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0GICAL REVIEWS
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Physiology and Pharmacology of Corticotr
releasing Factor*} logy and Experimental Therapeutics
 Pharmacology of Co:
 releasing Factor*

FEL J. OWENS AND CHARLES B. NEMEROFF† **Teleasing Factor***
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on Schizophrenia and Depression.
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Atlanta, GA 30322.

I. Introduction and Historical Perspectives

CRF^{\ddagger} is the major physiological regulator of the secre-**1. Introduction and Historical Perspectives**
CRF‡ is the major physiological regulator of the secre-
tion of ACTH, β -endorphin, and other POMC-derived
peptides from the anterior pituitary gland. Simply stated, I. Introduction and Historical Perspectives
CRF‡ is the major physiological regulator of the secre-
tion of ACTH, β -endorphin, and other POMC-derived
peptides from the anterior pituitary gland. Simply stated,

peptides from the anterior pituitary gland. Simply stated,

[†]Abbreviations: CRF, corticotropin-releasing factor; ACTH, adre-

nocorticotropic hormone; POMC, pro-opiomelanocortin; CNS, central

nervous system; LHRH, lutei that the previations: CRF, corticotropin-releasing factor; ACTH, adre-
nocorticotropic hormone; POMC, pro-opiomelanocortin; CNS, central
nervous system; LHRH, luteinizing hormone-releasing hormone HPA,
hypothalamic-pituita \dagger Abbreviations: CRF, corticotropin-releasing factor; ACTH, adre-
nocorticotropic hormone; POMC, pro-opiomelanocortin; CNS, central
nervous system; LHRH, luteinizing hormone-releasing hormone HPA,
thypothalamic-pituitar ‡Abbreviations: CRF, corticotropin-releasing factor; ACTH, adre-
nocorticotropic hormone; POMC, pro-opiomelanocortin; CNS, central
nervous system; LHRH, luteinizing hormone-releasing hormone HPA,
hypothalamic-pituitary-adr nocorticotropic hormone; POMC, pro-opiomelanocortin; CNS, central enervous system; LHRH, luteinizing hormone-releasing hormone HP
hypothalamic-pituitary-adrenal; LH, luteinizing hormone; oCRF, ovi
CRF; mRNA, messenger ribo nervous system; LHRH, luteinizing hormone-releasing hormone HPA,
hypothalamic-pituitary-adrenal; LH, luteinizing hormone; oCRF, ovine
CRF; mRNA, messenger ribonucleic acid; PVN, paraventricular nu-
cleus; BNST, bed nucleus CRF; mRNA, messenger ribonucleic acid; PVN, paraventricular nucleus; BNST, bed nucleus of the stria terminalis; cAMP, cyclic adenosine monophosphate; i.c.v., intracerebroventricular(ly); AVP, arginine vasopressin; GABA, cleus; BNST, bed nucleus of the stria terminalis; cAMP, cyclic adeno-
sine monophosphate; i.c.v., intracerebroventricular(ly); AVP, arginine
vasopressin; GABA, γ -aminobutyric acid; 5-HT, 5-hydroxytryptamine;
i.v., intra cleus; BNST, bed nucleus of the stria terminalis; cAMP, cyclic adenosine monophosphate; i.c.v., intracerebroventricular(ly); AVP, arginine vasopressin; GABA, γ -aminobutyric acid; 5-HT, 5-hydroxytryptamine; i.v., intrave sine monophosphate; i.c.v., intracerebroventricular(ly); AVP, arterleukin; GABA, γ -aminobutyric acid; 5-HT, 5-hydroxytrypteliv., intravenous(ly); FSL, Flinders sensitive line; SHR, spontanely
hypertensive rat; ECT, elec **vasopressin; GABA, γ-aminobutyric**
i.v., intravenous(ly); FSL, Flinders
hypertensive rat; ECT, electroconv
IL, interleukin; MAP, mean arteria
graphic; CSF, cerebrospinal fluid.

CRF is the predominant chemical messenger by which
the CNS controls the activity of the pituitary-adrenal CRF is the predominant chemical messenger by whithe CNS controls the activity of the pituitary-adrenalis and is, therefore, ultimately responsible for orch CRF is the predominant chemical messenger by whithe CNS controls the activity of the pituitary-adrendistical responsible for orches-
axis and is, therefore, ultimately responsible for orches-
trating the endocrine response CRF is the predominant chemical messenger by which
the CNS controls the activity of the pituitary-adrenal
axis and is, therefore, ultimately responsible for orches-
trating the endocrine response to stress. This has been
h CKF is the predominant chemical messenger by which
the CNS controls the activity of the pituitary-adrenal
axis and is, therefore, ultimately responsible for orches-
trating the endocrine response to stress. This has been
h the CNS controls the activity of the pituitary-adrenal
axis and is, therefore, ultimately responsible for orches-
trating the endocrine response to stress. This has been
hypothesized to be the case since the 1950s and has axis and is, therefore, ultimately responsible for orches-
trating the endocrine response to stress. This has been
hypothesized to be the case since the 1950s and has been
decisively demonstrated to be so for nearly a deca hypothesized to be the case since the 1950s and has been
decisively demonstrated to be so for nearly a decade. In
the past 5 years, overwhelming evidence has accumulated
that is concordant with the hypothesis that CRF also nypothesized to be the case since the 1950s and has been
decisively demonstrated to be so for nearly a decade. In
the past 5 years, overwhelming evidence has accumulated
that is concordant with the hypothesis that CRF also decisively demonstrated to be so for nearly a decade. In
the past 5 years, overwhelming evidence has accumulated
that is concordant with the hypothesis that CRF also
acts as a neurotransmitter within the CNS. Taken to-
get the past 5 years, overwhelming evidence has accumulated
that is concordant with the hypothesis that CRF also
acts as a neurotransmitter within the CNS. Taken to-
gether, the extant CRF literature strongly suggests that
CRF that is concordant with the hypothesis that CKF also
acts as a neurotransmitter within the CNS. Taken to-
gether, the extant CRF literature strongly suggests that
CRF integrates not only the endocrine but also the
autonomi acts as a neurotransmitter within the CNS. Taken
gether, the extant CRF literature strongly suggests t
CRF integrates not only the endocrine but also
autonomic, immunological, and behavioral responses
mammalian organisms t gether, the extant CRF literature strongly suggests that
CRF integrates not only the endocrine but also the
autonomic, immunological, and behavioral responses of
mammalian organisms to stress. Moreover, inappro-
priate CRF CKF integrates not only the endocrine but also the
autonomic, immunological, and behavioral responses of
mammalian organisms to stress. Moreover, inappro-
priate CRF neuronal activity may manifest itself in a
number of psy

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CORTICOTROPIN-
Orders, anxiety disorders, anorexia nervosa, and Alz-
heimer's disease. orders, anxiety c
heimer's disease.
Although such

CORTICOTROPIN-RELI

imer's disease.

Although such an all-encompassing role for a single trurotransmitter substance may initially seem somewhat orders, anxiety disorders, anorexia nervosa, and Alz-
heimer's disease.
Although such an all-encompassing role for a single
neurotransmitter substance may initially seem somewhat
surprising, the burgeoning database support heimer's disease. and all-encompassing role for a single trom
neurotransmitter substance may initially seem somewhat late
surprising, the burgeoning database supports what is the
quite simple and elegant teleologically. Th Although such an all-encompassing role for a single
neurotransmitter substance may initially seem somewhat
surprising, the burgeoning database supports what is
quite simple and elegant teleologically. The amino acid
sequen neurotransmitter substance may initially seem somewhat late
surprising, the burgeoning database supports what is the
quite simple and elegant teleologically. The amino acid fact
sequence of CRF has been highly conserved th surprising, the burgeoning database supports what
quite simple and elegant teleologically. The amino a
sequence of CRF has been highly conserved through
the evolutionary process. CRF has been identified
mammals and birds, quite simple and elegant teleologically. The amino acid
sequence of CRF has been highly conserved throughout
the evolutionary process. CRF has been identified in
mammals and birds, with homologs of CRF demon-
strated in am the evolutionary process. CRF has been identified in mammals and birds, with homologs of CRF demonstrated in amphibians and fish. Therefore, it appears that CRF-like compounds have been utilized by orga-
nisms for millions the evolutionary process. CRF has been identified in (Burgus et al., 1969).

mammals and birds, with homologs of CRF demon-Because Hans Selye (1936) observed that the "general

strated in amphibians and fish. Therefore, it mammals and birds, with homologs of CRF demonstrated in amphibians and fish. Therefore, it appears
that CRF-like compounds have been utilized by orga-
nisms for millions of years in which they apparently
function in an ada strated in amphibians and fish. Therefore, it appear
that CRF-like compounds have been utilized by orga
nisms for millions of years in which they apparentl
function in an adaptive role to mediate stress responses
Although that CRF-like compounds have been utilized by orga-
nisms for millions of years in which they apparently che
function in an adaptive role to mediate stress responses. po
Although these compounds may have originally func-
n misms for millions of years in which they apparently
function in an adaptive role to mediate stress responses.
Although these compounds may have originally func-
tioned simply to mobilize sources of energy to help flee
pre function in an adaptive role to mediate stress responses. port
Although these compounds may have originally func-
tioned simply to mobilize sources of energy to help flee stre
predators or other threatening conditions, as Although these compounds may have originally functioned simply to mobilize sources of energy to help flee predators or other threatening conditions, as animals developed evolutionarily, CRF appears to have taken on a more tioned simply to mobilize sources of energy to help fl
predators or other threatening conditions, as anima
developed evolutionarily, CRF appears to have taken
a more complex role in integrating the organism's
sponses (endo predators or other threatening conditions, as animals avadeveloped evolutionarily, CRF appears to have taken on ers a more complex role in integrating the organism's rechasionses (endocrine, behavioral, autonomic, and immu developed evolutionarily, CRF appears to have taken on
a more complex role in integrating the organism's re-
sponses (endocrine, behavioral, autonomic, and immu-
nological) to stress. Recent evidence suggests that a
simila a more complex role in integrating the organism's responses (endocrine, behavioral, autonomic, and immu-
nological) to stress. Recent evidence suggests that a
similar evolutionary sequence of events may have oc-
curred for sponses (endocrine, behavioral, autonomic, and immunological) to stress. Recent evidence suggests that similar evolutionary sequence of events may have o curred for LHRH (gonadotropin-releasing hormone Thus, not only does similar evolutionary sequence of events may have occurred for LHRH (gonadotropin-releasing hormone).
Thus, not only does this decapeptide control the secrecurred for LHRH (gonadotropin-releasing hormone). the Thus, not only does this decapeptide control the secretion of sex steroids by functioning as the major physiolical regulator of pituitary gonadotropin release but it C tion of sex steroids by functioning as the major physio-
logical regulator of pituitary gonadotropin release but it
also appears to directly influence behavioral aspects of
reproductive behavior by acting on CNS neurons.
I In the present review, it is our intention to sex steroids by functioning as the major physio-
gical regulator of pituitary gonadotropin release but it
so appears to directly influence behavioral aspects of
productive beha logical regulator of pituitary gonadotropin release but it also appears to directly influence behavioral aspects of reproductive behavior by acting on CNS neurons. In the present review, it is our intention to summarize th

also appears to directly influence behavioral aspects of ex-
reproductive behavior by acting on CNS neurons. Summarize
In the present review, it is our intention to summarize
withe well-established data concerning CRF (i.e reproductive behavior by acting on CNS neurons. sub
In the present review, it is our intention to summarize was
the well-established data concerning CRF (i.e., physical to properties, localization, neuroendocrine function) In the present review, it is our intention to summarize
the well-established data concerning CRF (i.e., physical
properties, localization, neuroendocrine function), as
well as to scrutinize the experimental data suggesting the well-established data concerning CRF (i.e., physical to properties, localization, neuroendocrine function), as means well as to scrutinize the experimental data suggesting a radehavioral, autonomic, and immunological f properties, localization, neuroendocrine function), as n
well as to scrutinize the experimental data suggesting a
behavioral, autonomic, and immunological function for la
CRF in the organism's response to stress. Moreover, well as to scrutinize the experimental data suggesting a behavioral, autonomic, and immunological function for CRF in the organism's response to stress. Moreover, is dysregulation of CRF neuronal activity responsible for s behavioral, autonomic, and immunological function for CRF in the organism's response to stress. Moreover, is dysregulation of CRF neuronal activity responsible for some aspects of mental illness and, if this is the case, w CRF in the organism's response to stress. Moreover, is fidysregulation of CRF neuronal activity responsible for some aspects of mental illness and, if this is the case, between what are the clinical implications for future dysregulation of CRF neuronal
some aspects of mental illness a
what are the clinical implication
strategies? We have used pertin
up until the early part of 1991.
Early morphological investiga what are the clinical implications for future treatment
strategies? We have used pertinent references gathered
up until the early part of 1991.
Early morphological investigation of the anterior pi-
tuitary showed that it w

adrenal and gonadal atrophy. It was not until the late 1940s that Harris (1948) and colleagues in England confirmed the neurohumoral control of anterior pituitary hormone secretion. In this "chemotransmitter-portal vessel what are the clinical implications for future treatment
strategies? We have used pertinent references gathered
up until the early part of 1991.
Early morphological investigation of the anterior pi-
tuitary showed that it w strategies? We have used pertinent references gather
up until the early part of 1991.
Early morphological investigation of the anterior p
tuitary showed that it was completely free of dire
neuronal innervation. In the earl up until the early part of 1991.
Early morphological investigation of the anteri
tuitary showed that it was completely free of
neuronal innervation. In the early 1930s, Popa and
ing (1933) described the existence of a hypo Early morphological investigation of the anterior pituitary showed that it was completely free of direct neuronal innervation. In the early 1930s, Popa and Fielding (1933) described the existence of a hypothalamohy-pophysi tuitary showed that it was completely free of direct
neuronal innervation. In the early 1930s, Popa and Field-
ing (1933) described the existence of a hypothalamohy-
pophysial portal vessel system. However, controversy
aro neuronal innervation. In the early 1930s, Popa and Fielding (1933) described the existence of a hypothalamoh,
pophysial portal vessel system. However, controvers
arose concerning the direction of blood flow, and the
findin ing (1933) described the existence of a hypothalamohy-
pophysial portal vessel system. However, controversy co
arose concerning the direction of blood flow, and their A
(findings were subsequently disregarded as unimportan pophysial portal vessel system. However, controve
arose concerning the direction of blood flow, and the
findings were subsequently disregarded as unimporta
At this same time, the notion of humoral control of
anterior pitui arose concerning the direction of blood flow, and their A

findings were subsequently disregarded as unimportant. (G

At this same time, the notion of humoral control of the this

anterior pituitary gland by the brain was findings were subsequently disregarded as unimportant. (At this same time, the notion of humoral control of the tanterior pituitary gland by the brain was first hypothe-
sized. In a number of animal and human studies which At this same time, the notion of humoral control of the anterior pituitary gland by the brain was first hypothe-
sized. In a number of animal and human studies which
utilized laboratory animals or soldiers who had been war anterior pituitary gland by the brain was first hypothe-

sized. In a number of animal and human studies which

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utilized laboratory animals or soldiers who had been war

intercasualties, lesions of the hypothalamus r sized. In a number of animal and human studies which 19
utilized laboratory animals or soldiers who had been war int
casualties, lesions of the hypothalamus resulted in pro-
iso
found decreases in pituitary function as evi utilized laboratory animals or soldiers who had been ware
casualties, lesions of the hypothalamus resulted in pro-
found decreases in pituitary function as evidenced by
adrenal and gonadal atrophy. It was not until the lat casualties, lesions of the hypothalamus resulted in pro-
found decreases in pituitary function as evidenced by
firmed the isolation and adrenal and gonadal atrophy. It was not until the late
firmed and gonadal atrophy. It found decreases in pituitary function as evidenced adrenal and gonadal atrophy. It was not until the 1940s that Harris (1948) and colleagues in England firmed the neurohumoral control of anterior pit hormone secretion. In

heimer's disease. The animal encompassing role for a single trol of anterior pituitary. However, although the humoral con-
Although such an all-encompassing role for a single trol of anterior pituitary function was confirm LEASING FACTOR
via the portal vessels from the hypothalamus to the
anterior pituitary. However, although the humoral con-LEASING FACTOR
via the portal vessels from the hypothalamus to the
anterior pituitary. However, although the humoral con-
trol of anterior pituitary function was confirmed in the 427

via the portal vessels from the hypothalamus to the

anterior pituitary. However, although the humoral con-

trol of anterior pituitary function was confirmed in the

late 1940s and early 1950s, nearly 20 years elapse via the portal vessels from the hypothalamus to the
anterior pituitary. However, although the humoral con-
trol of anterior pituitary function was confirmed in the
late 1940s and early 1950s, nearly 20 years elapsed before via the portal vessels from the hypothalamus to the
anterior pituitary. However, although the humoral con-
trol of anterior pituitary function was confirmed in the
late 1940s and early 1950s, nearly 20 years elapsed before anterior pituitary. However, although the humoral control of anterior pituitary function was confirmed in the late 1940s and early 1950s, nearly 20 years elapsed before the chemical identity of the first hypothalamic relea trol of anterior pituitary function was confirmed in the
late 1940s and early 1950s, nearly 20 years elapsed before
the chemical identity of the first hypothalamic releasing
factor, thyrotropin-releasing hormone, was achie late 1940s and early 19.
the chemical identity c
factor, thyrotropin-rele
Schally's group (Bøler (
(Burgus et al., 1969).
Because Hans Selye e chemical identity of the first hypothalamic releasing
ctor, thyrotropin-releasing hormone, was achieved by
hally's group (Bøler et al., 1969) and Guilleman's group
urgus et al., 1969).
Because Hans Selye (1936) observed Schally's group (Bøler et al., 1969) and Guilleman's group
(Burgus et al., 1969).
Because Hans Selve (1936) observed that the "general

similar evolutionary sequence of events may have oc-

curred for LHRH (gonadotropin-releasing hormone). the HPA axis in experimental animals has confounded

Thus, not only does this decapeptide control the secre-

tion of Schally's group (Bøler et al., 1969) and Guilleman's group
(Burgus et al., 1969).
Because Hans Selye (1936) observed that the "general
adaptation syndrome" following exposure to stress acti-
vated the pituitary-adrenocorti (Burgus et al., 1969).
Because Hans Selye (1936) observed that the "general
adaptation syndrome" following exposure to stress acti-
vated the pituitary-adrenocortical axis, elucidation of the
chemical identity of CRF was c Because Hans Selye (1936) observed that the "general
adaptation syndrome" following exposure to stress acti-
vated the pituitary-adrenocortical axis, elucidation of the
chemical identity of CRF was clearly of paramount imadaptation syndrome" following exposure to stress activated the pituitary-adrenocortical axis, elucidation of the chemical identity of CRF was clearly of paramount importance to any comprehensive understanding of the neura vated the pituitary-adrenocortical axis, elucidation of the
chemical identity of CRF was clearly of paramount im-
portance to any comprehensive understanding of the
neural mechanisms that mediate the HPA response to
stress chemical identity of CRF was clearly of paramount
portance to any comprehensive understanding of
neural mechanisms that mediate the HPA respons
stress. The clinical importance of the HPA axis, and
availability of bioassays portance to any comprehensive understanding of the
neural mechanisms that mediate the HPA response to
stress. The clinical importance of the HPA axis, and the
availability of bioassays to measure ACTH, led research-
ers in stress. The clinical importance of the HPA axis, and the
availability of bioassays to measure ACTH, led research-
ers in the early 1950s to focus on CRF prior to attempting
characterization of other putative hypothalamic r stress. The clinical importance of the HPA axis, and the
availability of bioassays to measure ACTH, led research-
ers in the early 1950s to focus on CRF prior to attempting
characterization of other putative hypothalamic r availability of bioassays to measure ACTH, led research-
ers in the early 1950s to focus on CRF prior to attempting
characterization of other putative hypothalamic releas-
ing factors. However, elucidation of the structure ers in the early 1950s to focus on CRF prior to attempting
characterization of other putative hypothalamic releas-
ing factors. However, elucidation of the structure of CRF
proved difficult for several reasons. First, the characterization of other putative hypothalamic releasing factors. However, elucidation of the structure of CRF proved difficult for several reasons. First, the ease with which almost any novel stimulus (mild stressor) act proved difficult for several reasons. First, the ease with proved difficult for several reasons. First, the ease with
which almost any novel stimulus (mild stressor) activates
the HPA axis in experimental animals has confounded
many studies. Second, because many neurotransmitters
 which almost any novel stimulus (mild stressor) activates
the HPA axis in experimental animals has confounded
many studies. Second, because many neurotransmitters
in tissue extracts other than authentic CRF possess
CRF-lik in tissue extracts other than authentic CRF possess CRF-like activity and can enhance ACTH secretion, extreme caution was necessary before any endogenous substance could be deemed the physiological CRF. This many studies. Second, because many neurotransmitters
in tissue extracts other than authentic CRF possess
CRF-like activity and can enhance ACTH secretion,
extreme caution was necessary before any endogenous
substance could in tissue extracts other than authentic CRF possess
CRF-like activity and can enhance ACTH secretion,
extreme caution was necessary before any endogenous
substance could be deemed the physiological CRF. This
was a particul CRF-like activity and can enhance ACTH secretion,
extreme caution was necessary before any endogenous
substance could be deemed the physiological CRF. This
was a particular problem with regard to the bioassay used
to ident extreme caution was necessary before any endogenous
substance could be deemed the physiological CRF. This
was a particular problem with regard to the bioassay used
to identify CRF activity in which ACTH release was
measure substance could be deemed the physiological CRF. T
was a particular problem with regard to the bioassay u
to identify CRF activity in which ACTH release
measured from hemipituitaries in vitro. Finally,
radioimmunoassay for to identify CRF activity in which ACTH release was
measured from hemipituitaries in vitro. Finally, the
radioimmunoassay for ACTH also proved to be particu-
larly problematic, because of poor sensitivity and speci-
ficity. ficity. easured from hemipituitaries in vitro. Finally, the
dioimmunoassay for ACTH also proved to be particu-
rly problematic, because of poor sensitivity and speci-
ity.
The systematic search for CRF in hypothalamic tissue
gan w

radioimmunoassay for ACTH also proved to be particularly problematic, because of poor sensitivity and specificity.
The systematic search for CRF in hypothalamic tissue
began with the work of Saffran and Schally (1955) and
 larly problematic, because of poor sensitivity and specificity.

The systematic search for CRF in hypothalamic tissue

began with the work of Saffran and Schally (1955) and

Guillemin and Rosenberg (1955). Thereafter, Scha ficity.
The systematic search for CRF in hypothalamic tissue
began with the work of Saffran and Schally (1955) and
Guillemin and Rosenberg (1955). Thereafter, Schally and
Guillemin working together at McGill University use The systematic search for CRF in hypothalamic tissue
began with the work of Saffran and Schally (1955) and
Guillemin and Rosenberg (1955). Thereafter, Schally and
Guillemin working together at McGill University used
extrac began with the work of Saffran and Schally (1955) and
Guillemin and Rosenberg (1955). Thereafter, Schally and
Guillemin working together at McGill University used
extracts of neurohypophysial tissue and gel filtration
chr Guillemin and Rosenberg (1955). Thereafter, Schally and

Guillemin working together at McGill University used

extracts of neurohypophysial tissue and gel filtration

chromatography to identify CRF-like activity in three
 Guillemin working together at McGill University used
extracts of neurohypophysial tissue and gel filtration
chromatography to identify CRF-like activity in three
separate fractions which they labeled α_1 , α_2 (simil extracts of neurohypophysial tissue and gel filtration
chromatography to identify CRF-like activity in three
separate fractions which they labeled α_1 , α_2 (similar to
 α -melanocyte-stimulating hormone) and β (chromatography to identify CRF-like activity in three
separate fractions which they labeled α_1 , α_2 (similar to
 α -melanocyte-stimulating hormone) and β (similar to
vasopressin) (Schally et al., 1960, 1962). T separate fractions which they labeled α_1 , α_2 (similar to α -melanocyte-stimulating hormone) and β (similar to vasopressin) (Schally et al., 1960, 1962). They also discovered that extracts of porcine hypothala α -melanocyte-stimulating hormone) and β (similar to vasopressin) (Schally et al., 1960, 1962). They also discovered that extracts of porcine hypothalamus contained ACTH and α - and β -melanocyte-stimulating horm vasopressin) (Schally et al., 1960, 1962). They also dis-
covered that extracts of porcine hypothalamus contained
ACTH and α - and β -melanocyte-stimulating hormone
(Guillemin et al., 1962). Although remarkable in tha covered that extracts of porcine hypothalamus contained ACTH and α - and β -melanccyte-stimulating hormone (Guillemin et al., 1962). Although remarkable in that this finding anticipated by 16 years the discovery of PO ACTH and α - and β -melanocyte-stimulating hormone (Guillemin et al., 1962). Although remarkable in that this finding anticipated by 16 years the discovery of POMC-derived peptides in the brain (Krieger and Liotta, 19 (Guillemin et al., 1962). Although remarkable in that
this finding anticipated by 16 years the discovery of
POMC-derived peptides in the brain (Krieger and Liotta,
1979), this finding further increased the difficulty of
in this finding anticipated by 16 years the discovery
POMC-derived peptides in the brain (Krieger and Liot
1979), this finding further increased the difficulty
interpreting the assay data, and serious work on t
isolation of C DMC-derived peptides in the brain (Krieger and Liotta,
79), this finding further increased the difficulty of
terpreting the assay data, and serious work on the
plation of CRF was brought to a halt (Fink, 1981).
The more th interpreting the assay data, and serious work on the isolation of CRF was brought to a halt (Fink, 1981).
The more than 25-year delay in the isolation and

interpreting the assay data, and serious work on the isolation of CRF was brought to a halt (Fink, 1981).
The more than 25-year delay in the isolation and characterization of CRF after unequivocal evidence for its existenc isolation of CRF was brought to a halt (Fink, 1981).
The more than 25-year delay in the isolation and
characterization of CRF after unequivocal evidence for
its existence can be attributed, as noted above, to several
facto The more than 25-year delay in the isolation and
characterization of CRF after unequivocal evidence for
its existence can be attributed, as noted above, to several
factors. The bioassays were problematic because of their
l characterization of CRF after unequivocal evidence for
its existence can be attributed, as noted above, to several
factors. The bioassays were problematic because of their
lack of specificity, although their sensitivity wa

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says could be confounded by the fact that other substances can directly stimulate ACTH release, albeit less Solution 128 COMENS AND NE

stances can directly stimulate ACTH release, albeit less of

potently than authentic CRF, and/or potentiate the efowend also says could be confounded by the fact that other substances can directly stimulate ACTH release, albeit less potently than authentic CRF, and/or potentiate the effects of CRF itself. Whole hypothalamic extracts a says could be confounded by the fact that other sub-
stances can directly stimulate ACTH release, albeit less of t
potently than authentic CRF, and/or potentiate the ef-
fects of CRF itself. Whole hypothalamic extracts als says could be confounded by the fact that other sub-
stances can directly stimulate ACTH release, albeit less of t
potently than authentic CRF, and/or potentiate the ef-
fects of CRF itself. Whole hypothalamic extracts als stances can directly stimulate ACTH release, albeit less
potently than authentic CRF, and/or potentiate the ef-
fects of CRF itself. Whole hypothalamic extracts also
contain ACTH. Furthermore, because the sizes of CRF
(41 potently than authentic CRF, and/or potentiate the ef-
fects of CRF itself. Whole hypothalamic extracts also sequentain ACTH. Furthermore, because the sizes of CRF mR
(41 amino acids) and ACTH (39 amino acids) are similar fects of CRF itself. Whole hypothalamic extracts also
contain ACTH. Furthermore, because the sizes of CRF
(41 amino acids) and ACTH (39 amino acids) are similar,
the two peptides are generally not easily separable by
liqui contain ACTH. Furthermore, because the sizes of CRF m1
(41 amino acids) and ACTH (39 amino acids) are similar, 19
the two peptides are generally not easily separable by aci
liquid chromatography. The in vitro bioassay sys (41 amino acids) and ACTH (39 amino acids) are similar, the two peptides are generally not easily separable by liquid chromatography. The in vitro bioassay systems were also vulnerable to nonspecific secretagogues found i the two peptides are generally not easily separable by
liquid chromatography. The in vitro bioassay systems β -li
were also vulnerable to nonspecific secretagogues found cur
in tissue extracts, such as myelin basic prot liquid chromatography. The
were also vulnerable to nonsp
in tissue extracts, such as mye
K⁺, and the components of
solvents (Vale et al., 1983a).
In 1981, Wylie Vale and coll In the also vulnerable to nonspecific secretagogues found

In tissue extracts, such as myelin basic protein, histones,

^t, and the components of a variety of buffers and

lvents (Vale et al., 1983a).

In 1981, Wylie Vale

in tissue extracts, such as myelin basic protein, histones, K^+ , and the components of a variety of buffers and solvents (Vale et al., 1983a).
In 1981, Wylie Vale and colleagues at the Salk Institute (Vale et al., 1981; K⁻, and the components of a variety of buffers and solvents (Vale et al., 1983a).

In 1981, Wylie Vale and colleagues at the Salk Institute 1986, C

(Vale et al., 1981; Spiess et al., 1981; Rivier et al., 1982c)

isolate solvents (Vale et al., 1983a).

In 1981, Wylie Vale and colleagues at the Salk Institute

(Vale et al., 1981; Spiess et al., 1981; Rivier et al., 1982c)

isolated and characterized a 41-amino acid peptide from

extracts of In 1981, Wylie Vale and colleagues at the
(Vale et al., 1981; Spiess et al., 1981; Rivie
isolated and characterized a 41-amino acie
extracts of ovine hypothalamus with the
mary structure: H-Ser-Gln-Glu-Pro-Pr
Asp-Leu-Thr-P Asp-Leu-Thr-Phe-His-Leu-Leu-Arg-Glu-Val-Leu-Glu-Met-Thr-Lys-Ala-Asp-Gln-Leu-Ala-Gln-Gln-Ala-His-Ser-Asn-Arg-Lys-Leu-Leu-Asp-Ile-Ala-NH₂. Starting A. Corticotropin-r
material for this purification was a side fraction of pearly. RNA Localization mary structure: H-Ser-Gln-Glu-Pro-Pro-Ile-Ser-Leu-
Asp-Leu-Thr-Phe-His-Leu-Leu-Arg-Glu-Val-Leu-Glu-
Met-Thr-Lys-Ala-Asp-Gln-Leu-Ala-Gln-Gln-Ala-His-
Ser-Asn-Arg-Lys-Leu-Leu-Asp-Ile-Ala-NH₂. Starting A.
material for this Asp-Leu-Thr-Phe-His-Leu-Leu-Arg-Glu-Val-Leu-Glu
Met-Thr-Lys-Ala-Asp-Gln-Leu-Ala-Gln-Gln-Ala-His
Ser-Asn-Arg-Lys-Leu-Leu-Asp-Ile-Ala-NH₂. Startin
material for this purification was a side fraction of nearl
500,000 fragmen Met-Thr-Lys-Ala-Asp-Gln-Leu-Ala-Gln-Gln-Ala-H
Ser-Asn-Arg-Lys-Leu-Leu-Asp-Ile-Ala-NH₂. Start
material for this purification was a side fraction of nea
500,000 fragments of ovine hypothalamus initially pr
essed during the Ser-Asn-Arg-Lys-Leu-Leu-Asp-Ile-Ala-NH₂. Starting α
material for this purification was a side fraction of nearly
500,000 fragments of ovine hypothalamus initially proc-
essed during the characterization of LHRH. A co material for this purification was a side from 500,000 fragments of ovine hypothalamu essed during the characterization of LH hensive review of the isolation and change CRF was written by Vale et al. (1983a). The structure 0,000 fragments of ovine hypothalamus initially proc-
sed during the characterization of LHRH. A compre-
nsive review of the isolation and characterization of
RF was written by Vale et al. (1983a).
The structure of oCRF is

essed during the characterization of LHRH. A compre-
hensive review of the isolation and characterization of te
CRF was written by Vale et al. (1983a). ge
The structure of oCRF is homologous with several in
known peptides hensive review of the isolation and characterization of ter

CRF was written by Vale et al. (1983a). See ger

The structure of oCRF is homologous with several im

known peptides including sauvagine and urotensin I stu

(Pa CRF was written by Vale et al. (1983a). get
The structure of oCRF is homologous with several in
known peptides including sauvagine and urotensin I st
(Pallai et al., 1983). Sauvagine was isolated from the skin be
of the So The structure of oCRF is homologous with several im
known peptides including sauvagine and urotensin I stu
(Pallai et al., 1983). Sauvagine was isolated from the skin
of the South American frog *Phylomedusa sauvagei*. Mor known peptides including sauvagine and urotensin I
(Pallai et al., 1983). Sauvagine was isolated from the skin
of the South American frog *Phylomedusa sauvagei*. More
than 50% of the residues in sauvagine are identical wi (Pallai et al., 1983). Sauvagine was isolated from the skin
of the South American frog *Phylomedusa sauvagei*. More
than 50% of the residues in sauvagine are identical with
those in oCRF; the majority of the remaining res of the South American frog *Phylomedusa sauvagei*. More than 50% of the residues in sauvagine are identical with those in oCRF; the majority of the remaining residues is are conservative substitutions. Both sauvagine and than 50% of the residues in sauvagine are identical with
those in oCRF; the majority of the remaining residues
are conservative substitutions. Both sauvagine and oCRF
are closely related to a third peptide, urotensin I, is those in oCRF; the majority of the remaining residues
are conservative substitutions. Both sauvagine and oCRF
are closely related to a third peptide, urotensin I, isolated
from the urohypophysis of two species of fish, *Ca* are conservative substitutions. Both sauvagine and oClare closely related to a third peptide, urotensin I, isolat
from the urohypophysis of two species of fish, Catostom
cyprimus and Catostomus catostomus. CRF also shai
so are closely related to a third peptide, urotensin I, isolated
from the urohypophysis of two species of fish, *Catostomus*
ala
cyprimus and *Catostomus catostomus*. CRF also shares
some homology with calmodulin and angioten from the urohypophysis of two species of fish, Catostor cyprimus and Catostomus catostomus. CRF also shas
some homology with calmodulin and angiotensinos
The tetrapeptide Phe-His-Leu-Leu is common to b
angiotensinogen and some homology with calmodulin and angiotensinogen.
The tetrapeptide Phe-His-Leu-Leu is common to both
angiotensinogen and oCRF and is the site in angioten-
sinogen of renin and converting enzyme cleavage. This
may reflect The tetrapeptide Phe-His-Leu-Leu is common to both
angiotensinogen and oCRF and is the site in angioten-
sinogen of renin and converting enzyme cleavage. This
may reflect a distant ancestral relationship between an-
gioten may reflect a distant ancestral relationship between an-
giotensinogen and oCRF, each of which can modulate
adrenocortical function (Vale et al., 1983a).
Rat and human CRF have an identical structure and reflect a distant ancestral relationship between and the set of which can modulate the distant and occurs of which can modulate the remocortical function (Vale et al., 1983a).
Rat and human CRF have an identical structure

may reflect a distant ancestral relationship between an-
giotensinogen and oCRF, each of which can modulate
adrenocortical function (Vale et al., 1983a).
Rat and human CRF have an identical structure and
differ from oCRF i adrenocortical function (Vale et al., 1983a).

Rat and human CRF have an identical structure and

differ from oCRF in only seven of the 41 residues (Spiess

et al., 1983). Although detailed determination of the

active por Rat and human CRF have an identical structure and
differ from oCRF in only seven of the 41 residues (Spiess
et al., 1983). Although detailed determination of the
active portion of the CRF molecule has been studied by
a nu differ from oCRF in only seven of the 41 residues (Spiess

et al., 1983). Although detailed determination of the

active portion of the CRF molecule has been studied by

a number of investigators, other than the work of Je et al., 1983). Although detailed determination of the $\frac{1}{10}$ active portion of the CRF molecule has been studied by $\frac{1}{10}$ a number of investigators, other than the work of Jean Rivier and colleagues (1984) at the active portion of the CRF molecule has been studied by
a number of investigators, other than the work of Jean
Rivier and colleagues (1984) at the Salk Institute, little
has been published. However, utilizing ACTH secretion a number of investigators, other than the work of Jean 19.

Rivier and colleagues (1984) at the Salk Institute, little als

has been published. However, utilizing ACTH secretion present

and adenylate cyclase activity in v Rivier and colleagues (1984) at the Salk Institute, little
has been published. However, utilizing ACTH secretion
and adenylate cyclase activity in vitro, Aguilera et al.
(1983) determined that bioactivity resides within t has been published. However, utilizing ACTH secretion provided and adenylate cyclase activity in vitro, Aguilera et al. (1983) determined that bioactivity resides within the coCOOH-terminal 27 amino acid residues. However and adenylate cyclase activity in vitro, Aguilera et al.

(1983) determined that bioactivity resides within the

COOH-terminal 27 amino acid residues. However, the

much weaker affinity for the

used as an antagonist, has (1983) determined that bioactivity resides within the COOH-terminal 27 amino acid residues. However, the weak CRF partial agonist, α -helical CRF₉₋₄₁, which is used as an antagonist, has much weaker affinity for the C

NEMEROFF
taining the first eight residues. Therefore, many regions
of the CRF molecule are necessary for full function. NEMEROFF
taining the first eight residues. Therefore, many reg
of the CRF molecule are necessary for full function.
Numa and colleagues were the first to clone the L

MEROFF
ining the first eight residues. Therefore, many regions
the CRF molecule are necessary for full function.
Numa and colleagues were the first to clone the DNA
quences complementary to the human and ovine taining the first eight residues. Therefore, many regions
of the CRF molecule are necessary for full function.
Numa and colleagues were the first to clone the DNA
sequences complementary to the human and ovine
mRNA encodin taining the first eight residues. Therefore, many regions
of the CRF molecule are necessary for full function.
Numa and colleagues were the first to clone the DNA
sequences complementary to the human and ovine
mRNA encodin of the CRF molecule are necessary for full function.

Numa and colleagues were the first to clone the DNA

sequences complementary to the human and ovine

mRNA encoding the CRF precursor (Furutani et al.,

1983; Shibahara Numa and colleagues were the first to clone the DNA
sequences complementary to the human and ovine
mRNA encoding the CRF precursor (Furutani et al.,
1983; Shibahara et al., 1983). Comparison of the amino
acid sequence of sequences complementary to the human and ovine
mRNA encoding the CRF precursor (Furutani et al.,
1983; Shibahara et al., 1983). Comparison of the amino
acid sequence of oCRF precursor with that of the ACTH-
 β -lipotropin 1983; Shibahara et al., 1983). Comparison of the amino acid sequence of oCRF precursor with that of the ACTH- β -lipotropin precursor and the AVP-neurophysin II precursor suggests that these precursor proteins may be evo evolutionarily related as alluded to earlier. The strucacid sequence of oCRF precursor with that of the ACTH- β -lipotropin precursor and the AVP-neurophysin II precursor suggests that these precursor proteins may be evolutionarily related as alluded to earlier. The structur β -lipotropin precursor and the AVP-neurophysin II precursor suggests that these precursor proteins may be evolutionarily related as alluded to earlier. The structures of porcine, caprine, and bovine CRF have also been cursor suggests that these precursor proteins may be
evolutionarily related as alluded to earlier. The struc-
tures of porcine, caprine, and bovine CRF have also been
isolated and sequenced (Ling et al., 1984; Patthy et al evolutionarily related as alluded to earlier. The structures of porcine, caprine, and bovine CRF have also been
isolated and sequenced (Ling et al., 1984; Patthy et al.,
1986, Gouth et al., 1987). The structure of porcine tures of porcine, caprine, and bovine CRF have also been
isolated and sequenced (Ling et al., 1984; Patthy et al.,
1986, Gouth et al., 1987). The structure of porcine CRF
shows greater homology to rat and human CRF than it isolated and sequenced (
1986, Gouth et al., 1987)
shows greater homology
does to caprine and bov
closely resemble oCRF. II. Superstoner and bovine CRF; the latter to caprine and bovine CRF; the latter to
II. Distribution of Corticotropin-releas
Factor-containing Neurons and Recept to caprine and bovine CRF; the latter two mely resemble oCRF.
II. Distribution of Corticotropin-releasing
Factor-containing Neurons and Receptors
orticotropin-releasing Factor Peptide and Messen

A. Cosety resemble ockr.
 **A. Corticotropin-releasing Factor-containing Neurons and Receptors
** *A. Corticotropin-releasing Factor Peptide and Messenger***
** *RNA Localization* **H. Distribution
Factor-contain**
A. Corticotropin-relee
RNA Localization
1. Localization of

some homology with calmodulin and angiotensinogen. et al., 1983; Liposits et al., 1983a,b; Liposits and Paull,
The tetrapeptide Phe-His-Leu-Leu is common to both
angiotensinogen and oCRF and is the site in angioten-
sinoge et al., 1983). Although detailed determination of the al., 1983; Daikoku et al., 1983; Piekut and Joseph, and numerical function of the CRF molecule has been studied by the PVN. These CRF-positive cell bodies have been dif **7. Factor-containing Neurons and Receptors**
1. Corticotropin-releasing Factor Peptide and Messenger
1. Localization of corticotropin-releasing factor in the
central nervous system. Following the isolation, charac-*A. Corticotropin-releasing Factor Peptide and Messeng*
RNA Localization
1. Localization of corticotropin-releasing factor in
central nervous system. Following the isolation, chare
terization, and synthesis of CRF, a The diameter of the diameter and the sensor
RNA Localization
1. Localization of corticotropin-releasing factor in the
central nervous system. Following the isolation, charac-
terization, and synthesis of CRF, a number of g 1. Localization of corticotropin-releasing factor in the
central nervous system. Following the isolation, charac-
terization, and synthesis of CRF, a number of groups
generated polyclonal antibodies against CRF for use in
 1. Localization of corticotropin-releasing factor in the
central nervous system. Following the isolation, charac-
terization, and synthesis of CRF, a number of groups
generated polyclonal antibodies against CRF for use in
 central nervous system. Following the isolation, characterization, and synthesis of CRF, a number of groups
generated polyclonal antibodies against CRF for use in
immunohistochemical and radioimmunoassay mapping
studies of terization, and synthesis of CRF, a number of grogenerated polyclonal antibodies against CRF for use immunohistochemical and radioimmunoassay mapp studies of CRF-containing neurons. Cell bodies and bers that stain positive generated polyclonal antibodies against CRF for use
immunohistochemical and radioimmunoassay mappii
studies of CRF-containing neurons. Cell bodies and
bers that stain positively for CRF are located heterog
neously througho immunohistochemical and radioimmunoassay mapping
studies of CRF-containing neurons. Cell bodies and fi-
bers that stain positively for CRF are located heteroge-
neously throughout the CNS. The most widely recog-
nized and studies of CRF-containing neurons. Cell bodies and fibers that stain positively for CRF are located heterogeneously throughout the CNS. The most widely recognized and intensively studied population of CRF neurons is locate bers that stain positively for CRF are located heteroge-
neously throughout the CNS. The most widely recog-
nized and intensively studied population of CRF neurons
is located in the parvocellular region of the PVN of the
h neously throughout the CNS. The most widely rec
nized and intensively studied population of CRF neuro
is located in the parvocellular region of the PVN of
hypothalamus. Their major projection is to the med
eminence, the si nized and intensively studied population of CRF neurons
is located in the parvocellular region of the PVN of the
hypothalamus. Their major projection is to the median
eminence, the site of the primary plexus of the hypothis located in the parvocellular region of the PVN of the hypothalamus. Their major projection is to the median eminence, the site of the primary plexus of the hypothalamohypophysial portal system (Bloom et al., 1982; Kawat hypothalamus. Their major projection is to the median
eminence, the site of the primary plexus of the hypoth-
alamohypophysial portal system (Bloom et al., 1982;
Kawata et al., 1982, 1983; Pelletier et al., 1982; Antoni
et eminence, the site of the primary plexus of the hypoth-
alamohypophysial portal system (Bloom et al., 1982;
Kawata et al., 1982, 1983; Pelletier et al., 1982; Antoni
et al., 1983; Liposits et al., 1983a,b; Liposits and Pau alamohypophysial portal system (Bloom et al., 1982;
Kawata et al., 1982, 1983; Pelletier et al., 1982; Antoni
et al., 1983; Liposits et al., 1983a,b; Liposits and Paull,
1985; Schipper et al., 1984; Daikoku et al., 1985; P Kawata et al., 1982, 1983; Pelletier et al., 1982; Antoni et al., 1983; Liposits et al., 1983a,b; Liposits and Paull, 1985; Schipper et al., 1984; Daikoku et al., 1985; Piekut and Joseph, 1985; Rho and Swanson, 1987), although some fibers project to other hypothalamic nuclei and 1985; Schipper et al., 1984; Daikoku et al., 1985; Pie
and Joseph, 1985; Rho and Swanson, 1987), altho
some fibers project to other hypothalamic nuclei
extrahypothalmic brain areas. CRF-immunoreactive
bodies are also prese and Joseph, 1985; Rho and Swanson, 1987), although
some fibers project to other hypothalamic nuclei and
extrahypothalmic brain areas. CRF-immunoreactive cell
bodies are also present in a number of other hypotha-
lamic nucl some fibers project to other hypothalamic nuclei and
extrahypothalmic brain areas. CRF-immunoreactive cell
bodies are also present in a number of other hypotha-
lamic nuclei as well, although to a lesser extent than in
the observed in the supraoptic, suprachiasmatic, preoptic, bodies are also present in a number of other hypothalamic nuclei as well, although to a lesser extent than in
the PVN. These CRF-positive cell bodies have been
observed in the supraoptic, suprachiasmatic, preoptic,
premammillary, periventricular, arcuate, and magnocel-
lula the PVN. These CRF-positive cell bodies have been
observed in the supraoptic, suprachiasmatic, preoptic,
premammillary, periventricular, arcuate, and magnocel-
lular paraventricular nuclei (Kawata et al., 1982; Antoni
et a observed in the supraoptic, suprachiasmatic, preoptic,
premammillary, periventricular, arcuate, and magnocel-
lular paraventricular nuclei (Kawata et al., 1982; Antoni
et al., 1983; Daikoku et al., 1984, 1985; Piekut and J premammillary, periventricular, arcuate, and magnocel-
lular paraventricular nuclei (Kawata et al., 1982; Antoni
et al., 1983; Daikoku et al., 1984, 1985; Piekut and Joseph,
1985). Although some of these other hypothalamic lular paraventricular nuclei (K
et al., 1983; Daikoku et al., 1984
1985). Although some of these
also project to the median emir
projection fields are unknown.
During the past decade, nui al., 1983; Daikoku et al., 1984, 1985; Piekut and Joseph,
85). Although some of these other hypothalamic nuclei
so project to the median eminence, the majority of their
ojection fields are unknown.
During the past decade, 1985). Although some of these other hypothalamic nucleus also project to the median eminence, the majority of the projection fields are unknown.
During the past decade, numerous investigators has convincingly demonstrated

also project to the median eminence, the majority of their
projection fields are unknown.
During the past decade, numerous investigators have
convincingly demonstrated that several chemical trans-
mitters may be colocalize projection fields are unknown.
During the past decade, numerous investigators has convincingly demonstrated that several chemical tran
mitters may be colocalized within the same neuron. Thas also been shown to be true for During the past decade, numerous investigators have
convincingly demonstrated that several chemical trans-
mitters may be colocalized within the same neuron. This
has also been shown to be true for CRF. Thus, immu-
nohisto convincingly demonstrated that several chemical transmitters may be colocalized within the same neuron. This
has also been shown to be true for CRF. Thus, immu-
nohistochemical double-staining methods have revealed
that a

aspet

CORTICOTROPIN-RELE

vasopressin. Moreover, adrenalectomy induces the 19

expression of vasopressin in the majority of CRF cells in cORTICOTROPIN-RELEA

vasopressin. Moreover, adrenalectomy induces the 198

expression of vasopressin in the majority of CRF cells in Mer

the PVN (Roth et al., 1982; Sawchenko et al., 1984; vide CORTICOTROPIN-RE
vasopressin. Moreover, adrenalectomy induces the
expression of vasopressin in the majority of CRF cells in
the PVN (Roth et al., 1982; Sawchenko et al., 1984;
Whitnall et al., 1985, 1987; Piekut and Joseph vasopressin. Moreover, adrenalectomy induces the expression of vasopressin in the majority of CRF cells in the PVN (Roth et al., 1982; Sawchenko et al., 1984; Whitnall et al., 1985, 1987; Piekut and Joseph, 1986; Alonso et vasopressin. Moreover, adrenalectomy induces the 198
expression of vasopressin in the majority of CRF cells in Mei
the PVN (Roth et al., 1982; Sawchenko et al., 1984; vide
Whitnall et al., 1985, 1987; Piekut and Joseph, 19 expression of vasopressin in the majority of CRF cells
the PVN (Roth et al., 1982; Sawchenko et al., 19
Whitnall et al., 1985, 1987; Piekut and Joseph, 19
Alonso et al., 1986). The increase in the number of C
neurons also the PVN (Roth et al., 1982; Sawchenko et al., 1984; vid
Whitnall et al., 1985, 1987; Piekut and Joseph, 1986; sch
Alonso et al., 1986). The increase in the number of CRF and
neurons also containing vasopressin following ad Whitnall et al., 1985, 1987; Piekut and Joseph, 1986;
Alonso et al., 1986). The increase in the number of CRF
neurons also containing vasopressin following adrenal-
ectomy is clearly beneficial because vasopressin not only neurons also containing vasopressin following adrenal-
ectomy is clearly beneficial because vasopressin not only
stimulates ACTH secretion but also potentiates the ac-
tions of CRF on anterior pituitary corticotrophs. Oxyneurons also containing vasopressin following adrenal-
ectomy is clearly beneficial because vasopressin not only
attenuates ACTH secretion but also potentiates the ac-
tions of CRF on anterior pituitary corticotrophs. Oxyectomy is clearly beneficial because vasopressin not c
stimulates ACTH secretion but also potentiates the
tions of CRF on anterior pituitary corticotrophs. C
tocin has also been found to coexist with CRF i
number of cells tions of CRF on anterior pituitary corticotrophs. Oxytocin has also been found to coexist with CRF in a number of cells in both the parvocellular and magnocel-
lular regions of the PVN (Sawchenko et al., 1984; Pa-
padopoul tions of CRF on anterior pituitary corticotrophs. Oxy-BNST,
tocin has also been found to coexist with CRF in a central
number of cells in both the parvocellular and magnocel-
lular regions of the PVN (Sawchenko et al., 198 tocin has also been found to coexist with CRF in a c
number of cells in both the parvocellular and magnocel-
lular regions of the PVN (Sawchenko et al., 1984; Pa-
padopoulos et al., 1985; Pretel and Piekut, 1990a). A c
num number of cells in both the parvocellular and magnocel-
lular regions of the PVN (Sawchenko et al., 1984; Pa-
padopoulos et al., 1985; Pretel and Piekut, 1990a). A
number of CRF cells in the PVN also stain positively for
e lular regions of the PVN (Sawchenko et al., 1984; Pa-
padopoulos et al., 1985; Pretel and Piekut, 1990a). A
number of CRF cells in the PVN also stain positively for
enkephalin (Hökfelt et al., 1983; Hisano et al., 1986;
Ce padopoulos et al., 1985; Pretel and Piekut, 1990a). A contrained rote al., 1985; Pretel and Piekut, 1990a). A contract enterphalin (Hökfelt et al., 1983; Hisano et al., 1986; a Ceccatelli et al., 1989a; Sakanaka et al., 19 number of CRF cells in the PVN also stain positively for
enkephalin (Hökfelt et al., 1983; Hisano et al., 1986;
Ceccatelli et al., 1989a; Sakanaka et al., 1989) or express
enkephalin mRNA (Pretel and Piekut, 1990b). There
 enkephalin (Hökfelt et al., 1983; Hisano et al., 1986;
Ceccatelli et al., 1989a; Sakanaka et al., 1989) or express
enkephalin mRNA (Pretel and Piekut, 1990b). There
have been singular reports of colocalization of dynorphin Ceccatelli et al., 1989a; Sakanaka et al., 1989) or express
enkephalin mRNA (Pretel and Piekut, 1990b). There
have been singular reports of colocalization of dynorphin
(Roth et al., 1983), neurotensin (Ceccatelli et al., 1 enkephalin mRNA (Pretel and Piekut, 1990b). There
have been singular reports of colocalization of dynorphin
(Roth et al., 1983), neurotensin (Ceccatelli et al., 1989a),
and peptide histidine isoleucine amide (Hökfelt et al

have been singular reports of colocalization of dynorp
(Roth et al., 1983), neurotensin (Ceccatelli et al., 198
and peptide histidine isoleucine amide (Hökfelt et
1983; Berkenbosch et al., 1986) with CRF in the P
The physi (Roth et al., 1983), neurotensin (Ceccatelli et al., 1989a),
and peptide histidine isoleucine amide (Hökfelt et al., t
1983; Berkenbosch et al., 1986) with CRF in the PVN.
The physiological function of colocalization of n and peptide histidine isoleucine amide (Hökfelt et al., 1983; Berkenbosch et al., 1986) with CRF in the PVN.
The physiological function of colocalization of neuropeptides remains obscure, but it is plausible that one pepti 1983; Berkenbosch et al., 1986) with CRF in the PVI The physiological function of colocalization of neuropeeides remains obscure, but it is plausible that one peptic may modulate the function of the other at the anterior p The physiological function of colocalization of neuropeptides remains obscure, but it is plausible that one peptide may modulate the function of the other at the anterior pituitary. Alternatively, several different anterio tides remains obscure, but it is plausible t
may modulate the function of the other
pituitary. Alternatively, several different
tary hormones could be released following
of neurons containing multiple peptides.
As noted ea ay modulate the function of the other at the anterior
tuitary. Alternatively, several different anterior pitui-
ry hormones could be released following depolarization
neurons containing multiple peptides.
As noted earlier,

pituitary. Alternatively, several different anterior pitui-
tary hormones could be released following depolarization
of neurons containing multiple peptides.
As noted earlier, CRF neurons have a widespread, but
selective, of neurons containing multiple peptides.
As noted earlier, CRF neurons have a widespread,
selective, distribution throughout the CNS. A numbe
investigators have examined the CNS distribution
CRF utilizing either immunohist As noted earlier, CRF neurons have a widespread, but apprecive, distribution throughout the CNS. A number of show investigators have examined the CNS distribution of act CRF utilizing either immunohistochemical (Merchentha selective, distribution throughout the CNS. A number of
investigators have examined the CNS distribution of
CRF utilizing either immunohistochemical (Merchen-
thaler et al., 1982; Cummings et al., 1983; Joseph and
Knigge, investigators have examined the CNS distribution of CRF utilizing either immunohistochemical (Merchenthaler et al., 1982; Cummings et al., 1983; Joseph and Knigge, 1983; Swanson et al., 1983; Merchenthaler, 1984; Sakanaka CRF utilizing either immunohistochemical (Merchenthaler et al., 1982; Cummings et al., 1983; Joseph and Knigge, 1983; Swanson et al., 1983; Merchenthaler, 1984; Sakanaka et al., 1987a) or radioimmunoassay techniques (Fisch thaler et al., 1982; Cummings et al., 1983; Joseph and tical lamenae (Lewis et al., 1989; Lewis and Lund, 1990).
Knigge, 1983; Swanson et al., 1983; Merchenthaler, 1984; Gray and colleagues have provided detailed descrip-

LEASING FACTOR 429
1987). Of these studies, those of Swanson et al. (1983),
Merchenthaler (1984) and Sakanaka et al. (1987a) pro-LEASING FACTOR
1987). Of these studies, those of Swanson et al. (1983).
Merchenthaler (1984) and Sakanaka et al. (1987a) pro-
vide an excellent overview with a large number of detailed 429
1987). Of these studies, those of Swanson et al. (1983),
Merchenthaler (1984) and Sakanaka et al. (1987a) pro-
vide an excellent overview with a large number of detailed
schematic diagrams of CRF-immunopositive perikar 1987). Of these studies, those of Swanson et al. (1983), Merchenthaler (1984) and Sakanaka et al. (1987a) provide an excellent overview with a large number of detailed schematic diagrams of CRF-immunopositive perikarya an 1987). Of these studies, those of Swanson et al. (1983)
Merchenthaler (1984) and Sakanaka et al. (1987a) pro-
vide an excellent overview with a large number of detailed
schematic diagrams of CRF-immunopositive perikary
and Merchenthaler (1984) and Sakanaka et al. (1987a) provide an excellent overview with a large number of detail schematic diagrams of CRF-immunopositive perikan and fibers (fig. 1). CRF neurons are localized throughc the cort vide an excellent overview with a large number of detailed
schematic diagrams of CRF-immunopositive perikarya
and fibers (fig. 1). CRF neurons are localized throughout
the cortex, limbic system, and brainstem nuclei associ schematic diagrams of CRF-immunopositive perikarya
and fibers (fig. 1). CRF neurons are localized throughout
the cortex, limbic system, and brainstem nuclei associ-
ated with autonomic functioning. Briefly, the highest
den and fibers (fig. 1). CRF neurons are localized throughout
the cortex, limbic system, and brainstem nuclei associ-
ated with autonomic functioning. Briefly, the highest
density of CRF neurons are found in the amygdala,
BNST the cortex, limbic system, and brainstem nuclei associated with autonomic functioning. Briefly, the highest density of CRF neurons are found in the amygdala BNST, lateral hypothalamus (distinct from the PVN) central gray a ated with autonomic functioning. Briefly, the highest
density of CRF neurons are found in the amygdala,
BNST, lateral hypothalamus (distinct from the PVN),
central gray area, dorsal tegmentum, locus ceruleus, par-
abrachia density of CRF neurons are found in the amygdal
BNST, lateral hypothalamus (distinct from the PVN
central gray area, dorsal tegmentum, locus ceruleus, pa
abrachial nucleus, dorsal vagal complex, and inferite
olive. It is o BNST, lateral hypothalamus (distinct from the PVN), central gray area, dorsal tegmentum, locus ceruleus, parabrachial nucleus, dorsal vagal complex, and inferior olive. It is of interest to note that these areas are interc central gray area, dorsal tegmentum, locus ceruleus, parabrachial nucleus, dorsal vagal complex, and inferior
olive. It is of interest to note that these areas are inter-
connected via the median forebrain bundle and its c abrachial nucleus, dorsal vagal complex, and inferior
olive. It is of interest to note that these areas are inter-
connected via the median forebrain bundle and its caudal
extension in the reticular formation or dorsally t olive. It is of interest to note that these areas are inter-
connected via the median forebrain bundle and its caudal
extension in the reticular formation or dorsally through
a periventricular system in the thalamus and ce connected via the median forebrain bundle and its caudal
extension in the reticular formation or dorsally through
a periventricular system in the thalamus and central
gray area. Although CRF fibers are found coursing
throu extension in the reticular formation or dorsally through
a periventricular system in the thalamus and central
gray area. Although CRF fibers are found coursing
throughout the median forebrain bundle, the direction of
fiber a periventricular system in the thalamus and cent
gray area. Although CRF fibers are found coursi
throughout the median forebrain bundle, the direction
fibers in these systems is unclear. Therefore, there is
unfortunate pa gray area. Although CRF fibers are found co
throughout the median forebrain bundle, the direct
fibers in these systems is unclear. Therefore, there
unfortunate paucity of data regarding the actual μ
tion fields of the v

of neurons containing multiple peptides. Iocalized to layers II and III of the cortex where they
As noted earlier, CRF neurons have a widespread, but appear to represent cortical interneurons. However, it
selective, distri roughout the median forebrain bundle, the direction of
pers in these systems is unclear. Therefore, there is an
infortunate paucity of data regarding the actual projec-
on fields of the various groups of CRF perikarya.
Rec fibers in these systems is unclear. Therefore, there is an unfortunate paucity of data regarding the actual projection fields of the various groups of CRF perikarya.
Recently, a small number of CRF pathways outside of the unfortunate paucity of data regarding the actual projection fields of the various groups of CRF perikarya.
Recently, a small number of CRF pathways outside of the hypothalamus have been traced. CRF cell bodies are widely d tion fields of the various groups of CRF perikarya.
Recently, a small number of CRF pathways outside of
the hypothalamus have been traced. CRF cell bodies are
widely distributed throughout the neocortex, but rela
tively mo Recently, a small number of CRF pathways outside of
the hypothalamus have been traced. CRF cell bodies are
widely distributed throughout the neocortex, but rela-
tively more CRF neurons are observed in the prefrontal,
cing the hypothalamus have been traced. CRF cell bodies are widely distributed throughout the neocortex, but relatively more CRF neurons are observed in the prefrontal, cingulate, and insular cortical areas (Swanson et al., 198 widely distributed throughout the neocortex, but rela-
tively more CRF neurons are observed in the prefrontal,
cingulate, and insular cortical areas (Swanson et al.,
1983). These CRF neurons appear to be predominantly
loca tively more CRF neurons are observed in the prefrontal, cingulate, and insular cortical areas (Swanson et al., 1983). These CRF neurons appear to be predominantly localized to layers II and III of the cortex where they app cingulate, and insular cortical areas (Swanson et al., 1983). These CRF neurons appear to be predominantly localized to layers II and III of the cortex where they appear to represent cortical interneurons. However, it shou 1983). These CRF neurons appear to be predominantl
localized to layers II and III of the cortex where the
appear to represent cortical interneurons. However,
should be noted that recent data suggest that CRF
actually prese localized to layers II and III of the cortex where they appear to represent cortical interneurons. However, it should be noted that recent data suggest that CRF is actually present in a diverse group of neurons and process appear to represent cortical interneurons. However, it
should be noted that recent data suggest that CRF is
actually present in a diverse group of neurons and proc-
esses in the neocortex dispersed throughout various cor-
 ould be noted that recent data suggest that CRF
tually present in a diverse group of neurons and pr
ses in the neocortex dispersed throughout various c
al lamenae (Lewis et al., 1989; Lewis and Lund, 199
Gray and colleague

actually present in a diverse group of neurons and processes in the neocortex dispersed throughout various cortical lamenae (Lewis et al., 1989; Lewis and Lund, 1990). Gray and colleagues have provided detailed description esses in the neocortex dispersed throughout various cortical lamenae (Lewis et al., 1989; Lewis and Lund, 1990).
Gray and colleagues have provided detailed descriptions of the morphology of CRF neurons in the central nucle tical lamenae (Lewis et al., 1989; Lewis and Lund, 1990).
Gray and colleagues have provided detailed descrip-
tions of the morphology of CRF neurons in the central
nucleus of the amygdala (Cassell and Gray, 1989) and
have

FIG. 1. Major CRF-stained cell groups (dots) and fiber systems in the rat brain. CC, corpus callosum; HIP, hippocampus; SEPT, septal
region; AC, anterior commissure; BST, bed nucleus of the stria terminalis; SI substantia FIG. 1. Major CRF-stained cell groups (dots) and fiber systems in the rat brain. CC, corpus callosum; HIP, hippocampus; SEPT, septal
region; AC, anterior commissure; BST, bed nucleus of the stria terminalis; SI substantia FIG. 1. Major CRF-stained cell groups (dots) and fiber systems in the rat brain. CC, corpus callosum; HIP, hippocampus; SEPT, septal region; AC, anterior commissure; BST, bed nucleus of the stria terminalis; SI substantia region; AC, anterior commissure; BST, bed nucleus of the stria terminalis; SI substantia innominata; CcA, central
MPO, medial preoptic area; PVH, PVN of hypothalamus; ME, median eminence; PP, posterior pituitary; LHA, late

430
Tegion of the PVN (Gray et al., 1989). Additionally, they rep
(Moga and Gray, 1985) have traced a pathway from the tur (Moga and Gray, 1985) have traced a pathway from the pays (Moga and Gray, 1985) have traced a pathway from the traced owens al

region of the PVN (Gray et al., 1989). Additionally, the

(Moga and Gray, 1985) have traced a pathway from the

central nucleus of the amygdala to the parabrachia

nuclei in the brainstem which play a role in con region of the PVN (Gray et al., 1989). Additionally, they
(Moga and Gray, 1985) have traced a pathway from the
central nucleus of the amygdala to the parabrachial
nuclei in the brainstem which play a role in controlling
ca region of the PVN (Gray et al., 1989). Additionally, they rep
(Moga and Gray, 1985) have traced a pathway from the tun
central nucleus of the amygdala to the parabrachial I
nuclei in the brainstem which play a role in cont (Moga and Gray, 1985) have traced a pathway from the tum to central nucleus of the amygdala to the parabrachial It is nuclei in the brainstem which play a role in controlling the hypcardiovascular and respiratory responses central nucleus of the amygdala to the parabrachial
nuclei in the brainstem which play a role in controlling
cardiovascular and respiratory responses. Sakanaka and
Lederis (1986) have also reported a similar pathway from
t nuclei in the brainstem which play a role in controlling the cardiovascular and respiratory responses. Sakanaka and in Lederis (1986) have also reported a similar pathway from the amygdala to the parabrachial nuclei. They cardiovascular and respiratory responses. Sakanaka and
Lederis (1986) have also reported a similar pathway from
the amygdala to the parabrachial nuclei. They found that
this descending amygdalofugal projection appears to p Lederis (1986) have also reported a similar pathway from
the amygdala to the parabrachial nuclei. They found that
this descending amygdalofugal projection appears to pass
through the BNST, the lateral hypothalamus, and the the amygdala to the parabrachial nuclei. They found that
this descending amygdalofugal projection appears to pass
through the BNST, the lateral hypothalamus, and the
reticular formation to these brainstem nuclei. Moreover, this descending amygdalofugal projection appears to pas
through the BNST, the lateral hypothalamus, and the
reticular formation to these brainstem nuclei. Moreover
along this pathway, a number of CRF neurons in the
amygdal through the BNST, the lateral hypothalamus, and the reticular formation to these brainstem nuclei. Moreover along this pathway, a number of CRF neurons in the amygdala terminated in the BNST and ventromedia hypothalamus ra reticular formation to these brainstem nuclei. Moreover,
along this pathway, a number of CRF neurons in the the
amygdala terminated in the BNST and ventromedial opto
hypothalamus rather than in the brainstem. These find-
 along this pathway, a number of CRF neurons in the that
amygdala terminated in the BNST and ventromedial op-
hypothalamus rather than in the brainstem. These find-
ings are similar to those of Moga et al. (1990) who
repor amygdala terminated in the BNST and ventromedial op-
hypothalamus rather than in the brainstem. These find-
ings are similar to those of Moga et al. (1990) who
reported that large numbers of CRF-staining cells are
found i hypothalamus rather than in the brainstem. These find-
ings are similar to those of Moga et al. (1990) who
reported that large numbers of CRF-staining cells are infe
found in the lateral hypothalamus which project to the
p ings are similar to those of Moga et al. (1990) who and
reported that large numbers of CRF-staining cells are infe
found in the lateral hypothalamus which project to the
parabrachial nuclei. The observed staining was not i reported that large numbers of CRF-staining cells are found in the lateral hypothalamus which project to the parabrachial nuclei. The observed staining was not in cell bodies but, rather, primarily in fibers of passage. In found in the lateral hypothalamus which project to the parabrachial nuclei. The observed staining was not in cell bodies but, rather, primarily in fibers of passage. In addition to this lack of direct projections from the parabrachial nuclei. The obsercell bodies but, rather, primaril
addition to this lack of direct pr
hypothalamus, <1% of CRF pe
ect to the parabrachial nuclei.
The largest concentration of Il bodies but, rather, primarily in fibers of passage. In dition to this lack of direct projections from the lateral fiber pothalamus, $\lt 1\%$ of CRF perikarya in the PVN projection of CRF cell bodies outside (The larges

addition to this lack of direct projections from the lateral hypothalamus, $\langle 1\%$ of CRF perikarya in the PVN pro
ect to the parabrachial nuclei.
The largest concentration of CRF cell bodies outside
the hypothalamus is f hypothalamus, $\lt 1\%$ of CRF perikarya in the PVN project to the parabrachial nuclei.

The largest concentration of CRF cell bodies outside

the hypothalamus is found in the BNST. Anatomically,

the BNST is the major pat ect to the parabrachial nuclei.
The largest concentration of CRF cell bodies outs
the hypothalamus is found in the BNST. Anatomica
the BNST is the major pathway for amygdaloid inp
into the hypothalamus as well as being a r The largest concentration of CRF cell bodies outside
the hypothalamus is found in the BNST. Anatomically,
the BNST is the major pathway for amygdaloid inputs
into the hypothalamus as well as being a region contain-
ing a the hypothalamus is found in the BNST. Anatomically,
the BNST is the major pathway for amygdaloid inputs
into the hypothalamus as well as being a region contain-
ing a number of reciprocal connections with brainstem
nucle the BNST is the major pathway for amygdaloid inputs
into the hypothalamus as well as being a region contain-
ing a number of reciprocal connections with brainstem
nuclei involved in autonomic functioning. As in the
amygdal into the hypothalamus as well as being a region contain-
ing a number of reciprocal connections with brainstem
nuclei involved in autonomic functioning. As in the
amygdala, CRF neurons of the BNST project directly to
the p ing a number of reciprocal connections with brainster
nuclei involved in autonomic functioning. As in th
amygdala, CRF neurons of the BNST project directly t
the parabrachial nuclei (Moga et al., 1989) and to th
dorsal vag nuclei involved in autonomic functioning. As in the
amygdala, CRF neurons of the BNST project directly to
the parabrachial nuclei (Moga et al., 1989) and to the
dorsal vagal complex, both of which can regulate auto-
nomic amygdala, CRF neurons of the BNST project directly to
the parabrachial nuclei (Moga et al., 1989) and to the
dorsal vagal complex, both of which can regulate auto-
momic functioning (Gray and Magnuson, 1987). Some
CRF neu the parabrachial nuclei (Moga et al., 1989) and to the
dorsal vagal complex, both of which can regulate auto-
momic functioning (Gray and Magnuson, 1987). Some
CRF neurons in the central nucleus of the amygdala and
BNST al dorsal vagal complex, both of which canonic functioning (Gray and Magnus CRF neurons in the central nucleus of t
BNST also contain neurotensin immu
and Han, 1989; Shimada et al., 1989).
In addition to the above mentioned

projections, ascending projections from these nuclei have
been reported. Within the dorsal vagal complex, the BNST also contain neurotensin immunoreactivity (Ju
and Han, 1989; Shimada et al., 1989).
In addition to the above mentioned descending CRF
projections, ascending projections from these nuclei have
been reported. Within th and Han, 1989; Shimada et al., 1989).

In addition to the above mentioned descending CRF to

projections, ascending projections from these nuclei have

been reported. Within the dorsal vagal complex, the

nucleus of the s In addition to the above mentioned descending CRF
projections, ascending projections from these nuclei have
been reported. Within the dorsal vagal complex, the
nucleus of the solitary tract contains CRF cell bodies
that a projections, ascending projections from these nuclei have
been reported. Within the dorsal vagal complex, the
nucleus of the solitary tract contains CRF cell bodies
that ascend to the parabrachial nuclei (Herbert and
Sape been reported. Within the dorsal vagal complex, the nucleus of the solitary tract contains CRF cell bodie that ascend to the parabrachial nuclei (Herbert an Saper, 1990). Neuroanatomically, the nucleus of the solitary trac that ascend to the parabrachial nuclei (Herbert and

Saper, 1990). Neuroanatomically, the nucleus of the sol-

Turthermore, considerable variance in the concentra-

itary tract provides a major projection to the parabrachi that ascend to the parabrachial nuclei (Herbert and dition
Saper, 1990). Neuroanatomically, the nucleus of the sol-
itary tract provides a major projection to the parabrachial
nuclei. This ascending projection is believed Saper, 1990). Neuroanatomically, the nucleus of the solitary tract provides a major projection to the parabrachial nuclei. This ascending projection is believed to be the main source of somatosensory visceral information t itary tract provides a major projection to the parabrachia
nuclei. This ascending projection is believed to be th
main source of somatosensory visceral information t
the forebrain. Moreover, the nucleus of the solitary tra nuclei. This ascending projection is believed to be the
main source of somatosensory visceral information to
the forebrain. Moreover, the nucleus of the solitary tract
is a major relay for descending pathways from the para main source of somatosensory visceral information to in
the forebrain. Moreover, the nucleus of the solitary tract
is a major relay for descending pathways from the para-
brachial nuclei and forebrain implicated in autonom the forebrain. Moreover, the nucleus of the solitary traction is a major relay for descending pathways from the parabrachial nuclei and forebrain implicated in autonomic regulation. Lind and Swanson (1984) reported a pathw is a major relay for descending pathways from the para-
brachial nuclei and forebrain implicated in autonomic
regulation. Lind and Swanson (1984) reported a pathway
originating from CRF cell bodies in the parabrachial
nucl brachial nuclei and forebrain implicated in autonomic
regulation. Lind and Swanson (1984) reported a pathway
experimenting from CRF cell bodies in the parabrachial
nucleus and terminating in the medial preoptic nucleus
mo regulation. Lind and Swanson (1984) reported a pathway echolamine and indoleamine transmitters. Thus, CRF is
originating from CRF cell bodies in the parabrachial strategically positioned to influence the activity of the
nu originating from CRF cell bodies in the parabrachial
nucleus and terminating in the medial preoptic nucleus
of the hypothalamus. CRF was found alone as well as
colocalized in a subpopulation of cholinergic cell bodies
in t nucleus and terminating in the medial preoptic nucleus
of the hypothalamus. CRF was found alone as well as
colocalized in a subpopulation of cholinergic cell bodies
in the lateral dorsal tegmentum near the locus ceruleus
a colocalized in a subpopulation of cholinergic cell bodies 2. Localization of corticotropin-releasing factor in en-
in the lateral dorsal tegmentum near the locus ceruleus docrine, gastrointestinal, immune, and other periph in the lateral dorsal tegmentum near the locus ceruleus

NEMEROFF
reported CRF projections from the lateral dorsal tegme
tum to the sacral spinal cord. NEMEROFF
reported CRF projections from t
tum to the sacral spinal cord.
It is important to note that

MEROFF
ported CRF projections from the lateral dorsal tegmen-
m to the sacral spinal cord.
It is important to note that not all CRF neurons in
e hypothalamus project to the median eminence. Cells reported CRF projections from the lateral dorsal tegmentum to the sacral spinal cord.
It is important to note that not all CRF neurons in
the hypothalamus project to the median eminence. Cells
in the PVN and anterior hypot reported CRF projections from the lateral dorsal tegmentum to the sacral spinal cord.
It is important to note that not all CRF neurons in
the hypothalamus project to the median eminence. Cells
in the PVN and anterior hypot tum to the sacral spinal cord.
It is important to note that not all CRF neurons in
the hypothalamus project to the median eminence. Cells
in the PVN and anterior hypothalamus have been shown
to terminate in the lateral sep It is important to note that not all CRF neurons in
the hypothalamus project to the median eminence. Cells
in the PVN and anterior hypothalamus have been shown
to terminate in the lateral septum (Sakanaka et al.,
1988). So the hypothalamus project to the median eminence. Cells
in the PVN and anterior hypothalamus have been shown
to terminate in the lateral septum (Sakanaka et al.,
1988). Some of those in the lateral hypothalamus project
to t in the PVN and anterior hypothalamus have been shown
to terminate in the lateral septum (Sakanaka et al.,
1988). Some of those in the lateral hypothalamus project
to the inferior colliculus where they may play a role in
mo terminate in the lateral septum (Sakanaka et al., 88). Some of those in the lateral hypothalamus project the inferior colliculus where they may play a role in odulating auditory processing (Sakanaka et al., 1987b). An oliv

1988). Some of those in the lateral hypothalamus project
to the inferior colliculus where they may play a role in
modulating auditory processing (Sakanaka et al., 1987b).
An olivocerebellar CRF pathway has been reported in modulating auditory processing (Sakanaka et al., 1987b).
An olivocerebellar CRF pathway has been reported in
the cat (Cummings et al., 1988; Kitahama et al., 1988),
opossum (Cummings et al., 1989, Cummings and King,
1990), modulating auditory processing (Sakanaka et al., 1987b).

An olivocerebellar CRF pathway has been reported in

the cat (Cummings et al., 1988; Kitahama et al., 1988),

opossum (Cummings et al., 1989, Cummings and King,

19 An olivocerebellar CRF pathway has been reported in
the cat (Cummings et al., 1988; Kitahama et al., 1988),
opossum (Cummings et al., 1989, Cummings and King,
1990), and primate brain (Cha and Foote, 1988; Foote
and Cha, 1 the cat (Cummings et al., 1988; Kitahama et al., 1988), opossum (Cummings et al., 1989, Cummings and King, 1990), and primate brain (Cha and Foote, 1988; Foote and Cha, 1988). These CRF neurons originating in the inferior opossum (Cummings et al., 1990), and primate brain (Chand Cha, 1988). These CRF inferior olive project through
inferior olive project through the flocculus and paraflocculu
CRF-immunoreactive fibers 90), and primate brain (Cha and Foote, 1988; Foote
d Cha, 1988). These CRF neurons originating in the
ferior olive project throughout the cerebellum within
e flocculus and paraflocculus.
CRF-immunoreactive fibers have been

and Cha, 1988). These CRF neurons originating in the
inferior olive project throughout the cerebellum within
the flocculus and paraflocculus.
CRF-immunoreactive fibers have been found to ter-
minate in various layers of th inferior olive project throughout the cerebellum within
the flocculus and paraflocculus.
CRF-immunoreactive fibers have been found to ter-
minate in various layers of the spinal cord. Some of these
fibers originate in the the flocculus and paraflocculus.

CRF-immunoreactive fibers have been found to ter-

minate in various layers of the spinal cord. Some of these

fibers originate in the Edinger-Westphal nucleus (Chung

et al., 1987), sympa CRF-immunoreactive fibers have been found to ter-
minate in various layers of the spinal cord. Some of these
fibers originate in the Edinger-Westphal nucleus (Chung
et al., 1987), sympathetic (Krukoff, 1986) and sensory
ga minate in various layers of the spinal cord. Some of these
fibers originate in the Edinger-Westphal nucleus (Chung
et al., 1987), sympathetic (Krukoff, 1986) and sensory
ganglia (Skofitsch et al., 1985), and the spinal cor fibers originate in the Edinger-Westphal nucleus (Chung
et al., 1987), sympathetic (Krukoff, 1986) and sensory
ganglia (Skofitsch et al., 1985), and the spinal cord itself
(Merchenthaler et al., 1983). Although the functio et al., 1987), sympathetic (Krukoff, 1986) and sensory
ganglia (Skofitsch et al., 1985), and the spinal cord itself
(Merchenthaler et al., 1983). Although the function of
CRF neurons in the spinal cord is unclear, it is pl ganglia (Skofitsch et al., 1983)
(Merchenthaler et al., 1983)
CRF neurons in the spinal that they may play a role
and/or autonomic outflow.
This heterogeneous dist Merchenthaler et al., 1983). Although the function of RF neurons in the spinal cord is unclear, it is plausible at they may play a role in modulating sensory input d/or autonomic outflow.
This heterogeneous distribution of

The above mention of these nuclei have

In a role for CRF as a hypothalamic releasing factor

CRF neurons in the central nucleus of the amygdala and

ENST also contain neurotensin immunoreactivity (Ju

and Han, 1989; Shima CRF neurons in the spinal cord is unclear, it is plausible
that they may play a role in modulating sensory input
and/or autonomic outflow.
This heterogeneous distribution of CRF discussed
above is concordant with a role fo that they may play a role in modulating sensory input
and/or autonomic outflow.
This heterogeneous distribution of CRF discussed
above is concordant with a role for the peptide as a
neurotransmitter in the CNS. To some ext and/or autonomic outflow.
This heterogeneous distribution of CRF discussed
above is concordant with a role for the peptide as a
neurotransmitter in the CNS. To some extent, functional
roles for chemical messengers in the C This heterogeneous distribution of CRF discussed
above is concordant with a role for the peptide as a
neurotransmitter in the CNS. To some extent, functional
roles for chemical messengers in the CNS can be inferred
from ne above is concordant with a role for the peptide as a
neurotransmitter in the CNS. To some extent, functional
roles for chemical messengers in the CNS can be inferred
from neuroanatomical localization. Thus, consistent
with requively and the CNS. To some extent, functions
roles for chemical messengers in the CNS can be inferre-
from neuroanatomical localization. Thus, consisten
with a role for CRF as a hypothalamic releasing facto-
regulating roles for chemical messengers in the CNS can be inferred
from neuroanatomical localization. Thus, consistent
with a role for CRF as a hypothalamic releasing factor
regulating pituitary-adrenocortical activity is the pres-
 from neuroanatomical localization. Thus, consistent
with a role for CRF as a hypothalamic releasing factor
regulating pituitary-adrenocortical activity is the pres-
ence of CRF in high concentrations in the PVN and
median with a role for CRF as a hypothalamic releasing fa
regulating pituitary-adrenocortical activity is the p
ence of CRF in high concentrations in the PVN
median eminence, two of the so-called hypophysiotr
areas of the hypotha regulating pituitary-adrenocortical activity is the pence of CRF in high concentrations in the PVN
median eminence, two of the so-called hypophysiotiareas of the hypothalamus. Relatively high concer
tions of CRF have been median eminence, two of the so-called hypophysiotropic median eminence, two of the so-called hypophysiotropic
areas of the hypothalamus. Relatively high concentra-
tions of CRF have been observed following immunohis-
tochemistry and radioimmunoassay studies in subcorti-
cal li areas of the hypothalamus. Relatively high concentra-
tions of CRF have been observed following immunohis-
tochemistry and radioimmunoassay studies in subcorti-
cal limbic and brainstem structures (e.g., amygdala,
BNST, ra tions of CRF have been observed following immunohis-
tochemistry and radioimmunoassay studies in subcorti-
cal limbic and brainstem structures (e.g., amygdala,
BNST, raphe nuclei, locus ceruleus), brain regions tra-
dition tochemistry and radioimmunoassay studies in subceal limbic and brainstem structures (e.g., amyge BNST, raphe nuclei, locus ceruleus), brain regions ditionally associated with control of arousal and af Furthermore, consider BNST, raphe nuclei, locus ceruleus), brain regions traamygdala and hypothalamus (Kilts et a!., 1987), suggestditionally associated with control of arousal and affect.
Furthermore, considerable variance in the concentra-
tions of CRF is observed among component nuclei of the
amygdala and hypothalamus (Kilts et al., 1987), suggest-Furthermore, considerable variance in the concentra-
tions of CRF is observed among component nuclei of the
amygdala and hypothalamus (Kilts et al., 1987), suggest-
ing that the functional role of CRF would most likely
var tions of CRF is observed among component nuclei of the
amygdala and hypothalamus (Kilts et al., 1987), suggest-
ing that the functional role of CRF would most likely
vary among these individual nuclei. High concentrations
 amygdala and hypothalamus (Kilts et al., 1987), suggesting that the functional role of CRF would most likely vary among these individual nuclei. High concentrations and dense staining are also noted in many of the brain re ing that the functional role of CRF would most likely
vary among these individual nuclei. High concentrations
and dense staining are also noted in many of the brain
regions containing the major perikarya for the cat-
echol vary among these individual nuclei. High concentrations
and dense staining are also noted in many of the brain
regions containing the major perikarya for the cat-
echolamine and indoleamine transmitters. Thus, CRF is
strat and dense staining are also noted in many of the brain
regions containing the major perikarya for the cat-
echolamine and indoleamine transmitters. Thus, CRF is
strategically positioned to influence the activity of the
maj CNS. *2. holamine and indoleamine transmitters. Thus, CRF is* rategically positioned to influence the activity of the ajor monoamine-containing neuronal systems in the NS.

2. *Localization of corticotropin-releasing factor in*

docrinally positioned to influence the activity of the major monoamine-containing neuronal systems in the CNS.
 docrine, gastrointestinal, immune, and other peripheral tissues. Although generally thought of as a brain p major monoamine-containing neuronal systems in the

CNS.

2. Localization of corticotropin-releasing factor in en-

docrine, gastrointestinal, immune, and other peripheral

tissues. Although generally thought of as a brain CNS.

2. Localization of corticotropin-releasing factor in

docrine, gastrointestinal, immune, and other perip

tissues. Although generally thought of as a brain per

regulating pituitary-adrenal function, CRF immuno

tivi docrine, gastrointestinal, immune, and other peripheral

aspet

PHARMACOLOGICAL REVIEWS

aspet

CORTICOTROPIN-RELEASI
sues, many of which are apparently unrelated to HPA in net
axis activity. CRF-like immunoreactivity is present in Wolte CORTICOTROPIN-RELEA
sues, many of which are apparently unrelated to HPA in r
axis activity. CRF-like immunoreactivity is present in Wol
the pituitary stalk and neurointermediate lobe of the terior CORTICOTROPIN-RELE
sues, many of which are apparently unrelated to HPA in
axis activity. CRF-like immunoreactivity is present in W
the pituitary stalk and neurointermediate lobe of the ten
posterior pituitary gland in rats sues, many of which are apparently unrelated to HPA
axis activity. CRF-like immunoreactivity is present in
the pituitary stalk and neurointermediate lobe of the
posterior pituitary gland in rats (Saavedra et al., 1984;
Jea sues, many of which are apparently unrelated to HPA
axis activity. CRF-like immunoreactivity is present in
the pituitary stalk and neurointermediate lobe of the
posterior pituitary gland in rats (Saavedra et al., 1984;
Jea axis activity. CRF-like immunoreactivity is present in Withe pituitary stalk and neurointermediate lobe of the ten posterior pituitary gland in rats (Saavedra et al., 1984; aris Jeandel et al., 1987) and humans (Ohtani et the pituitary stalk and neurointermediate lobe of the ten posterior pituitary gland in rats (Saavedra et al., 1984; aris Jeandel et al., 1987) and humans (Ohtani et al., 1987). su This CRF-like immunoreactivity is thought posterior pituitary gland in rats (Saavedra et al., 1984;
Jeandel et al., 1987) and humans (Ohtani et al., 1987).
This CRF-like immunoreactivity is thought to be of brain
origin. The physiological role of CRF in these area Jeandel et al., 1987) and humans (Ohtani et al., 19
This CRF-like immunoreactivity is thought to be of b
origin. The physiological role of CRF in these area
unclear at present. However, it has been suggested
CRF in the neu This CRF-like immunoreactivity is thought to be of brain
origin. The physiological role of CRF in these areas is
unclear at present. However, it has been suggested that
cRF in the neurointermediate lobe might act presynapt origin. The physiological role of CRF in these areas is unclear at present. However, it has been suggested tha
CRF in the neurointermediate lobe might act presynapt
ically on autoreceptors located on CRF terminals in th
me unclear at present. However, it has been suggested tl
CRF in the neurointermediate lobe might act presyna
ically on autoreceptors located on CRF terminals in
median eminence and/or act locally in a paracrine fas
ion to rel CRF in the neurointermediate lobe might act presynaptically on autoreceptors located on CRF terminals in the median eminence and/or act locally in a paracrine fashion to release ACTH from anterior pituitary corticotrophs. median eminence and/or act locally in a paracrine fashion to release ACTH from anterior pituitary corticotrophs. Both of these hypotheses must be considered highly speculative at this time.

CRF is present in the adrenal medulla of rats (Hashimoto et al., 1984), cows (Edwards and Jones, 1988; Minamino et al., 1988), humans (Suda et al., 1984a), and moto et al., 1984), cows (Edwards and Jones, 1988; Mintrophs. Both of these hypotheses must be considered rhypotheses this time.

CRF is present in the adrenal medulla of rats (Hashimoto et al., 1984), cows (Edwards and Jones, 1988; Min-

amino et al., 1988), humans (Suda et highly speculative at this time.

CRF is present in the adrenal medulla of rats (Hashinanto et al., 1984), cows (Edwards and Jones, 1988; Minanino et al., 1988), humans (Suda et al., 1984a), and place is appears to be in CRF is present in the adrenal medulla of rats (Hashimoto et al., 1984), cows (Edwards and Jones, 1988; Minamino et al., 1988), humans (Suda et al., 1984a), and dogs (Bruhn et al., 1987) where it appears to be in close prox moto et al., 1984), cows (Edwards and Jones, 1988; lamino et al., 1988), humans (Suda et al., 1984a), dogs (Bruhn et al., 1987) where it appears to be in oproximity to small blood vessels. In contrast to convestigators, Ru amino et al., 1988), humans (Suda et al., 1984a), and
dogs (Bruhn et al., 1987) where it appears to be in close
proximity to small blood vessels. In contrast to other
investigators, Rundle et al. (1988) utilized immunohis dogs (Bruhn et al., 1987) where it appears to be in close
proximity to small blood vessels. In contrast to other
investigators, Rundle et al. (1988) utilized immunohis-
tochemical methods to demonstrate the presence of CR proximity to small blood vessels. In contrast to other investigators, Rundle et al. (1988) utilized immunohistochemical methods to demonstrate the presence of CRF in sheep adrenal cortex where it appears in small nerve fib tochemical methods to demonstrate the presence of CRF
in sheep adrenal cortex where it appears in small nerve
fibers associated with blood vessels. They suggested that
this CRF may be present in postganglionic autonomic
ne in sheep adrenal cortex where it appears in small nerve
fibers associated with blood vessels. They suggested that
this CRF may be present in postganglionic autonomic
nerve fibers. Although the physiological role of adrena fibers associated with blood vessels. They suggested that this CRF may be present in postganglionic autonominerve fibers. Although the physiological role of adrena CRF is not known, both direct stimulation of the splanchni this CRF may be present in postganglionic autonom
nerve fibers. Although the physiological role of adre
CRF is not known, both direct stimulation of
splanchnic nerve (Edwards and Jones, 1988) and he
orrhagic stress (Bruhn nerve fibers. Although the physiological role of adrenal CRF is not known, both direct stimulation of the splanchnic nerve (Edwards and Jones, 1988) and hemorrhagic stress (Bruhn et al., 1987) increase the concentration o splanchnic nerve (Edwards and Jones, 1988) and hemorrhagic stress (Bruhn et al., 1987) increase the concentration of CRF in adrenal venous plasma. Such a plasma concentration of CRF is too low to increase pituitary-
adrena splanchnic nerve (Edwards and Jones, 1988) and hemorrhagic stress (Bruhn et al., 1987) increase the concentration of CRF in adrenal venous plasma. Such a plasma concentration of CRF is too low to increase pituitary-adrenal orrhagic stress (Brutation of CRF in a
concentration of C.
adrenal activity, an
role in the adrenal.
In a preliminary ation of CRF in adrenal venous plasma. Such a plasma
ncentration of CRF is too low to increase pituitary-
renal activity, and, therefore, it may play a paracrine
le in the adrenal.
In a preliminary study, we (Ritchie et al

concentration of CRF is too low to increase pituitary-
adrenal activity, and, therefore, it may play a paracrine
role in the adrenal.
In a preliminary study, we (Ritchie et al., 1986) de-
tected CRF immunoreactivity in lym adrenal activity, and, therefore, it may play a paracrine (S
role in the adrenal. (S
may perform that it is the different density in lymphocytes. This im-
tected CRF immunoreactivity in lymphocytes. This im-
munoreactivity role in the adrenal.
In a preliminary study, we (Ritchie et al., 1986) de-
tected CRF immunoreactivity in lymphocytes. This im-
munoreactivity was dilutable, suggesting that it is the
authentic peptide. This finding has re tected CRF immunoreactivity in lymphocytes. This in
munoreactivity was dilutable, suggesting that it is tl
authentic peptide. This finding has recently been confirmed by Stephanou et al. (1990) who detected boo
immunoreact unoreactivity was dilutable, suggesting that it is
thentic peptide. This finding has recently been c
med by Stephanou et al. (1990) who detected b
munoreactive CRF and CRF mRNA in lymphocyt
Yoon and colleagues (1988) ident

authentic peptide. This finding has recently been confirmed by Stephanou et al. (1990) who detected both immunoreactive CRF and CRF mRNA in lymphocytes.
Yoon and colleagues (1988) identified CRF immuno-
reactivity in the r firmed by Stephanou et al. (1990) who detected both immunoreactive CRF and CRF mRNA in lymphocytes.

Yoon and colleagues (1988) identified CRF immuno-

reactivity in the rat testis by both radioimmunoassay

and immunocyto immunoreactive CRF and CRF mRNA in lymphocytes.

Yoon and colleagues (1988) identified CRF immuno-

reactivity in the rat testis by both radioimmunoassay

and immunocytochemistry. This immunoreactivity was

relatively the Yoon and colleagues (1988) identified CRF immuno-
reactivity in the rat testis by both radioimmunoassay
and immunocytochemistry. This immunoreactivity was
observed in Leydig cells, advanced germ cells, and even
epididymal reactivity in the rat testis by both radioimmunoa
and immunocytochemistry. This immunoreactivity
observed in Leydig cells, advanced germ cells, and e
pididymal spermatozoa. These investigators found
hypophysectomy signific observed in Leydig cells, advanced germ cells, and even
epididymal spermatozoa. These investigators found that
hypophysectomy significantly reduced the concentra-
tions of CRF observed in the testis. This suggests that
the pituitary hormones, perhaps gonadotropin.

CRF has also been found in the pancreas, stomach, tions of CRF observed in the testis. This suggests that
the CRF-containing cells are under the influence of
pituitary hormones, perhaps gonadotropin.
CRF has also been found in the pancreas, stomach,
and small intestine in the CRF-containing cells are under the influence of P
pituitary hormones, perhaps gonadotropin. W
CRF has also been found in the pancreas, stomach, in
and small intestine in a number of different mammals. If
For example, C pituitary hormones, perhaps gonadotropin.
CRF has also been found in the pancreas, stomach,
and small intestine in a number of different mammals.
For example, CRF is found in a large number of cells
within the endocrine pa CRF has also been found in the pancreas, stomach,
and small intestine in a number of different mammals.
For example, CRF is found in a large number of cells
within the endocrine pancreas (Petrusz et al., 1983, 1
1984), wh and small intestine in a number of different mammals.
For example, CRF is found in a large number of cells
within the endocrine pancreas (Petrusz et al., 1983,
1984), where they are in close topographical association
with For example, CRF is found in a large number of cells
within the endocrine pancreas (Petrusz et al., 1983,
1984), where they are in close topographical association
with glucagon-secreting cells. In addition, Petrusz et al.
 within the endocrine pancreas (Petrusz et al., 1983, plane 1984), where they are in close topographical association iol with glucagon-secreting cells. In addition, Petrusz et al. (1984) and Kruseman et al. (1984) identifie with glucagon-secreting cells. In addition, Petrusz et al. (1984) and Kruseman et al. (1984) identified CRF-containing cells in the gastric epithelium. Similar to the localization of CRF in the adrenal, CRF immunostaining

LEASING FACTOR 431
in nerve fibers in the rat duodenum was reported by
Wolter (1984, 1985) to be closely associated with myen-LEASING FACTOR

in nerve fibers in the rat duodenum was reported

Wolter (1984, 1985) to be closely associated with mye

teric and submucosal blood vessels. These fibers m 431
in nerve fibers in the rat duodenum was reported by
Wolter (1984, 1985) to be closely associated with myen-
teric and submucosal blood vessels. These fibers may
arise from autonomic neurons in the myenteric and in nerve fibers in the rat duodenum was reported by Wolter (1984, 1985) to be closely associated with myenteric and submucosal blood vessels. These fibers may arise from autonomic neurons in the myenteric and submucosal pl Wolter (1984, 1985) to be closely associated with myenteric and submucosal blood vessels. These fibers may arise from autonomic neurons in the myenteric and submucosal plexus. olter (1984, 1985) to be closely associated with myen-
ric and submucosal blood vessels. These fibers may
ise from autonomic neurons in the myenteric and
bmucosal plexus.
CRF has been measured in blood plasma obtained from

proximity to small blood vessels. In contrast to other
investigators, Rundle et al. (1988) utilized immunohis-
tochemical methods to demonstrate the presence of CRF
in sheep adrenal cortex where it appears in small nerve
f tected CRF immunoreactivity in lymphocytes. This im-
munoreactivity was dilutable, suggesting that it is the
authentic peptide. This finding has recently been con-
firmed by Stephanou et al. (1990) who detected both
immuno epididymal spermatozoa. These investigators found that
hypophysectomy significantly reduced the concentra-
tions of CRF observed in the testis. This suggests that axis activity during gestation. This is likely due to the
t teric and submucosal blood vessels. These fibers may
arise from autonomic neurons in the myenteric and
submucosal plexus.
CRF has been measured in blood plasma obtained from
the peripheral circulation of rats, horses, and arise from autonomic neurons in the myenteric and
submucosal plexus.
CRF has been measured in blood plasma obtained from
the peripheral circulation of rats, horses, and humans,
albeit at much lower concentrations than that submucosal plexus.
CRF has been measured in blood plasma obtained from
the peripheral circulation of rats, horses, and human
albeit at much lower concentrations than that found is
the plasma of portal vessels supplying the CRF has been measured in blood plasma obtained from
the peripheral circulation of rats, horses, and humans,
albeit at much lower concentrations than that found in
the plasma of portal vessels supplying the anterior pitui-
 the peripheral circulation of rats, horses, and humans,
albeit at much lower concentrations than that found in
the plasma of portal vessels supplying the anterior pitui-
tary (Suda et al., 1985a; Sumitomo et al., 1987; Ale albeit at much lower concentrations than that found in
the plasma of portal vessels supplying the anterior pitui-
tary (Suda et al., 1985a; Sumitomo et al., 1987; Alexander
et al., 1991; Hohtari et al., 1988). Because plas the plasma of portal vessels supplying the anterior pit
tary (Suda et al., 1985a; Sumitomo et al., 1987; Alexancet al., 1991; Hohtari et al., 1988). Because plasma C
concentrations in humans exhibited an apparent diuri
rhy tary (Suda et al., 1985a; Sumitomo et al., 1987; Alexan
et al., 1991; Hohtari et al., 1988). Because plasma C
concentrations in humans exhibited an apparent diur
rhythm paralleling plasma ACTH and cortisol conc
trations, p et al., 1991; Hohtari et al., 1988). Because plasma CRF concentrations in humans exhibited an apparent diurnal
rhythm paralleling plasma ACTH and cortisol concentrations, plasma CRF was proposed to be of hypotha-
lamic ori rhythm paralleling plasma ACTH and cortisol concentrations, plasma CRF was proposed to be of hypotha-
lamic origin (Watabe et al., 1987). However, recent evi-
dence from the rat suggests that this is not the case;
Plotsky rhythm paralleling plasma ACTH and cortisol concentrations, plasma CRF was proposed to be of hypotha-
lamic origin (Watabe et al., 1987). However, recent evi-
dence from the rat suggests that this is not the case;
Plotsky trations, plasma CRF was proposed to be of hypotha
lamic origin (Watabe et al., 1987). However, recent evidence from the rat suggests that this is not the case
Plotsky et al. (1990) reported that neither bilateral de
struc lamic origin (Watabe et al., 1987). However, recent effence from the rat suggests that this is not the callends plotsky et al. (1990) reported that neither bilateral contraction of CRF perikarya in the PVN nor stalk transe dence from the rat suggests that this is not the case;
Plotsky et al. (1990) reported that neither bilateral de-
struction of CRF perikarya in the PVN nor stalk tran-
section alters peripheral plasma CRF concentrations.
Mo Plotsky et al. (1990) reported that neither bilateral destruction of CRF perikarya in the PVN nor stalk transection alters peripheral plasma CRF concentrations.
Moreover, the increase in plasma CRF concentrations following struction of CRF perikarya in the PVN nor stalk transection alters peripheral plasma CRF concentrations.
Moreover, the increase in plasma CRF concentrations following nitroprusside-induced hypotension was shown to be neith section alters peripheral plasma CRF concentrations.
Moreover, the increase in plasma CRF concentrations
following nitroprusside-induced hypotension was shown
to be neither of hypothalamic nor adrenal origin. Thus,
the sou at present, and any measurement of its concentration as following nitroprusside-induced hypotension was shot to be neither of hypothalamic nor adrenal origin. The source(s) and function of plasma CRF is uncertat present, and any measurement of its concentration a marker of HPA to be neither of hypothalamic nor adrenal origin. Thus
the source(s) and function of plasma CRF is uncertair
at present, and any measurement of its concentration as
a marker of HPA activity should be viewed with skepti-
ci the source(s) and function of plasma CRF is uncertain
at present, and any measurement of its concentration as
a marker of HPA activity should be viewed with skepti-
cism. However, this is not the case during pregnancy.
Pla at present, and any measurement of its concentration as
a marker of HPA activity should be viewed with skepti-
cism. However, this is not the case during pregnancy.
Plasma CRF in pregnant women, the source of which is
the a marker of HPA activity should be viewed with skep
cism. However, this is not the case during pregnan
Plasma CRF in pregnant women, the source of which
the placenta, undergoes a sharp increase during the th
trimester of p cism. However, this is not the case during pregnancy.
Plasma CRF in pregnant women, the source of which is
the placenta, undergoes a sharp increase during the third
trimester of pregnancy. Although plasma CRF concen-
trati Plasma CRF in pregnant women, the source of which is
the placenta, undergoes a sharp increase during the third
trimester of pregnancy. Although plasma CRF concen-
trations were either undetectable early in pregnancy
(Sasak the placenta, undergoes a sharp increase during the third
trimester of pregnancy. Although plasma CRF concen-
trations were either undetectable early in pregnancy
(Sasaki et al., 1984; Goland et al., 1986; Laatikainen et
a trimester of pregnancy. Although plasma CRF concentrations were either undetectable early in pregnancy (Sasaki et al., 1984; Goland et al., 1986; Laatikainen et al., 1987) or low (Campbell et al., 1987), concentrations inc (Sasaki et al., 1984; Goland et al., 1986; Laatikainen et al., 1987) or low (Campbell et al., 1987), concentrations parturition. Plasma CRF concentrations do not increase increased 6- to 40-fold late in the third trimester or at
parturition. Plasma CRF concentrations do not increase
during the stress of labor nor are plasma ACTH or
cortisol concentrations increased at any time during the
co parturition. Plasma CRF concentrations do not increase
during the stress of labor nor are plasma ACTH or
cortisol concentrations increased at any time during the
course of pregnancy (Goland et al., 1986; Laatikainen et
al. during the stress of labor nor are plasma ACTH or
cortisol concentrations increased at any time during the
course of pregnancy (Goland et al., 1986; Laatikainen et
al., 1987; Campbell et al., 1987). In contrast to the
sugg cortisol concentrations increased at any time during the
course of pregnancy (Goland et al., 1986; Laatikainen et
al., 1987; Campbell et al., 1987). In contrast to the
suggestion of Goland et al. (1986), the lack of any co course of pregnancy (Goland et al., 1986; Laatikainen et al., 1987; Campbell et al., 1987). In contrast to the suggestion of Goland et al. (1986), the lack of any correlation between plasma CRF concentrations during pregna al., 1987; Campbell et al., 1987). In contrast to the suggestion of Goland et al. (1986), the lack of any correlation between plasma CRF concentrations during pregnancy and pituitary-adrenocortical hormone concentrations s suggestion of Goland et al. (1986), the lack of any correlation between plasma CRF concentrations during
pregnancy and pituitary-adrenocortical hormone concentrations strongly suggests that maternal CRF of pla-
cental orig pregnancy and pituitary-adrenocortical hormone conpregnancy and pituitary-adrenocortical hormone concentrations strongly suggests that maternal CRF of placental origin does not modulate maternal or fetal HPA axis activity during gestation. This is likely due to the presen centrations strongly suggests that maternal CRF of placental origin does not modulate maternal or fetal HPA axis activity during gestation. This is likely due to the presence of a specific circulating CRF-binding protein w axis activity during gestation. This is likely due to the presence of a specific circulating CRF-binding protein which was first semipurified from maternal plasma during pregnancy (Suda et al., 1988a, 1989; Linton et al., axis activity during gestation. This is likely due to the presence of a specific circulating CRF-binding protein which was first semipurified from maternal plasma during pregnancy (Suda et al., 1988a, 1989; Linton et al., presence of a specific circulating CRF-binding protein
which was first semipurified from maternal plasma dur-
ing pregnancy (Suda et al., 1988a, 1989; Linton et al.,
1990) and has now been purified and sequenced by Potter
 which was first semipurified from maternal plasma du
ing pregnancy (Suda et al., 1988a, 1989; Linton et a
1990) and has now been purified and sequenced by Pott
et al. (1991). This CRF-binding protein is present in bot
plas ing pregnancy (Suda et al., 1988a, 1989; 1
1990) and has now been purified and sequen
et al. (1991). This CRF-binding protein is pr
plasma and brain and may well play an imp
iological role in regulating CRF availability
Co 90) and has now been purified and sequenced by Potter
al. (1991). This CRF-binding protein is present in both
asma and brain and may well play an important phys-
logical role in regulating CRF availability.
Considerable va

plasma and brain and may well play an important physiological role in regulating CRF availability.
Considerable variability in the concentrations of plasma CRF has been reported by different investigators.
This is almost c plasma and brain and may well play an important physiological role in regulating CRF availability.
Considerable variability in the concentrations of plasma CRF has been reported by different investigators.
This is almost c iological role in regulating CRF availability.
Considerable variability in the concentrations of
plasma CRF has been reported by different investigators.
This is almost certainly due to differences in extraction
and radioi

vestigator comparisons of experimental data are difficult, owens and
vestigator comparisons of experimental data are difficult,
if not impossible, to interpret at present.
3. Localization of corticotropin-releasing factor messen-

²

3. Localization of experimental data are difficu

3. Localization of corticotropin-releasing factor messen
 7 RNA. In 1983, Numa and colleagues succeeded **germs** vestigator comparisons of experimental data are difficult, port
if not impossible, to interpret at present.
3. Localization of corticotropin-releasing factor messen-
ger RNA. In 1983, Numa and colleagues succeeded vestigator comparisons of experimental data are difficult, point in the general of contempt at present.

S. Localization of corticotropin-releasing factor messen-

ger RNA. In 1983, Numa and colleagues succeeded in and

cl if not impossible, to interpret at present.
3. Localization of corticotropin-releasing factor messen-
ger RNA. In 1983, Numa and colleagues succeeded in
cloning the gene encoding the CRF prohormone in ovine
(Furutani et al 3. Localization of corticotropin-releasing factor mess
ger RNA. In 1983, Numa and colleagues succeeded
cloning the gene encoding the CRF prohormone in ov
(Furutani et al., 1983), human (Shibahara et al., 198
and rat genomi ger RNA. In 1983, Numa and colleagues succeeded in an cloning the gene encoding the CRF prohormone in ovine definition (Furutani et al., 1983), human (Shibahara et al., 1983), (Jand rat genomic libraries (Jingami et al., 1 cloning the gene encoding the CRF prohormone in ovine

(Furutani et al., 1983), human (Shibahara et al., 1983),

and rat genomic libraries (Jingami et al., 1985b; Thompion

son et al., 1987). Southern blot analysis has si (Furutani et al., 1983), human (Shibahara et al., 1983), and rat genomic libraries (Jingami et al., 1985b; Thompson et al., 1987). Southern blot analysis has since tracked the locus of the human CRF gene to the long arm of and rat genomic libraries (Jingami et al., 1985b; Thompion et al., 1987). Southern blot analysis has since tracked rate rate rate rate rate of the human CRF gene to the long arm of lite chromosome 8 (Arbiser et al., 1988) son et al., 1987). Southern blot analysis has since tracture the locus of the human CRF gene to the long arm chromosome 8 (Arbiser et al., 1988). Thompson et (1987) found that the rat and human CRF gene w quite similar in the locus of the human CRF gene to the long arm of liter
chromosome 8 (Arbiser et al., 1988). Thompson et al. of t
(1987) found that the rat and human CRF gene were
quite similar in sequence homology and basic organiza-
re chromosome 8 (Arbiser et al., 1988). Thompson et al. of
(1987) found that the rat and human CRF gene were
quite similar in sequence homology and basic organiza-
tion. Both genes contain two exons separated by an
interveni (1987) found that the rat and human CRF gene were
quite similar in sequence homology and basic organiza-
regions previously found to contain CRF-immunoreac-
tion. Both genes contain two exons separated by an
intervening i quite similar in sequence homology and basic organiza-
tion. Both genes contain two exons separated by an
intervening intron. The first exon encodes most of the
5'-untranslated region of the mRNA, and the second
exon cont tion. Both genes contain two exons separated by an
intervening intron. The first exon encodes most of the
5'-untranslated region of the mRNA, and the second
exon contains all the prohormone-coding sequences and
some 3'-un intervening intron. The first exon encodes most of the
5'-untranslated region of the mRNA, and the second
exon contains all the prohormone-coding sequences and
some 3'-untranslated regions of the mRNA (fig. 2). The
5'-fla 5'-untranslated region of the mRNA, and the second
exon contains all the prohormone-coding sequences and
some 3'-untranslated regions of the mRNA (fig. 2). The
5'-flanking DNA sequences are likely to contain the
DNA sequen exon contains all the prohormone-coding sequences and
some 3'-untranslated regions of the mRNA (fig. 2). The
5'-flanking DNA sequences are likely to contain the
DNA sequence elements responsible for glucocorticoic
regulati some 3'-untranslated regions of the mRNA (fig. 2). The
5'-flanking DNA sequences are likely to contain the
DNA sequence elements responsible for glucocorticoid
regulation, tissue-specific expression, and second mes-
senge 5'-flanking DNA sequences are likely to contain the DNA sequence elements responsible for glucocorticoid regulation, tissue-specific expression, and second messenger regulation of CRF gene expression. In fact, a cAMP-respo DNA sequence elements responsible for glucocorticoion
regulation, tissue-specific expression, and second mes
senger regulation of CRF gene expression. In fact, a
cAMP-responsive element from the CRF gene was iso
lated foll regulation, tissue-specific expression, and second mes-
senger regulation of CRF gene expression. In fact, a
cAMP-responsive element from the CRF gene was iso-
lated following transfection into rat pheochromocytoma
(PC-12) senger regulation of CRF gene expression. In fact
cAMP-responsive element from the CRF gene was i
lated following transfection into rat pheochromocyto
(PC-12) cells in which the cAMP-responsive elem
allows the cells to exp $\begin{array}{ll}\n\text{cAMP-responsive element from the CRF gene was isolated following transfection into rat pheochromocytoma} \\
\text{(PC-12) cells in which the cAMP-responsive element} & \text{19} \\
\text{allows the cells to express the gene encoding chloram-} & \text{phenicol acetyltransferase (Seasholtz et al., 1988).} \quad \text{St} \\
\text{cAMP-responsive element was localized to a 59-base pair} & \text{al.} \n\end{array}$ lated following transfection into rat pheochromocytoma (PC-12) cells in which the cAMP-responsive element
allows the cells to express the gene encoding chloram-
phenicol acetyltransferase (Seasholtz et al., 1988). The
cAMP (PC-12) cells in which the cAMP-responsive element
allows the cells to express the gene encoding chloram-
phenicol acetyltransferase (Seasholtz et al., 1988). The
cAMP-responsive element was localized to a 59-base pair
al allows the cells to exprese
phenicol acetyltransfer:
cAMP-responsive eleme
region located between
CRF mRNA cap site.
Localization of CRF cAMP-responsive element was localized to a 59-base pair
region located between 238 and 180 base pairs 5' to the
CRF mRNA cap site.
Localization of CRF mRNA by in situ hybridization
or Northern blot analysis coincides quit

region located between 238 and 180 base pairs 5' to the CRF mRNA cap site.
CRF mRNA cap site.
Localization of CRF mRNA by in situ hybridization
or Northern blot analysis coincides quite well with im-
munohistochemical loca region located between 238 and 180 base pairs 5' to the
CRF mRNA cap site.
Localization of CRF mRNA by in situ hybridization exi
or Northern blot analysis coincides quite well with im-
with munohistochemical localization o CRF mRNA cap site.

Localization of CRF mRNA by in situ hybridization

or Northern blot analysis coincides quite well with im-

munohistochemical localization of CRF, although high

concentrations of peptide do not necessa

RAT CRH PROTEIN PRECURSOR

FIG. 2. Structural organization of the rat corticotropin-releasir

hormone gene, mRNA, and protein precursor. Top, schematic repre-

sentation of the rat corticotropin-releasing hormone (CRH) gen RAT CRH PROTEIN PRECURSOR

FIG. 2. Structural organization of the rat corticotropin-releasing

hormone gene, mRNA, and protein precursor. Top, schematic repre-

sentation of the rat corticotropin-releasing hormone (CRH) ge FIG. 2. Structural organization of the rat corticotropin-releasing
hormone gene, mRNA, and protein precursor. Top, schematic repre-
sentation of the rat corticotropin-releasing hormone (CRH) gene. The
exons are shown as bl FIG. 2. Structural organization of the rat corticotropin-releasing
hormone gene, mRNA, and protein precursor. Top, schematic repre-
sentation of the rat corticotropin-releasing hormone (CRH) gene. The
exons are shown as b hormone gene, mRNA, and protein precursor. Top, schematic representation of the rat corticotropin-releasing hormone (CRH) gene. The exons are shown as blocks; the intron, 5'-flanking and 3'-flanking sequences are shown as sentation of the rat corticotropin-releasing hormone (CRH) gene. The phases are shown as blocks; the intron, 5'-flanking and 3'-flanking Classequences are shown as lines. The 5'-untranslated and 3'-untranslated al. regions exons are shown as blocks; the intron, 5'-flanking and 3'-flanking
sequences are shown as lines. The 5'-untranslated and 3'-untranslated
regions of the exons are shaded. The cAMP-responsive element (CRE),
CAAT and TATA seq sequences are shown as lines. The 5'-untranslated and 3'-untranslated regions of the exons are shaded. The cAMP-responsive element (CRE) CAAT and TATA sequences, cap site, translation initiation ATG, and translation termin regions of the exons are shaded. The cAMP-responsive element (CRE),
CAAT and TATA sequences, cap site, translation initiation ATG, and
translation termination TGA are indicated. Four polyadenylation ad-
dition signals (AA CAAT and TATA sequences, cap site, translation initiation ATG, and
translation termination TGA are indicated. Four polyadenylation addition signals (AATAAA) are indicated. All hypothalamic CRH com-
plementary DNA clones i translation termination TGA are indicated. Four polyadenylation addition signals (AATAAA) are indicated. All hypothalamic CRH complementary DNA clones isolated to date appear to use the second or restructure of the rat CRH dition signals (AATAAA) are indicated. All hypothalamic CRH com-
plementary DNA clones isolated to date appear to use the second or
third polyadenylation addition signals. The location of the CRH peptide
is indicated by CR plementary DNA clones isolated to date appear to use the second or third polyadenylation addition signals. The location of the CRH peptide is indicated by CRH. The structure of the rat CRH mRNA (1400 nucleotides) and rat C

NEMEROFF
portional amounts of mRNA and vice versa. This is a
result of mRNA being localized in cell bodies, whereas NEMEROFF
portional amounts of mRNA and vice versa. This is a
result of mRNA being localized in cell bodies, whereas
CRF, or its prohormone, is localized in terminal fields, NEMEROFF
portional amounts of mRNA and vice versa. This is a
result of mRNA being localized in cell bodies, whereas
CRF, or its prohormone, is localized in terminal fields,
axons, and cell bodies. However, there is increas portional amounts of mRNA and vice versa. This is a
result of mRNA being localized in cell bodies, whereas
CRF, or its prohormone, is localized in terminal fields,
axons, and cell bodies. However, there is increasing evi-
 portional amounts of mRNA and vice versa. This is a
result of mRNA being localized in cell bodies, whereas
CRF, or its prohormone, is localized in terminal fields,
axons, and cell bodies. However, there is increasing evi-
 result of mRNA being localized in cell bodies, whereas
CRF, or its prohormone, is localized in terminal fields,
axons, and cell bodies. However, there is increasing evi-
dence for the presence of mRNA in axonal processes
(CRF, or its prohormone, is localized in terminal fields,
axons, and cell bodies. However, there is increasing evi-
dence for the presence of mRNA in axonal processes
(Jirikowski et al., 1990). Although the antisera used in axons, and cell bodies. However, there is increasing evi-
dence for the presence of mRNA in axonal processes
(Jirikowski et al., 1990). Although the antisera used in
immunocytochemical and radioimmunoassay studies is
raise dence for the presence of mRNA in axonal processes
(Jirikowski et al., 1990). Although the antisera used in
immunocytochemical and radioimmunoassay studies is
raised against CRF, it is unclear while reviewing the
literatur (Jirikowski et al., 1990). Although the antisera used in
immunocytochemical and radioimmunoassay studies is
raised against CRF, it is unclear while reviewing the
literature as to whether these antisera recognize any form
o immunocytochemical and radioimmunoassay studies is
raised against CRF, it is unclear while reviewing the
literature as to whether these antisera recognize any form
of the CRF prohormone or just the final processed pep-
tid raised against CRF, it is unclear while reviewing
literature as to whether these antisera recognize are of the CRF prohormone or just the final processe
tide. Nonetheless, CRF mRNA is certainly found if
regions previously literature as to
of the CRF pr
tide. Nonethel
regions previo
tive perikarya.
In situ hyb the CRF prohormone or just the final processed pep-
le. Nonetheless, CRF mRNA is certainly found in those
gions previously found to contain CRF-immunoreac-
re perikarya.
In situ hybridization studies have identified CRF
RN

tide. Nonetheless, CRF mRNA is certainly found in the regions previously found to contain CRF-immunores
tive perikarya.
In situ hybridization studies have identified Cl
mRNA in a number of brain areas including the parvo-
 regions previously found to contain CRF-immunores
tive perikarya.
In situ hybridization studies have identified CF
mRNA in a number of brain areas including the parv
cellular region of the PVN (Young et al., 1986a; Light-
 tive perikarya.

In situ hybridization studies have identified CRF

mRNA in a number of brain areas including the parvo-

cellular region of the PVN (Young et al., 1986a; Light-

man and Young, 1987), magnocellular regions In situ hybridization studies have identified CRF mRNA in a number of brain areas including the parvocellular region of the PVN (Young et al., 1986a; Lightman and Young, 1987), magnocellular regions of the PVN and supraopt mRNA in a number of brain areas including the parvocellular region of the PVN (Young et al., 1986a; Lightman and Young, 1987), magnocellular regions of the PVN and supraoptic nucleus of the hypothalamus (Lightman and Young cellular region of the PVN (Young et al., 1986a; Lightman and Young, 1987), magnocellular regions of the PVN and supraoptic nucleus of the hypothalamus (Lightman and Young, 1987), inferior olive (Young et al., 1986b; Palko man and Young, 1987), magnocellular regions of the
PVN and supraoptic nucleus of the hypothalamus
(Lightman and Young, 1987), inferior olive (Young et
al., 1986b; Palkovits et al., 1987; Barmack and Young,
1990), and olfac PVN and supraoptic nucleus of the hypothalamus
(Lightman and Young, 1987), inferior olive (Young et
al., 1986b; Palkovits et al., 1987; Barmack and Young,
1990), and olfactory bulb (Imaki et al., 1989). Similarly,
CRF mRNA (Lightman and Young, 1987), inferior olive (Young et al., 1986b; Palkovits et al., 1987; Barmack and Young, 1990), and olfactory bulb (Imaki et al., 1989). Similarly, CRF mRNA has been found in the PVN (Jingami et al., 198 1990), and olfactory bulb (Imaki et al., 1989). Similarly, CRF mRNA has been found in the PVN (Jingami et al., 1985b; Thompson et al., 1987; Beyer et al., 1988; Suda et al., 1988b) and cerebral cortex (Thompson et al., 198 1990), and olfactory bulb (Imaki et al., 1989). Similarly,
CRF mRNA has been found in the PVN (Jingami et al.,
1985b; Thompson et al., 1987; Beyer et al., 1988; Suda et
al., 1988b) and cerebral cortex (Thompson et al., 198 CRF mRNA has been found in the PVN (Jingami et al., 1985b; Thompson et al., 1987; Beyer et al., 1988; Suda et al., 1988b) and cerebral cortex (Thompson et al., 1987; Suda et al., 1988b) by Northern blot analysis. Beyer et 1985b; Thompson et al., 1987; Beyer et al., 1988; Suda
al., 1988b) and cerebral cortex (Thompson et al., 19
Suda et al., 1988b) by Northern blot analysis. Beye:
al. (1988) reported the presence of CRF mRNA in
tracts of tis al., 1988b) and cerebral cortex (Thompson et al., 1987;
Suda et al., 1988b) by Northern blot analysis. Beyer et
al. (1988) reported the presence of CRF mRNA in ex-
tracts of tissue from the amygdala, BNST, and supraop-
tic Suda et al., 1988b) by Northern blot analysis. Beyer et al. (1988) reported the presence of CRF mRNA in extracts of tissue from the amygdala, BNST, and supraoptic nucleus. In fact, Thompson et al. (1987) reported the exist al. (1988) reported the presence of CRF mRNA in ex-
tracts of tissue from the amygdala, BNST, and supraop-
tic nucleus. In fact, Thompson et al. (1987) reported the
existence of CRF mRNA in every major brain region
with th tic nucleus. In fact, Thompson et al. (1987) reported the existence of CRF mRNA in every major brain region with the exception of the cerebellum. When expressed as a percentage of total polyadenylated mRNA, the concentrat tic nucleus. In fact, Thompson et al. (1987) reported the
existence of CRF mRNA in every major brain region
with the exception of the cerebellum. When expressed as
a percentage of total polyadenylated mRNA, the concen-
tr existence of CRF mRNA in every major brain region
with the exception of the cerebellum. When expressed a
a percentage of total polyadenylated mRNA, the concentration of CRF mRNA can be represented as: brainsten
>> cerebra tration of CRF mRNA can be represented as: brainstem
 \gg cerebral cortex = hypothalamus > midbrain > stria-

tum > hippocampus. This should not be totally unex-

pected because immunohistochemical and radioimmunoa percentage of total polyadenylated mRNA, the cointration of CRF mRNA can be represented as: brain $>$ creebral cortex = hypothalamus > midbrain > tum > hippocampus. This should not be totally pected because immunohistoc tration of CRF mRNA can be represented as: brainstem
 $>>$ cerebral cortex = hypothalamus > midbrain > stria-

tum > hippocampus. This should not be totally unex-

pected because immunohistochemical and radioimmuno-

assay \gg cerebral cortex = hypothalamus > midbrain > s
tum > hippocampus. This should not be totally u
pected because immunohistochemical and radioimm
assay studies have previously demonstrated a widesp
distribution of CRF ne m > hippocampus. This should not be totally unex-
cted because immunohistochemical and radioimmuno-
say studies have previously demonstrated a widespread
stribution of CRF neurons throughout the CNS.
As with CRF itself, CR

pected because immunohistochemical and radioimmuno-
assay studies have previously demonstrated a widespread
distribution of CRF neurons throughout the CNS.
As with CRF itself, CRF mRNA has been observed in
a number of peri assay studies have previously demonstrated a widespread
distribution of CRF neurons throughout the CNS.
As with CRF itself, CRF mRNA has been observed in
a number of peripheral tissues including the human
placenta (Grino e distribution of CRF neurons throughout the CNS.
As with CRF itself, CRF mRNA has been observed in
a number of peripheral tissues including the human
placenta (Grino et al., 1987; Frimm et al., 1988). In
concert with an inc As with CRF itself, CRF mRNA has been observed in
a number of peripheral tissues including the human
placenta (Grino et al., 1987; Frimm et al., 1988). In
concert with an increase in placental CRF peptide con-
centrations, a number of peripheral tissues including the humain placenta (Grino et al., 1987; Frimm et al., 1988). In concert with an increase in placental CRF peptide concentrations, CRF mRNA concentrations increased more than 20-fol placenta (Grino et al., 1987; Frimm et al., 1988). In concert with an increase in placental CRF peptide concentrations, CRF mRNA concentrations increased more than 20-fold in the 5-week period preceding parturition. Lightm concert with an increase in placental CRF peptide contrations, CRF mRNA concentrations increased methan 20-fold in the 5-week period preceding parturition Lightman and coworkers (Stephanou et al., 1990) eserved CRF mRNA in than 20-fold in the 5-week period preceding parturition.
Lightman and coworkers (Stephanou et al., 1990) observed CRF mRNA in T and B lymphocytes and neutro-
phils. Thompson et al. (1987) reported the existence of
CRF mRNA than 20-fold in the 5-week period preceding parturition.
Lightman and coworkers (Stephanou et al., 1990) observed CRF mRNA in T and B lymphocytes and neutro-
phils. Thompson et al. (1987) reported the existence of
CRF mRNA Lightman and coworkers (Stephanou et al., 1990) observed CRF mRNA in T and B lymphocytes and neutro-
phils. Thompson et al. (1987) reported the existence of
CRF mRNA in the testes and, in contrast to Jingami et
al. (1985b) served CRF mRNA in T and B lymphocytes and neutro-
phils. Thompson et al. (1987) reported the existence of
CRF mRNA in the testes and, in contrast to Jingami et
al. (1985b), in whole pituitary and adrenal glands. CRF
mRNA phils. Thompson et al. (1987) reported the existence
CRF mRNA in the testes and, in contrast to Jingami
al. (1985b), in whole pituitary and adrenal glands. C
mRNA was not found in samples taken from kidn
duodenum, thymus, CRF mRNA in the testes and, in contrast to Jingami et
al. (1985b), in whole pituitary and adrenal glands. CRF
mRNA was not found in samples taken from kidney,
duodenum, thymus, or liver. The reason for this discrep-
ancy b al. (1985b), in whole pituitary and adrenal glands. CRF
mRNA was not found in samples taken from kidney,
duodenum, thymus, or liver. The reason for this discrep-
ancy between these two groups is unclear but may be the
resu mRNA was not found in sample
duodenum, thymus, or liver. The $\frac{1}{10}$ ancy between these two groups is
result of methodological difference
transient CRF mRNA expression
A number of investigators h odenum, thymus, or liver. The reason for this discrep-
cy between these two groups is unclear but may be the
sult of methodological differences or the possibility of
ansient CRF mRNA expression.
A number of investigators h ancy between these two groups is unclear but may be the
result of methodological differences or the possibility of
transient CRF mRNA expression.
A number of investigators have scrutinized CRF
mRNA in the PVN, and these da

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CORTICOTROPIN
the section concerning CRF regulation of endocrine func
tion (section III) the section concernition
tion (section III).
B. Certicetronin-rel CORTI

the section concerning CRF regulation of endc

tion (section III).
 B. Corticotropin-releasing Factor Receptors

1. *Biochemical characterization of the co*

**1. Biochemical characterization of endocrine for the corticotropin-releasing Factor Receptors

1. Biochemical characterization of the corticotron

1. Biochemical characterization of the corticotron

Leasing factor recepto** *Frelignant* (*receptor Receptors*
 releasing factor receptors
 releasing factor receptor. Initial attempts to biochemically

characterize the ligand-binding subunit of the CRF re-B. Corticotropin-releasing Factor Receptors
1. Biochemical characterization of the corticotropin-
releasing factor receptor. Initial attempts to biochemically
characterize the ligand-binding subunit of the CRF re-
ceptor r B. Corticotropin-releasing Factor Receptors

1. Biochemical characterization of the corticotropin-

releasing factor receptor. Initial attempts to biochemically

characterize the ligand-binding subunit of the CRF re-

cep 1. Biochemical characterization of the corticotropin
releasing factor receptor. Initial attempts to biochemical
characterize the ligand-binding subunit of the CRF receptor revealed that in a number of species there wee
dis releasing factor receptor. Initial attempts to biochemically
characterize the ligand-binding subunit of the CRF re-
ceptor revealed that in a number of species there were
distinct differences between cortical and anterior characterize the ligand-binding subunit of the CRF receptor revealed that in a number of species there were
distinct differences between cortical and anterior pitui-
tary CRF receptors (Grigoriadis and De Souza, 1988;
Grig ceptor revealed that in a number of species there were
distinct differences between cortical and anterior pitui-
tary CRF receptors (Grigoriadis and De Souza, 1988;
Grigoriadis et al., 1989b). The ligand-binding portion of distinct differences between cortical and anterior pituitary CRF receptors (Grigoriadis and De Souza, 1988; idid
Grigoriadis et al., 1989b). The ligand-binding portion of the CRF receptor in cortex consisted of a protein tary CRF receptors (Grigoriadis and De Souza, 1988;
Grigoriadis et al., 1989b). The ligand-binding portion of oth
the CRF receptor in cortex consisted of a protein with
an apparent molecular weight of 58,000, whereas the Grigoriadis et al., 1989b). The ligand-binding portion of
the CRF receptor in cortex consisted of a protein with
an apparent molecular weight of 58,000, whereas the
anterior pituitary receptor binding subunit resided on a
 the CRF receptor in cortex consisted of a protein with
an apparent molecular weight of 58,000, whereas the
anterior pituitary receptor binding subunit resided on a
protein with an apparent molecular weight of 75,000.
This anterior pituitary receptor binding subunit resided on a
protein with an apparent molecular weight of 75,000.
This difference has since been found to be the result of
differential glycosylation of cortical and pituitary re protein with an apparent molecular weight of 75,000.
This difference has since been found to be the result of
differential glycosylation of cortical and pituitary recep-
tors; deglycosylation generated virtually identical This difference has since been found to be the result of
differential glycosylation of cortical and pituitary recep-
tors; deglycosylation generated virtually identical peptide
fragments which indicates that the ligand-bi differential glycosylation of cortical and pituitary receptors; deglycosylation generated virtually identical peptide fragments which indicates that the ligand-binding portion of the CRF receptor in both tissues resides on tors; deglycosylation generated virtually identical peptide
fragments which indicates that the ligand-binding por-
tion of the CRF receptor in both tissues resides on a
polypeptide of approximately 40,000 to 45,000 molecu fragments which indicates that the ligand-binding por-
tion of the CRF receptor in both tissues resides on a
polypeptide of approximately 40,000 to 45,000 molecular
weight (Grigoriadis and De Souza, 1989a). Binding of
var tion of the CRF receptor in both tissues resides on a polypeptide of approximately 40,000 to 45,000 molecular weight (Grigoriadis and De Souza, 1989a). Binding of various CRF ligands to the receptor is increased by divalen polypeptide of approximately 40,000 to 45,000 molecular
weight (Grigoriadis and De Souza, 1989a). Binding of
various CRF ligands to the receptor is increased by
divalent cations and decreased by guanyl nucleotides
(Perrin weight (Grigoriadis and De Souza, 1989a). Binding of various CRF ligands to the receptor is increased by divalent cations and decreased by guanyl nucleotides (Perrin et al., 1986; De Souza, 1987). This is consistent with C various CRF ligan
divalent cations are
(Perrin et al., 1986;
with CRF receptors.
family of receptors.
2. Localization of c *2. Valent cations and decreased by guanyl nucleotides*
 2. Localization of corticotropin-releasing factor receptors
 2. Localization of corticotropin-releasing factor receptors
 2. Localization of corticotropin-relea (Perrin et al., 1986; De Souza, 1987). This is consistent
with CRF receptors as members of the G protein-coupled
family of receptors.
2. Localization of corticotropin-releasing factor receptors
in pituitary and brain. A nu

with CRF receptors as members of the G protein-coupled
family of receptors.
2. Localization of corticotropin-releasing factor receptors
in pituitary and brain. A number of biochemical and
autoradiographic studies have desc family of receptors.

2. Localization of corticotropin-releasing factor receptors

in pituitary and brain. A number of biochemical and

autoradiographic studies have described CRF receptors

throughout the pituitary and C 2. Localization of corticotropin-releasing factor receptors
in pituitary and brain. A number of biochemical and
autoradiographic studies have described CRF receptors
throughout the pituitary and CNS. CRF receptors are
foun in pituitary and brain. A number of biochemical and
autoradiographic studies have described CRF receptors
throughout the pituitary and CNS. CRF receptors are
found in greatest density in the anterior pituitary but
are also autoradiographic studies have described CRF receptors
throughout the pituitary and CNS. CRF receptors are
found in greatest density in the anterior pituitary but
are also found in the neurointermediate lobe as well,
albeit throughout the pituitary and CNS. CRF receptors are
found in greatest density in the anterior pituitary but
are also found in the neurointermediate lobe as well,
albeit in much lower numbers (Wynn et al., 1983, 1984;
De S found in greatest density in the anterior pituitary but
are also found in the neurointermediate lobe as well,
albeit in much lower numbers (Wynn et al., 1983, 1984;
De Souza et al., 1984b, 1985a; De Souza, 1987; Millan et
 e also found in the neurointermediate lobe as well,
beit in much lower numbers (Wynn et al., 1983, 1984;
 $\frac{1}{2}$ Souza et al., 1984b, 1985a; De Souza, 1987; Millan et
 $\frac{1}{2}$, 1987; Grigoriadis and De Souza, 1989b).
M

albeit in much lower numbers (Wynn et al., 1983, 1984;

De Souza et al., 1984b, 1985a; De Souza, 1987; Millan et

al., 1987; Grigoriadis and De Souza, 1989b).

Many investigators have studied the distribution of

CRF rece De Souza et al., 1984b, 1985a; De Souza, 1987; Millan et al., 1987; Grigoriadis and De Souza, 1989b).
Many investigators have studied the distribution of CRF receptors in the CNS. De Souza (1987) described in detail the bi al., 1987; Grigoriadis and De Souza, 1989b).
Many investigators have studied the distribution of
CRF receptors in the CNS. De Souza (1987) described
in detail the binding characteristics of CRF in membrane
homogenates from in detail the binding characteristics of CRF in membrane
homogenates from the anterior pituitary and 11 other
brain regions. This binding is saturable, reversible, and,
on Scatchard analysis, reveals a high-affinity compon CRF receptors in the CNS. De Souza (1987) described
in detail the binding characteristics of CRF in membrane
homogenates from the anterior pituitary and 11 other
brain regions. This binding is saturable, reversible, and,
 in detail the binding characteristics of CRF in membrane
homogenates from the anterior pituitary and 11 other
brain regions. This binding is saturable, reversible, and,
on Scatchard analysis, reveals a high-affinity compo homogenates from the anterior pituitary and 11 other
brain regions. This binding is saturable, reversible, and,
on Scatchard analysis, reveals a high-affinity component
 (K_d) of 0.1 to 0.2 nM and a low-affinity-binding si brain regions. This binding is saturable, reversible, and,
on Scatchard analysis, reveals a high-affinity component
 (K_d) of 0.1 to 0.2 nM and a low-affinity-binding site (K_d)
of 20 nM (fig. 3). In brain tissues, highest on Scatchard analysis, reveals a high-affinity component (K_d) of 0.1 to 0.2 nM and a low-affinity-binding site (K_d) of 20 nM (fig. 3). In brain tissues, highest concentrations of CRF receptors are found in the olfactory (K_d) of 0.1 to 0.2 nM and a low-affinity-binding site (K_d)
of 20 nM (fig. 3). In brain tissues, highest concentrations
of CRF receptors are found in the olfactory bulb, followed
by cerebellum, followed by cortical and l of 20 nM (fig. 3). In brain tissues, highest concentrations
of CRF receptors are found in the olfactory bulb, followed
by cerebellum, followed by cortical and limbic regions.
This was initially somewhat surprising because of CRF receptors are found in the olfactory bulb, followed
by cerebellum, followed by cortical and limbic regions.
This was initially somewhat surprising because the ol-
factory bulb and cerebellum appear to possess relati by cerebellum, followed by cortical and limbic regions. C.
This was initially somewhat surprising because the ol-
factory bulb and cerebellum appear to possess relatively 1
few CRF-containing fibers, although a olivocereb factory bulb and cerebellum appear to possess relatively CRF pathway does exist. However, as will be discussed later, many of these receptors may not be functional or the possess limited second messenger-generating capability. the More precise anatomical localization of CRF rec

More precise anatomical localization of CRF receptors
can be found in the detailed autoradiographic studies of
De Souza et al. (1984a, 1985b) and Wynn et al. (1984). later, many of these receptors may not be functional or possess limited second messenger-generating capability.
More precise anatomical localization of CRF receptors can be found in the detailed autoradiographic studies of possess limited second messenger-generating capability. tume
More precise anatomical localization of CRF receptors with
can be found in the detailed autoradiographic studies of prepa
De Souza et al. (1984a, 1985b) and Wynn More precise anatomical localization of CRF receptors wit
can be found in the detailed autoradiographic studies of pre
De Souza et al. (1984a, 1985b) and Wynn et al. (1984). cre-
Highest densities were again found in the c

LEASING FACTOR
cortex. Although high concentrations of CRF receptors
were visualized in these regions, substantial heterogene-LEASING FACTOR
cortex. Although high concentrations of CRF recep
were visualized in these regions, substantial heterog
ity was exhibited among the component nuclei of 433

cortex. Although high concentrations of CRF receptors

were visualized in these regions, substantial heterogene-

ity was exhibited among the component nuclei of the

brainstem as well as the different laminae and are cortex. Although high concentrations of CRF receptors
were visualized in these regions, substantial heterogene-
ity was exhibited among the component nuclei of the
brainstem as well as the different laminae and areas of
co cortex. Although high concentrations of CRF receptors
were visualized in these regions, substantial heterogene-
ity was exhibited among the component nuclei of the
brainstem as well as the different laminae and areas of
co were visualized in these regions, substantial heterogenty was exhibited among the component nuclei of thrainstem as well as the different laminae and areas cortex. Lower, although substantial, binding was fou throughout th ity was exhibited am
brainstem as well as
cortex. Lower, althou
throughout the major
ing the spinal cord.
Two novel methods ainstem as well as the different laminae and areas of
rtex. Lower, although substantial, binding was found
roughout the majority of brain regions studied includ-
g the spinal cord.
Two novel methods of identifying CRF rece

throughout the majority of brain regions studied includ-
ing the spinal cord.
Two novel methods of identifying CRF receptors have
recently been reported. One involves the use of anti-
idiotypic antibodies (Piekut and Knigg throughout the majority of brain regions studied includ-
ing the spinal cord.
Two novel methods of identifying CRF receptors have
recently been reported. One involves the use of anti-
idiotypic antibodies (Piekut and Knigg ing the spinal cord.
Two novel methods of identifying CRF receptors have
recently been reported. One involves the use of anti-
idiotypic antibodies (Piekut and Knigge, 1989) and the
other uses a fluorescent analog of CRF (1986). *3. Localization of corticotropin-releasing factor receptors and the her uses a fluorescent analog of CRF (Schwartz et al.,* $3.$ *Localization of corticotropin-releasing factor receptors other endocrine, gastrointesti*

This differential glycosylation generated virtually identical peptide
tissues. Although CRF immunoreactivity has been ob-
this differential glycosylation of cortical and pituitary recep-
tors; deglycosylation generated vir *idiotypic antibodies (Piekut and Knigge, 1989) and the*

other uses a fluorescent analog of CRF (Schwartz et al.,

1986).

3. Localization of corticotropin-releasing factor receptors

in other endocrine, gastrointestinal, other uses a fluorescent analog of CRF (Schwartz et al., 1986).

3. Localization of corticotropin-releasing factor receptors

in other endocrine, gastrointestinal, and immune system

tissues. Although CRF immunoreactivity 1986).
3. Localization of corticotropin-releasing factor receptors
in other endocrine, gastrointestinal, and immune system
tissues. Although CRF immunoreactivity has been ob-
served in a number of peripheral tissues (vide 3. Localization of corticotropin-releasing factor recept
in other endocrine, gastrointestinal, and immune syst
tissues. Although CRF immunoreactivity has been exerved in a number of peripheral tissues (vide supp
CRF recept medulla (Dave et al., 1985; Udelsman et al., 1986b) and tissues. Although CRF immunoreactivity has been observed in a number of peripheral tissues (vide supra), CRF receptors have been identified in only a few peripheral tissues. CRF receptors are present in the adrenal medulla served in a number of peripheral tissues (vide supra),
CRF receptors have been identified in only a few periph-
eral tissues. CRF receptors are present in the adrenal
medulla (Dave et al., 1985; Udelsman et al., 1986b) and CRF receptors have been identified in only a few peripheral tissues. CRF receptors are present in the adrenal
medulla (Dave et al., 1985; Udelsman et al., 1986b) and
sympathetic ganglia (Udelsman et al., 1986b). Adrenal
CR eral tissues. CRF receptors are present in the adrenal
medulla (Dave et al., 1985; Udelsman et al., 1986b) and
sympathetic ganglia (Udelsman et al., 1986b). Adrenal
CRF receptors are functionally coupled to adenylate
cycla medulla (Dave et al., 1985; Udelsman et al., 1986b) and
sympathetic ganglia (Udelsman et al., 1986b). Adrenal
CRF receptors are functionally coupled to adenylate
cyclase and have been postulated to modulate the release
of sympathetic ganglia (Udelsman et al., 1986b). Adrenal
CRF receptors are functionally coupled to adenylate
cyclase and have been postulated to modulate the release
of catecholamines. Alternatively, we believe they may
resid CRF receptors are functionally coupled to adenylate cyclase and have been postulated to modulate the release of catecholamines. Alternatively, we believe they may reside on the walls of local blood vessels within the adren cyclase and have been postulated to modulate the release
of catecholamines. Alternatively, we believe they may
reside on the walls of local blood vessels within the
adrenal where they may alter local blood flow patterns.
I of catecholamines. Alternatively, we believe they may
reside on the walls of local blood vessels within the
adrenal where they may alter local blood flow patterns.
In fact, Dashwood et al. (1987) obtained autoradiographic
 reside on the walls of local blood vessels within the
adrenal where they may alter local blood flow patterns.
In fact, Dashwood et al. (1987) obtained autoradiographic
evidence of CRF receptors present on rabbit aortic enadrenal where they may alter local blood flow patterns.
In fact, Dashwood et al. (1987) obtained autoradiographic
evidence of CRF receptors present on rabbit aortic en-
dothelium where they were hypothesized to play a role In fact, Dashwood et al. (1987) obtained autoradiographic
evidence of CRF receptors present on rabbit aortic en-
dothelium where they were hypothesized to play a role
in regulating vascular tone. Dave et al. (1985) also re evidence of CRF receptors present on rabbit aortic en-
dothelium where they were hypothesized to play a role
in regulating vascular tone. Dave et al. (1985) also re-
ported the existence of small numbers of CRF receptors
i dothelium where they were hypothesized to play a role
in regulating vascular tone. Dave et al. (1985) also re-
ported the existence of small numbers of CRF receptors
in the prostate, spleen, liver, kidneys, and testis. De
 in regulating vascular tone. Dave et al. (1985) also reported the existence of small numbers of CRF receptors
in the prostate, spleen, liver, kidneys, and testis. De
Souza and colleagues (Webster and De Souza, 1988;
Webste ported the existence of small numbers of CRF receptors
in the prostate, spleen, liver, kidneys, and testis. De
Souza and colleagues (Webster and De Souza, 1988;
Webster et al., 1989, 1990) also identified CRF receptors
in in the prostate, spleen, liver, kidneys, and testis. De
Souza and colleagues (Webster and De Souza, 1988;
Webster et al., 1989, 1990) also identified CRF receptors
in the spleen. These receptors appear to be restricted to
 Souza and colleagues (Webster and De Souza, 1988;
Webster et al., 1989, 1990) also identified CRF receptors
in the spleen. These receptors appear to be restricted to
a population of resident splenic macrophages and are
als in the spleen. These receptors appear to be restricted to a population of resident splenic macrophages and are also coupled to adenylate cyclase. Neither our group nor De Souza's group (E. B. De Souza, personal communiin the spleen. These receptors appear to be restricted to
a population of resident splenic macrophages and are
also coupled to adenylate cyclase. Neither our group nor
De Souza's group (E. B. De Souza, personal communi-
ca a population of resident splenic macrophages and are
also coupled to adenylate cyclase. Neither our group nor
De Souza's group (E. B. De Souza, personal communi-
cation) have found any evidence of CRF receptor binding
on l cation) have found any evidence of CRF receptor binding
on lymphocytes or erythrocytes as was previously sug-
gested by Smith et al. (1986) and Dave and Eskay (1986). respectively. *4. Signal transduction via second messenger systems*
 4. Signal transduction via second messenger systems.
 4. Signal transduction via second messenger systems.
 4. Signal transduction via second messenger systems.

This was initially somewhat surprising because the ol-
factory bulb and cerebellum appear to possess relatively
few CRF-containing fibers, although a olivocerebellar
Litvin et al., 1983; Giguere et al., 1982; Wynn et al., on lymphocytes or erythrocytes as was previously suggested by Smith et al. (1986) and Dave and Eskay (1986), respectively.

4. Signal transduction via second messenger systems.

Following binding, the CRF receptor is posit gested by Smith et al. (1986) and Dave and Eskay (1986),
respectively.
4. Signal transduction via second messenger systems.
Following binding, the CRF receptor is positively coupled
to adenylate cyclase. The resultant incr respectively.
4. Signal transduction via second messenger systems.
Following binding, the CRF receptor is positively coupled
to adenylate cyclase. The resultant increases in cellular
cAMP represent the second messenger ass 4. Signal transduction via second messenger systems.
Following binding, the CRF receptor is positively coupled
to adenylate cyclase. The resultant increases in cellular
cAMP represent the second messenger associated with
C Following binding, the CRF receptor is positively coupled
to adenylate cyclase. The resultant increases in cellular
cAMP represent the second messenger associated with
CRF receptor activation in the CNS (Labrie et al.,
198 to adenylate cyclase. The resultant increases in cellular cAMP represent the second messenger associated with CRF receptor activation in the CNS (Labrie et al., 1982a,b, 1983; Giguere et al., 1982; Wynn et al., 1984; Litvi cAMP represent the second messenger associated wit
CRF receptor activation in the CNS (Labrie et a
1982a,b, 1983; Giguere et al., 1982; Wynn et al., 198
Litvin et al., 1984; Hoffman et al., 1985; Sobel, 198
Millan et al., CRF receptor activation in the CNS (Labrie et al., 1982a,b, 1983; Giguere et al., 1982; Wynn et al., 1984; Litvin et al., 1984; Hoffman et al., 1985; Sobel, 1985; Millan et al., 1987). When pituitary cell cultures, pituita 1982a,b, 1983; Giguere et al., 1982; Wynn et al., 1984;
Litvin et al., 1984; Hoffman et al., 1985; Sobel, 1985;
Millan et al., 1987). When pituitary cell cultures, pitui-
tary membrane homogenates, or AtT-20 mouse pituitar Litvin et al., 1984; Hoffman et al., 1985; Sobel, 1985;
Millan et al., 1987). When pituitary cell cultures, pitui-
tary membrane homogenates, or AtT-20 mouse pituitary
tumor cells are studied, increases in cAMP are observe Millan et al., 1987). When pituitary cell cultures, pituitary membrane homogenates, or AtT-20 mouse pituitary
tumor cells are studied, increases in cAMP are observed
within minutes following the addition of CRF to these
pr tary membrane homogenates, or AtT-20 mouse pituitary
tumor cells are studied, increases in cAMP are observed
within minutes following the addition of CRF to these
preparations. Giguere et al. (1982) observed 4-fold in-
cre tumor cells are studied, increases in cAMP are observed within minutes following the addition of CRF to the preparations. Giguere et al. (1982) observed 4-fold is creases in cAMP 2 minutes following addition of CF and 8-fo within minutes following the addition of CRF to these
preparations. Giguere et al. (1982) observed 4-fold in-
creases in cAMP 2 minutes following addition of CRF
and 8-fold increases between 10 and 180 minutes. Aguil-
era

FIG. 3. Characterization of the pharmacological specificty of ¹²⁵I-Tyr^o rat/human CRF binding in rat olfactory bulb membranes. Crude
mitochondrial/synaptosomal membranes were incubated for 120 minutes at room temperat CRF and varying concentrations of the pharmacological specificty of ¹²⁵I-Tyr^o rat/human CRF binding in rat olfactory bulb membranes. Crude mitochondrial/synaptosomal membranes were incubated for 120 minutes at room tem FIG. 3. Characterization of the pharmacological specificty of ¹²⁵I-Tyr⁰ rat/human CRF binding in rat olfactory bulb membranes. Crud mitochondrial/synaptosomal membranes were incubated for 120 minutes at room temperatu mitochondrial/synaptosomal membranes were incubated for 120 minutes at room temperature in the presence of 0.1 nM ¹²⁵I-Tyr^o rat/human CRF and varying concentrations of CRF-related and unrelated peptides. Nonspecific b mitochondrial/synaptosomal membranes were incubated for 120 minutes at room temperature in the presence of 0.1
CRF and varying concentrations of CRF-related and unrelated peptides. Nonspecific binding was determined in th and was subtracted from total binding. The data shown are from representative experiments. Each point, mean of a triplicate determination SEM <10%. Shown are acetyl (Ac) oCRF (4-41)NH₂; rCRF (1-41)NH₂; oCRF (1-41)NH₂ SEM <10%. Shown are acetyl (Ac) oCRF (4-41)NH₂; rCRF (1-41)NH₂; oCRF (1-41)NH₂; α -helical oCRF (9-41)NH₂; oCRF (1-39)NH₂, and
one of several noncompeting rCRF fragments or unrelated peptides. Reprinted with p

SEM <10%. Shown are acetyl (Ac) oCRF (4-41)NH₂; rCRF (1-41)Nl
one of several noncompeting rCRF fragments or unrelated peptides. Re
levels 3 minutes following CRF stimulation with maxi-
mal 10- to 15-fold increases occurr one of several noncompeting rCRF fragments or unrelated peptides. Reprinted
levels 3 minutes following CRF stimulation with maxi-
mal 10- to 15-fold increases occurring by 30 minutes. and
Litvin et al. (1984) reported that levels 3 minutes following CRF stimulation with maxi-
mal 10- to 15-fold increases occurring by 30 minutes. and
Litvin et al. (1984) reported that a 2-fold increase in posi
cAMP following the addition of 30 nM CRF resulted levels 3 minutes following CRF stimulation with maximal 10- to 15-fold increases occurring by 30 minutes.
Litvin et al. (1984) reported that a 2-fold increase in cAMP following the addition of 30 nM CRF resulted in maximal mal 10- to 15-fold increases occurring by 30 minutes. and
Litvin et al. (1984) reported that a 2-fold increase in pose
cAMP following the addition of 30 nM CRF resulted in
maximal ACTH secretion in vitro; however, ACTH re cAMP following the addition of 30 nM CRF resulted in As suggested above, other second messenger systems
maximal ACTH secretion in vitro; however, ACTH re-
may be involved in CRF receptor-mediated signal trans-
lease was n lease was not substantially increased, although cAMP maximal ACTH secretion in vitro; however, ACTH re-
lease was not substantially increased, although cAMP due
levels were eventually increased up to 20-fold using the
phosphodiesterase inhibitor 3-methylisobutylxanthine. se lease was not substantially increased, although cAMP
levels were eventually increased up to 20-fold using the
phosphodiesterase inhibitor 3-methylisobutylxanthine.
These observed increases in cAMP were produced with
CRF co levels were eventually increased up to 20-fold using the

phosphodiesterase inhibitor 3-methylisobutylxanthine. ser

These observed increases in cAMP were produced with

CRF concentrations near the reported K_d for recep phosphodiesterase inhibitor 3-methylisobutylxanthine. ser
These observed increases in cAMP were produced with
CRF concentrations near the reported K_d for receptor (19
binding [i.e., 0.28 to 1.3 nM (Aguilera et al., 1983 These observed increases in cAMP were produced with
CRF concentrations near the reported K_d for receptor (in
binding [i.e., 0.28 to 1.3 nM (Aguilera et al., 1983) and 3.3 nM (Millan et al., 1987)]. These increases in binding [i.e., 0.28 to 1.3 nM (Aguilera et al., 1983) and 3.3 nM (Millan et al., 1987)]. These increases in cAMP apparently are essential for CRF-induced ACTH release because the cAMP-dependent protein kinase inhibitor blo binding [i.e., 0.28 to 1.3 nM (Aguilera et al., 1983) and
3.3 nM (Millan et al., 1987)]. These increases in cAMP active
apparently are essential for CRF-induced ACTH release not because the cAMP-dependent protein kinase i 3.3 nM (Millan et al., 1987)]. These increases in cAMP
apparently are essential for CRF-induced ACTH release
because the cAMP-dependent protein kinase inhibitor
blocks both the ACTH secretory response and the POMC
gene exp parently are essential for CRF-induced ACTH release

cause the cAMP-dependent protein kinase inhibitor

ocks both the ACTH secretory response and the POMC

ne expression produced by CRF (Reisine et al., 1985).

De Souza a

because the cAMP-dependent protein kinase inhibitor
blocks both the ACTH secretory response and the POMC
gene expression produced by CRF (Reisine et al., 1985).
De Souza and colleagues conducted a detailed study of
CRF-me blocks both the ACTH secretory response and the POMC gene expression produced by CRF (Reisine et al., 1985).

De Souza and colleagues conducted a detailed study of CRF -mediated cAMP production in a variety of brain regio gene expression produced by CRF (Reisine et al., 1985).
De Souza and colleagues conducted a detailed study of
CRF-mediated cAMP production in a variety of brain
regions (Battaglia et al., 1987). The rank order of potency
f De Souza and colleagues conducted a detailed study of

CRF-mediated cAMP production in a variety of brain

regions (Battaglia et al., 1987). The rank order of potency

for CRF analogs and fragments in stimulating adenylate CRF-mediated cAMP production in a variety of brain
regions (Battaglia et al., 1987). The rank order of potency
for CRF analogs and fragments in stimulating adenylate
cyclase activity was directly correlated to their bindin for CRF analogs and fragments in stimulating adenylate cyclase activity was directly correlated to their binding affinities for CRF receptors. However, the regional distribution of receptor density (vide supra) did not cor for CRF analogs and fragments in stimulating adenylate
cyclase activity was directly correlated to their binding
affinities for CRF receptors. However, the regional dis-
tribution of receptor density (vide supra) did not cyclase activity was directly correlated to their binding
affinities for CRF receptors. However, the regional dis
tribution of receptor density (vide supra) did not corre
spond with regional CRF-stimulated adenylate cycla affinities for CRF receptors. However, the regional distribution of receptor density (vide supra) did not correspond with regional CRF-stimulated adenylate cyclas activity (frontoparietal cortex $>$ olfactory bulb $>$ cer tribution of receptor density (vide supra) did not corre-
spond with regional CRF-stimulated adenylate cyclase
activity (frontoparietal cortex $>$ olfactory bulb $>$ cere-
bellum $>$ midbrain $>$ hippocampus $>$ striatum spond with regional CRF-stimulated adenylate cyclase
activity (frontoparietal cortex $>$ olfactory bulb $>$ cere-
bellum $>$ midbrain $>$ hippocampus $>$ striatum $>$ hypo-
thalamus $>$ spinal cord). The authors suggest t activity (frontoparietal cortex $>$ olfactory bulb $>$ cerebellum $>$ midbrain $>$ hippocampus $>$ striatum $>$ hypothalamus $>$ spinal cord). The authors suggest that this disparity may derive from some populations of CR bellum > midbrain > hippocampus > striatum > hypo-
thalamus > spinal cord). The authors suggest that this
disparity may derive from some populations of CRF
receptors being coupled to other second messenger sys-
tems (vide thalamus > spinal cord). The authors suggest that this cell
disparity may derive from some populations of CRF inh
receptors being coupled to other second messenger sys-
in tems (vide infra). Alternatively, certain populati disparity may derive from some populations of CRF in
receptors being coupled to other second messenger sys-
tems (vide infra). Alternatively, certain populations of n
CRF receptors may not be functionally coupled to any it receptors being coupled to other second messenger sys-
tems (vide infra). Alternatively, certain populations of
CRF receptors may not be functionally coupled to any
isecond messenger system and/or may represent "spare"
rec

positively coupled to adenylate cyclase.

As suggested above, other second messenger systems the spleen (Webster et al., 1989), rat adrenal membrane
and bovine chromaffin cells (Dave et al., 1985), are al
positively coupled to adenylate cyclase.
As suggested above, other second messenger syster
may be involved in and bovine chromaffin cells (Dave et al., 1985), are also
positively coupled to adenylate cyclase.
As suggested above, other second messenger systems
may be involved in CRF receptor-mediated signal trans-
duction. For exam positively coupled to adenylate cyclase.
As suggested above, other second messenger systems
may be involved in CRF receptor-mediated signal trans-
duction. For example, in a pilot study our group (C. D.
Kilts and C. B. Nem As suggested above, other second messenger systems
may be involved in CRF receptor-mediated signal trans-
duction. For example, in a pilot study our group (C. D.
Kilts and C. B. Nemeroff, personal communication) ob-
served Kilts and C. B. Nemeroff, personal communication) observed CRF-induced increases in phosphoinositide hydrolysis in rat hypothalamic brain slices. Cronin et al. (1986) obtained evidence that protein kinase C can poduction. For example, in a pilot study our group (C. D.
Kilts and C. B. Nemeroff, personal communication) observed CRF-induced increases in phosphoinositide hy-
drolysis in rat hypothalamic brain slices. Cronin et al.
(198 Kilts and C. B. Nemeroff, personal communication) observed CRF-induced increases in phosphoinositide hydrolysis in rat hypothalamic brain slices. Cronin et al. (1986) obtained evidence that protein kinase C can potentiate served CRF-induced increases in phosphoinositide hy-
drolysis in rat hypothalamic brain slices. Cronin et al.
(1986) obtained evidence that protein kinase C can po-
tentiate cAMP production subsequent to CRF receptor
activ drolysis in rat hypothalamic brain slices. Cronin et al.
(1986) obtained evidence that protein kinase C can po-
tentiate cAMP production subsequent to CRF receptor
activation. It should be noted that in this case this woul (1986) obtained evidence that protein kinase C can po-
tentiate cAMP production subsequent to CRF receptor
activation. It should be noted that in this case this would
not be a direct result of CRF receptor occupancy but a
 tentiate cAMP production subset activation. It should be noted that
not be a direct result of CRF rec
synergistic effect of other neurotr
that activate protein kinase C.
Using electrophysiological met tivation. It should be noted that in this case this would
t be a direct result of CRF receptor occupancy but a
nergistic effect of other neurotransmitters on that cell
at activate protein kinase C.
Using electrophysiologic

not be a direct result of CRF receptor occupancy bu
synergistic effect of other neurotransmitters on that α
that activate protein kinase C.
Using electrophysiological methods, Aldenhoff (194
demonstrated that the calciu synergistic effect of other neurotransmitters on that
that activate protein kinase C.
Using electrophysiological methods, Aldenhoff (19
demonstrated that the calcium channel blocker, vera
mil, blocked the excitatory effect that activate protein kinase C.
Using electrophysiological methods, Aldenhoff (1986)
demonstrated that the calcium channel blocker, verapa-
mil, blocked the excitatory effects of CRF on hippocam-
pal neuronal activity. Thi Using electrophysiological methods, Aldenhoff (1986)
demonstrated that the calcium channel blocker, verapa-
mil, blocked the excitatory effects of CRF on hippocam-
pal neuronal activity. This raises the possibility that
CR demonstrated that the calcium channel blocker, verapa-
mil, blocked the excitatory effects of CRF on hippocam-
pal neuronal activity. This raises the possibility that
CRF alters membrane calcium fluxes with possible re-
su mil, blocked the excitatory effects of CRF on hippocampal neuronal activity. This raises the possibility that CRF alters membrane calcium fluxes with possible resultant alterations in potassium ion conductance and membrane pal neuronal activity. This raises the possibility that CRF alters membrane calcium fluxes with possible resultant alterations in potassium ion conductance and membrane potentials. In addition, there has been one report de CRF alters membrane calcium fluxes with possible resultant alterations in potassium ion conductance and membrane potentials. In addition, there has been one report describing a role for calcium-mediated second messenger sy sultant alterations in potassium ion conductance and
membrane potentials. In addition, there has been one
report describing a role for calcium-mediated second
messenger systems in modulating the actions of CRF. It
is known membrane potentials. In addition, there has been one
report describing a role for calcium-mediated second
messenger systems in modulating the actions of CRF. It
is known that binding of calcium to calmodulin leads to
activ report describing a role for calcium-mediated second
messenger systems in modulating the actions of CRF. It
is known that binding of calcium to calmodulin leads to
activation of a calmodulin-dependent kinase that may be
im messenger systems in modulating the actions of CRF. It
is known that binding of calcium to calmodulin leads to
activation of a calmodulin-dependent kinase that may be
important in the stimulus-secretion coupling in various is known that binding of calcium to calmodulin leads to
activation of a calmodulin-dependent kinase that may be
important in the stimulus-secretion coupling in various
cells. Murakami et al. (1985) found that the calmoduli activation of a calmodulin-dependent kinase that may b
important in the stimulus-secretion coupling in variou
cells. Murakami et al. (1985) found that the calmoduli
inhibitor (W-7) inhibits CRF-stimulated ACTH releas
in vi important in the stimulus-secretion coupling in various
cells. Murakami et al. (1985) found that the calmodulin
inhibitor (W-7) inhibits CRF-stimulated ACTH release
in vitro without effecting CRF-stimulated cAMP accu-
mula cells. Murakami et al. (1985) found that the calmodulin
inhibitor (W-7) inhibits CRF-stimulated ACTH release
in vitro without effecting CRF-stimulated cAMP accu-
mulation. Although these results suggest that CRF exerts
its inhibitor (W-7) inhibits CRF-stimulated ACTH release
in vitro without effecting CRF-stimulated cAMP accu-
mulation. Although these results suggest that CRF exerts
its effects on ACTH release through both a cAMP system
and in vitro without effecting CR
imulation. Although these result
its effects on ACTH release thr
and a calcium-calmodulin syst
further study and confirmation

CORTICOTROPIN-RELE
Following coupling to its receptor, CRF increases the alce
thylation of phosphatidylethanolamine to phosphati-CORTICOTRO
Following coupling to its receptor, CRF increases
methylation of phosphatidylethanolamine to phosph
dylcholine (Hook et al., 1982). Although this reac CORTICOTROPIN-RELI

Following coupling to its receptor, CRF increases the

almethylation of phosphatidylethanolamine to phosphati-

dylcholine (Hook et al., 1982). Although this reaction

has not been well studied, it has Following coupling to its receptor, CRF increases the
methylation of phosphatidylethanolamine to phosphati-
dylcholine (Hook et al., 1982). Although this reaction
has not been well studied, it has been suggested that
phosp Following coupling to its receptor, CRF increases the
methylation of phosphatidylethanolamine to phosphati-
dylcholine (Hook et al., 1982). Although this reaction
has not been well studied, it has been suggested that
phosp methylation of phosphatidylethanolamine to phosphatidylcholine (Hook et al., 1982). Although this reaction has not been well studied, it has been suggested that phospholipid methylation may be a possible membrane transduct dylcholine (Hook et al., 1982). Although this reaction
has not been well studied, it has been suggested that
phospholipid methylation may be a possible membrane
transduction mechanism for receptor-mediated events.
In addit has not been well studied, it has been suggested that nephospholipid methylation may be a possible membrane morntanal transduction mechanism for receptor-mediated events. In In addition, this same group (Heisler et al., 19 phospholipid methylation may be a possible membrane
transduction mechanism for receptor-mediated events. In
In addition, this same group (Heisler et al., 1983) re-
ported that CRF also stimulates methylation of free
carbox In addition, this same group (Heisler et al., 1983) re-
ported that CRF also stimulates methylation of free
carboxyl groups on glutamyl and/or aspartyl residues of
various protein substrates by the enzyme protein carbox-
y ported that CRF also stimulates methylation of free
carboxyl groups on glutamyl and/or aspartyl residues of
various protein substrates by the enzyme protein carbox-
ymethylase. This latter action of CRF appears to be
impor and in CRF-mediated ACTH release in particular. rious protein substrates by the enzyme protein carbox-
nethylase. This latter action of CRF appears to be
portant in exocytosis secretion mechanisms in general
d in CRF-mediated ACTH release in particular.
Little is known methylase. This latter action of CRF appears to be
important in exocytosis secretion mechanisms in general of
and in CRF-mediated ACTH release in particular.
Little is known regarding termination of the action of
CRF foll

important in exocytosis secretion mechanisms in genera
and in CRF-mediated ACTH release in particular.
Little is known regarding termination of the action or
CRF following its synaptic release. Although there is
evidence t and in CRF-mediated ACTH release in particular.

Little is known regarding termination of the action of

CRF following its synaptic release. Although there is

evidence that CRF is degraded by one or more peptidases,

the Little is known regarding termination of the action
CRF following its synaptic release. Although there
evidence that CRF is degraded by one or more peptidas
there is evidence that the ligand-receptor complex
internalized f CRF following its synaptic release. Although there is evidence that CRF is degraded by one or more peptidases, there is evidence that the ligand-receptor complex is internalized following receptor activation and metabolize CRF was measured in hypophysial portal blood (Plotsky
evidence that CRF is degraded by one or more peptidases,
there is evidence that the ligand-receptor complex is
internalized following receptor activation and metabo-
li The internalized following receptor control of the al. 2. Ontogeny of the hypophysiotropic corticotropin-re-

internalized following receptor activation and metabo-

lized internally. In a preliminary report, Ritchie et al internalized following receptor activation and metabo-
lized internally. In a preliminary report, Ritchie et al.
(1990) observed that, following incubation of rat/human
CRF with brain tissue extracts, high-pressure liquid lized internally. In a preliminary report, Ritchie et al.
(1990) observed that, following incubation of rat/human
CRF with brain tissue extracts, high-pressure liquid
chromatography fractionation showed diminution of the
p CRF with brain tissue extracts, high-pressure liquid
chromatography fractionation showed diminution of the
parent CRF peak as well as the presence of two other
peaks not previously observed. The latter peaks may
represent chromatography fractionation showed diminution of the
parent CRF peak as well as the presence of two other
peaks not previously observed. The latter peaks may
represent CRF metabolites resulting from the action of
peptidas parent CRF peak as well as the presence of two other
peaks not previously observed. The latter peaks may
represent CRF metabolites resulting from the action of
peptidases. Leroux and Pelletier (1984), using ¹²⁵I-CRF
elec peaks not previously observed. The latter peaks may
represent CRF metabolites resulting from the action of
peptidases. Leroux and Pelletier (1984), using ¹²⁵I-CRF
electron microscopic autoradiography, found that, within
 represent CRF metabolites resulting from the action of
peptidases. Leroux and Pelletier (1984), using ¹²⁵I-CRF Cc
electron microscopic autoradiography, found that, within
15 minutes of administration to intact animals, s 15 minutes of administration to intact animals, silver 15 minutes of administration to intact animals, silver grains were observed primarily over lysosomes and the Golgi apparatus of anterior pituitary corticotrophs. I addition, by 30 minutes, no labeling could be detected Thi grains were observed primarily over lysosomes and the Golgi apparatus of anterior pituitary corticotrophs. In addition, by 30 minutes, no labeling could be detected. This suggested that, following binding to plasma membran Golgi apparatus of anterior pituitary corticotrophs. In ges
addition, by 30 minutes, no labeling could be detected. mF
This suggested that, following binding to plasma mem-
CR
brane receptors, CRF is rapidly internalized. addition, by 30 minutes, no labeling could be detected. m
This suggested that, following binding to plasma mem-
brane receptors, CRF is rapidly internalized. Similar pindings were reported by Childs et al. (1986) who used
 brane receptors, CRF is rapidly internalized. Similar period, but CRF mRNA concentrations did not change.

findings were reported by Childs et al. (1986) who used Although exposure to stress does not elicit marked

a bioti brane receptors, CRF is rapidly internalized. Similar perfindings were reported by Childs et al. (1986) who used a biotinylated CRF analog. Internalization was observed in as early as 1 to 3 minutes following exposure to p findings were reported by Childs et al. (1986) who used
a biotinylated CRF analog. Internalization was observed
as early as 1 to 3 minutes following exposure to pituitary
cell cultures. Although further work is needed, the a biotinylated CRF analog. Internalization was observed
as early as 1 to 3 minutes following exposure to pituitary
cell cultures. Although further work is needed, these
studies suggest that internalization of CRF-receptor as early as 1 to 3 minutes following exposure to pituitary
cell cultures. Although further work is needed, these
studies suggest that internalization of CRF-receptor
complexes, cleavage of the CRF molecule in the synaptic
 cell cultures. Although further work is needed, these ex-
studies suggest that internalization of CRF-receptor
complexes, cleavage of the CRF molecule in the synaptic
incleft, and binding of CRF by its binding protein repr complexes, cleavage of the CRF molecule in the synaptic
cleft, and binding of CRF by its binding protein represent
three complimentary methods for termination of the
action of CRF. All three of these mechanisms represent complexes, cleavage of the CRF molecule in the synaptic
cleft, and binding of CRF by its binding protein represent
three complimentary methods for termination of the
action of CRF. All three of these mechanisms represent
p rotransmission. **III. Corticotropin-releasing Factor Regulation of**
 III. Corticotropin-releasing Factor Regulation of
 III. Corticotropin-releasing Factor Regulation of
 III. Corticotropin-releasing Factor Regulation of

Neuroendocrine Function *A. Regulation Continertion-releasing Factor Regularion of the Pituitary-Adrenal Axis*
A. Regulation of the Pituitary-Adrenal Axis
A. Corticotronin-releasing factor as the major

1. Corticotropin-releasing Factor Regulation of
*Regulation of the Pituitary-Adrenal Axis***
1. Corticotropin-releasing factor as the major regulator**
pro-opiomelanocortin-derived anterior pituitary hor-A. Regulation of the Pituitary-Adrenal Axis
 1. Corticotropin-releasing factor as the major regulator
 of pro-opiomelanocortin-derived anterior pituitary hor-
 mone secretion. In this section we briefly review the A. Regulation of the Pituitary-Adrenal Axis

1. Corticotropin-releasing factor as the major regulator and

of pro-opiomelanocortin-derived anterior pituitary hor-

mone secretion. In this section we briefly review the expl different and the Trundary-Autenal Axis
1. Corticotropin-releasing factor as the major regula
of pro-opiomelanocortin-derived anterior pituitary h
mone secretion. In this section we briefly review
literature supporting a s 1. Corticotropin-releasing factor as the major regulator
of pro-opiomelanocortin-derived anterior pituitary hor-
mone secretion. In this section we briefly review the
literature supporting a seminal role for CRF in neuroen of pro-opiomelanocortin-derived anterior pituitary hor-
mone secretion. In this section we briefly review the
literature supporting a seminal role for CRF in neuroen-
docrine function. As noted earlier, Vale et al. (1981) mone secretion. In this section we briefly review the expresient expression in this section of CRF in neuroen-
docrine function. As noted earlier, Vale et al. (1981) spons
elucidated the structure of CRF approximately a d literature supporting a seminal role for CRF in neuroen
docrine function. As noted earlier, Vale et al. (1981
elucidated the structure of CRF approximately a decad
ago. CRF was found to stimulate the release of ACTI
and

In addition, this same group (Heisler et al., 1983) re-
ported that CRF also stimulates methylation of free
ported that CRF also stimulates methylation of free
carboxyl groups on glutamyl and/or aspartyl residues of
regul LEASING FACTOR 435
ald et al., 1983) and in vitro (Vale et al., 1983b). These
actions of CRF are antagonized by the CRF antagonist, LEASING FACTOR
ald et al., 1983) and in vitro (Vale et al., 1983b). These
actions of CRF are antagonized by the CRF antagonist
 α -helical CRF₉₋₄₁ (Rivier et al., 1984c), or by immuno LEASING FACTOR
ald et al., 1983) and in vitro (Vale et al., 1983b). Th
actions of CRF are antagonized by the CRF antagon
 α -helical CRF₉₋₄₁ (Rivier et al., 1984c), or by immu
neutralization with polyclonal (Rivier et ald et al., 1983) and in vitro (Vale et al., 1983b). These
actions of CRF are antagonized by the CRF antagonist,
 α -helical CRF₉₋₄₁ (Rivier et al., 1984c), or by immuno-
neutralization with polyclonal (Rivier et al., ald et al., 1983) and in vitro (Vale et al., 1983b). These
actions of CRF are antagonized by the CRF antagonist
 α -helical CRF₉₋₄₁ (Rivier et al., 1984c), or by immuno-
neutralization with polyclonal (Rivier et al., 1 actions of CRF are antagonized by the CRF antagonist, α -helical CRF₉₋₄₁ (Rivier et al., 1984c), or by immuno-
neutralization with polyclonal (Rivier et al., 1982b) or
monoclonal (van Oers et al., 1989) anti-CRF antib α -helical CRF₉₋₄₁ (Rivier et al., 1984c), or by immuno-
neutralization with polyclonal (Rivier et al., 1982b) or
monoclonal (van Oers et al., 1989) anti-CRF antibodies.
In addition, CRF administered i.c.v. also stimu neutralization with polyclonal (Rivier et al., 1982b) on
monoclonal (van Oers et al., 1989) anti-CRF antibodies
In addition, CRF administered i.c.v. also stimulates ac
tivation of the HPA axis (Rock et al., 1984; Ono et al monoclonal (van Oers et al., 1989) anti-CRF antibodies.
In addition, CRF administered i.c.v. also stimulates activation of the HPA axis (Rock et al., 1984; Ono et al., 1985a). Final proof that CRF is the major physiologica In addition, CRF administered i.c.v. also stimulates activation of the HPA axis (Rock et al., 1984; Ono et al.
1985a). Final proof that CRF is the major physiologica
regulator of the increased HPA activity that occurs in
r tivation of the HPA axis (Rock et al., 1984; Ono et al., 1985a). Final proof that CRF is the major physiological regulator of the increased HPA activity that occurs in response to stress comes from data showing almost comp 1985a). Final proof that CRF is the major physiological
regulator of the increased HPA activity that occurs in
response to stress comes from data showing almost com-
plete blockade of pituitary-adrenal responses to a varie regulator of the increased HPA activity that occurs in
response to stress comes from data showing almost com-
plete blockade of pituitary-adrenal responses to a variety
of stressors following administration of CRF antisera response to stress comes from data showing almost com-
plete blockade of pituitary-adrenal responses to a variety
of stressors following administration of CRF antisera
(Rivier and Vale, 1983a; Linton et al., 1985; Nakane e plete blockade of pituitary-adrenal responses to a variety
of stressors following administration of CRF antisera
(Rivier and Vale, 1983a; Linton et al., 1985; Nakane et
al., 1985; Ono et al., 1985b) and from studies in whi of stressors follow
(Rivier and Vale,
al., 1985; Ono et
CRF was measure
and Vale, 1984).
2. Ontogeny of Zuver and Vale, 1983a; Linton et al., 1985; Naka, 1985; Ono et al., 1985b) and from studies in NRF was measured in hypophysial portal blood (Plance Vale, 1984).
 2. Ontogeny of the hypophysiotropic corticotrop using fact

chromatography fractionation showed diminution of the
parent CRF peak as well as the presence of two other
peaks into previously observed. The latter peaks may
represent CRF metabolites resulting from the action of the tec electron microscopic autoradiography, found that, within through birth, then decreased during the perinatal
15 minutes of administration to intact animals, silver period, before finally increasing to adult levels thereafte al., 1985; Ono et al., 1985b) and from studies in which

CRF was measured in hypophysial portal blood (Plotsky

and Vale, 1984).

2. Ontogeny of the hypophysiotropic corticotropin-re-

leasing factor system. CRF immunoreac CRF was measured in hypophysial portal blood (Plot.
and Vale, 1984).
2. Ontogeny of the hypophysiotropic corticotropin-
leasing factor system. CRF immunoreactivity in the P
of the rat fetus can be observed beginning at app and Vale, 1984).

2. Ontogeny of the hypophysiotropic corticotropin-re-

leasing factor system. CRF immunoreactivity in the PVN

of the rat fetus can be observed beginning at approxi-

mately gestation day 18 or 19 and gra 2. Ontogeny of the hypophysiotropic corticotropin-re-
leasing factor system. CRF immunoreactivity in the PVN
of the rat fetus can be observed beginning at approxi-
mately gestation day 18 or 19 and gradually increases in
d leasing factor system. CRF immunoreactivity in the PVN
of the rat fetus can be observed beginning at approxi-
mately gestation day 18 or 19 and gradually increases in
density during development before finally attaining adu of the rat fetus can be observed beginning at approxi-
mately gestation day 18 or 19 and gradually increases in
density during development before finally attaining adult
levels (Bugnon et al., 1982; Chatelain et al., 1988; mately gestation day 18 or 19 and gradually increases in
density during development before finally attaining adult
levels (Bugnon et al., 1982; Chatelain et al., 1988; Rundle
and Funder, 1988). Similarly, Grino et al. (198 density during development before finally attaining adult
levels (Bugnon et al., 1982; Chatelain et al., 1988; Rundle
and Funder, 1988). Similarly, Grino et al. (1989b) de-
tected CRF mRNA in the PVN on day 17 of gestation levels (Bugnon et al., 1982; Chatelain et al., 1988; Rundle
and Funder, 1988). Similarly, Grino et al. (1989b) de-
tected CRF mRNA in the PVN on day 17 of gestation.
Concentrations of CRF mRNA increased gradually
through b and Funder, 1988). Similarly, Grino et al. (1989b) de
tected CRF mRNA in the PVN on day 17 of gestation
Concentrations of CRF mRNA increased gradually
through birth, then decreased during the perinata
period, before finall tected CRF mRNA in the PVN on day 17 of gestation.
Concentrations of CRF mRNA increased gradually
through birth, then decreased during the perinatal
period, before finally increasing to adult levels thereafter.
Emanuel et through birth, then decreased during the perinatal period, before finally increasing to adult levels thereafter. period, before finally increasing to adult levels thereafter.
Emanuel et al. (1989) first detected CRF mRNA on
gestation day 20 and measured both the peptide and
mRNA from this prenatal period until postnatal day 15.
CRF c Emanuel et al. (1989) first detected CRF mRNA on
gestation day 20 and measured both the peptide and
mRNA from this prenatal period until postnatal day 15.
CRF concentrations increased throughout the study
period, but CRF m

Although exposure to stress does not elicit marked increases in plasma ACTH concentrations until 14 days CRF concentrations increased throughout the study
period, but CRF mRNA concentrations did not change.
Although exposure to stress does not elicit marked
increases in plasma ACTH concentrations until 14 days
of age (vide in period, but CRF mRNA concentrations did not change.
Although exposure to stress does not elicit marked
increases in plasma ACTH concentrations until 14 days
of age (vide infra), Walker et al. (1986) showed that
exogenous C Although exposure to stress does not elicit mand increases in plasma ACTH concentrations until 14 to 4 of age (vide infra), Walker et al. (1986) showed rexogenous CRF can directly stimulate ACTH relation-
throughout postna increases in plasma ACTH concentrations until 14 days

of age (vide infra), Walker et al. (1986) showed that

exogenous CRF can directly stimulate ACTH release

throughout postnatal days 3 to 21. Moreover, urethane-

indu of age (vide infra), Walker et al. (1986) showe
exogenous CRF can directly stimulate ACTH is
throughout postnatal days 3 to 21. Moreover, ure
induced stress can result in a small increase in .
secretion that can be blocked exogenous CRF can directly stimulate ACTH relearthroughout postnatal days 3 to 21. Moreover, urethainduced stress can result in a small increase in ACT secretion that can be blocked by CRF immunoneutrization as early as da throughout postnatal days 3 to 21. Moreover, urethane-
induced stress can result in a small increase in ACTH
secretion that can be blocked by CRF immunoneutrali-
zation as early as day 3 postnatally. The limited capabil-
i induced stress can result in a small increase in ACTH
secretion that can be blocked by CRF immunoneutrali-
zation as early as day 3 postnatally. The limited capabil-
ity of the rat to mount a robust ACTH and corticosterone secretion that can be blocked by CRF immunoneutralization as early as day 3 postnatally. The limited capability of the rat to mount a robust ACTH and corticosterone response to stress during the first week of life has been zation as early as day 3 postnatally. The limited capabity of the rat to mount a robust ACTH and corticosteron
response to stress during the first week of life has bee
termed the stress-nonresponsive period. Whereas on
cur ity of the rat to mount a robust ACTH and corticosterone
response to stress during the first week of life has been
termed the stress-nonresponsive period. Whereas one
current hypothesis to explain the stress-nonresponsive
 response to stress during the first week of life has been
termed the stress-nonresponsive period. Whereas one
current hypothesis to explain the stress-nonresponsive
period is an increased glucocorticoid negative feedback
o current hypothesis to explain the stress-nonresponsive
period is an increased glucocorticoid negative feedback
on POMC and CRF peptide synthesis during this time,
Grino et al. (1989a) showed that, in contrast to the adult, current hypothesis to explain the stress-nonresponsive
period is an increased glucocorticoid negative feedback
on POMC and CRF peptide synthesis during this time,
Grino et al. (1989a) showed that, in contrast to the adult, period is an increased glucocorticoid negative feedback
on POMC and CRF peptide synthesis during this time,
Grino et al. (1989a) showed that, in contrast to the adult,
adrenalectomy does not alter CRF gene expression in th on POMC and CRF peptide synthesis during this time,
Grino et al. (1989a) showed that, in contrast to the adult,
adrenalectomy does not alter CRF gene expression in the
PVN of 7 day old rats. This suggests that CRF gene
exp Grino et al. (1989a) showed that, in contrast to the aduladrenalectomy does not alter CRF gene expression in th
PVN of 7 day old rats. This suggests that CRF genexpression, rather than being particularly sensitive t
glucoc adrenalectomy does not alter CRF gene expression in the
PVN of 7 day old rats. This suggests that CRF gene
expression, rather than being particularly sensitive to
glucocorticoid negative feedback, may in fact be unre-
spon PVN of 7 day old rats. This suggests that CRF gene
expression, rather than being particularly sensitive to
glucocorticoid negative feedback, may in fact be unre-
sponsive to feedback of any sort, such as the ability to
res expression, rather than being particularly sensitive if glucocorticoid negative feedback, may in fact be unresponsive to feedback of any sort, such as the ability if respond to the need for increased CRF and glucocorticoid glucocorticoid negative feedback, may in fact be unresponsive to feedback of any sort, such as the ability t
respond to the need for increased CRF and glucocorticoid
production under any circumstance. It would be of inter-

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a
sponsive elements in the promoter region of the CRF to a
gene during this stress-nonresponsive period. 436
gene during this stress-nonresponsive period.
CRF receptors in pituitary and cerebral of

G

CRF receptors in the promoter region of the CRF to

the during this stress-nonresponsive period.

CRF receptors in pituitary and cerebral cortex are the

tectable by prenatal day 17 (Insel et al., 1988). Intersponsive elements in the promoter region of the CR
gene during this stress-nonresponsive period.
CRF receptors in pituitary and cerebral cortex a
detectable by prenatal day 17 (Insel et al., 1988). Inte
estingly, receptor sponsive elements in the promoter region of the CRF to a
gene during this stress-nonresponsive period. These
CRF receptors in pituitary and cerebral cortex are the
detectable by prenatal day 17 (Insel et al., 1988). Intergene during this stress-nonresponsive period. The result CRF receptors in pituitary and cerebral cortex are the detectable by prenatal day 17 (Insel et al., 1988). Inter-exce estingly, receptor number in whole brain increa CRF receptors in pituitary and cerebral cortex are the detectable by prenatal day 17 (Insel et al., 1988). Inter-
estingly, receptor number in whole brain increases to nun
three times their adult concentration by postnatal detectable by prenatal day 17 (Insel et al., 1988). Inter-
estingly, receptor number in whole brain increases to
three times their adult concentration by postnatal day 8
and then decreases to adult concentrations by day 21 three times their adult concentration by postnatal day 8 and then decreases to adult concentrations by day 21. In addition to changes in the density of CRF receptors, there are alterations in the distribution of CRF recept three times their adult concentration by postnatal day
and then decreases to adult concentrations by day 21.
addition to changes in the density of CRF receptor
there are alterations in the distribution of CRF recepto
that and then decreases to adult concentrations by day 21. In occupaddition to changes in the density of CRF receptors, of PC there are alterations in the distribution of CRF receptors Reisithat occur during development. For ex addition to changes in the density of CRF receptor
there are alterations in the distribution of CRF receptor
that occur during development. For example, CRF rece
tors are found in very high density in the striature
prenata there are alterations in the distribution of CRF receptors Re
that occur during development. For example, CRF recep-
tors are found in very high density in the striatum ad
prenatally, but postnatally and in the adult, CRF prenatally, but postnatally and in the adult, CRF receptor binding is much more dense in the cerebral cortex with minimal binding in the striatum.
3. Circadian rhythmicity. It is well established that the *3. The striatum* adentically, but postnatally and in the adult, CRF recep-
 3. Circadian rhythmicity. It is well established that the of
 PA axis exhibits a circadian rhythm in humans, rats, must be also interest that

prenatally, but postnatally and in the adult, CRF receptor binding is much more dense in the cerebral cortex
with minimal binding in the striatum.
3. Circadian rhythmicity. It is well established that the
HPA axis exhibits tor binding is much more dense in the cerebral cortex
with minimal binding in the striatum.
3. Circadian rhythmicity. It is well established that the
HPA axis exhibits a circadian rhythm in humans, rats,
and other mammals. with minimal binding in the striatum. The controlled predominantly is well established that the offerential release in the differential release in the controlled predominantly by the differential release in of CRF from ner 3. Circadian rhythmicity. It is well established that the HPA axis exhibits a circadian rhythm in humans, rats, and other mammals. This rhythm is generally thought to be controlled predominantly by the differential release HPA axis exhibits a circadian rhythm in humans, rats, nearly other mammals. This rhythm is generally thought et be controlled predominantly by the differential release in of CRF from nerve terminals in the median eminence and other mammals. This rhythm is generally thought et
to be controlled predominantly by the differential release in
of CRF from nerve terminals in the median eminence ce
into the portal vessels supplying the anterior pitu to be controlled predominantly by the differential release intraperitoneal injections of CRF increased corticotroph
of CRF from nerve terminals in the median eminence cell volume. Gertz et al. (1987) demonstrated that CRF into the portal vessels supplying the anterior pituitary
corticotrophs. However, other neuroregulators such as
vasopressin, oxytocin, and epinephrine also are known
to possess ACTH-releasing activity, and immunoneu-
traliz corticotrophs. However, other neuroregulators such as
vasopressin, oxytocin, and epinephrine also are known
to possess ACTH-releasing activity, and immunoneu-
tralization of CRF does not completely abolish circadian
rhythm corticotrophs. However, other neuroregulators such a
vasopressin, oxytocin, and epinephrine also are know:
to possess ACTH-releasing activity, and immunoneu
tralization of CRF does not completely abolish circadia:
rhythms sopressin, oxytocin, and epinephrine also are kno
possess ACTH-releasing activity, and immunon
alization of CRF does not completely abolish circadi
ythms of plasma ACTH (Carnes et al., 1989, 1990).
We (Owens et al., 1990a) to possess ACTH-releasing activity, and immunoneu-
tralization of CRF does not completely abolish circadian
rhythms of plasma ACTH (Carnes et al., 1989, 1990).
We (Owens et al., 1990a) reported that CRF concen-
trations in

tralization of CRF does not completely abolish circadia
rhythms of plasma ACTH (Carnes et al., 1989, 1990).
We (Owens et al., 1990a) reported that CRF concertrations in the median eminence and hypothalamus (m
nus median em rhythms of plasma ACTH (Carnes et al., 1989, 1990).
We (Owens et al., 1990a) reported that CRF concentrations in the median eminence and hypothalamus (n
nus median eminence) increase with the normal circ
dian increase in p We (Owens et al., 1990a) reported that CRF concentrations in the median eminence and hypothalamus (minus median eminence) increase with the normal circadian increase in plasma corticosterone concentrations.
These increases trations in the median eminence and hypothalamus (minumus median eminence) increase with the normal circadian increase in plasma corticosterone concentrations.
These increases in CRF concentrations may reflect increased sy nus median eminence) increase with the normal circa-
dian increase in plasma corticosterone concentrations.
These increases in CRF concentrations may reflect in-
creased synthesis, storage, and release (i.e., turnover) of dian increase in plasma corticosterone concentration
These increases in CRF concentrations may reflect increased synthesis, storage, and release (i.e., turnover) CRF necessitated by the greater secretion of ACTH an
cortic These increases in CRF concentrations may reflect increased synthesis, storage, and release (i.e., turnover) of CRF necessitated by the greater secretion of ACTH and corticosterone that occurs in rodents in the late aftern creased synthesis, storage, and release (i.e., turnover) of and
CRF necessitated by the greater secretion of ACTH and in recorticosterone that occurs in rodents in the late after-
noon. Although it is likely that CRF conce CRF necessitated by the greater secretion of ACTH
corticosterone that occurs in rodents in the late af
noon. Although it is likely that CRF concentrati
measured in the median eminence reflect stored CRI
vesicles, the major corticosterone that occurs in rodents in the late after-
noon. Although it is likely that CRF concentrations
measured in the median eminence reflect stored CRF in
vesicles, the majority of CRF measured in the hypothal-
amu noon. Although it is likely that CRF concentrations CRI
measured in the median eminence reflect stored CRF in part
vesicles, the majority of CRF measured in the hypothal-
amus minus median eminence probably represents pepmeasured in the median eminence reflect stored CRF in
vesicles, the majority of CRF measured in the hypothal-
amus minus median eminence probably represents pep-
tide found in cell bodies in the PVN and their axons. In
con vesicles, the majority of CRF measured in the hypothal-
amus minus median eminence probably represents pep-
tide found in cell bodies in the PVN and their axons. In
contrast to our findings, Moldow and Fischman (1984)
repo amus minus median eminence probably represents pep-
tide found in cell bodies in the PVN and their axons. In
contrast to our findings, Moldow and Fischman (1984)
reported that the lowest hypothalamic concentrations of
CRF tide found in cell bodies in the PVN and their axons. In
contrast to our findings, Moldow and Fischman (1984) to
reported that the lowest hypothalamic concentrations of cou
CRF occur at the time of peak plasma corticostero contrast to our findings, Moldow and Fischman (1984) to
reported that the lowest hypothalamic concentrations of
CRF occur at the time of peak plasma corticosterone sconcentrations. More recently, and in agreement with
our reported that the lowest hypothalamic concentrations of coup
CRF occur at the time of peak plasma corticosterone seer
concentrations. More recently, and in agreement with (198
our findings, Yokoe et al. (1988) reported tha CRF occur at the time of peak plasma corticosterone see
concentrations. More recently, and in agreement with (19
our findings, Yokoe et al. (1988) reported that increased dec
hypothalamic and plasma concentrations of CRF v concentrations. More recently, and in agreement with
our findings, Yokoe et al. (1988) reported that increased
hypothalamic and plasma concentrations of CRF vary in
parallel with alterations in the pituitary-adrenal axis a hypothalamic and plasma concentrations of CRF vary in pituitary, but no changes were observed in the neuroin-
parallel with alterations in the pituitary-adrenal axis and termediate lobe. This CRF receptor down-regulation p hypothalamic and plasma concentrations of CRF vary in
parallel with alterations in the pituitary-adrenal axis and
circulating glucocorticoids. Further evidence supporting
our findings comes from the work of Watts and Swans parallel with alterations in the pituitary-adrenal axis and
circulating glucocorticoids. Further evidence supporting si
our findings comes from the work of Watts and Swanson
d(1989) who found that the content of CRF precur our findings comes from the work of Watts and Swanson detailed study, Wynn et al. (1985) observed significant (1989) who found that the content of CRF precursor (29%) down-regulation of anterior pituitary CRF recepmRNA in (1989) who found that the content of CRF precursor mRNA in the PVN begins to decline sometime between midday and the beginning of the dark phase. This decline in mRNA synthesis occurs at or near the time of maximal peptid mRNA in the PVN begins to decline sometime between
midday and the beginning of the dark phase. This decline
in mRNA synthesis occurs at or near the time of maximal
peptide accumulation in the neurons.
4. Actions of cortico **EXAM** in the PVN begins to decline sometime between idday and the beginning of the dark phase. This decline mRNA synthesis occurs at or near the time of maximal pitide accumulation in the neurons.
4. Actions of corticotro midday and the beginning of the dark phase. This declim
in mRNA synthesis occurs at or near the time of maxim-
peptide accumulation in the neurons.
4. Actions of corticotropin-releasing factor on pituitar
corticotrophs. As

in mRNA synthesis occurs at or near the time of maximal pa
peptide accumulation in the neurons. actions of corticotropin-releasing factor on pituitary
ecorticotrophs. As mentioned previously, following inter-
action of CRF peptide accumulation in the neurons. a
4. Actions of corticotropin-releasing factor on pituitary
corticotrophs. As mentioned previously, following inter-
action of CRF with its receptor on the corticotrophs, the
formation

NEMEROFF
to a cascade of little understood events that ultimately
results in the secretion of POMC-derived peptides into NEMEROFF
to a cascade of little understood events that ultimately
results in the secretion of POMC-derived peptides into
the peripheral circulation. However, during chronic or NEMEROFF
to a cascade of little understood events that ultimately
results in the secretion of POMC-derived peptides into
the peripheral circulation. However, during chronic or
excessive exposure to CRF, the corticotrophs u to a cascade of little understood events that ultimately results in the secretion of POMC-derived peptides into the peripheral circulation. However, during chronic or excessive exposure to CRF, the corticotrophs undergo a results in the secretion of POMC-derived peptides into
the peripheral circulation. However, during chronic or
excessive exposure to CRF, the corticotrophs undergo a
number of changes.
It has consistently been shown that CR sults in the secretion of POMC-derived peptides into
e peripheral circulation. However, during chronic or
cessive exposure to CRF, the corticotrophs undergo a
mber of changes.
It has consistently been shown that CRF recept

the peripheral circulation. However, during chronic or excessive exposure to CRF, the corticotrophs undergo a
number of changes.
It has consistently been shown that CRF receptor
occupancy or cAMP analogs increase the conce excessive exposure to CRF, the corticotrophs undergo a
number of changes.
It has consistently been shown that CRF receptor
occupancy or cAMP analogs increase the concentration
of POMC mRNA both in vivo and in vitro (Affolt number of changes.
It has consistently been shown that CRF receptor
occupancy or cAMP analogs increase the concentration
of POMC mRNA both in vivo and in vitro (Affolter and
Reisine, 1985; Gagner and Drouin, 1985, 1987; Lo It has consistently been shown that CRF receptor
occupancy or cAMP analogs increase the concentration
of POMC mRNA both in vivo and in vitro (Affolter and
Reisine, 1985; Gagner and Drouin, 1985, 1987; Loeffler
et al., 1985 occupancy or cAMP analogs increase the concentration
of POMC mRNA both in vivo and in vitro (Affolter and
Reisine, 1985; Gagner and Drouin, 1985, 1987; Loeffler
et al., 1985; Dave et al., 1987; Knight et al., 1987). In
add of POMC mRNA both in vivo and in vitro (Affolter and
Reisine, 1985; Gagner and Drouin, 1985, 1987; Loeffler
et al., 1985; Dave et al., 1987; Knight et al., 1987). In
addition to these increases in POMC peptide synthesis,
C Reisine, 1985; Gagner and Drouin, 1985, 1987; Loeffler
et al., 1985; Dave et al., 1987; Knight et al., 1987). In
addition to these increases in POMC peptide synthesis,
CRF also appears to possess trophic actions on the
pit addition to these increases in POMC peptide synthesis, CRF also appears to possess trophic actions on the pituitary as well. For example, Westlund et al. (1985) reported that following a 48-hour subcutaneous infusion of CR pituitary as well. For example, Westlund et al. (1985) reported that following a 48-hour subcutaneous infusion of CRF in rats, corticotroph cell area and ACTH-im-
munoreactive staining was increased. Similarly, McNicol et CRF also appears to possess trophic actions on the pituitary as well. For example, Westlund et al. (1985) reported that following a 48-hour subcutaneous infusion of CRF in rats, corticotroph cell area and ACTH-im-munoreact pituitary as well. For example, Westlund et al. (1985)
reported that following a 48-hour subcutaneous infusion
of CRF in rats, corticotroph cell area and ACTH-im-
munoreactive staining was increased. Similarly, McNicol
et reported that following a 48-hour subcutaneous infusion
of CRF in rats, corticotroph cell area and ACTH-im-
munoreactive staining was increased. Similarly, McNicol
et al. (1988) reported that both adrenalectomy or daily
in of CRF in rats, corticotroph cell area and ACTH-im-
munoreactive staining was increased. Similarly, McNicol
et al. (1988) reported that both adrenalectomy or daily
intraperitoneal injections of CRF increased corticotroph
 munoreactive staining was increased. Similarly, McNicol
et al. (1988) reported that both adrenalectomy or daily
intraperitoneal injections of CRF increased corticotroph
cell volume. Gertz et al. (1987) demonstrated that CR et al. (1988) reported that both adrenalectomy or dail intraperitoneal injections of CRF increased corticotrop
cell volume. Gertz et al. (1987) demonstrated that CR.
infusion (10 μ g/day × 52 days) resulted in continuou intraperitoneal injections of CRF increased cort
cell volume. Gertz et al. (1987) demonstrated the
infusion (10 μ g/day × 52 days) resulted in cont
elevated corticosterone concentrations, increased
nal weight, increased cell volume. Gertz et al. (1987) demonstrated that CRF
infusion (10 μ g/day × 52 days) resulted in continuously
elevated corticosterone concentrations, increased adre-
nal weight, increased numbers of ACTH-immunostain-
 infusion $(10 \mu g/day \times 52 \text{ days})$ resulted in continuously
elevated corticosterone concentrations, increased adre-
nal weight, increased numbers of ACTH-immunostain-
ing cells, and increased diameter of peptide-forming and
sto elevated corticosterone concentrations, increased adrenal weight, increased numbers of ACTH-immunostaining cells, and increased diameter of peptide-forming and storage granules, but no increase in corticotroph cell area. I nal weight, increased numbers of ACTH-immunostain-
ing cells, and increased diameter of peptide-forming and
storage granules, but no increase in corticotroph cell
area. It is unclear from a review of the literature whether ing cells, and increased diameter of peptide-forming and
storage granules, but no increase in corticotroph cell
area. It is unclear from a review of the literature whether
the increased number of ACTH-staining cells is the area. It is unclear from a review of the literature whether
the increased number of ACTH-staining cells is the
result of hyperplasia or expression of the POMC gene in
cells previously quiescent. the increased number of ACTH-staining cells is the
result of hyperplasia or expression of the POMC gene in
cells previously quiescent.
However, in contrast to the above cited actions of CRF
on corticotrophs, which bolster

the increased number of ACTH-staining cells is the
result of hyperplasia or expression of the POMC gene in
cells previously quiescent.
However, in contrast to the above cited actions of CRF
on corticotrophs, which bolster result of hyperplasia or expression of the POMC gene in
cells previously quiescent.
However, in contrast to the above cited actions of CRF
on corticotrophs, which bolster the production of ACTH
and related peptides, is the cells previously quiescent.

However, in contrast to the above cited actions of CRF

on corticotrophs, which bolster the production of ACTH

and related peptides, is the desensitization that occurs

in response to continuo However, in contrast to the above cited actions of CRF
on corticotrophs, which bolster the production of ACTH
and related peptides, is the desensitization that occurs
in response to continuous or excessive exposure to CRF. on corticotrophs, which bolster the production of ACTH and related peptides, is the desensitization that occur
in response to continuous or excessive exposure to CRF
In vivo studies clearly show that continuous exposure t
 and related peptides, is the desensitization that occur
in response to continuous or excessive exposure to CRI
In vivo studies clearly show that continuous exposure t
CRF substantially reduces ACTH secretion when com
pared in response to continuous or excessive exposure to CRF.
In vivo studies clearly show that continuous exposure to
CRF substantially reduces ACTH secretion when com-
pared to initial responsiveness; however, CRF still stim-
 CRF substantially reduces ACTH secretion when compared to initial responsiveness; however, CRF still stimulates ACTH secretion above baseline (Rivier and Vale, 1983b, 1985a; Evans et al., 1985). The tolerance that develops RF substantially reduces ACTH secretion when com-
red to initial responsiveness; however, CRF still stim-
ates ACTH secretion above baseline (Rivier and Vale,
83b, 1985a; Evans et al., 1985).
The tolerance that develops to

pared to initial responsiveness; however, CRF still stimulates ACTH secretion above baseline (Rivier and Vale, 1983b, 1985a; Evans et al., 1985).
The tolerance that develops to CRF exposure appears
to be primarily at the l ulates ACTH secretion above baseline (Rivier and Vale, 1983b, 1985a; Evans et al., 1985).
The tolerance that develops to CRF exposure appears
to be primarily at the level of the CRF receptor and its
coupling to adenylate c 1983b, 1985a; Evans et al., 1985).
The tolerance that develops to CRF exposure appears
to be primarily at the level of the CRF receptor and its
coupling to adenylate cyclase in a manner similar to that
seen with other G pr The tolerance that develops to CRF exposure appears
to be primarily at the level of the CRF receptor and its
coupling to adenylate cyclase in a manner similar to that
seen with other G protein receptors. De Souza et al.
(to be primarily at the level of the CRF receptor and its coupling to adenylate cyclase in a manner similar to that seen with other G protein receptors. De Souza et al. (1985a) initially reported that adrenalectomy markedl coupling to adenylate cyclase in a manner similar to t
seen with other G protein receptors. De Souza et
(1985a) initially reported that adrenalectomy marke
decreased CRF receptor density ($\approx 70\%$) in the anter
pituitary seen with other G protein receptors. De Souza et al.
(1985a) initially reported that adrenalectomy markedly
decreased CRF receptor density $(\approx 70\%)$ in the anterior
pituitary, but no changes were observed in the neuroin-
 (1985a) initially reported that adrenalectomy markedly
decreased CRF receptor density $(\approx 70\%)$ in the anterior
pituitary, but no changes were observed in the neuroin-
termediate lobe. This CRF receptor down-regulation pe decreased CRF receptor density $(\approx 70\%)$ in the anterior
pituitary, but no changes were observed in the neuroin-
termediate lobe. This CRF receptor down-regulation per-
sisted for as many as 9 weeks postsurgery. In a more pituitary, but no changes were observed in the neuroi
termediate lobe. This CRF receptor down-regulation pe
sisted for as many as 9 weeks postsurgery. In a mo
detailed study, Wynn et al. (1985) observed significa
(29%) dow termediate lobe. This CRF receptor down-regulation per-
sisted for as many as 9 weeks postsurgery. In a more
detailed study, Wynn et al. (1985) observed significant
(29%) down-regulation of anterior pituitary CRF recep-
to sisted for as many as 9 weeks postsurgery. In a mometrailed study, Wynn et al. (1985) observed significar
(29%) down-regulation of anterior pituitary CRF receptors 24 hours following adrenalectomy. Receptor number
progress detailed study, Wynn et al. (1985) observed significant (29%) down-regulation of anterior pituitary CRF receptors 24 hours following adrenalectomy. Receptor number progressively declined by another 20% by day 4. Comparable (29%) down-regulation of anterior pituitary CRF rectors 24 hours following adrenalectomy. Receptor num progressively declined by another 20% by day 4. Co parable decreases in CRF-stimulated adenylate cyclensity and s tors 24 hours following adrenalectomy. Receptor number
progressively declined by another 20% by day 4. Com-
parable decreases in CRF-stimulated adenylate cyclase
activity and sensitivity were observed in these adrenal-
ect progressively declined by another 20% by day 4. Comparable decreases in CRF-stimulated adenylate cyclase
activity and sensitivity were observed in these adrenal-
ectomized animals. In addition, these changes, like many
oth parable decreases in CRF-stimulated adenylate cyclase
activity and sensitivity were observed in these adrenal-
ectomized animals. In addition, these changes, like many
others induced by adrenalectomy, were reversed by dexactivity and sensitivity were observed in these adrenal-
ectomized animals. In addition, these changes, like many
others induced by adrenalectomy, were reversed by dex-
amethasone supplementation. The same group per-
forme

aspet

CORTICOTROPIN-RE
CRF infusion rather than adrenalectomy (Wynn et al.,
1988). A 46% decrease in CRF receptor binding was CRF infusion rather than adrenalectomy (Wynn et al., st
1988). A 46% decrease in CRF receptor binding was 19
observed following 48 hours of CRF infusion (100 ng/ A CORTICOTROPIN-RE
CRF infusion rather than adrenalectomy (Wynn et al.,
1988). A 46% decrease in CRF receptor binding was
observed following 48 hours of CRF infusion (100 ng/
minute). Again, the changes in CRF receptor numbe CRF infusion rather than adrenalectomy (Wynn et al., 1988). A 46% decrease in CRF receptor binding was observed following 48 hours of CRF infusion (100 ng/ minute). Again, the changes in CRF receptor number were accompanie CRF infusion rather than adrenalectomy (Wynn et al
1988). A 46% decrease in CRF receptor binding wa
observed following 48 hours of CRF infusion (100 ng
minute). Again, the changes in CRF receptor numbe
were accompanied by 1988). A 46% decrease in CRF receptor binding wa
observed following 48 hours of CRF infusion (100 ng
minute). Again, the changes in CRF receptor numbe
were accompanied by comparable decreases in CRF
stimulated adenylate cy observed following 48 hours of CRF infusion (100 ng/
minute). Again, the changes in CRF receptor number
were accompanied by comparable decreases in CRF-
stimulated adenylate cyclase activity. The findings com-
paring chron minute). Again, the changes in CRF receptor number C
were accompanied by comparable decreases in CRF-
stimulated adenylate cyclase activity. The findings com-
paring chronic CRF infusion to adrenalectomy suggest ti
that ad were accompanied by comparable decreases in CRF-
stimulated adenylate cyclase activity. The findings com-
paring chronic CRF infusion to adrenalectomy suggest ti
that additional factors (vasopressin?) may be involved A
in stimulated adenylate cyclase activity. The findings comparing chronic CRF infusion to adrenalectomy suggest
that additional factors (vasopressin?) may be involved
in the modulation of CRF receptor kinetics following
adrena paring chronic CRF infusion to adrenalectomy suggest ties
that additional factors (vasopressin?) may be involved
in the modulation of CRF receptor kinetics following
adrenalectomy. In vitro studies by Reisine's group (Rethat additional factors (vasopressin?) may be involve
in the modulation of CRF receptor kinetics followin
adrenalectomy. In vitro studies by Reisine's group (Re
isine and Hoffman, 1983; Hoffman et al., 1985) hav
shown that in the modulation of CRF receptor kinetics following
adrenalectomy. In vitro studies by Reisine's group (Re-
isine and Hoffman, 1983; Hoffman et al., 1985) have
shown that the ability of CRF to stimulate cAMP accu-
mulatio adrenalectomy. In vitro studies by Reisine's group (Re-
isine and Hoffman, 1983; Hoffman et al., 1985) have
shown that the ability of CRF to stimulate cAMP accu-
mulation and the ability of cAMP analogs to stimulate
ACTH shown that the ability of CRF to stimulate cAMP accumulation and the ability of cAMP analogs to stimulate ACTH secretion are decreased following exposure to CRF for short periods of time. Moreover, the HPA stimshown that the ability of CRF to stimulate cAMP accumulation and the ability of cAMP analogs to stimulate ACTH secretion are decreased following exposure to CRF for short periods of time. Moreover, the HPA stimulatory acti mulation and the ability of cAMP analogs to stin
ACTH secretion are decreased following exposu
CRF for short periods of time. Moreover, the HPA
ulatory actions of CRF recovered rapidly within se
hours following removal of

**FREF for short periods of time. Moreover, the HPA stimulatory actions of CRF recovered rapidly within several hours following removal of chronic CRF treatment.

5. Potentiation of the action of corticotropin-releasing fac** ulatory actions of CRF recovered rapidly within several
hours following removal of chronic CRF treatment.
5. Potentiation of the action of corticotropin-releasing
factor on the corticotroph. It is well established that a
n hours following removal of chronic CRF treatment.

5. Potentiation of the action of corticotropin-releasing

factor on the corticotroph. It is well established that a

number of endogenous substances in addition to CRF

a 5. Potentiation of the action of corticotropin-releasing
factor on the corticotroph. It is well established that a
mumber of endogenous substances in addition to CRF
also possess ACTH-releasing properties. These include
m factor on the corticotroph. It is well established that a
number of endogenous substances in addition to CRF
also possess ACTH-releasing properties. These include
neurohypophyseal peptides and catecholamines. The
most wide number of endogenous substances in addition to CRF
also possess ACTH-releasing properties. These include
neurohypophyseal peptides and catecholamines. The
most widely studied of these hormones is AVP. A number
of in vivo (also possess ACTH-releasing properties. These include
neurohypophyseal peptides and catecholamines. The
most widely studied of these hormones is AVP. A number
of in vivo (Rivier and Vale, 1983c; Rivier et al., 1984b;
Fisch neurohypophyseal peptides and catecholamines. The
most widely studied of these hormones is AVP. A number
of in vivo (Rivier and Vale, 1983c; Rivier et al., 1984b;
Fischman and Moldow, 1984) and in vitro (Culler et al.,
198 most widely studied of these hormones is AVP. A numb
of in vivo (Rivier and Vale, 1983c; Rivier et al., 1984
Fischman and Moldow, 1984) and in vitro (Culler et a
1983; Murakami et al., 1984) studies have shown th
AVP weakl of in vivo (Rivier and Vale, 1983c; Rivier et al., 1984b;
Fischman and Moldow, 1984) and in vitro (Culler et al., 1983; Murakami et al., 1984) studies have shown that
AVP weakly stimulates ACTH release alone but markedly (Schoenenberg et al., 1987). It appears that these actions of CRF interpretence, therefore, only briefly review these findings.

(Sing a specific immunocytochemical marker for cat-

1983; Murakami et al., 1984) studies hav 1983; Murakami et al., 1984) studies have shown that
AVP weakly stimulates ACTH release alone but mark-
edly potentiates the actions of CRF on ACTH release
(Schoenenberg et al., 1987). It appears that these actions
of AVP AVP weakly stimulates ACTH release alone but markedly potentiates the actions of CRF on ACTH release (Schoenenberg et al., 1987). It appears that these actions of AVP are not mediated through alterations of CRF binding (H edly potentiates the actions of CRF on ACTH relearties (Schoenenberg et al., 1987). It appears that these action of AVP are not mediated through alterations of Cl binding (Holmes et al., 1984); rather, AVP interacts with i (Schoenenberg et al., 1987). It appears that these actions
of AVP are not mediated through alterations of CRF
binding (Holmes et al., 1984); rather, AVP interacts with
its receptor subtype, V_1 (Rivier et al., 1984b), t of AVP are not mediated through alterations of CRF
binding (Holmes et al., 1984); rather, AVP interacts with
its receptor subtype, V_1 (Rivier et al., 1984b), to poten-
tiate CRF-stimulated cAMP accumulation (Giguere an binding (Holmes et al., 1984); rather, AVP interacts wit
its receptor subtype, V₁ (Rivier et al., 1984b), to potentiate CRF-stimulated cAMP accumulation (Giguere an
Labrie, 1982; Hoffman et al., 1985; Bilezikjian et al
1 binding (Tromes et al., 1984), tatilet, AVP interacts with
its receptor subtype, V_1 (Rivier et al., 1984b), to poten-
tiate CRF-stimulated cAMP accumulation (Giguere and
Labrie, 1982; Hoffman et al., 1985; Bilezikijian Labrie, 1982; Hoffman et al., 1985; Bilezikijan et al., and the CRF external of the PVN CRF-containing peri-

1987). Interestingly, although AVP does potentiate CRF-

stimulated cAMP accumulation, it appears that AVP

acts 1987). Interestingly, although AVP does potentiate CRF-
stimulated cAMP accumulation, it appears that AVP
acts on functionally distinct corticotrophs that do not
contain CRF receptors (Schwartz and Vale, 1988; Jia et
al., 1987). Interestingly, although AVP does potentiate CRF-
stimulated cAMP accumulation, it appears that AVP
acts on functionally distinct corticotrophs that do not
contain CRF receptors (Schwartz and Vale, 1988; Jia et
al., stimulated cAMP accumulation, it appears that AVP acts on functionally distinct corticotrophs that do not particular contain CRF receptors (Schwartz and Vale, 1988; Jia et al., 1991). In fact, Plotsky et al. (1985) reporte acts on functionally distinct corticotrophs that do not
contain CRF receptors (Schwartz and Vale, 1988; Jia et
al., 1991). In fact, Plotsky et al. (1985) reported that
during hypoglycemic stress CRF plays predominantly a
p contain CRF receptors (Schwartz and Vale, 1988; Jia et al., 1991). In fact, Plotsky et al. (1985) reported that al. during hypoglycemic stress CRF plays predominantly a happermissive role, whereas AVP represents the dynami al., 1991). In fact, Plotsky et al. (1985) reported that
during hypoglycemic stress CRF plays predominantly a
permissive role, whereas AVP represents the dynamic
mediator of ACTH secretion. Also of interest is the
report b during hypoglycemic stress CRF plays predominantly a
permissive role, whereas AVP represents the dynamic
mediator of ACTH secretion. Also of interest is the
report by Levin et al. (1989) who replicated the findings
of AVP permissive role, whereas AVP represents the dynamic
mediator of ACTH secretion. Also of interest is the
report by Levin et al. (1989) who replicated the findings
of AVP potentiation of ACTH release but observed that,
ica
w mediator of ACTH secretion. Also of interest is the CRF
report by Levin et al. (1989) who replicated the findings man
of AVP potentiation of ACTH release but observed that, ical
whereas CRF increased POMC gene transcriptio of AVP potentiation of ACTH release but observed that,
whereas CRF increased POMC gene transcription and
peptide synthesis, AVP, if anything, decreased POMC
gene expression.
There are a number of reports that suggest that of AVP potentiation of ACTH release but observed that, ical evidence for modulation of hypothalamic CRF secre-
whereas CRF increased POMC gene transcription and
peptide synthesis, AVP, if anything, decreased POMC Because o whereas CRF increased POMC gene transcription and
peptide synthesis, AVP, if anything, decreased POMC
gene expression.
There are a number of reports that suggest that in the
sheep, in contrast to the rat and most other mam

peptide synthesis, AVP, if anything, decreased POMC
gene expression.
There are a number of reports that suggest that in the
sheep, in contrast to the rat and most other mammals, n
AVP is a more potent stimulator of ACTH s gene expression.
There are a number of reports that suggest that in the
sheep, in contrast to the rat and most other mammals,
AVP is a more potent stimulator of ACTH secretion
than is CRF (Familari et al., 1989). This appe There are a number of reports that suggest that in the sheep, in contrast to the rat and most other mammals, AVP is a more potent stimulator of ACTH secretion than is CRF (Familari et al., 1989). This appears to result fro sheep, in contrast to the rat and most other mammals,
AVP is a more potent stimulator of ACTH secretion
than is CRF (Familari et al., 1989). This appears to result
from the fact that the concentration of AVP receptors
in t AVP is a more potent stimulator of ACTH secretion field
than is CRF (Familari et al., 1989). This appears to result cher
from the fact that the concentration of AVP receptors has
in the sheep anterior pituitary is twice th than is CRF (Familari et al.,
from the fact that the conc
in the sheep anterior pituit
whereas CRF receptor dens
the rat (Shen et al., 1990).
In addition to AVP, oxyt om the fact that the concentration of AVP receptor
the sheep anterior pituitary is twice that of the ra-
nereas CRF-receptor density is only 10% of those is
e rat (Shen et al., 1990).
In addition to AVP, oxytocin also pote

LEASING FACTOR
stimulated ACTH release both in vitro (Gibbs et al.,
1984; Schwartz and Vale, 1988) and in vivo (Gibbs, 1985). LEASING FACTOR

1984; Schwartz and Vale, 1988) and in vitro (Gibbs, 1985).

1984; Schwartz and Vale, 1988) and in vivo (Gibbs, 1985).

Another hormone that exerts synergistic effects with 437

stimulated ACTH release both in vitro (Gibbs et al.,

1984; Schwartz and Vale, 1988) and in vivo (Gibbs, 1985).

Another hormone that exerts synergistic effects with

CRF on ACTH secretion is angiotensin II, which als stimulated ACTH release both in vitro (Gibbs et al., 1984; Schwartz and Vale, 1988) and in vivo (Gibbs, 1985).
Another hormone that exerts synergistic effects with
CRF on ACTH secretion is angiotensin II, which also
stimul 1984; Schwartz and Vale, 1988) and in vivo (Gibbs, 1985).
Another hormone that exerts synergistic effects with
CRF on ACTH secretion is angiotensin II, which also
stimulates ACTH release alone as well as potentiating CRF-stimulated cAMP accumulation and ACTH secre-Another hormone that exerts synergistic effects with
CRF on ACTH secretion is angiotensin II, which also
stimulates ACTH release alone as well as potentiating
CRF-stimulated cAMP accumulation and ACTH secre-
tion. Another CRF on ACTH secretion is angiotensin II, which also
stimulates ACTH release alone as well as potentiating
CRF-stimulated cAMP accumulation and ACTH secre-
tion. Another peptide that potentiates CRF-stimulated
ACTH release stimulates ACTH release alone as well as potentiating CRF-stimulated cAMP accumulation and ACTH secretion. Another peptide that potentiates CRF-stimulated ACTH release in vitro is the intestinal peptide PHI-27, which is pr 1984). *ACTH release in vitro is the intestinal peptide PHI-27, which is present in the median eminence (Tilders et al...)*

Neuron 1. Regulation of the Corticotropin-releasing Factor
Neuron
1. Neurotransmitter regulation of corticotropin-releas

B. Regulation of the Corticotropin-releasing Factor
Neuron
*1. Neurotransmitter regulation of corticotropin-releas-
ing factor release.* A decade prior to elucidation of the
sequence of CRF, investigators were already B. Regulation of the Corticotropin-releasing Factor
Neuron
1. Neurotransmitter regulation of corticotropin-releas-
ing factor release. A decade prior to elucidation of the
sequence of CRF, investigators were already studyi neuron

1. Neurotransmitter regulation of corticotropin-releas-

ing factor release. A decade prior to elucidation of the

sequence of CRF, investigators were already studying the

neurotransmitter regulation of CRF releas 1. Neurotransmitter regulation of corticotropin-releasing factor release. A decade prior to elucidation of the sequence of CRF, investigators were already studying the neurotransmitter regulation of CRF release in vitro us ing factor release. A decade prior to elucidation of the sequence of CRF, investigators were already studying the neurotransmitter regulation of CRF release in vitro using bioassays for ACTH and adrenal glucocorticoids as sequence of CRF, investigators were already studying the
neurotransmitter regulation of CRF release in vitro using
bioassays for ACTH and adrenal glucocorticoids as a
measure of "CRF" activity. Even with the availability o neurotransmitter regulation of CRF release in vitro using
bioassays for ACTH and adrenal glucocorticoids as a
measure of "CRF" activity. Even with the availability of
sensitive and specific radioimmunoassays for CRF, con-
 bioassays for ACTH and adrenal glucocorticoids as a
measure of "CRF" activity. Even with the availability of
sensitive and specific radioimmunoassays for CRF, con-
siderable controversy exists concerning the role of var-
i measure of "CRF" activity. Even with the availability of
sensitive and specific radioimmunoassays for CRF, con-
siderable controversy exists concerning the role of var-
ious neurotransmitters in regulating the secretion of sensitive and specific radioimmunoassays for CRF, considerable controversy exists concerning the role of various neurotransmitters in regulating the secretion of hypothalamic CRF. We have previously discussed these finding siderable controversy exists concerning the
ious neurotransmitters in regulating the s
hypothalamic CRF. We have previously disc
findings in detail (Owens and Nemeroff, 199
therefore, only briefly review these findings.
Us us neurotransmitters in regulating the secretion of
pothalamic CRF. We have previously discussed these
ndings in detail (Owens and Nemeroff, 1990) and will,
erefore, only briefly review these findings.
Using a specific imm

hypothalamic CRF. We have previously discussed th
findings in detail (Owens and Nemeroff, 1990) and w
therefore, only briefly review these findings.
Using a specific immunocytochemical marker for c
echolaminergic neurons, findings in detail (Owens and Nemeroff, 1990) and will,
therefore, only briefly review these findings.
Using a specific immunocytochemical marker for cat-
echolaminergic neurons, Liposits et al. (1986b) demon-
strated tyro therefore, only briefly review these findings.
Using a specific immunocytochemical marker for cat-
echolaminergic neurons, Liposits et al. (1986b) demon-
strated tyrosine hydroxylase-immunoreactive nerve ter-
minals innerv Using a specific immunocytochemical marker for cat-
echolaminergic neurons, Liposits et al. (1986b) demon-
strated tyrosine hydroxylase-immunoreactive nerve ter-
minals innervating CRF-containing perikarya in the
PVN. This echolaminergic neurons, Liposits et al. (1986b) dem
strated tyrosine hydroxylase-immunoreactive nerve t
minals innervating CRF-containing perikarya in
PVN. This same group, using a specific marker
epinephrine-containing ne strated tyrosine hydroxylase-immunoreactive nerve ter-
minals innervating CRF-containing perikarya in the
PVN. This same group, using a specific marker for
epinephrine-containing neurons, also found that phenyl-
ethanolam PVN. This same group, using a specific marker for nerve terminals arising from the C_1 (ventral lateral meepinephrine-containing neurons, also found that phenyl
ethanolamine-N-methyl transferase immunoreactiv
nerve terminals arising from the C_1 (ventral lateral me
dulla) and C_2 (dorsal vagal complex) cell groups establi ethanolamine-N-methyl transferase immunoreactive
nerve terminals arising from the C_1 (ventral lateral me-
dulla) and C_2 (dorsal vagal complex) cell groups establish
direct synaptic contact with PVN CRF-containing pe nerve terminals arising from the C_1 (ventral lateral me-
dulla) and C_2 (dorsal vagal complex) cell groups establish
direct synaptic contact with PVN CRF-containing peri-
karya (Liposits et al., 1986a; Cunningham et dulla) and C₂ (dorsal vagal complex) cell groups establish
direct synaptic contact with PVN CRF-containing peri-
karya (Liposits et al., 1986a; Cunningham et al., 1990).
Recently, evidence for direct serotonergic (Liposi direct synaptic contact with PVN CRF-containing peri-
karya (Liposits et al., 1986a; Cunningham et al., 1990).
Recently, evidence for direct serotonergic (Liposits and
Paull, 1987; Soghomonian et al., 1988), dopaminergic
(karya (Liposits et al., 1986a; Cunningham et al., 1990).

Recently, evidence for direct serotonergic (Liposits and

Paull, 1987; Soghomonian et al., 1988), dopaminergic

(Liposits and Paull, 1989), and GABAergic (Meister Paull, 1987; Soghomonian et al., 1988), dopaminergic (Liposits and Paull, 1989), and GABAergic (Meister et al., 1988) innervation of the CRF perikarya of the PVN has also been provided. In addition, it appears that CRF neu neurons may possess recurrent collaterals that innervate (Liposits and Paull, 1989), and GABAergic (Meister
al., 1988) innervation of the CRF perikarya of the P
has also been provided. In addition, it appears that C
neurons may possess recurrent collaterals that innerv
CRF neuro al., 1988) innervation of the CRF perikarya of the P
has also been provided. In addition, it appears that C
neurons may possess recurrent collaterals that innerv
CRF neurons, presumably as a form of feedback (Silv
man et a has also been provided. In addition, it appears that CF
neurons may possess recurrent collaterals that innerva
CRF neurons, presumably as a form of feedback (Silve
man et al., 1989). These findings provide direct anator
ic neurons may possess recurrent collaterals that i
CRF neurons, presumably as a form of feedbacl
man et al., 1989). These findings provide direct
ical evidence for modulation of hypothalamic Cl
tion by a number of neurotrans RF neurons, presumably as a form of feedback (Silver-
an et al., 1989). These findings provide direct anatom-
al evidence for modulation of hypothalamic CRF secre-
on by a number of neurotransmitter systems.
Because of the

man et al., 1989). These findings provide direct anatomical evidence for modulation of hypothalamic CRF secretion by a number of neurotransmitter systems.
Because of the tortuous pathway taken by the CRF neuron from the PV ical evidence for modulation of hypothalamic CRF secre-
tion by a number of neurotransmitter systems.
Because of the tortuous pathway taken by the CRF
neuron from the PVN to the median eminence, in vitro
hypothalamic expla tion by a number of neurotransmitter systems.
Because of the tortuous pathway taken by the CRF
neuron from the PVN to the median eminence, in vitro
hypothalamic explants are by necessity large (2 to 3
mm³). However, the Because of the tortuous pathway taken by the CRF
neuron from the PVN to the median eminence, in vitro
hypothalamic explants are by necessity large (2 to 3
mm³). However, the vast majority of literature from other
fields neuron from the PVN to the median eminence, in vitro
hypothalamic explants are by necessity large (2 to 3
mm³). However, the vast majority of literature from other
fields that utilize in vitro incubations (i.e., cerebral hypothalamic explants are by necessity large (2 to 3 mm³). However, the vast majority of literature from other fields that utilize in vitro incubations (i.e., cerebral ischemia studies, hippocampal slice physiology) repe mm³). However, the vast majority of literature from other fields that utilize in vitro incubations (i.e., cerebral ischemia studies, hippocampal slice physiology) repeatedly has established the fact that tissue explants fields that utilize in vitro incubations (i.e., cerebral is-
chemia studies, hippocampal slice physiology) repeatedly
has established the fact that tissue explants of this size
quickly become hypoxic. Of the large number o chemia studies, hippocampal slice physiology) repeatedly
has established the fact that tissue explants of this size
quickly become hypoxic. Of the large number of groups
who have attempted to study the in vitro release of has established the fact that tissue explants of this size
quickly become hypoxic. Of the large number of groups
who have attempted to study the in vitro release of CRF
using nearly identical incubation setups, only a sele

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que the same of the published work to date.
The sponsible for nearly all of the published work to date.
The sponsible further proof is independently provided, it would 438

until further proof is independently provided, it would

Until further proof is independently provided, it would

be prudent to regard many of the reports as preliminary
 $(\pm$ owends and presponsible for nearly all of the published work to date.
Until further proof is independently provided, it would
be prudent to regard many of the reports as preliminary
as almost all neurotransmitter systems s responsible for nearly all of the published work to date. those
Until further proof is independently provided, it would μ g/l
be prudent to regard many of the reports as preliminary (\pm) .
as almost all neurotransmitter Until further proof is independently provided, it would
be prudent to regard many of the reports as preliminary
as almost all neurotransmitter systems studied appear to
directly alter CRF secretion. As might be expected, negative feedback effects of concerned all neurotransmitter systems studied appear to concelly alter CRF secretion.
As might be expected, negative feedback effects of C accocorticoids, ACTH, and CRF

be prudent to regard many of the reports as preliminary (:
as almost all neurotransmitter systems studied appear to objectly alter CRF secretion.
As might be expected, negative feedback effects of C
glucocorticoids, ACTH, glucocorticoids, ACTH, and CRF itself on CRF release
have been demonstrated in these in vitro experiments.
Both Suda et al. (1985b) and Calogero et al. (1988b) directly alter CRF secretion.
As might be expected, negative feedback effects of
glucocorticoids, ACTH, and CRF itself on CRF release
have been demonstrated in these in vitro experiments.
Both Suda et al. (1985b) and Calog As might be expected, negative feedback effects of C
glucocorticoids, ACTH, and CRF itself on CRF release H
have been demonstrated in these in vitro experiments. a
Both Suda et al. (1985b) and Calogero et al. (1988b) repor glucocorticoids, ACTH, and CRF itself on CRF release
have been demonstrated in these in vitro experiments.
Both Suda et al. (1985b) and Calogero et al. (1988b)
reported a dose-dependent inhibition of CRF secretion 2
by glu have been demonstrated in these in vitro experiments.
Both Suda et al. (1985b) and Calogero et al. (1988b) reported a dose-dependent inhibition of CRF secretion for glucocorticoids, suggesting a direct long-loop negative c Both Suda et al. (1985b) and Calogero et al. (1988b) repreported a dose-dependent inhibition of CRF secretion 2-8-
by glucocorticoids, suggesting a direct long-loop negative cos
feedback of adrenal steroids on the hypothal reported a dose-dependent inhibition of CRF secretion 2-aminopropane administration increased plasma corti-
by glucocorticoids, suggesting a direct long-loop negative costerone concentrations. Similarly, Bagdy et al. (198 by glucocorticoids, suggesting a direct long-loop negativeled
back of adrenal steroids on the hypothalamus. Suda
group reported that the effects of dexamethasone on th
hypothalamic explant were exerted above the level of t feedback of adrenal steroids on the hypothalamus. Sudigroup reported that the effects of dexamethasone on thypothalamic explant were exerted above the level of t
median eminence. A rebound increase in the basal section of group reported that the effects of dexamethasone on the
hypothalamic explant were exerted above the level of the
median eminence. A rebound increase in the basal secre-
tion of CRF was seen after removal of dexamethasone,
 hypothalamic explant were exerted above the level of the
median eminence. A rebound increase in the basal secre-
tion of CRF was seen after removal of dexamethasone,
suggesting that short-term incubation with the steroid
c median eminence. A rebound increase in the basal secretion of CRF was seen after removal of dexamethasone
suggesting that short-term incubation with the steroic
could decrease release without altering CRF synthesis
These f tion of CRF was seen after removal of dexamethasone, tor
suggesting that short-term incubation with the steroid 199
could decrease release without altering CRF synthesis. 198
These findings are concordant with several stud suggesting that short-term incubation with the steroid could decrease release without altering CRF synthesis These findings are concordant with several studies dem onstrating the presence of glucocorticoid receptors or PVN could decrease release without altering CRF synthesis
These findings are concordant with several studies dem
onstrating the presence of glucocorticoid receptors o
PVN CRF neurons (Liposits et al., 1987; Sawchenka
1987b). F onstrating the presence of glucocorticoid receptors on PVN CRF neurons (Liposits et al., 1987; Sawchenko, 1987b). Furthermore, both Suda et al. (1986) and Calogero et al. (1988b) reported a short-loop negative feed-back ro PVN CRF neurons (Liposits et al., 1987; Sawchenko, 1987b). Furthermore, both Suda et al. (1986) and Calogero et al. (1988b) reported a short-loop negative feedback role for ACTH on CRF release. The exact anatomical site(s) PVN CRF neurons (Liposits et al., 1987; Sawchenko, 1987b). Furthermore, both Suda et al. (1986) and Calogero et al. (1988b) reported a short-loop negative feedback role for ACTH on CRF release. The exact anatomical site(s) 1987b). Furthermore, both Suda et al. (1986) and Calo-
gero et al. (1988b) reported a short-loop negative feed-
back role for ACTH on CRF release. The exact anatom-
jected
cial site(s) where ACTH acts within the hypothalam (i.e., PVN or median eminence) or where the ACTH The effects of norepinephrine and the opioid peptides originates has not yet been determined. Calogero et al. on CRF release in vitro are less clear. Suda et al. (1987c) (19 back role for ACTH on CRF release. The exact anatomical site(s) where ACTH acts within the hypothalamus (i.e., PVN or median eminence) or where the ACTH originates has not yet been determined. Calogero et al. (1988b) furth ical site(s) where ACTH acts within the hypothalamus co
(i.e., PVN or median eminence) or where the ACTH
originates has not yet been determined. Calogero et al.
(1988b) further reported on a possible ultrashort-loop re
neg (i.e., PVN or median eminence) or where the ACTH
originates has not yet been determined. Calogero et al.
(1988b) further reported on a possible ultrashort-loop
negative feedback of CRF directly on itself. Evidence of
local originates has not yet been (1988b) further reported on
negative feedback of CRF dilocal CRF neuronal circuits
this possibility (vide supra).
The majority of in vitro a 988b) further reported on a possible ultrashort-logative feedback of CRF directly on itself. Evidence
cal CRF neuronal circuits in the PVN also suppo
is possibility (vide supra).
The majority of in vitro and in vivo studie

negative feedback of CRF directly on itself. Evidence of local CRF neuronal circuits in the PVN also supports
this possibility (vide supra).
The majority of in vitro and in vivo studies demon-
strate both stimulatory choli local CRF neuronal circuits in the PVN also supports
this possibility (vide supra).
The majority of in vitro and in vivo studies demon-
strate both stimulatory cholinergic and serotonergic la
components to hypothalamic CRF this possibility (vide supra).
The majority of in vitro and in vivo studies demonstrate both stimulatory cholinergic and serotonergic
components to hypothalamic CRF release. Although
there certainly appears to be a stimula The majority of in vitro and in vivo studies demonstrate both stimulatory cholinergic and serotonergic
components to hypothalamic CRF release. Although
there certainly appears to be a stimulatory cholinergic
component, it components to hypothalamic CRF release. Although nergic stimulation of CRF release via β -receptors in rat
there certainly appears to be a stimulatory cholinergic hypothalamic cell cultures obtained from 1-week-old
comp components to hypothalamic CRF release. Although nethere certainly appears to be a stimulatory cholinergic hypomponent, it remains to be clarified whether it is pre-
dominantly muscarinic or nicotinic or a combination of v there certainly appears to be a stimulatory component, it remains to be clarified whethe dominantly muscarinic or nicotinic or a comb
the two receptor subclasses (Suda et al., 1987).
et al., 1988a, 1989c; Tsagarakis et al. mponent, it remains to be clarified whether it is pre-
minantly muscarinic or nicotinic or a combination of
e two receptor subclasses (Suda et al., 1987b; Calogero
al., 1988a, 1989c; Tsagarakis et al., 1988).
In vitro stud

dominantly muscarinic or nicotinic or a combination of
the two receptor subclasses (Suda et al., 1987b; Calogero
et al., 1988a, 1989c; Tsagarakis et al., 1988).
In vitro studies clearly suggest a robust stimulatory
role fo the two receptor subclasses (Suda et al., 1987b; Calogero st al., 1988a, 1989c; Tsagarakis et al., 1988). In vitro studies clearly suggest a robust stimulatory where for serotonin on CRF release (Nakagami et al., 1986; a C et al., 1988a, 1989c; Tsagarakis et al., 1988). The property in vitro studies clearly suggest a robust stimulatory with role for serotonin on CRF release (Nakagami et al., 1986; and Calogero et al., 1989a). Calogero et al. In vitro studies clearly suggest a robust stimulatory wivele for serotonin on CRF release (Nakagami et al., 1986; an Calogero et al., 1989a). Calogero et al. (1989b) reported Arthat the effects of 5-HT were completely blo role for serotonin on CRF release (Nakagami et al., 1986;
Calogero et al., 1989a). Calogero et al. (1989b) reported
that the effects of 5-HT were completely blocked by
ritanserin, suggesting that the action of serotonin is Calogero et al., 1989a). Calogero et al. (1989b) reported Ar
that the effects of 5-HT were completely blocked by of
ritanserin, suggesting that the action of serotonin is al.
mediated by the 5-HT₂ receptor subtype; this that the effects of 5-HT were completely blo
ritanserin, suggesting that the action of sero
mediated by the 5-HT₂ receptor subtype; this v
confirmed through stimulation of CRF release
relatively specific 5-HT₂ agonist ritanserin, suggesting that the action of serotonin i
mediated by the 5-HT₂ receptor subtype; this was late
confirmed through stimulation of CRF release by th
relatively specific 5-HT₂ agonist (\pm) -1-(2,5-dimethoxy
4 mediated by the 5-HT₂ receptor subtype; this was later Bucconfirmed through stimulation of CRF release by the peptic
relatively specific 5-HT₂ agonist (\pm) -1- $(2,5$ -dimethoxy-only $(4$ -iodophenyl)-2-aminopropane. The confirmed through stimulation of CRF release by the perturbatively specific 5-HT₂ agonist (\pm) -1-(2,5-dimethoxy-
4-iodophenyl)-2-aminopropane. They also report a dose-
dependent stimulation of CRF release by the 5-HT₁ relatively specific 5-HT₂ agonist (\pm) -1-(2,5-dimethoxy-
4-iodophenyl)-2-aminopropane. They also report a dose-
dependent stimulation of CRF release by the 5-HT₁₄
agonist 8-hydroxydipropylaminotetralin and by the 5-
 4-iodophenyl)-2-aminopropane. They also report a dose-
dependent stimulation of CRF release by the 5-HT_{1A}
agonist 8-hydroxydipropylaminotetralin and by the 5-
HT_{1B} agonist *m*-chlorophenylpiperazine, albeit at lower
m dimethoxy-4-iodophenyl)-2-aminopropane. agonist 8-hydroxydipropylaminotetralin and by the 5-
HT_{1B} agonist *m*-chlorophenylpiperazine, albeit at lower
maximal responses than that produced by (\pm) -1- $(2,5$ -
dimethoxy-4-iodophenyl)-2-aminopropane.
We (Owens et

doses of the 5-HT₂ and 5-HT_{1C} agonist (\pm) -1- $(2,5$ -dime-

NEMEROFF
thoxy-4-bromophenyl)-2-aminopropane as low as 100
µg/kg. However, tolerance to the stimulatory effects of NEMEROFF
thoxy-4-bromophenyl)-2-aminopropane as low as 100
 μ g/kg. However, tolerance to the stimulatory effects of
(±)-1-(2,5-dimethoxy-4-bromophenyl)-2-aminopropane (\pm) -1- $(2,5$ -dimethoxy-4-bromophenyl)-2-aminopropane thoxy-4-bromophenyl)-2-aminopropane as low as $100 \mu g/kg$. However, tolerance to the stimulatory effects of (\pm) -1-(2,5-dimethoxy-4-bromophenyl)-2-aminopropane on HPA axis activity were evident by 7 days of treatment as ev thoxy-4-bromophenyl)-2-aminopropane as low as 100 μ g/kg. However, tolerance to the stimulatory effects of (\pm) -1-(2,5-dimethoxy-4-bromophenyl)-2-aminopropane on HPA axis activity were evident by 7 days of treatment as μ g/kg. However, tolerance to the stimulatory effects of (\pm) -1-(2,5-dimethoxy-4-bromophenyl)-2-aminopropane
on HPA axis activity were evident by 7 days of treatment
as evidenced by down-regulation of anterior pituitar (\pm)-1-(2,5-dimethoxy-4-bromophenyl)-2-aminopropane
on HPA axis activity were evident by 7 days of treatment
as evidenced by down-regulation of anterior pituitary
CRF receptor binding and cortical and hypothalamic 5-
HT on HPA axis activity were evident by 7 days of treatment
as evidenced by down-regulation of anterior pituitary
CRF receptor binding and cortical and hypothalamic 5-
HT₂ receptor binding (Owens et al., 1991b). These resu as evidenced by down-regulation of anterior $|CRF|$ receptor binding and cortical and hypothe HT_2 receptor binding (Owens et al., 1991b). Thes are in agreement with those of Nash et al. (19) reported that acute (\pm) -1-(CRF receptor binding and cortical and hypothalamic t
HT₂ receptor binding (Owens et al., 1991b). These result
are in agreement with those of Nash et al. (1989) wh
reported that acute (\pm) -1-(2,5-dimethoxy-4-iodophe HT_2 receptor binding (Owens et al., 1991b). These results
are in agreement with those of Nash et al. (1989) who
reported that acute (\pm) -1-(2,5-dimethoxy-4-iodophenyl)-
2-aminopropane administration increased plasma co are in agreement with those of Nash et al. (19
reported that acute (\pm) -1-(2,5-dimethoxy-4-iodo
2-aminopropane administration increased plasr
costerone concentrations. Similarly, Bagdy et a
reported that (\pm) -1-(2,5-dim reported that acute (\pm) -1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane administration increased plasma corticosterone concentrations. Similarly, Bagdy et al. (1989)
reported that (\pm) -1-(2,5-dimethoxy-4-iodophenyl)-2-am 2-aminopropane administration increased plasma cort
costerone concentrations. Similarly, Bagdy et al. (198
reported that (\pm) -1- $(2,5$ -dimethoxy-4-iodophenyl)-
aminopropane dose dependently increased plasm
ACTH and corti

In agreement with the in vitro work on $5\text{-}HT_{1A}$ receptor stimulation of CRF release, our group (Owens et al., 1990b) and others (Koenig et al., 1987; Aulakh et al., aminopropane dose dependently increased plasma
ACTH and corticosterone concentrations in the rat.
In agreement with the in vitro work on 5-HT_{1A} recep-
tor stimulation of CRF release, our group (Owens et al.,
1990b) and ACTH and corticosterone concentrations in the rat.

In agreement with the in vitro work on $5\text{-}HT_{1A}$ receptor stimulation of CRF release, our group (Owens et al., 1990b) and others (Koenig et al., 1987; Aulakh et al., In agreement with the in vitro work on 5-HT_{1A} receptor stimulation of CRF release, our group (Owens et al., 1990b) and others (Koenig et al., 1987; Aulakh et al., 1988; Lorens and van de Kar, 1987) reported that the 5-H tor stimulation of CRF release, our group (Owens et a 1990b) and others (Koenig et al., 1987; Aulakh et a 1988; Lorens and van de Kar, 1987) reported that the HT_{1A} agonists, 8-hydroxydipropylaminotetralin and ip apiron 1990b) and others (Koenig et al., 1987; Aulakh et al., 1988; Lorens and van de Kar, 1987) reported that the 5- HT_{1A} agonists, 8-hydroxydipropylaminotetralin and ips-
apirone, stimulate HPA axis activity in intact rats. 1988; Lorens and van de Kar, 1987) reported that the 5-
 HT_{1A} agonists, 8-hydroxydipropylaminotetralin and ips-
apirone, stimulate HPA axis activity in intact rats. More-
over, Haleem et al. (1989) reported that this is HT_{1A} agonists, 8-hydroxydipropylaminotetralin and i
apirone, stimulate HPA axis activity in intact rats. Mo
over, Haleem et al. (1989) reported that this is proba
a direct serotonergic effect on CRF neurons because
hyd apirone, stimulate HPA axis activity in intact rats. More-
over, Haleem et al. (1989) reported that this is probably
a direct serotonergic effect on CRF neurons because 8-
hydroxydipropylaminotetralin (500 to 1500 ng) micr concentrations. direct serotonergic effect on CRF neurons because 8-
droxydipropylaminotetralin (500 to 1500 ng) microin-
ted into the PVN increases plasma corticosterone
ncentrations.
The effects of norepinephrine and the opioid peptides jected into the PVN increases plasma corticosterone
concentrations.
The effects of norepinephrine and the opioid peptides

jected into the PVN increases plasma corticosterone
concentrations.
The effects of norepinephrine and the opioid peptides
on CRF release in vitro are less clear. Suda et al. (1987c)
reported that norepinephrine has a pote concentrations.
The effects of norepinephrine and the opioid peptides
on CRF release in vitro are less clear. Suda et al. (1987c)
reported that norepinephrine has a potent inhibitory
effect mediated by α_1 - and β -re The effects of norepinephrine and the opioid peptides
on CRF release in vitro are less clear. Suda et al. (1987c)
reported that norepinephrine has a potent inhibitory
effect mediated by α_1 - and β -receptors. In cont on CRF release in vitro are less clear. Suda et al. (1987c)
reported that norepinephrine has a potent inhibitory
effect mediated by α_1 - and β -receptors. In contrast, Tsa-
garakis et al. (1988) and Joanny et al. (19 reported that norepinephrine has a potent inhibitory
effect mediated by α_1 - and β -receptors. In contrast, Tsa-
garakis et al. (1988) and Joanny et al. (1989) report a
stimulatory effect of norepinephrine on CRF rel garakis et al. (1988) and Joanny et al. (1989) report a stimulatory effect of norepinephrine on CRF release mediated through β -receptors. In agreement with the two latter reports, Widmaier et al. (1989) reported noradr garakis et al. (1988) and Joanny et al. (1989) report a stimulatory effect of norepinephrine on CRF release mediated through β -receptors. In agreement with the two latter reports, Widmaier et al. (1989) reported noradr stimulatory effect of norepinephrine on CRF release
mediated through β -receptors. In agreement with the two
latter reports, Widmaier et al. (1989) reported noradre-
nergic stimulation of CRF release via β -receptors mediated through β -receptors. In agreement with the two
latter reports, Widmaier et al. (1989) reported noradre-
nergic stimulation of CRF release via β -receptors in rat
hypothalamic cell cultures obtained from 1-we latter reports, Widmaier et al. (1989) reported noradre-
nergic stimulation of CRF release via β -receptors in rat
hypothalamic cell cultures obtained from 1-week-old
rats. The elegant work of Plotsky (1987), using port nergic stimulation of CRF release via β -receptors in
hypothalamic cell cultures obtained from 1-week-
rats. The elegant work of Plotsky (1987), using por
vessel cannulation for sampling CRF release in vivo, a
supports hypothalamic cell cultures obtained from 1-week-old
rats. The elegant work of Plotsky (1987), using portal
vessel cannulation for sampling CRF release in vivo, also
supports a stimulatory role for norepinephrine. Norepi-
 rats. The elegant work of Plotsky (1987), using portal vessel cannulation for sampling CRF release in vivo, also supports a stimulatory role for norepinephrine. Norepinephrine produces a bell-shaped dose-response curve, w vessel cannulation for sampling CRF release in vivo, also supports a stimulatory role for norepinephrine. Norepinephrine produces a bell-shaped dose-response curve with low doses stimulating CRF release via α_1 -recepto supports a stimulatory role for norepinephrine. Norepi-
nephrine produces a bell-shaped dose-response curve,
with low doses stimulating CRF release via α_1 -receptors
and higher doses inhibiting CRF release via β -rec nephrine produces a bell-shaped dose-response curve,
with low doses stimulating CRF release via α_1 -receptors
and higher doses inhibiting CRF release via β -receptors.
An excellent review of the catecholaminergic reg with low doses stimulating CRF release via α_1 -receptors
and higher doses inhibiting CRF release via β -receptors.
An excellent review of the catecholaminergic regulation
of HPA axis activity was recently provided by d higher doses inhibiting CRF release via β -receptors.

a excellent review of the catecholaminergic regulation

HPA axis activity was recently provided by Plotsky et

(1989).

Buckingham (1986, 1987) reported that vari

maximal responses than that produced by (\pm) -1-(2,5-variety of opioid peptides, including β -endorphin, inhib-
dimethoxy-4-iodophenyl)-2-aminopropane.
We (Owens et al., 1991a) reported significant increases et al. (198 An excellent review of the catecholaminergic regulation
of HPA axis activity was recently provided by Plotsky et
al. (1989).
Buckingham (1986, 1987) reported that various opioid
peptides directly stimulate CRF release in v of HPA axis activity was recently provided by Plotsky et al. (1989).

Buckingham (1986, 1987) reported that various opioid

peptides directly stimulate CRF release in vitro. The

only exception is the bell-shaped dose-res al. (1989).
Buckingham (1986, 1987) reported that various opic
peptides directly stimulate CRF release in vitro. T
only exception is the bell-shaped dose-response cur
generated by β -endorphin. Concentrations of β -en Buckingham (1986, 1987) reported that various opioid
peptides directly stimulate CRF release in vitro. The
only exception is the bell-shaped dose-response curve
generated by β -endorphin. Concentrations of β -endor-
p peptides directly stimulate CRF release in vitro. The
only exception is the bell-shaped dose-response curve
generated by β -endorphin. Concentrations of β -endor-
phin >100 nM were found to inhibit basal CRF release,
 only exception is the bell-shaped dose-response curve
generated by β -endorphin. Concentrations of β -endor-
phin >100 nM were found to inhibit basal CRF release,
whereas concentrations <100 nM retain their stimulator generated by β -endorphin. Concentrations of β -endo
phin >100 nM were found to inhibit basal CRF releas
whereas concentrations <100 nM retain their stimulato
activity. In contrast, Yajima et al. (1986) reported that
 phin >100 nM were found to inhibit basal CRF release,
whereas concentrations <100 nM retain their stimulatory
activity. In contrast, Yajima et al. (1986) reported that a
variety of opioid peptides, including β -endorphin whereas concentrations <100 nM retain their stimulatory
activity. In contrast, Yajima et al. (1986) reported that a
variety of opioid peptides, including β -endorphin, inhib-
ited CRF release at all concentrations teste variety of opioid peptides, including β -endorphin, inhibited CRF release at all concentrations tested. Tsagarakis

corricotraching corricotron agreement with the findings of studies using the μ - may agonist morphine, Nikolarakis et al. (1987) utilizing CRF adminimmunoneutralization techniques reported that endog-CORTICOTROPI
agreement with the findings of studies using the
agonist morphine, Nikolarakis et al. (1987) utilizing CI
immmunoneutralization techniques reported that endo
enous opioids tonically inhibit CRF release but tha agreement with the findings of studies using the μ -
agonist morphine, Nikolarakis et al. (1987) utilizing CRF
immmunoneutralization techniques reported that endog-
enous opioids tonically inhibit CRF release but that $\$ agonist morphine, Nikolarakis et al. (1987) utilizing CRF immmunoneutralization techniques reported that endogenous opioids tonically inhibit CRF release but that μ -agonists release ACTH via non CRF-dependent mechanism

enous opioids tonically inhibit CRF release but that μ agonists release ACTH via non CRF-dependent mechanisms and that κ -agonists stimulate CRF release directl Of the in vitro studies not previously discussed in ou agonists release ACTH via non CRF-dependent mecha-
nisms and that κ -agonists stimulate CRF release directly. Othe
Of the in vitro studies not previously discussed in our
recent review (Owens and Nemeroff, 1990), both misms and that κ -agonists stimulate CRF release directly
Of the in vitro studies not previously discussed in our
recent review (Owens and Nemeroff, 1990), both hypo-
glycemia (Widmaier et al., 1988) and neuropeptide Y Of the in vitro studies not previously discussed in our
recent review (Owens and Nemeroff, 1990), both hypo-
glycemia (Widmaier et al., 1988) and neuropeptide Y
(Tsagarakis et al., 1989c) stimulate, whereas GABAergic/
benz recent review (Owens and Nemeroff, 1990), both hypo-
glycemia (Widmaier et al., 1988) and neuropeptide Y
(Tsagarakis et al., 1989c) stimulate, whereas GABAergic/
subenzodiazepine (Kalogeras et al., 1990) mechanisms in-
in glycemia (Widmaier et al., 1988) and neuropeptide Y c
(Tsagarakis et al., 1989c) stimulate, whereas GABAergic/
benzodiazepine (Kalogeras et al., 1990) mechanisms in-
hibit, CRF release. In addition, cocaine has been report (Tsagarakis et al., 1989c) stimulate, whereas GABAergic/
benzodiazepine (Kalogeras et al., 1990) mechanisms in-
hibit, CRF release. In addition, cocaine has been reported
to stimulate CRF release through mechanisms unrelat not adequately understood (Calogero et al., 1989b).

As we have implied previously, the in vivo techniques
in which viability of the tissue is not a problem, such as
the portal vessel cannulations used by Plotsky and colto its actions on monoamine-containing neurons but, in rather, through its local anesthetic properties which are Theorem and a problem. As we have implied previously, the in vivo techniques stim which viability of the tiss rather, through its local anesthetic properties which are
not adequately understood (Calogero et al., 1989b).
As we have implied previously, the in vivo techniques
in which viability of the tissue is not a problem, such as not adequately understood (Calogero et al., 1989b).
As we have implied previously, the in vivo technique
in which viability of the tissue is not a problem, such a
the portal vessel cannulations used by Plotsky and col
leag As we have implied previously, the in vivo techniques
in which viability of the tissue is not a problem, such as
the portal vessel cannulations used by Plotsky and col-
leagues, are superior to the hypothalamic explant inc in which viability of the tissue is not a problem, such as
the portal vessel cannulations used by Plotsky and col-
leagues, are superior to the hypothalamic explant incu-
bations. However, this technique can suffer from th the portal vessel cannulations used by Plotsky and colleagues, are superior to the hypothalamic explant incubations. However, this technique can suffer from the fact that the secretagogue under study, if administered syste leagues, are superior to the hypothalamic explant incu-
bations. However, this technique can suffer from the fact
that the secretagogue under study, if administered sys-
gluenically, must be able to cross the blood-brain b bations. However, this technique can suffer from the fact
that the secretagogue under study, if administered sys-
temically, must be able to cross the blood-brain barrier adr
and those that do will certainly be acting at o that the secretagogue under study, if administered sys-
temically, must be able to cross the blood-brain barrier and
those that do will certainly be acting at other brain in
areas in addition to the PVN, thus confounding a temically, must be able to cross the blood-brain barrier add and those that do will certainly be acting at other brain invareas in addition to the PVN, thus confounding any fir attempt to study transmitter regulation at th and those that do will certainly be acting at other brain
areas in addition to the PVN, thus confounding an
attempt to study transmitter regulation at the level of
the hypothalamic CRF perikarya themselves. It should
be re areas in addition to the PVN, thus confounding any
attempt to study transmitter regulation at the level of
the hypothalamic CRF perikarya themselves. It should
be remembered that this problem is common to all stud-
ies in attempt to study the hypothalamic
be remembered the
ies in which syste
cluding our own.
2. Feedback and : **2. Feedback and stress-induced effects on the corticotro-**
2. Feedback and stress-induced effects on the corticotro-
2. Feedback and stress-induced effects on the cortico-
2. Feedback and stress-induced effects on th

be remembered that this problem is common to all studeries in which systemic drug administration is used, including our own.
 pin-releasing factor neuron. Feedback regulation of the difference regulation of the differenc ies in which systemic drug administration is used, including our own.
2. Feedback and stress-induced effects on the corticotro-
pin-releasing factor neuron. Feedback regulation of the
HPA axis, in general, and CRF neurons, cluding our own.

2. Feedback and stress-induced effects on the corticotro-

pin-releasing factor neuron. Feedback regulation of the

HPA axis, in general, and CRF neurons, in particular,

by glucocorticoids is complex and 2. Feedback and stress-induced effects on the corticotro-
pin-releasing factor neuron. Feedback regulation of the
HPA axis, in general, and CRF neurons, in particular,
by glucocorticoids is complex and a detailed descripti pin-releasing factor neuron. Feedback regulation of the different HPA axis, in general, and CRF neurons, in particular, alteration by glucocorticoids is complex and a detailed description (198) is beyond the scope of this by glucocorticoids is complex and a detailed description
is beyond the scope of this review. Nevertheless, we will
briefly review recent studies focusing on alterations in
paraventricular CRF neuronal function. Those seeki is beyond the scope of this review. Nevertheless, we will or covertly review recent studies focusing on alterations in streparaventricular CRF neuronal function. Those seeking CRI more detailed, although already somewhat o briefly review reparaventricular
more detailed, a
information woo
Antoni (1986).
There is unde raventricular CRF neuronal function. Those seek
ore detailed, although already somewhat out of diformation would do well to start with the review
ntoni (1986).
There is undeniably convincing evidence that circulating gluco

information would do well to start with the review by

Antoni (1986). pa

There is undeniably convincing evidence that circulat-

ing glucocorticoids exhibit part of their negative feedback

the effects directly at the lev Antoni (1986).
There is undeniably convincing evidence that circulat-
ing glucocorticoids exhibit part of their negative feedback
effects directly at the level of the CRF perikarya of the
PVN. Strong evidence of such effec There is undeniably convincing evidence that circulat-
ing glucocorticoids exhibit part of their negative feedback
effects directly at the level of the CRF perikarya of the
FVN. Strong evidence of such effects comes from r ing glucocorticoids exhibit part of their negative feedback the effects directly at the level of the CRF perikarya of the FVN. Strong evidence of such effects comes from recent 2. immunocytochemical studies revealing the p effects directly at the level of the CRF perikarya of the PVN. Strong evidence of such effects comes from recent immunocytochemical studies revealing the presence of glucocorticoid receptors in CRF-containing neurons of th PVN. Strong evidence of such effects comes from recent
immunocytochemical studies revealing the presence of
glucocorticoid receptors in CRF-containing neurons of
the PVN (Liposits et al., 1987; Sawchenko, 1987b; Uht
et al. immunocytochemical studies revealing the presence of glucocorticoid receptors in CRF-containing neurons of the PVN (Liposits et al., 1987; Sawchenko, 1987b; Uht et al., 1988). In addition to observing glucocorticoid recept glucocorticoid receptors in CRF-containing neurons
the PVN (Liposits et al., 1987; Sawchenko, 1987b; let al., 1988). In addition to observing glucocortic
receptor immunoreactivity in the PVN, Cintra et
(1987) also reported the PVN (Liposits et al., 1987; Sawchenko, 1987b; Uht
et al., 1988). In addition to observing glucocorticoid
receptor immunoreactivity in the PVN, Cintra et al.
(1987) also reported glucocorticoid receptor immuno-
reactivi et al., 1988). In addition to observing glucocorticoid particle receptor immunoreactivity in the PVN, Cintra et al. has (1987) also reported glucocorticoid receptor immuno-
reactivity in CRF cell bodies in the BNST and in receptor immunoreactivity in the PVN, Cintra
(1987) also reported glucocorticoid receptor imm
reactivity in CRF cell bodies in the BNST and in cand
medial amygdaloid nuclei. Although it is not k
what effect glucocorticoids (1987) also reported glucocorticoid receptor immuno-
reactivity in CRF cell bodies in the BNST and in central et and medial amygdaloid nuclei. Although it is not known nifit
what effect glucocorticoids exert on these extr reactivity in CRF cell bodies in the BNST and in central
and medial amygdaloid nuclei. Although it is not known
what effect glucocorticoids exert on these extrahypotha-
lamic CRF neurons, it does not necessarily involve a
 what effect glucocorticoids exert on these extrahypotha-
lamic CRF neurons, it does not necessarily involve a was followed by increases at 60 minutes that could be
reduction in CRF gene expression because the role of block

LEASING FACTOR
may differ among brain regions. In fact, glucocorticoid
administration has been reported to increase (Swanson LEASING FACTOR 439
may differ among brain regions. In fact, glucocorticoid
administration has been reported to increase (Swanson
and Simmons, 1989) or have no effect (Beyer et al., 1988) 439
may differ among brain regions. In fact, glucocorticoid
administration has been reported to increase (Swanson
and Simmons, 1989) or have no effect (Beyer et al., 1988)
on CRF mRNA concentrations in the central nucleus may differ among brain regions. In fact, glucocorticoid
administration has been reported to increase (Swanson
and Simmons, 1989) or have no effect (Beyer et al., 1988)
on CRF mRNA concentrations in the central nucleus of
t administration has been reported to increase (Swanson
and Simmons, 1989) or have no effect (Beyer et al., 1988)
on CRF mRNA concentrations in the central nucleus of
the amygdala.
Other evidence for glucocorticoid regulatio ministration has been reported to increase (Swanson
d Simmons, 1989) or have no effect (Beyer et al., 1988)
c CRF mRNA concentrations in the central nucleus of
e amygdala.
Other evidence for glucocorticoid regulation of CR

immmunoneutralization techniques reported that endog-
enous opioids tonically inhibit CRF release but that μ -
enous opioids tonically inhibit CRF release but that μ -
enous on CRF mRNA concentrations in the central n benzodiazepine (Kalogeras et al., 1990) mechanisms in-
hibit, CRF release. In addition, cocaine has been reported
to stimulate CRF release through mechanisms unrelated
to stimulate CRF release through mechanisms unrelated and Simmons, 1989) or have no effect (Beyer et al., 1988)
on CRF mRNA concentrations in the central nucleus of
the amygdala.
Other evidence for glucocorticoid regulation of CRF
neurons comes from the technically difficult on CRF mRNA concentrations in the central nucleus of
the amygdala.
Other evidence for glucocorticoid regulation of CRF
neurons comes from the technically difficult studies of
Plotsky and colleagues who directly measured th the amygdala.

Other evidence for glucocorticoid regulation of CRF

neurons comes from the technically difficult studies of

Plotsky and colleagues who directly measured the release

of CRF from the median eminence into th Other evidence for glucocorticoid regulation of CRF
neurons comes from the technically difficult studies of
Plotsky and colleagues who directly measured the release
of CRF from the median eminence into the portal vessels
s neurons comes from the technically difficult studies of
Plotsky and colleagues who directly measured the release
of CRF from the median eminence into the portal vessels
supplying the anterior pituitary. Plotsky and Vale (1 Plotsky and colleagues who directly measured the release
of CRF from the median eminence into the portal vessels
supplying the anterior pituitary. Plotsky and Vale (1984)
initially reported that hemorrhage stress increase of CRF from the median eminence into the portal vessels
supplying the anterior pituitary. Plotsky and Vale (1984)
initially reported that hemorrhage stress increased portal
vessel concentrations of CRF from an initial lev supplying the anterior pituitary. Plotsky and Vale (1984)
initially reported that hemorrhage stress increased portal
vessel concentrations of CRF from an initial level of 430
 \pm 34 (approximately 0.1 nM) to 839 \pm 170 initially reported that hemorrhage stress increased portal
vessel concentrations of CRF from an initial level of 430
 \pm 34 (approximately 0.1 nM) to 839 \pm 170 pg/ml. These
increases were blocked by dexamethasone (100 vessel concentrations of CRF from an initial level of 430 \pm 34 (approximately 0.1 nM) to 839 \pm 170 pg/ml. These increases were blocked by dexamethasone (100 μ g/kg). The calculated basal secretory rate from the me \pm 34 (approximately 0.1 nM) to 839 \pm 170 pg/ml. These
increases were blocked by dexamethasone (100 μ g/kg).
The calculated basal secretory rate from the median
eminence was approximately 1.6 pg/minute. Hypotensive increases were blocked by dexamethasone $(100 \mu g/kg)$.
The calculated basal secretory rate from the median
eminence was approximately 1.6 pg/minute. Hypotensive
stress-induced increases in CRF release were suppressed
by pla The calculated basal secretory rate from the median
eminence was approximately 1.6 pg/minute. Hypotensive
stress-induced increases in CRF release were suppressed
by plasma corticosterone concentrations between 80 and
120 n eminence was approximately 1.6 pg/minute. Hypoten
stress-induced increases in CRF release were suppre
by plasma corticosterone concentrations between 80
120 ng/ml (Plotsky et al., 1986). However, basal (
release was only d by plasma corticosterone concentrations between 80 and 120 ng/ml (Plotsky et al., 1986). However, basal CRF release was only decreased by corticosterone concentrations >400 ng/ml. Conversely, the effects of a lack of gluco 120 ng/ml (Plotsky et al., 1986). However, basal CRF release was only decreased by corticosterone concentra-
tions >400 ng/ml. Conversely, the effects of a lack of
glucocorticoid feedback, produced by pharmacological
adrenalectomy with metyrapone and aminoglutethimide,
initi release was only decreased by corticosterone concentra-
tions >400 ng/ml. Conversely, the effects of a lack of
glucocorticoid feedback, produced by pharmacological
adrenalectomy with metyrapone and aminoglutethimide,
initi tions >400 ng/ml. Conversely, the effects of a lack of glucocorticoid feedback, produced by pharmacological adrenalectomy with metyrapone and aminoglutethimide, initially produced decreases in CRF release during the first glucocorticoid feedback, produced by pharm
adrenalectomy with metyrapone and aminoglu
initially produced decreases in CRF release
first 24 hours but increases in CRF secretion
by 72 hours (Plotsky and Sawchenko, 1987).
A n renalectomy with metyrapone and aminoglutethimide,
itially produced decreases in CRF release during the
st 24 hours but increases in CRF secretion (2.2-fold)
72 hours (Plotsky and Sawchenko, 1987).
A number of investigator

by glucocorticoids is complex and a detailed description (1986) reported that acute (3-hour cold immobilization)
is beyond the scope of this review. Nevertheless, we will or chronic (a series of different stressors for 14 information would do well to start with the review by

acute situation and continued release in the chronic

Antoni (1986).

There is undeniably convincing evidence that circulat-

There is undeniably convincing evidence t initially produced decreases in CRF release during
first 24 hours but increases in CRF secretion (2.2-f
by 72 hours (Plotsky and Sawchenko, 1987).
A number of investigators have directly examined
effects of stress on CRF c first 24 hours but increases in CRF secretion (2.2-fo
by 72 hours (Plotsky and Sawchenko, 1987).
A number of investigators have directly examined t
effects of stress on CRF concentrations in the hypoth
amus as well. Althou by 72 hours (Plotsky and Sawchenko, 1987).
A number of investigators have directly examined the
effects of stress on CRF concentrations in the hypothal-
amus as well. Although measurement of peptide concen-
trations alone A number of investigators have directly examined the
effects of stress on CRF concentrations in the hypothal
amus as well. Although measurement of peptide concentrations alone is insufficient to determine whethe
changes in effects of stress on CRF concentrations in the hypothal-
amus as well. Although measurement of peptide concen-
trations alone is insufficient to determine whether
changes in release, storage, or synthesis are responsible,
 amus as well. Although measurement of peptide concentrations alone is insufficient to determine whether changes in release, storage, or synthesis are responsible, differences between treatment groups clearly represent alte trations alone is insufficient to determine whethe
changes in release, storage, or synthesis are responsible
differences between treatment groups clearly represen
alterations in the activity of the neurons. Chappell et a
(changes in release, storage, or synthesis are responsible,
differences between treatment groups clearly represent
alterations in the activity of the neurons. Chappell et al.
(1986) reported that acute (3-hour cold immobili differences between treatment groups clearly represent
alterations in the activity of the neurons. Chappell et al.
(1986) reported that acute (3-hour cold immobilization)
or chronic (a series of different stressors for 14 alterations in the activity of the neurons. Chappell et al.
(1986) reported that acute (3-hour cold immobilization)
or chronic (a series of different stressors for 14 days)
stress resulted in a 50% decrease in median emine (1986) reported that acute (3-hour cold immobilization)
or chronic (a series of different stressors for 14 days)
stress resulted in a 50% decrease in median eminence
CRF concentrations. These decreases are thought to
repr or chronic (a series of different stressors for 14 days)
stress resulted in a 50% decrease in median eminence
CRF concentrations. These decreases are thought to
represent the release of CRF from terminal stores in the
acut stress resulted in a 50% decrease in median eminence
CRF concentrations. These decreases are thought to
represent the release of CRF from terminal stores in the
acute situation and continued release in the chronic
paradigm CRF concentrations. These decreases are thought to
represent the release of CRF from terminal stores in the
acute situation and continued release in the chronic
paradigm where new synthesis cannot keep pace with
the demand represent the release of CRF from terminal stores in the acute situation and continued release in the chronic paradigm where new synthesis cannot keep pace with the demands for more secretion. Whether this is actually the acute situation and continued release in the chronic
paradigm where new synthesis cannot keep pace with
the demands for more secretion. Whether this is actually
the case is unclear. Murakami et al. (1989) reported a
rapid paradigm where new synthesis cannot keep pace with
the demands for more secretion. Whether this is actually
the case is unclear. Murakami et al. (1989) reported a
rapid increase in the content of median eminence CRF
2.5 mi the demands for more secretion. Whether this is actually
the case is unclear. Murakami et al. (1989) reported a
rapid increase in the content of median eminence CRF
2.5 minutes after ether stress. This transient increase
d the case is unclear. Murakami et al. (1989) reported a rapid increase in the content of median eminence CRF 2.5 minutes after ether stress. This transient increase disappeared by 5 minutes. The increase was thought to be t rapid increase in the content of median eminence CRF
2.5 minutes after ether stress. This transient increase
disappeared by 5 minutes. The increase was thought to
be too rapid to be explained by new synthesis but more
like 2.5 minutes after ether stress. This transient increase disappeared by 5 minutes. The increase was thought to be too rapid to be explained by new synthesis but more likely represented rapid changes in the processing or pac disappeared by 5 minutes. The increase was thought to
be too rapid to be explained by new synthesis but more
likely represented rapid changes in the processing or
packaging of CRF in granules. ACTH concentrations
had alrea be too rapid to be explained by new synthesis but more likely represented rapid changes in the processing or packaging of CRF in granules. ACTH concentrations had already risen by this time point; therefore, CRF was though likely represented rapid changes in the processing or packaging of CRF in granules. ACTH concentrations had already risen by this time point; therefore, CRF was thought to have been secreted during this time. Moldow et al. packaging of CRF in granules. ACTH concentrations
had already risen by this time point; therefore, CRF was
thought to have been secreted during this time. Moldow
et al. (1987) reported that during restraint stress a sig-
n had already risen by this time point; therefore, CRF was
thought to have been secreted during this time. Moldow
et al. (1987) reported that during restraint stress a sig-
nificant decrease in hypothalamic CRF concentration thought to have been secreted during this time. Moldow
et al. (1987) reported that during restraint stress a sig-
nificant decrease in hypothalamic CRF concentrations
occurred 15 minutes after the initiation of stress. Thi et al. (1987) reported that during restraint stress a significant decrease in hypothalamic CRF concentrations
occurred 15 minutes after the initiation of stress. This
was followed by increases at 60 minutes that could be
b new synthesis was the likely cause of the increased CRF

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concentrations observed at this time point. Finally, in inta

agreement with the mRNA data (vide infra), Haas and dire owens and networks

concentrations observed at this time point. Finally, in interpresement with the mRNA data (vide infra), Haas and direction

George (1988) reported that 24 hours after a single 5-GENS AND NU

Concentrations observed at this time point. Finally, in

in agreement with the mRNA data (vide infra), Haas and d

George (1988) reported that 24 hours after a single 5-

minute foot shock, significant increas concentrations observed at this time point. Finally, in agreement with the mRNA data (vide infra), Haas and George (1988) reported that 24 hours after a single 5-
minute foot shock, significant increases in median emi-
nen concentrations observed at this time point. Finally, in in agreement with the mRNA data (vide infra), Haas and diffeorge (1988) reported that 24 hours after a single 5- minute foot shock, significant increases in median em agreement with the mRNA data (vide infra), Haas and George (1988) reported that 24 hours after a single 5-
minute foot shock, significant increases in median emi-
nence CRF content were observed. Inhibition of protein
synt George (1988) reported that 24 hours after a single 5-
minute foot shock, significant increases in median emi-
nence CRF content were observed. Inhibition of protein
synthesis with anisomycin completely abolished the in-
c minute foot shock, significant increases in median ϵ nence CRF content were observed. Inhibition of pro synthesis with anisomycin completely abolished the crease in CRF and resulted in decreased hypothala concentration nence CRF content were observed. Inhibition of protein
synthesis with anisomycin completely abolished the in-
crease in CRF and resulted in decreased hypothalamic
concentrations; this was undoubtedly due to unreplen-
ished nthesis with anisomycin completely abolished the in
ease in CRF and resulted in decreased hypothalamic
ncentrations; this was undoubtedly due to unreplen
ed stores being released during the previous 24 hours
In addition to

crease in CRF and resulted in decreased hypothalam:
concentrations; this was undoubtedly due to unrepler
ished stores being released during the previous 24 hour
In addition to feedback at the level of the CRF per
karya, gl concentrations; this was undoubtedly due to unrepler
ished stores being released during the previous 24 hour
In addition to feedback at the level of the CRF per
karya, glucocorticoids can act at both the anterior pitu
tary ished stores being released during the previous 24 house In addition to feedback at the level of the CRF per karya, glucocorticoids can act at both the anterior pitutary and at higher CNS areas such as the hippocampu At th In addition to feedback at the level of the CRF I
karya, glucocorticoids can act at both the anterior pi
tary and at higher CNS areas such as the hippocam
At the level of the anterior pituitary corticotroph, pr
cubation of karya, glucocorticoids can act at both the anterior pitui-
tary and at higher CNS areas such as the hippocampus. that
the level of the anterior pituitary corticotroph, prein-
cubation of pituitary cells in vitro with 10 nM tary and at higher CNS areas such as the hippocampus. the the level of the anterior pituitary corticotroph, preincubation of pituitary cells in vitro with 10 nM dexamethasone for 18 hours did not alter CRF-stimulated cAMP At the level of the anterior pituitary corticotroph, prein-
cubation of pituitary cells in vitro with 10 nM dexameth-
asone for 18 hours did not alter CRF-stimulated cAMP
accumulation but did markedly reduce ACTH release
(cubation of pituitary cells in vitro with 10 nM dexamethasone for 18 hours did not alter CRF-stimulated cAMP to accumulation but did markedly reduce ACTH release (Giguere et al., 1982). This suggests that glucocorticoids g asone for 18 hours did not alter CRF-stimulated cAMP tice
accumulation but did markedly reduce ACTH release A
(Giguere et al., 1982). This suggests that glucocorticoids gen
exerted their effect at a point distal to cAMP ge accumulation but did markedly reduce ACTH release
(Giguere et al., 1982). This suggests that glucocorticoids
exerted their effect at a point distal to cAMP generation
by CRF. In contrast, Sobel (1985) and Bilezikjian and
V (Giguere et al., 1982). This suggests that glucocortico
exerted their effect at a point distal to cAMP generation,
by CRF. In contrast, Sobel (1985) and Bilezikjian a
Vale (1983) reported that glucocorticoids significan
at exerted their effect at a point distal to cAMP generatio
by CRF. In contrast, Sobel (1985) and Bilezikjian an
Vale (1983) reported that glucocorticoids significantl
attenuated CRF-stimulated cAMP generation, suggess
ing th by CRF. In contrast, Sobel (1985) and Bilezikjian and h
Vale (1983) reported that glucocorticoids significantly n
attenuated CRF-stimulated cAMP generation, suggest-
sing that glucocorticoids exert at least part of their n Vale (1983) reported that glucocorticoids significantly
attenuated CRF-stimulated cAMP generation, suggest-
ing that glucocorticoids exert at least part of their nega-
tive feedback effects prior to cAMP generation. There
 attenuated CRF-stimulated cAMP generation, sugges
ing that glucocorticoids exert at least part of their neg
tive feedback effects prior to cAMP generation. The
are several methodological differences between these r
ports t ing that glucocorticoids exert at least part of their negative feedback effects prior to cAMP generation. There Y
are several methodological differences between these re-
ports that may account for the discrepancies. For e are several methodological differences between these re-
ports that may account for the discrepancies. For exam-
ple, an 18-hour preincubation with glucocorticoid was
used by Giguere et al. (1982), whereas only a 60-minute ports that may account for the discrepancies. For example, an 18-hour preincubation with glucocorticoid was used by Giguere et al. (1982), whereas only a 60-minute preincubation was used by the other investigators. It has ple, an 18-hour preincubation with glucocorticoid w
used by Giguere et al. (1982), whereas only a 60-minu
preincubation was used by the other investigators. It h
been suggested that local production of prostaglandin l
whic used by Giguere et al. (1982), whereas only a 60-minute preincubation was used by the other investigators. It has been suggested that local production of prostaglandin E_2 , which in turn alters intracellular calcium con preincubation was used by the other investigators. It has
been suggested that local production of prostaglandin E₂,
which in turn alters intracellular calcium concentrations,
may represent a portion of the negative feedb which in turn alters intracellular calcium concentrations,
may represent a portion of the negative feedback actions
of glucocorticoids at the corticotroph (Vlaskovska et al.,
1984; Sobel, 1987).

The most recent data have considerably strengthened
the hypothesis that the hippocampus plays a significant may represent a portion of the negative feedback actions
of glucocorticoids at the corticotroph (Vlaskovska et al.,
1984; Sobel, 1987).
The most recent data have considerably strengthened
the hypothesis that the hippocampu of glucocorticoids at the corticotroph (Vlaskovska et al., 1984; Sobel, 1987).
The most recent data have considerably strengthened
the hypothesis that the hippocampus plays a significant
role in glucocorticoid feedback. Sa 1984; Sobel, 1987).
The most recent data have considerably strengthen
the hypothesis that the hippocampus plays a significa
role in glucocorticoid feedback. Sapolsky et al. (198
showed that fornix transection, which disrup The most recent data have considerably strengthened
the hypothesis that the hippocampus plays a significant
role in glucocorticoid feedback. Sapolsky et al. (1989)
showed that fornix transection, which disrupts hippo-
it
c the hypothesis that the hippocampus plays a significant
role in glucocorticoid feedback. Sapolsky et al. (1989)
sice showed that fornix transection, which disrupts hippo-
its
campal input to the hypothalamus, renders the n role in glucocorticoid feedback. Sapolsky et al. (1989)
showed that fornix transection, which disrupts hippo-
campal input to the hypothalamus, renders the normally
glucocorticoid-sensitive increased release of CRF during
 showed that fornix transection, which disrupts hippo-
campal input to the hypothalamus, renders the normally
glucocorticoid-sensitive increased release of CRF during
stress resistant to glucocorticoid negative feedback. Ad campal input to the hypothalamus, renders the norma
glucocorticoid-sensitive increased release of CRF duri
stress resistant to glucocorticoid negative feedback. A
ditional studies by this group (Sapolsky et al., 199
sugges glucocorticoid-sensitive increased release of CRF during
stress resistant to glucocorticoid negative feedback. Ad-
ditional studies by this group (Sapolsky et al., 1990)
suggested that a major regulator of basal CRF concen stress resistant to glucocorticoid negative feedback. Additional studies by this group (Sapolsky et al., 1990) suggested that a major regulator of basal CRF concentrations in the portal vessel system is predominantly relat ditional studies by this group (Sapolsky et al., 19
suggested that a major regulator of basal CRF contrations in the portal vessel system is predomina
related to the occupancy of hippocampal type II glu
corticoid receptors suggested that a major regulator of basal CRF concentries increased CRF mRNA concentrations in the PVN, but trations in the portal vessel system is predominantly not in the cortex, to 130% of control values by 30 min-
rela trations in the portal vessel system is predominantly nelated to the occupancy of hippocampal type II gluco-
corticoid receptors, often in combination with hippocam-
pal type I or hypothalamic receptors, whereas secretion related to the occupancy of hippocampal type II gluco-
corticoid receptors, often in combination with hippocam-
pal type I or hypothalamic receptors, whereas secretion dian
of CRF induced by hypotensive stress is a functio corticoid receptors, often in combination with hippoca
pal type I or hypothalamic receptors, whereas secret
of CRF induced by hypotensive stress is a function
both hippocampal type I and II receptor occupancy.
addition to pal type I or hypothalamic receptors, whereas secretion of CRF induced by hypotensive stress is a function of (both hippocampul type I and II receptor occupancy. In addition to these studies, hippocampectomy or destruction of CRF induced by hypotensive stress is a function of (both hippocampal type I and II receptor occupancy. In paddition to these studies, hippocampectomy or destruction of the dorsal hippocampus results in a 4-fold increas both hippocampal type I and II receptor occupancy. In paddition to these studies, hippocampectomy or destruction of the dorsal hippocampus results in a 4-fold increase hin PVN CRF mRNA production and increases in plasma s addition to these studies, hippocampectomy or destruc-
tion of the dorsal hippocampus results in a 4-fold increase
in PVN CRF mRNA production and increases in plasma
speed following and corticosterone concentrations (Herm tion of the dorsal hippocampus results in a 4-fold increase
in PVN CRF mRNA production and increases in plasma
g-endorphin and corticosterone concentrations (Herman
aset al., 1989b). Similar findings were observed followi in PVN CRF mRNA production and increases in plasma
 β -endorphin and corticosterone concentrations (Herman

et al., 1989b). Similar findings were observed following

hypothalamic deafferentation that removed much of the β -endorphin and corticosterone concentrations (Herman asset al., 1989b). Similar findings were observed following bathopothalamic deafferentation that removed much of the Findippocampal input into the hypothalamus (Her

NEMEROFF
intact, it was shown that local actions of glucocorticoids
directly on CRF perikarya are insufficient to maintain NEMEROFF
intact, it was shown that local actions of glucocorticoids
directly on CRF perikarya are insufficient to maintain
normal CRF mRNA expression. NEMEROFF
intact, it was shown that local a
directly on CRF perikarya are
normal CRF mRNA expression
In addition to the previously tact, it was shown that local actions of glucocorticoids
rectly on CRF perikarya are insufficient to maintain
rmal CRF mRNA expression.
In addition to the previously described feedback ac-
ons on CRF release into portal ve directly on CRF perikarya are insufficient to maintain
normal CRF mRNA expression.
In addition to the previously described feedback ac-
tions on CRF release into portal vessels, glucocorticoids,

directly on CRF perikarya are insufficient to maintain
normal CRF mRNA expression.
In addition to the previously described feedback ac-
tions on CRF release into portal vessels, glucocorticoids,
or lack thereof, alter CRF normal CRF mRNA expression.
In addition to the previously described feedback actions on CRF release into portal vessels, glucocorticoids,
or lack thereof, alter CRF gene expression and peptide
content of the median eminenc In addition to the previously described feedback actions on CRF release into portal vessels, glucocorticoids, or lack thereof, alter CRF gene expression and peptide content of the median eminence. Our group (Owens et al., tions on CRF release into portal vessels, glucocorticoids,
or lack thereof, alter CRF gene expression and peptide
content of the median eminence. Our group (Owens et
al., 1990a) and others (Suda et al., 1984b; Yokoe et al. or lack thereof, alter CRF gene expression and peptide
content of the median eminence. Our group (Owens et
al., 1990a) and others (Suda et al., 1984b; Yokoe et al.,
1988; Jessop et al., 1990) have found that glucocorticoid content of the median eminence. Our group (Owens et al., 1990a) and others (Suda et al., 1984b; Yokoe et al., 1988; Jessop et al., 1990) have found that glucocorticoid administration decreases CRF immunoreactivity in the h al., 1990a) and others (Suda et al., 1984b; Yokoe et a
1988; Jessop et al., 1990) have found that glucocortico
administration decreases CRF immunoreactivity in t
hypothalamus. Conversely, Sawchenko (1987a) observ
that the administration decreases CRF immunoreactivity in the
hypothalamus. Conversely, Sawchenko (1987a) observed
that the lack of glucocorticoid feedback available follow-
ing adrenalectomy results in increased CRF immunohypothalamus. Conversely, Sawchenko (1987a) observed
that the lack of glucocorticoid feedback available follow-
ing adrenalectomy results in increased CRF immuno-
staining in the PVN; this effect is abolished by glucocor-
 hypothalamus. Co
that the lack of gluing adrenalectomy
staining in the PV
ticoid replacement
A number of in at the lack of glucocorticoid feedback available follow-
g adrenalectomy results in increased CRF immuno-
aining in the PVN; this effect is abolished by glucocor-
coid replacement.
A number of investigators have directly s

tive feedback effects prior to cAMP generation. There Young et al., 1986a; Beyer et al., 1988). These increases are several methodological differences between these re-
are also abolished by glucocorticoid replacement. In ing adrenalectomy results in increased CRF immuno-
staining in the PVN; this effect is abolished by glucocor-
ticoid replacement.
A number of investigators have directly studied CRF
gene expression by measuring CRF mRNA ei staining in the PVN; this effect is abolished by glucocor-
ticoid replacement.
A number of investigators have directly studied CRF
gene expression by measuring CRF mRNA either by
Northern blot gel analysis or by in situ hy ticoid replacement.
A number of investigators have directly studied CI
gene expression by measuring CRF mRNA either
Northern blot gel analysis or by in situ hybridizatie
histochemistry. Following adrenalectomy, c-fos imm
n A number of investigators have directly studied Clarence expression by measuring CRF mRNA either Northern blot gel analysis or by in situ hybridization histochemistry. Following adrenalectomy, c-fos immore activity in CRFgene expression by measuring CRF mRNA either by
Northern blot gel analysis or by in situ hybridization
histochemistry. Following adrenalectomy, c-fos immu-
noreactivity in CRF-containing cells of the PVN (Jacob-
son et al. Northern blot gel analysis or by in situ hybridization
histochemistry. Following adrenalectomy, c-fos immu-
noreactivity in CRF-containing cells of the PVN (Jacob-
son et al., 1990) and CRF mRNA concentrations increase
any histochemistry. Following adrenalectomy, c-fos immu-
noreactivity in CRF-containing cells of the PVN (Jacob-
son et al., 1990) and CRF mRNA concentrations increase
anywhere from 90% to 275% (Jingami et al., 1985a;
Young et noreactivity in CRF-containing cells of the PVN (Jacobson et al., 1990) and CRF mRNA concentrations increase
anywhere from 90% to 275% (Jingami et al., 1985a;
Young et al., 1986a; Beyer et al., 1988). These increases
are a son et al., 1990) and CRF mRNA concentrations increase
anywhere from 90% to 275% (Jingami et al., 1985a;
Young et al., 1986a; Beyer et al., 1988). These increases
are also abolished by glucocorticoid replacement. In fact,
 anywhere from 90% to 275% (Jingami et al., 1985a
Young et al., 1986a; Beyer et al., 1988). These increase
are also abolished by glucocorticoid replacement. In fact
dexamethasone implants into the PVN (Kovács and
Mezey, 198 Young et al., 1986a; Beyer et al., 1988). These increase
are also abolished by glucocorticoid replacement. In fact
dexamethasone implants into the PVN (Kovács an
Mezey, 1987) have been reported to cause a total inhi
bition are also abolished by glucocorticoid replacement. In fact,
dexamethasone implants into the PVN (Kovács and
Mezey, 1987) have been reported to cause a total inhi-
bition of hybridizable CRF mRNA above background.
Similarly, dexamethasone implants into the PVN (Kovács and
Mezey, 1987) have been reported to cause a total inhi-
bition of hybridizable CRF mRNA above background.
Similarly, Swanson and Simmons (1989) observed that
CRF mRNA hybridiz Mezey, 1987) have been reported to cause a total inhibition of hybridizable CRF mRNA above background.
Similarly, Swanson and Simmons (1989) observed that
CRF mRNA hybridization remains normal at plasma
corticosterone con bition of hybridizable CRF mRNA above background.
Similarly, Swanson and Simmons (1989) observed that
CRF mRNA hybridization remains normal at plasma
corticosterone concentrations ≤ 50 ng/ml, declines
sharply at stero CRF mRNA hybridization remains normal at plasma
corticosterone concentrations ≤ 50 ng/ml, declines
sharply at steroid concentrations between approximately
60 and 130 ng/ml, and is barely detectable at higher
concentra CRF mRNA hybridization rer
corticosterone concentrations
sharply at steroid concentration
60 and 130 ng/ml, and is bar
concentrations of corticosteroid
As expected, various physical rticosterone concentrations ≤ 50 ng/ml, declines
arply at steroid concentrations between approximately
and 130 ng/ml, and is barely detectable at higher
ncentrations of corticosteroids.
As expected, various physical a

sharply at steroid concentrations between approximate 60 and 130 ng/ml, and is barely detectable at high concentrations of corticosteroids.
As expected, various physical and behavioral stresses that activate the HPA axis a 60 and 130 ng/ml, and is barely detectable at concentrations of corticosteroids.
As expected, various physical and behavioral streat hat activate the HPA axis also alter CRF gene e sion. Intraperitoneal hypertonic saline, concentrations of corticosteroids.
As expected, various physical and behavioral stressors
that activate the HPA axis also alter CRF gene expres-
sion. Intraperitoneal hypertonic saline, naloxone-precip-
itated opiate withd As expected, various physical and behavioral stressors
that activate the HPA axis also alter CRF gene expres-
sion. Intraperitoneal hypertonic saline, naloxone-precip-
itated opiate withdrawal, swimming, or restraint stres that activate the HPA axis also alter CRF gene expression. Intraperitoneal hypertonic saline, naloxone-precipitated opiate withdrawal, swimming, or restraint stress increased CRF mRNA expression within 4 hours and remained sion. Intraperitoneal hypertonic saline, naloxone-precipitated opiate withdrawal, swimming, or restraint stress
increased CRF mRNA expression within 4 hours and
remained elevated for 24 hours (Lightman and Young,
1988; Har itated opiate withdrawal, swimming, or restraint stress
increased CRF mRNA expression within 4 hours and
remained elevated for 24 hours (Lightman and Young,
1988; Harbuz and Lightman, 1989a,b). Further studies
by Suda et a increased CRF mRNA expression within 4 hours and
remained elevated for 24 hours (Lightman and Young,
1988; Harbuz and Lightman, 1989a,b). Further studies
by Suda et al. (1988b) revealed that hypoglycemic stress
increased C remained elevated for 24 hours (Lightman and Young
1988; Harbuz and Lightman, 1989a,b). Further studies
by Suda et al. (1988b) revealed that hypoglycemic stress
increased CRF mRNA concentrations in the PVN, bu
not in the c 1988; Harbuz and Lightman, 1989a,b). Further studies
by Suda et al. (1988b) revealed that hypoglycemic stress
increased CRF mRNA concentrations in the PVN, but
not in the cortex, to 130% of control values by 30 min-
utes, by Suda et al. (1988b) revealed that hypoglycemic stress
increased CRF mRNA concentrations in the PVN, but
not in the cortex, to 130% of control values by 30 min-
utes, and these increases reached a peak of 186% by 2
hours increased CRF mRNA concentrations in the PVN, but
not in the cortex, to 130% of control values by 30 min-
utes, and these increases reached a peak of 186% by 2
hours (fig. 4). These changes followed decreases in me-
dian e not in the cortex, to 130% of control values by 30 minutes, and these increases reached a peak of 186% by 2 hours (fig. 4). These changes followed decreases in median eminence CRF concentrations at earlier time points (30 utes, and these increases reached a peak of 186% by 2
hours (fig. 4). These changes followed decreases in me-
dian eminence CRF concentrations at earlier time points
(30 to 60 minutes). Lightman and Young (1989a) re-
porte hours (fig. 4). These changes followed decreases in me-
dian eminence CRF concentrations at earlier time points
(30 to 60 minutes). Lightman and Young (1989a) re-
ported that dexamethasone administration in the fast or
int dian eminence CRF concentrations at earlier time points
(30 to 60 minutes). Lightman and Young (1989a) re-
ported that dexamethasone administration in the fast or
intermediate feedback time domains, 5 minutes and 2
hours, (30 to 60 minutes). Lightman and Young (1989a)
ported that dexamethasone administration in the fas
intermediate feedback time domains, 5 minutes ar
hours, respectively, did not alter the CRF mRNA
sponse to hypertonic salin intermediate feedback time domains, 5 minutes and 2 hours, respectively, did not alter the CRF mRNA response to hypertonic saline stress. However, dexamethasone administered during a 2-day period reduced both basal and str sponse to hypertonic saline stress. However, dexameth-
asone administered during a 2-day period reduced both
basal and stress-induced CRF mRNA concentrations.
Finally, Lightman and Young (1989b) also reported that,
althoug hours, respectively, did not alter the CRF mRNA response to hypertonic saline stress. However, dexamethasone administered during a 2-day period reduced both basal and stress-induced CRF mRNA concentrations. Finally, Lightm sponse to hypertonic saline stress. However, dexameth-
asone administered during a 2-day period reduced both
basal and stress-induced CRF mRNA concentrations.
Finally, Lightman and Young (1989b) also reported that,
althoug asone administered during a 2-day period reduced both
basal and stress-induced CRF mRNA concentrations.
Finally, Lightman and Young (1989b) also reported that,
although there are a number of hypothalamic changes
that are k

aspet

120 180 120 180 120 180 1
FIG. 4. Effect of insulin-induced hypoglycemia on CRF mRNA
levels in the hypothalamus without the median eminence. Relative
changes in CRF mRNA compared with control values are shown **Time (min)**
FIG. 4. Effect of insulin-induced hypoglycemia on CRF mRNA
levels in the hypothalamus without the median eminence. Relative
changes in CRF mRNA compared with control values are shown above.
There were four poo FIG. 4. Effect of insulin-induced hypoglycemia on CRF mRNA
levels in the hypothalamus without the median eminence. Relative
changes in CRF mRNA compared with control values are shown above.
There were four pools of animal FIG. 4. Effect of insulin-induced hypoglycemia on CRF mRNA levels in the hypothalamus without the median eminence. Relative changes in CRF mRNA compared with control values are shown above. There were four pools of animal levels in the hypothalam
changes in CRF mRNA co
There were four pools of a
saline. $*P < 0.05$. Values
from Suda et al. (1988b). Fine were four pools of animals with four rats per pool. \bullet , insussiline. $*P < 0.05$. Values are mean \pm SE. Reprinted with perform Suda et al. (1988b).
found to abolish stress-induced, but not adrenalectinduced, CRF

saline. * $P < 0.05$. Values are mean \pm SE. Reprinted with permission from Suda et al. (1988b).
found to abolish stress-induced, but not adrenalectomy-induced, CRF mRNA responses. These findings suggest that normal hypot from Suda et al. (1988b). and the stress induced, but not adrenalectomy-
found to abolish stress-induced, but not adrenalectomy-
identical induced, CRF mRNA responses. These findings suggest ult
that normal hypothalamic st he found to abolish stress-induced, but not adrenalectomy-
induced, CRF mRNA responses. These findings suggest und that normal hypothalamic stress responses are altered b
during lactation but return to normal within 2 days found to abolish stress-induced, but not adrenalectomy-
induced, CRF mRNA responses. These findings suggest us
that normal hypothalamic stress responses are altered b
during lactation but return to normal within 2 days a
f induced, CRF mRNA responses. These findings suge that normal hypothalamic stress responses are alt during lactation but return to normal within 2 following removal of pups from their mother. Alther this is presumably an ad that normal hypothalamic stress responses are altereduring lactation but return to normal within 2 day following removal of pups from their mother. Althought this is presumably an adaptive response, the neurotrans mitter a ring lactation but return to normal within 2 days allowing removal of pups from their mother. Although bis is presumably an adaptive response, the neurotrans-
is is presumably an adaptive response, the neurotrans-
titer al

following removal of pups from their mother. Although by
this is presumably an adaptive response, the neurotrans-
mitter alterations responsible for this remain obscure.
Some of the most interesting current studies involve this is presumably an adaptive response, the neurotransmitter alterations responsible for this remain obscure.
Some of the most interesting current studies involve
examination of the regulatory elements preceding the
CRF g mitter alterations responsible for this remain obscure. Come of the most interesting current studies involve standarding the community CRF gene proper. Emanuel et al. (1990) showed that in both forskolin and phorbol ester Some of the most interesting current studies involve
examination of the regulatory elements preceding the
CRF gene proper. Emanuel et al. (1990) showed that
both forskolin and phorbol esters stimulate CRF gene
expression i examination of the regulatory elements preceding the

CRF gene proper. Emanuel et al. (1990) showed that

both forskolin and phorbol esters stimulate CRF gene

expression in dispersed rat fetal hypothalamic cultures.

A m CRF gene proper. Emanuel et al. (1990) showed that
both forskolin and phorbol esters stimulate CRF gene
expression in dispersed rat fetal hypothalamic cultures.
A more detailed analysis was performed by Holsboer and
cowor both forskolin and phorbol esters stimulate CRF gene
expression in dispersed rat fetal hypothalamic cultures.
A more detailed analysis was performed by Holsboer and
coworkers (Van et al., 1990) who transfected the human
CR expression in dispersed rat fetal hypothalamic cultures.
A more detailed analysis was performed by Holsboer and
coworkers (Van et al., 1990) who transfected the human
CRF gene promoter region containing a 760-base pair
seg A more detailed analysis was performed by Holsboer and
coworkers (Van et al., 1990) who transfected the human
CRF gene promoter region containing a 760-base pair
segment into AtT-20 cells and linked it to the bacterial
ch coworkers (Van et al., 1990) who transfected the human
CRF gene promoter region containing a 760-base pair
segment into AtT-20 cells and linked it to the bacterial
chloramphenicol acetyltransferase gene. Expression was
enh CRF gene promoter region containing a 760-base p.
segment into AtT-20 cells and linked it to the bacter
chloramphenicol acetyltransferase gene. Expression w
enhanced by 8-bromo-cAMP but not by phorbol este
They also obser choramphenicol acetyltransferase gene. Expression was

enhanced by 8-bromo-cAMP but not by phorbol esters.

They also observed that the core sequence for a cAMP-

responsive element was 5'-TGACGTCA-3' -221 base

pairs fro enhanced by 8-bromo-cAMP but not by phorbol esters. enhanced by 8-bromo-cAMP but not by phorbol esters.
They also observed that the core sequence for a cAMP-
responsive element was 5'-TGACGTCA-3' -221 base
pairs from the putative CRF mRNA cap site. In addition,
treatment w They also observed that the core sequence for a cAM
responsive element was 5'-TGACGTCA-3' -221 b
pairs from the putative CRF mRNA cap site. In additive
treatment with 500 nM dexamethasone reduced activ
approximately 2-f responsive element was 5'-TGACGTCA-3' -221 base
pairs from the putative CRF mRNA cap site. In addition,
treatment with 500 nM dexamethasone reduced activity
approximately 2-fold in cAMP-stimulated cells, suggest-
ing that pairs from the putative CRF mRNA cap site. In addition, tion
treatment with 500 nM dexamethasone reduced activity al.,
approximately 2-fold in cAMP-stimulated cells, suggest-
ing that a portion of the glucocorticoid regul treatment with 500 nM dexamethasone reduced activity
approximately 2-fold in cAMP-stimulated cells, suggest-
ing that a portion of the glucocorticoid regulatory ele-
ment(s) resides in this region. Similar findings with
de ing that a portion of the glucocorticoid regulatory element(s) resides in this region. Similar findings with dexamethasone were observed by Adler et al. (1988) following introduction of an 8-kilobase DNA fragment

LEASING FACTOR 441
containing the entire human CRF gene including ap-
proximately 6 kilobases of the 5'-flanking sequence and LEASING FACTOR 441

containing the entire human CRF gene including ap-

proximately 6 kilobases of the 5'-flanking sequence and

0.8 kilobases of the 3'-sequence into AtT-20 cells. LEASING FACTOR

containing the entire human CRF gene including

proximately 6 kilobases of the 5'-flanking sequence

0.8 kilobases of the 3'-sequence into AtT-20 cells.

3. Feedback- and stress-induced effects on anterio IT ISLAM THE PROTAGE THE PROPRIMENT PROVIDENT AT A SURVEYOR STRESS-induced effects on anterior pi-
 3. Feedback- and stress-induced effects on anterior pi-
 itary corticotropin-releasing factor receptors. The stim-

containing the entire human CRF gene including approximately 6 kilobases of the 5'-flanking sequence an 0.8 kilobases of the 3'-sequence into AtT-20 cells.
3. *Feedback- and stress-induced effects on anterior pituitary cor* proximately 6 kilobases of the 5'-flanking sequence and
0.8 kilobases of the 3'-sequence into AtT-20 cells.
3. Feedback- and stress-induced effects on anterior pi-
tuitary corticotropin-releasing factor receptors. The stim 0.8 kilobases of the 3'-sequence into AtT-20 cells.
3. Feedback- and stress-induced effects on anterior pi-
tuitary corticotropin-releasing factor receptors. The stim-
ulation of ACTH release is dependent upon three major 3. Feedback- and stress-induced effects on anterior
tuitary corticotropin-releasing factor receptors. The st
ulation of ACTH release is dependent upon three m
factors involving CRF neurotransmission. Actually,
can be said tuitary corticotropin-releasing factor receptors. The stimulation of ACTH release is dependent upon three major factors involving CRF neurotransmission. Actually, this can be said for most forms of neurochemical transmissi ulation of ACTH release is dependent upon three major
factors involving CRF neurotransmission. Actually, this
can be said for most forms of neurochemical transmis-
sion. These include (a) neurotransmitter synthesis,
which factors involving CRF neurotransmission. Actually, th
can be said for most forms of neurochemical transmi
sion. These include (*a*) neurotransmitter synthesi
which can be assessed by measurement of CRF mRN
expression, (*b* can be said for most forms of neurochemical transmis-
sion. These include (*a*) neurotransmitter synthesis,
which can be assessed by measurement of CRF mRNA
expression, (*b*) CRF secretion, as determined by meas-
urement o sion. These include (a) neurotransmitter synthesis,
which can be assessed by measurement of CRF mRNA
expression, (b) CRF secretion, as determined by meas-
urement of portal vessel concentrations of CRF, and (c)
neurotr which can be assessed by measurement of CRF mRNA
expression, (b) CRF secretion, as determined by meas-
urement of portal vessel concentrations of CRF, and (c)
neurotransmitter receptor functioning, as determined by
meas expression, (b) CRF secretion, as determined by measurement of portal vessel concentrations of CRF, and (c) neurotransmitter receptor functioning, as determined by measurement of receptor affinity and density or second urement of portal vessel concentrations of CRF, and (c) neurotransmitter receptor functioning, as determined by
measurement of receptor affinity and density or second
messenger generating capabilities, which constitutes a
portion of the final aspect of neurotransmission. Regard measurement of receptor affinity and density or second
messenger generating capabilities, which constitutes a
portion of the final aspect of neurotransmission. Regard-
ing receptor function, removal of the negative feedbac messenger generating capabilities, which constitutes
portion of the final aspect of neurotransmission. Regarting receptor function, removal of the negative feedbac
action of glucocorticoids by adrenalectomy results in
CRF portion of the final aspect of neurotransmission. Regarding receptor function, removal of the negative feedback
action of glucocorticoids by adrenalectomy results in
CRF hypersecretion and a reduction (down-regulation)
in ing receptor function, removal of the negative feed
action of glucocorticoids by adrenalectomy result
CRF hypersecretion and a reduction (down-regulat
in anterior pituitary CRF receptor concentrations
fects that can be pre action of glucocorticoids by adrenalectomy results in CRF hypersecretion and a reduction (down-regulation) in anterior pituitary CRF receptor concentrations, effects that can be prevented by glucocorticoid supplementation CRF hypersecretion a
in anterior pituitary (
fects that can be preve
tation (Wynn et al.,
Holmes et al., 1987).
In addition to these anterior pituitary CRF receptor concentrations, ef-
tts that can be prevented by glucocorticoid supplemen-
tion (Wynn et al., 1983, 1984; Aguilera et al., 1986;
olmes et al., 1987).
In addition to these changes, chronic a fects that can be prevented by glucocorticoid supplementation (Wynn et al., 1983, 1984; Aguilera et al., 1986;
Holmes et al., 1987).
In addition to these changes, chronic administration
of corticosterone (0.5 to 150 mg/day

FIG. 4. Effect of insulin-induced hypoglycemia on CRF mRNA
 EIG. 4. Effect of insulin-induced hypoglycemia on CRF mRNA
 EIG. 4. Effect of insulin-induced hypoglycemia on CRF mRNA
 EIG. 4. Effect of insulin-induced tation (Wynn et al., 1983, 1984; Aguilera et al., 1986;
Holmes et al., 1987).
In addition to these changes, chronic administration
of corticosterone (0.5 to 150 mg/day) for 1 to 4 days also
causes a dose-dependent decrease Holmes et al., 1987).
In addition to these changes, chronic administration
of corticosterone (0.5 to 150 mg/day) for 1 to 4 days also
causes a dose-dependent decrease in anterior pituitary
CRF receptor number (Hauger et al In addition to these changes, chronic administration
of corticosterone $(0.5 \text{ to } 150 \text{ mg/day})$ for 1 to 4 days also
causes a dose-dependent decrease in anterior pituitary
CRF receptor number (Hauger et al., 1987). This may of corticosterone (0.5 to 150 mg/day) for 1 to 4 days also causes a dose-dependent decrease in anterior pituitary CRF receptor number (Hauger et al., 1987). This may be the result of decreased synthesis of new CRF receptor causes a dose-dependent decrease in anterior pituitary
CRF receptor number (Hauger et al., 1987). This may be
the result of decreased synthesis of new CRF receptors
in light of excessive glucocorticoid tone or may represen CRF receptor number (Hauger et al., 1987). This may be
the result of decreased synthesis of new CRF receptors
in light of excessive glucocorticoid tone or may represent
another means by which circulating glucocorticoids in the result of decreased synthesis of new CRF receptors
in light of excessive glucocorticoid tone or may represent
another means by which circulating glucocorticoids in-
hibit further ACTH secretion. It will be interesting in light of excessive glucocorticoid tone or may represent
another means by which circulating glucocorticoids in-
hibit further ACTH secretion. It will be interesting to
identify the presence of a glucocorticoid responsive another means by which circulating glucocorticoids in-
hibit further ACTH secretion. It will be interesting to
identify the presence of a glucocorticoid responsive reg-
ulatory element near the CRF receptor gene after it h hibit further ACTH secretion. It will be interesting to identify the presence of a glucocorticoid responsive regulatory element near the CRF receptor gene after it has been sequenced. In agreement with these findings, Chil identify the presence of a glucocorticoid responsive regulatory element near the CRF receptor gene after it has
been sequenced. In agreement with these findings, Childs
and Unabia (1990), while trying to identify corticotr ulatory element near the CRF receptor gene after it has
been sequenced. In agreement with these findings, Childs
and Unabia (1990), while trying to identify corticotrophs
by cytochemical binding with biotinylated analogs o been sequenced. In agreement with these findings, Childs
and Unabia (1990), while trying to identify corticotrophs
by cytochemical binding with biotinylated analogs of
CRF, found that glucocorticoids decreased the ability and Unabia (1990), while trying to identify corticotrophs
by cytochemical binding with biotinylated analogs of
CRF, found that glucocorticoids decreased the ability of
cells to bind CRF within 60 minutes of exposure to the by cytochemical binding with biotinylated analogs of CRF, found that glucocorticoids decreased the ability of cells to bind CRF within 60 minutes of exposure to the steroids, findings that could be mediated by a reduction CRF, found that glucocorticoids decreased the ability of cells to bind CRF within 60 minutes of exposure to the steroids, findings that could be mediated by a reduction in CRF receptor numbers at the cell surface. However, cells to bind CRF within 60 minutes of exposure to the steroids, findings that could be mediated by a reduction in CRF receptor numbers at the cell surface. However, in contrast to these observations suggesting glucocortic steroids, findings that could be mediated by a reduction
in CRF receptor numbers at the cell surface. However,
in contrast to these observations suggesting glucocorti-
coid-induced reduction in CRF function at the level of in CRF receptor numbers at the cell surface. However,
in contrast to these observations suggesting glucocorti-
coid-induced reduction in CRF function at the level of
the pituitary corticotroph, Ceda and Hoffman (1986)
obse in contrast to these observations suggesting glucocorticoid-induced reduction in CRF function at the level of
the pituitary corticotroph, Ceda and Hoffman (1986)
observed that glucocorticoids are necessary to prevent
devel coid-induced reduction in CRF function at the level of
the pituitary corticotroph, Ceda and Hoffman (1986)
observed that glucocorticoids are necessary to prevent
development of CRF desensitization in vitro. This sug-
gests the pituitary corticotroph, Ceda and Hoffman (1986)
observed that glucocorticoids are necessary to prevent
development of CRF desensitization in vitro. This sug-
gests that a mechanism exists by which, even in the face
of observed that glucocorticoids are necessary to prevent
development of CRF desensitization in vitro. This sug-
gests that a mechanism exists by which, even in the face
of high circulating concentrations of glucocorticoids, development of CRF desensitization in vitro. This suggests that a mechanism exists by which, even in the face
gests that a mechanism exists by which, even in the face
of high circulating concentrations of glucocorticoids, gests that a mechanism exists by which, even in the face
of high circulating concentrations of glucocorticoids, the
development of substantial CRF desensitization is pre-
vented in vivo. This is, in fact, the case because of high circulating concentrations of glucocorticoids, the development of substantial CRF desensitization is prevented in vivo. This is, in fact, the case because no specific desensitization to exogenous CRF is seen in chr development of substantial CRF desensitization is
vented in vivo. This is, in fact, the case because
specific desensitization to exogenous CRF is seen
chronically stressed animals (Young and Akil, 1985;
vier and Vale, 1987 vented in vivo. This is, in fact, the case because no specific desensitization to exogenous CRF is seen in chronically stressed animals (Young and Akil, 1985; Rivier and Vale, 1987), although CRF receptor concentrations in specific desensitization to exogenous CRF is seen in chronically stressed animals (Young and Akil, 1985; Rivier and Vale, 1987), although CRF receptor concentrations in the anterior pituitary are decreased (Hauger et al., *C. Involvement of Corticotropin-releasing Factor Neurons in the anterior pituitary are decreased (Haugal., 1988).*
C. Involvement of Corticotropin-releasing Factor Neurons in Other Endocrine Functions Net and Vale, 1501), although ORF Teces
 Neurons in the anterior pituitary are decreasing
 Neurons in Other Endocrine Functions
 1. Effects on growth hormone secretic

1. Effects on growth hormone secretion. One of the C. Involvement of Corticotropin-releasing Factor
Neurons in Other Endocrine Functions
1. Effects on growth hormone secretion. One of the
most well-documented endocrine responses to stress in

que the rat is the inhibition of growth hormone secretion.

Recent evidence suggests that this response is controlled OWENS AND N

the rat is the inhibition of growth hormone secretion.

Recent evidence suggests that this response is controlled

by CRF neurons. Rivier and Vale (1984a) and McCann owens and N
the rat is the inhibition of growth hormone secretion.
Recent evidence suggests that this response is controlled
by CRF neurons. Rivier and Vale (1984a) and McCann
and colleagues (Ono et al., 1984) initially re the rat is the inhibition of growth hormone secretion.
Recent evidence suggests that this response is controlled
by CRF neurons. Rivier and Vale (1984a) and McCann
and colleagues (Ono et al., 1984) initially reported that
 the rat is the inhibition of growth hormone secretion.
Recent evidence suggests that this response is controlled
by CRF neurons. Rivier and Vale (1984a) and McCann
and colleagues (Ono et al., 1984) initially reported that
 Recent evidence suggests that this response is controlled
by CRF neurons. Rivier and Vale (1984a) and McCann
and colleagues (Ono et al., 1984) initially reported that
i.c.v. administration of CRF dose dependently decreases by CRF neurons. Rivier and Vale (1984a) and McCann can act and colleagues (Ono et al., 1984) initially reported that the me
i.c.v. administration of CRF dose dependently decreases CRF
growth hormone secretion. This appears and colleagues (Ono et al., 1984) initially reported that the i.c.v. administration of CRF dose dependently decreases C growth hormone secretion. This appears to be the result LH of CRF-induced stimulation of somatostatin i.c.v. administration of CRF dose dependently decreases
growth hormone secretion. This appears to be the result
of CRF-induced stimulation of somatostatin release from
the median eminence; this has been demonstrated in
vit growth hormone secretion. This appears to be the result
of CRF-induced stimulation of somatostatin release from
the median eminence; this has been demonstrated in
vitro (Peterfreund and Vale, 1983; Aguila and McCann,
1985) of CRF-induced stimulation of somatostatin release from
the median eminence; this has been demonstrated in
vitro (Peterfreund and Vale, 1983; Aguila and McCann, con
1985) and in vivo (Mitsugi et al., 1990). Corroborating b the median eminence; this has been demonstrated in tion
vitro (Peterfreund and Vale, 1983; Aguila and McCann, con
1985) and in vivo (Mitsugi et al., 1990). Corroborating but
studies by Rivier and Vale (1985b) showed that b vitro (Peterfreund and Vale, 1983; Aguila and McCann, con
1985) and in vivo (Mitsugi et al., 1990). Corroborating but
studies by Rivier and Vale (1985b) showed that both con
i.c.v. CRF-induced and stress-induced decreases 1985) and in vivo (Mitsugi et al., 1990). Corrobors
studies by Rivier and Vale (1985b) showed that
i.c.v. CRF-induced and stress-induced decrease
plasma growth hormone concentrations are blocke
the CRF antagonist, α -he studies by Rivier and Vale (1985b) showed that both condictive. CRF-induced and stress-induced decreases in activeled plasma growth hormone concentrations are blocked by tion the CRF antagonist, α -helical CRF₉₋₄₁, or i.c.v. CRF-induced and stress-induced decreases in plasma growth hormone concentrations are blocked by
the CRF antagonist, α -helical CRF₉₋₄₁, or immunoneu-
tralization of somatostatin. It should be noted that, in
con plasma growth hormone concentrations are blocked by tuon an
the CRF antagonist, α -helical CRF₉₋₄₁, or immunoneuvations
tralization of somatostatin. It should be noted that, in CRF or
contrast to rodents, stress incre the CRF antagonist, α -helical CRF₉₋₄₁, or immunoneutralization of somatostatin. It should be noted that, in contrast to rodents, stress increases growth hormone secretion in primates. Therefore, the data derived from contrast to rodents, stress increases growth hormone accretion in primates. Therefore, the data derived from investor rodent experiments may not be relevant to nonhuman st primates and humans. Unrelated to its actions on g secretion in primates. Therefore, the data derived from
rodent experiments may not be relevant to nonhuman
primates and humans. Unrelated to its actions on growth
hormone secretion, but of interest nevertheless, CRF has
a rodent experiments may not be relevant to nonhuman
primates and humans. Unrelated to its actions on growth
hormone secretion, but of interest nevertheless, CRF has
also been reported to stimulate the release of dynorphin
 primates and l
hormone secre
also been repo
and β -endorpl
et al., 1986).
Interestingl

stress-induced ACTH secretion from the anterior pituiand β -endorphin from hypothalami in vitro (Nikola
et al., 1986).
Interestingly, somatostatinergic neurons can
stress-induced ACTH secretion from the anterior
tary by one of two apparent mechanisms. Somatos
28 and desAA et al., 1986).

Interestingly, somatostatinergic neurons can alter

stress-induced ACTH secretion from the anterior pitui-

tary by one of two apparent mechanisms. Somatostatin-

28 and desAA^{1,2,4,5,12,13}[d-Trp⁸]somato Interestingly, somatostatinergic neurons can alter
stress-induced ACTH secretion from the anterior pitui-
tary by one of two apparent mechanisms. Somatostatin-
28 and desAA^{1,2,4,5,12,13}[d-Trp⁸]somatostatin, but not so stress-induced ACTH secretion from the anterior pitui-
tary by one of two apparent mechanisms. Somatostatin-
28 and desAA^{1,2,4,5,12,13}[d-Trp⁸]somatostatin, but not so-
matostatin-14, given i.c.v. prevent stress-induced tary by one of two apparent mechanisms. Somatostatin-
28 and desAA^{1,2,4,5,12,13}[d-Trp⁸]somatostatin, but not so-
matostatin-14, given i.c.v. prevent stress-induced ACTH
secretion by inhibition of CRF release (Brown et 28 and desAA^{1,2,4,5,12,13}[d-Trp^o]somatostatin, but not so-
matostatin-14, given i.c.v. prevent stress-induced ACTH secretion by inhibition of CRF release (Brown et al., are
1984). Additionally, CRF-stimulated adenylat matostatin-14, given i.c.v. prevent stress-induced ACT
secretion by inhibition of CRF release (Brown et a
1984). Additionally, CRF-stimulated adenylate cyclas
activity and ACTH secretion from AtT-20 cells can l
dose depend secretion by inhibition of CRF release (Brown et a
1984). Additionally, CRF-stimulated adenylate cycla
activity and ACTH secretion from AtT-20 cells can
dose dependently inhibited up to 50% by somatostat
Higher doses can f 1984). Additionally, CRF-stimulated adenylate cyclase
activity and ACTH secretion from AtT-20 cells can be
dose dependently inhibited up to 50% by somatostatin.
Higher doses can further inhibit ACTH secretion appar-
ently dose dependently inhibited up to 50% by somatostatin.
Higher doses can further inhibit ACTH secretion apparently through a non-cAMP-dependent protein kinase
mechanism (Litvin et al., 1986).
2. Effects on reproductive hormo implemently inhibited up to 50% by somatostatin.
 2. Effects can further inhibit ACTH secretion appartly through a non-cAMP-dependent protein kinase
 2. Effects on reproductive hormone function. It is well

tablished t

Higher doses can further inhibit ACTH secretion apparently through a non-cAMP-dependent protein kinas mechanism (Litvin et al., 1986).
2. Effects on reproductive hormone function. It is welestablished that stress inhibits ently through a non-cAMP-dependent protein kine
mechanism (Litvin et al., 1986).
2. Effects on reproductive hormone function. It is w
established that stress inhibits reproductive functionin
Although reproduction is clearl mechanism (Litvin et al., 1986).

2. Effects on reproductive hormone function. It is well

established that stress inhibits reproductive functioning.

Although reproduction is clearly of paramount impor-

tance to the surv 2. *Effects on reproductive hormone function*. It is well
established that stress inhibits reproductive functioning.
Although reproduction is clearly of paramount impor-
tance to the survival of an organism, during times established that stress inhibits reproductive functioning.
Although reproduction is clearly of paramount impor-
tance to the survival of an organism, during times of life-
threatening stress, energy is best expended solel tance to the survival of an organism, during times of life-
threatening stress, energy is best expended solely for
survival. It is, therefore, not surprising that activation of
CRF neurons may result in inhibited sexual fu nce to the survival of an organism, during times of liferent
reatening stress, energy is best expended solely for
rvival. It is, therefore, not surprising that activation of
RF neurons may result in inhibited sexual funct

threatening stress, energy is best expended solely f
survival. It is, therefore, not surprising that activation
CRF neurons may result in inhibited sexual functionin
Rivier and Vale (1984b) and Ono et al. (1984) report
tha survival. It is, therefore, not surprising that activation of CRF neurons may result in inhibited sexual functioning Rivier and Vale (1984b) and Ono et al. (1984) reported that i.c.v. CRF administration produced dose-depen CRF neurons may result in inhibited sexual functioning.
Rivier and Vale (1984b) and Ono et al. (1984) reported
that i.c.v. CRF administration produced dose-dependent
decreases in plasma LH, but not follicle-stimulating hor Rivier and Vale (1984b) and Ono et al. (1984) reported
that i.c.v. CRF administration produced dose-dependent
decreases in plasma LH, but not follicle-stimulating hor-
mone, concentrations in rats. Rivier and Vale (1984b)
 that i.c.v. CRF administration produced dose-dependent for decreases in plasma LH, but not follicle-stimulating hor-
mone, concentrations in rats. Rivier and Vale (1984b) te showed that this effect was powerful enough to i decreases in plasma LH, but not follicle-stimulating h
mone, concentrations in rats. Rivier and Vale (1986)
showed that this effect was powerful enough to inhi
ovulation and to disrupt pregnancy. In addition to the
finding mone, concentrations in rats. Rivier and Vale (1984b)
showed that this effect was powerful enough to inhibit
ovulation and to disrupt pregnancy. In addition to these
findings, Rivier et al. (1986) reported that i.c.v. admi showed that this effect was powerful enough to inhibit
ovulation and to disrupt pregnancy. In addition to these
findings, Rivier et al. (1986) reported that i.c.v. admin-
istration of the CRF antagonist blocked stress-indu ovulation and to disrupt pregnancy. In addition to these resp
findings, Rivier et al. (1986) reported that i.c.v. admin-
istration of the CRF antagonist blocked stress-induced CRI
decreases in plasma LH concentrations. In findings, Rivier et al. (1986) reported that i.c.v. administration of the CRF antagonist blocked stress-induced decreases in plasma LH concentrations. In vitro studies utilizing hypothalamic slices have shown that the CRF istration of the CRF antagonist blocked stress-induced
decreases in plasma LH concentrations. In vitro studies
utilizing hypothalamic slices have shown that the CRF
antagonist increases gonadotropin-releasing hormone
(LHRH decreases in plasma LH concentrations. In vitro studies reported that 6 weeks following surgery $\leq 5\%$ of the CRF utilizing hypothalamic slices have shown that the CRF in the median eminence observed in sham-operated r antagonist increases gonadotropin-releasing hormone

NEMEROFF
containing neurons in the rat hypothalamus (Maclusky
et al., 1988). These studies suggest that CRF neurons NEMEROFF
containing neurons in the rat hypothalamus (Maclusky
et al., 1988). These studies suggest that CRF neurons
can act centrally to directly inhibit LHRH release from NEMEROFF
containing neurons in the rat hypothalamus (Maclusky
et al., 1988). These studies suggest that CRF neurons
can act centrally to directly inhibit LHRH release from
the median eminence. containing neurons in the rat hypothalamus (Maclusky
et al., 1988). These studies suggest that CRF neurons
can act centrally to directly inhibit LHRH release from
the median eminence.
CRF, administered peripherally, also d ntaining neurons in the rat hypothalamus (Maclusky
al., 1988). These studies suggest that CRF neurons
n act centrally to directly inhibit LHRH release from
e median eminence.
CRF, administered peripherally, also decreases

tralization of somatostatin. It should be noted that, in CRF on LH secretion were mediated by pituitary-adrenal
contrast to rodents, stress increases growth hormone activation. A different set of findings have been observe also been reported to stimulate the release of dynorphin
and β -endorphin from hypothalami in vitro (Nikolarakis dexamethasone actually blocks the effects of CRF on
et al., 1986).
actually blocks the effects of CRF on
a et al., 1988). These studies suggest that CRF neurons
can act centrally to directly inhibit LHRH release from
the median eminence.
CRF, administered peripherally, also decreases plasma
LH concentrations. The mechanism(s) b can act centrally to directly inhibit LHRH release f
the median eminence.
CRF, administered peripherally, also decreases pla
LH concentrations. The mechanism(s) by which
occurs is unclear. CRF decreased plasma LH concer
ti the median eminence.
CRF, administered peripherally, also decreases plasma
LH concentrations. The mechanism(s) by which this
occurs is unclear. CRF decreased plasma LH concentra-
tions in male and female rats and plasma te CRF, administered peripherally, also decreases plasma
LH concentrations. The mechanism(s) by which this
occurs is unclear. CRF decreased plasma LH concentra-
tions in male and female rats and plasma testosterone
concentrat LH concentrations. The mechanism(s) by which this occurs is unclear. CRF decreased plasma LH concentrations in male and female rats and plasma testosterone concentrations and seminal vesicle weights in male rats but did no occurs is unclear. CRF decreased plasma LH concentrations in male and female rats and plasma testosterone concentrations and seminal vesicle weights in male rats but did not alter plasma follicle-stimulating hormone concen tions in male and female rats and plasma testoste
concentrations and seminal vesicle weights in male
but did not alter plasma follicle-stimulating horr
concentrations (Rivier and Vale, 1985a). Moreover, t
actions of CRF co concentrations and seminal vesicle weights in male rabut did not alter plasma follicle-stimulating hormo concentrations (Rivier and Vale, 1985a). Moreover, the actions of CRF could be mimicked by ACTH administration and we but did not alter plasma follicle-stimulating hormone concentrations (Rivier and Vale, 1985a). Moreover, these actions of CRF could be mimicked by ACTH administration and were abolished by adrenalectomy. These observations actions of CRF could be mimicked by ACTH administraactions of CRF could be mimicked by ACTH administration and were abolished by adrenalectomy. These observations strongly suggested that the peripheral actions of CRF on LH secretion were mediated by pituitary-adrenal activ tion and were abolished by adrenalectomy. These obs
vations strongly suggested that the peripheral actions
CRF on LH secretion were mediated by pituitary-adren
activation. A different set of findings have been observ
in pr vations strongly suggested that the peripheral actions of CRF on LH secretion were mediated by pituitary-adrenal activation. A different set of findings have been observed in primates. CRF decreases both plasma LH and foll CRF on LH secretion were mediated by pituitary-adrenal
activation. A different set of findings have been observed
in primates. CRF decreases both plasma LH and follicle-
stimulating hormone in rhesus monkeys when given i.v activation. A different set of findings have been observed
in primates. CRF decreases both plasma LH and follicle-
stimulating hormone in rhesus monkeys when given i.v.,
and this effect is independent of glucocorticoid sec in primates. CRF decreases both plasma LH and follicle-
stimulating hormone in rhesus monkeys when given i.v.,
and this effect is independent of glucocorticoid secretion
(Olster and Ferin, 1987; Gindoff and Ferin, 1987; Xi stimulating hormone in rhesus monkeys when given i.v.,
and this effect is independent of glucocorticoid secretion
(Olster and Ferin, 1987; Gindoff and Ferin, 1987; Xiao
et al., 1989). In fact, Gindoff et al. (1989) reporte and this effect is independent of glucocorticoid secretion (Olster and Ferin, 1987; Gindoff and Ferin, 1987; Xiao et al., 1989). In fact, Gindoff et al. (1989) reported that dexamethasone actually blocks the effects of CRF (Olster and Ferin, 1987; Gindoff and Ferin, 1987; Xiao
et al., 1989). In fact, Gindoff et al. (1989) reported that
dexamethasone actually blocks the effects of CRF on
gonadotropin secretion. Ferin and colleagues proposed
t et al., 1989). In fact, Gindoff et al. (1989) reported that
dexamethasone actually blocks the effects of CRF on
gonadotropin secretion. Ferin and colleagues proposed
that the mechanism involves CRF-stimulated release of
en gonadotropin secretion. Ferin and colleagues proposed
that the mechanism involves CRF-stimulated release of
endogenous opioids which then inhibit LHRH release
centrally. It is unclear how, or even whether, opioid
peptides gonadotropin secretion. Ferin and colleagues proposed
that the mechanism involves CRF-stimulated release of
endogenous opioids which then inhibit LHRH release
centrally. It is unclear how, or even whether, opioid
peptides that the mechanism involves CRF-stimulated release of
endogenous opioids which then inhibit LHRH release
centrally. It is unclear how, or even whether, opioid
peptides from the anterior pituitary are responsible for
this. endogenous opioids which then inhibit LHRH release
centrally. It is unclear how, or even whether, opioid
peptides from the anterior pituitary are responsible for
this. Finally, i.v. CRF decreases electrical activity in an
 peptides from the anterior pituitary are responsible for
this. Finally, i.v. CRF decreases electrical activity in an
area of the mediobasal hypothalamus thought to contain peptides from the anterior pituitary are responsible for
this. Finally, i.v. CRF decreases electrical activity in an
area of the mediobasal hypothalamus thought to contain
the LHRH pulse generator (Williams et al., 1990). this. Finally, i.v. CRF decreases electrical activity in an area of the mediobasal hypothalamus thought to contain the LHRH pulse generator (Williams et al., 1990). These actions of CRF were unrelated to glucocorticoid lev area of the mediobasal hypothalamus th
the LHRH pulse generator (Williams et
actions of CRF were unrelated to gluc
but were partially blocked by naloxon
credence to the above opioid hypothesis
Further study of the function e LHRH pulse generator (Williams et al., 1990). These
tions of CRF were unrelated to glucocorticoid levels
it were partially blocked by naloxone, lending some
edence to the above opioid hypothesis.
Further study of the fun but were partially blocked by naloxone, lending some

actions of CRF were unrelated to glucocorticoid levels
but were partially blocked by naloxone, lending some
credence to the above opioid hypothesis.
Further study of the function of CRF neurons in the
regulation of the hyp credence to the above opioid hypothesis.

Further study of the function of CRF neurons in

regulation of the hypothalamic-pituitary-gonadal

may provide potentially useful information regarding

pathophysiology and treatme *to The Hypothalame-pitulary-go*
 to Miscellaneous and treatment of fertility provide potentially useful information regathophysiology and treatment of fertility provident to Miscellaneous Experimental Manipulations
 1.

D. Responses of Corticotropin-releasing Factor Neurons

1. Lesionses of Corticotropin-releasing Factor Neurons
 1. Lesion studies. Several lesion studies have been
 1. Lesion studies. Several lesion studies have been
 1. Lesion studies. Several lesion studies have been
 performance of Corticotropin-releasing Factor Neurons
to Miscellaneous Experimental Manipulations
1. Lesion studies. Several lesion studies have been
performed that were not conceived primarily as indirect
methods of traci D. Responses of Corticotropin-releasing Factor Neurons
to Miscellaneous Experimental Manipulations
1. Lesion studies. Several lesion studies have been
performed that were not conceived primarily as indirect
methods of trac to Miscellaneous Experimental Manipulations
1. Lesion studies. Several lesion studies have been
performed that were not conceived primarily as indirect
methods of tracing anatomical pathways but, rather, as
an experimental 1. Lesion studies. Several lesion studies have been
performed that were not conceived primarily as indirect
methods of tracing anatomical pathways but, rather, as
an experimental manipulation. These have primarily
focused performed that were not conceived primarily as indirect
methods of tracing anatomical pathways but, rather, as
an experimental manipulation. These have primarily
focused on lesions of the PVN. Bruhn et al. (1984)
observed methods of tracing anatomical pathways but, rather, as
an experimental manipulation. These have primarily
focused on lesions of the PVN. Bruhn et al. (1984)
observed a 90% decrease in median eminence CRF con-
tent 4 to 6 d an experimental manipulation. These have primarily
focused on lesions of the PVN. Bruhn et al. (1984)
observed a 90% decrease in median eminence CRF con-
tent 4 to 6 days following bilateral lesions of the PVN.
This was as focused on lesions of the PVN. Bruhn et al. (1984)
observed a 90% decrease in median eminence CRF con-
tent 4 to 6 days following bilateral lesions of the PVN.
This was associated with a 75% reduction in the ACTH
response observed a 90% decrease in median eminence CRF content 4 to 6 days following bilateral lesions of the PVN.
This was associated with a 75% reduction in the ACTH
response to stress. In addition, hyperresponsiveness to
exogen tent 4 to 6 days following bilateral lesions of the PVN.
This was associated with a 75% reduction in the ACTH
response to stress. In addition, hyperresponsiveness to
exogenous CRF was observed, probably as a result of
CRF This was associated with a 75% reduction in the ACTH
response to stress. In addition, hyperresponsiveness to
exogenous CRF was observed, probably as a result of
CRF receptor up-regulation. Similarly, another group
reporte response to stress. In addition, hyperresponsiveness to exogenous CRF was observed, probably as a result of CRF receptor up-regulation. Similarly, another group reported that 6 weeks following surgery $<\!5\%$ of the CRF i exogenous CRF was observed, probably as a result of CRF receptor up-regulation. Similarly, another group reported that 6 weeks following surgery $<5\%$ of the CRF in the median eminence observed in sham-operated rats wa CRF receptor up-regulation. Similarly, another group
reported that 6 weeks following surgery $< 5\%$ of the CRF
in the median eminence observed in sham-operated rats
was seen in lesioned rats (Dohanics et al., 1986; Makar reported that 6 weeks following surgery $<5\%$ of the CRF
in the median eminence observed in sham-operated rats
was seen in lesioned rats (Dohanics et al., 1986; Makara
et al., 1986). Although these rats had normal basal
 in the median eminence observed in sham-operated rats
was seen in lesioned rats (Dohanics et al., 1986; Makara
et al., 1986). Although these rats had normal basal
plasma ACTH levels, probably maintained by other
ACTH secre

CORTICOTROPIN-REI
et al., 1986) or a markedly reduced (Dohanics et al., 1986)
ACTH response to surgical or ether stress, respectively. CORTICOTROPIN
ACTH response to surgical or ether stress, respectively.
Beaulieu et al. (1989) determined the effects of destruc

CORTICOTROP
Beaulieu et al., 1986) or a markedly reduced (Dohanics et al., 19
CTH response to surgical or ether stress, respective
Beaulieu et al. (1989) determined the effects of destruction
of the central nucleus of the et al., 1986) or a markedly reduced (Dohanics et al., 1986) Ge
ACTH response to surgical or ether stress, respectively. in
Beaulieu et al. (1989) determined the effects of destruc-
section of the central nucleus of the amy et al., 1986) or a markedly reduced (Dohanics et al., 1986)
ACTH response to surgical or ether stress, respectively.
Beaulieu et al. (1989) determined the effects of destruc-
tion of the central nucleus of the amygdala, a ACTH response to surgical or ether stress, respectively. in
Beaulieu et al. (1989) determined the effects of destruc-
tion of the central nucleus of the amygdala, a region
containing large numbers of CRF-staining cell bodi Beaulieu et al. (1989) determined the effects of destruction of the central nucleus of the amygdala, a region containing large numbers of CRF-staining cell bodies, on CRF immunoreactivity in the median eminence. The author tion of the central nucleus of the amygdala, a region
containing large numbers of CRF-staining cell bodies, S
on CRF immunoreactivity in the median eminence. The
authors found a >50% decrease in CRF immunostaining si
in th containing large numbers of CRF-staining cell bodies, SI
on CRF immunoreactivity in the median eminence. The
authors found a >50% decrease in CRF immunostaining sic
in the median eminence 2 weeks after bilateral lesions of on CRF immunoreactivity in the median eminence. The activations found a $>50\%$ decrease in CRF immunostaining sion
in the median eminence 2 weeks after bilateral lesions of ACT
the central amygdala. The interpretation of authors found a >50% decrease in CRF immunostaining sion
in the median eminence 2 weeks after bilateral lesions of AC'
the central amygdala. The interpretation of this finding hyp
is not easy. A direct pathway from the cen in the median eminence 2 weeks after bilateral lesions of ACTH
the central amygdala. The interpretation of this finding hyperc
is not easy. A direct pathway from the central nucleus to Howev
the median eminence may exist, the central amygdala. The interpretation of this finding
is not easy. A direct pathway from the central nucleus to
the median eminence may exist, although there is no
other evidence for this. More likely, the pathways from is not easy. A direct pathway from the central nucleus to H
the median eminence may exist, although there is no
in other evidence for this. More likely, the pathways from ra
the central amygdala to the PVN could alter the the median eminence may exist, although there is no
other evidence for this. More likely, the pathways from
the central amygdala to the PVN could alter the neuronal
activity of PVN CRF neurons that project to the median
em other evidence for this. More likely, the pathways from rats
the central amygdala to the PVN could alter the neuronal to e
activity of PVN CRF neurons that project to the median hyp
eminence. Alternatively, the existence o the central amygdala to the PVN could alter the neurons
activity of PVN CRF neurons that project to the media
eminence. Alternatively, the existence of projection
from the central amygdala to the brainstem and back t
the h activity of PVN CRF neurons that project to the median
eminence. Alternatively, the existence of projections
from the central amygdala to the brainstem and back to
the hypothalamus could help explain these observations.
Un from the central amygdala to the brainstem and back to
the hypothalamus could help explain these observations.
Unfortunately, measures of HPA axis activity were not
undertaken in this study to help determine the physio-
lo logical role of this decrease in CRF staining. Unfortunately, measures of HPA axis activity were not undertaken in this study to help determine the physiological role of this decrease in CRF staining.
2. *Role in animal models of genetic disorders*. A number of animal

Unfortunately, measures of HPA axis activity were not no

undertaken in this study to help determine the physio-

logical role of this decrease in CRF staining.

2. Role in animal models of genetic disorders. A number

of undertaken in this study to help determine the physio-
logical role of this decrease in CRF staining. op
2. Role in animal models of genetic disorders. A number
of animal models for various diseases have been shown of
to b logical role of this decrease in CRF staining.

2. Role in animal models of genetic disorders. A number

of animal models for various diseases have been shown

to be associated with alterations in HPA activity. With

this 2. Role in animal models of genetic disorders. A number
of animal models for various diseases have been shown
to be associated with alterations in HPA activity. With
a:
this in mind, several studies were conducted to exami of animal models for various diseases have been shown
to be associated with alterations in HPA activity. With
this in mind, several studies were conducted to examine
the role of CRF neurons in these models. The FSL of
rats the role of CRF neurons in these models. The FSL of the role of CRF neurons in these models. The FSL of
rats was developed by selective breeding for muscarinic
cholinergic receptor supersensitivity. These rats have
been proposed as a genetic model of depression because
they rats was developed by selective breeding for muscari
cholinergic receptor supersensitivity. These rats hi
been proposed as a genetic model of depression beca
they share many similarities with depressed patier
Because these cholinergic receptor supersensitivity. These rats have N
been proposed as a genetic model of depression because p
they share many similarities with depressed patients.
Because these rats and depressed humans have exagger-
 they share many similarities with depressed patients. separately.

Because these rats and depressed humans have exagger-

ated HPA responses to cholinergic agonists, and because nence CRF concentrations that precedes the i Because these rats and depressed humans have exagger-
ated HPA responses to cholinergic agonists, and because ner
many depressed patients are hypercortisolemic, our pla
group investigated CRF neuronal activity in FSL rats ated HPA responses to cholinergic agonists, and because ner
many depressed patients are hypercortisolemic, our pla
group investigated CRF neuronal activity in FSL rats injer
(Owens et al., 1991c). In nonstressed FSL animal many depressed patients are hypercortisolemic, our
group investigated CRF neuronal activity in FSL rats
(Owens et al., 1991c). In nonstressed FSL animals, we
found decreased basal plasma ACTH concentrations and
increased a group investigated CRF neuronal activity in FSL
(Owens et al., 1991c). In nonstressed FSL animals
found decreased basal plasma ACTH concentrations
increased anterior pituitary CRF receptor concentrat
with no differences in (Owens et al., 1991c). In nonstressed FSL animals, we found decreased basal plasma ACTH concentrations and increased anterior pituitary CRF receptor concentrations with no differences in median eminence CRF concentrations found decreased basal plasma ACTH concentrations and
increased anterior pituitary CRF receptor concentrations
with no differences in median eminence CRF concentra-
the with no differences in median eminence CRF concentra-
 increased anterior pituitary CRF receptor concentrations
with no differences in median eminence CRF concentra-
tions compared to control rats of the Flinders resistant
line. The Flinders resistant line rats have generally with no differences in median eminence CRF concentra-
tions compared to control rats of the Flinders resistant
line. The Flinders resistant line rats have generally been
shown to resemble normal Sprague-Dawley rats in pretions compared to control rats of the Flinders resistant nepline. The Flinders resistant line rats have generally been resshown to resemble normal Sprague-Dawley rats in pre-
shown to resemble normal Sprague-Dawley rats in line. The Flinders resistant line rats have generally been ress
shown to resemble normal Sprague-Dawley rats in pre-
vious studies. Thus, under basal conditions, this strain ne
of rat appears to possess diminished HPA acti shown to resemble no
vious studies. Thus,
of rat appears to pos
is, therefore, dissimi
depressed individuals
Genetically obese (ous studies. Thus, under basal conditions, this strain
rat appears to possess diminished HPA activity and
therefore, dissimilar to what is observed in many
pressed individuals.
Genetically obese (*fa/fa*) Zucker rats are c is, therefore, dissimilar to what is observed in many
depressed individuals. Genetically obese (fa/fa) Zucker rats are characterized
by increased parasympathetic and decreased sympathetic

is, therefore, dissimilar to what is observed in many
depressed individuals.
Genetically obese (fa/fa) Zucker rats are characterized
by increased parasympathetic and decreased sympathetic
tone. As a result, they are hypom depressed individuals.

Genetically obese (fa/fa) Zucker rats are characterized by increased parasympathetic and decreased sympathetic

tone. As a result, they are hypometabolic and gain weig

more efficiently than their Genetically obese $(fa)/fa$) Zucker rats are characterized ch
by increased parasympathetic and decreased sympathetic
tone. As a result, they are hypometabolic and gain weight (S.
more efficiently than their heterozygote cont by increased parasympathetic and decreased sympathetic
tone. As a result, they are hypometabolic and gain weight
more efficiently than their heterozygote controls. Hyper-
cortisolemia or enhanced adrenal responsiveness is
 tone. As a result, they are hypometabolic and gain weight (Sawchenko, 1988).

more efficiently than their heterozygote controls. Hyper-

cortisolemia or enhanced adrenal responsiveness is capable of disrupting membrane flu more efficiently than their heterozygote controls. Hyper-
cortisolemia or enhanced adrenal responsiveness is
thought to contribute to the etiology of this disorder
because adrenalectomy can reverse most facets of the
syndr cortisolemia or enhanced adrenal responsiveness
thought to contribute to the etiology of this disord
because adrenalectomy can reverse most facets of the
syndrome. These animals are hypercortisolemic and e
hibit a blunted thought to contribute to the etiology of this disorder liev
because adrenalectomy can reverse most facets of the caus
syndrome. These animals are hypercortisolemic and ex-
we
hibit a blunted ACTH response to exogenous CRF because adrenalectomy can reverse most facets of the syndrome. These animals are hypercortisolemic and exhibit a blunted ACTH response to exogenous CRF (Cunningham et al., 1986). Although there are few data to date, the in hibit a blunted ACTH response to exogenous CRF (Cunningham et al., 1986). Although there are few data to date, the increased HPA activity appears to be of central origin and involves excessive CRF secretion (Guillaume-

LEASING FACTOR 443
Gentil et al., 1990). It is not known whether alterations
in hypothalamic CRF neuronal activity is a primary or LEASING FACTOR 443
Gentil et al., 1990). It is not known whether alterations
in hypothalamic CRF neuronal activity is a primary or
secondary factor in the etiology of this syndrome. LEASING FACTOR
Gentil et al., 1990). It is not known whether alte
in hypothalamic CRF neuronal activity is a prin
secondary factor in the etiology of this syndrome.
The last syndrome that has been investigated secondary factor in the etiology of this syndrome.
The last syndrome that has been investigated is the

in hypothalamic CRF neuronal activity is a primary or
secondary factor in the etiology of this syndrome.
The last syndrome that has been investigated is the
SHR strain. SHRs appear to possess abnormal HPA
activity that con SHR strain. SHRs appear to possess abnormal HPA
activity that contributes to the development of hyperten-
sion. Like depressed patients, SHRs exhibit blunted
ACTH responses to exogenous CRF and are somewhat secondary factor in the etiology of this syndrome.
The last syndrome that has been investigated is the
SHR strain. SHRs appear to possess abnormal HPA
activity that contributes to the development of hyperten-
sion. Like de The last syndrome that has been investigated is the SHR strain. SHRs appear to possess abnormal HPA activity that contributes to the development of hypertension. Like depressed patients, SHRs exhibit blunted ACTH responses SHR strain. SHRs appear to possess abnormal HPA
activity that contributes to the development of hyperten-
sion. Like depressed patients, SHRs exhibit blunted
ACTH responses to exogenous CRF and are somewhat
hypercortisolem activity that contributes to the development of hypertension. Like depressed patients, SHRs exhibit blunted ACTH responses to exogenous CRF and are somewhat hypercortisolemic at all times (Hashimoto et al., 1989). However, sion. Like depressed patients, SHRs exhibit blunted
ACTH responses to exogenous CRF and are somewhat
hypercortisolemic at all times (Hashimoto et al., 1989).
However, these rats have lower concentrations of CRF
in the medi ACTH responses to exogenous CRF and are somewhat
hypercortisolemic at all times (Hashimoto et al., 1989).
However, these rats have lower concentrations of CRF
in the median eminence compared with normotensive
rats. It is b hypercortisolemic at all times (Hashimoto et al., 1989).
However, these rats have lower concentrations of CRF
in the median eminence compared with normotensive
rats. It is believed that excessive glucocorticoid tone due
to in the median eminence compared with normotensive
rats. It is believed that excessive glucocorticoid tone due
to enhanced adrenocortical function, rather than CRF
hypersecretion, is responsible for the hypercortisolemia in the median eminence compared with normotensive
rats. It is believed that excessive glucocorticoid tone du
to enhanced adrenocortical function, rather than CR
hypersecretion, is responsible for the hypercortisolem
and ma rats. It is believed that excessive glucocorticoid tone due
to enhanced adrenocortical function, rather than CRF
hypersecretion, is responsible for the hypercortisolemia
and may be essential to the development of hypertens to enhanced adrenocortical function, rather than CRF
hypersecretion, is responsible for the hypercortisolemia
and may be essential to the development of hypertension.
Recent evidence suggests that adrenalectomy delays the
 hypersecretion, is responsible for the hypercortisole
and may be essential to the development of hypertens
Recent evidence suggests that adrenalectomy delays
onset of hypertension in SHRs by several weeks but c
not prevent and may be essential to the development of hypertensio
Recent evidence suggests that adrenalectomy delays t
onset of hypertension in SHRs by several weeks but do
not prevent it. Neonatal sympathectomy with 6-hydro
ydopamin onset of hypertension in SHRs by several weeks but does
not prevent it. Neonatal sympathectomy with 6-hydrox-
ydopamine, on the other hand, does prevent the devel-
opment of the hypertension.

this in mind, several studies were conducted to examine on CRF neurons. The majority of these studies are sim-
the role of CRF neurons in these models. The FSL of ilar to those described in the section entitled, "Neuro-
ra *3. Miscellaneous pharmacological treatments.* A variety not prevent it. Neonatal sympathectomy with 6-hydrox-

ydopamine, on the other hand, does prevent the devel-

opment of the hypertension.

3. Miscellaneous pharmacological treatments. A variety

of compounds have been tes ydopamine, on the other hand, does prevent the devel-
opment of the hypertension.
3. Miscellaneous pharmacological treatments. A variety
of compounds have been tested for their actions on HPA
axis activity with particular opment of the hypertension.
3. Miscellaneous pharmacological treatments. A variety
of compounds have been tested for their actions on HPA
axis activity with particular emphasis on their actions
on CRF neurons. The majority 3. Miscellaneous pharmacological treatments. A variation of compounds have been tested for their actions on H
axis activity with particular emphasis on their action
on CRF neurons. The majority of these studies are si
ilar transmitter Regulation of Corticotropin-releasing Factor axis activity with particular emphasis on their actions
on CRF neurons. The majority of these studies are sim-
ilar to those described in the section entitled, "Neuro-
transmitter Regulation of Corticotropin-releasing Fact on CRF neurons. The majority of these studies are similar to those described in the section entitled, "Neuro-
transmitter Regulation of Corticotropin-releasing Factor
Neurons," but because they are poorly selective for any separately. ansmitter Regulation of Corticotropin-releasing Factor
eurons," but because they are poorly selective for any
rticular neurotransmitter system, they are discussed
parately.
Reserpine causes a transient decrease in median e

Neurons," but because they are poorly selective for any
particular neurotransmitter system, they are discussed
separately.
Reserpine causes a transient decrease in median emi-
nence CRF concentrations that precedes the inc particular neurotransmitter system, they are discussed
separately.
Reserpine causes a transient decrease in median emi-
nence CRF concentrations that precedes the increase in
plasma ACTH concentrations following a single a separately.
Reserpine causes a transient decrease in median emi-
nence CRF concentrations that precedes the increase in
plasma ACTH concentrations following a single acute
injection (Bugnon et al., 1983; Suda et al., 1987a Reserpine causes a transient decrease in median emi-
nence CRF concentrations that precedes the increase in
plasma ACTH concentrations following a single acute
injection (Bugnon et al., 1983; Suda et al., 1987a). Three
day nence CRF concentrations that precedes the increase in plasma ACTH concentrations following a single acute injection (Bugnon et al., 1983; Suda et al., 1987a). Three days of reserpine administration produced similar result plasma ACTH concentrations following a single acute
injection (Bugnon et al., 1983; Suda et al., 1987a). Three
days of reserpine administration produced similar results
in the median eminence and posterior pituitary (Tizab injection (Bugnon et al., 1983; Suda et al., 1987a). Th
days of reserpine administration produced similar resu
in the median eminence and posterior pituitary (Tiz
et al., 1985). It has been suggested from these data th
the days of reserpine administration produced similar results
in the median eminence and posterior pituitary (Tizabi
et al., 1985). It has been suggested from these data that
the initial release of monoamines, particularly nor in the median eminence and posterior pituitary (Tizabi
et al., 1985). It has been suggested from these data that
the initial release of monoamines, particularly norepi-
nephrine, prior to the depletion of these substances et al., 1985). It has been suggested from these data t
the initial release of monoamines, particularly nore
nephrine, prior to the depletion of these substances
reserpine may stimulate CRF release. These findi
support othe nephrine, prior to the depletion of these substances by reserpine may stimulate CRF release. These findings support other studies specifically focusing on noradre-
nergic stimulation of hypothalamic CRF release. More-
over nephrine, prior to the depletion of these substances by
reserpine may stimulate CRF release. These findings
support other studies specifically focusing on noradre-
nergic stimulation of hypothalamic CRF release. More-
over reserpine may stimulate CRF release. These findi
support other studies specifically focusing on norad
nergic stimulation of hypothalamic CRF release. Mo
over, lesions that decrease the noradrenergic innervat
of the hypotha support other studies specifically focusing on noradre
nergic stimulation of hypothalamic CRF release. More
over, lesions that decrease the noradrenergic innervation
of the hypothalamus result in decreases in CRF-im
munost nergic stimulation of hypothalamic CRF release. More-
over, lesions that decrease the noradrenergic innervation
of the hypothalamus result in decreases in CRF-im-
munostaining 14 to 17 days afterward. Without cate-
cholami over, lesions that decrease the noradrenergic innervation
of the hypothalamus result in decreases in CRF-im-
munostaining 14 to 17 days afterward. Without cate-
cholaminergic input, CRF neurons apparently do not
produce, a of the hypothalamus
munostaining 14 to
cholaminergic input,
produce, and presum
(Sawchenko, 1988).
Although some con unostaining 14 to 17 days afterward. Without cate-
olaminergic input, CRF neurons apparently do not
oduce, and presumably secrete, CRF at normal rates
awchenko, 1988).
Although some consider ethanol a nonspecific stressor
 produce, and presumably secrete, CRF at normal rates

lieved to act largely via a GABAergic mechanism. Be-(Sawchenko, 1988).

Although some consider ethanol a nonspecific stressor

capable of disrupting membrane fluidity, it is also be-

lieved to act largely via a GABAergic mechanism. Be-

cause it is unclear which, if either Although some consider ethanol a nonspecific stressor
capable of disrupting membrane fluidity, it is also be-
lieved to act largely via a GABAergic mechanism. Be-
cause it is unclear which, if either, mechanism is correct, capable of disrupting membrane fluidity, it is also be-
lieved to act largely via a GABAergic mechanism. Be-
cause it is unclear which, if either, mechanism is correct,
we have included it here rather than in the previous
 lieved to act largely via a GABAergic mechanism. Be-
cause it is unclear which, if either, mechanism is correct,
we have included it here rather than in the previous
section. Ethanol increases CRF release from hypotha-
lam cause it is unclear which, if either, mechanism is correct,
we have included it here rather than in the previous
section. Ethanol increases CRF release from hypotha-
lamic tissue in vitro (Redei et al., 1988). In addition, section. Ethanol increases CRF release from hypotha-
lamic tissue in vitro (Redei et al., 1988). In addition,
immunoneutralization of CRF abolishes the increase in
plasma ACTH observed following acute administration

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owens
144 owens
14 of ethanol (Rivier et al., 1984a). Animals exposed cont
14 days exhibited decreas uous 444

uous and the et al., 1984a). Animals exposed contin-

uously to ethanol vapors for 14 days exhibited decreased

anterior pituitary CRF receptors and CRF-stimulated n owens ANI

of ethanol (Rivier et al., 1984a). Animals exposed contin-

uously to ethanol vapors for 14 days exhibited decreased

anterior pituitary CRF receptors and CRF-stimulated

cyclase activity (Dave et al., 1986). Th of ethanol (Rivier et al., 1984a). Animals exposed continuously to ethanol vapors for 14 days exhibited decreased
anterior pituitary CRF receptors and CRF-stimulated
cyclase activity (Dave et al., 1986). This was associat of ethanol (Rivier et al., 1984a). Animals exposed compously to ethanol vapors for 14 days exhibited decreant
erior pituitary CRF receptors and CRF-stimu cyclase activity (Dave et al., 1986). This was assoc
with decreases vusly to ethanol vapors for 14 days exhibited decreased 10
terior pituitary CRF receptors and CRF-stimulated miclase activity (Dave et al., 1986). This was associated on
th decreases in plasma β -endorphin concentration

anterior pituitary CRF receptors and CRF-stimulated neurolease activity (Dave et al., 1986). This was associated of with decreases in plasma β -endorphin concentrations. (In unrelated studies, central administration of cyclase activity (Dave et al., 1986). This was associ
with decreases in plasma β -endorphin concentration
In unrelated studies, central administration of
putative neurotransmitter neuropeptide Y incre
plasma ACTH and me In unrelated studies, central administration of the
putative neurotransmitter neuropeptide Y increased
plasma ACTH and median eminence CRF concentra-
tions 45 minutes postinjection (Haas and George, 1987).
Finally, because In unrelated studies, central administration of the no
putative neurotransmitter neuropeptide Y increased tio
plasma ACTH and median eminence CRF concentra-
tions 45 minutes postinjection (Haas and George, 1987). tio
Final putative neurotransmitter neuropeptide Y increased
plasma ACTH and median eminence CRF concentra-
tions 45 minutes postinjection (Haas and George, 1987).
Finally, because alterations in CRF neurons have been
proposed to pl plasma ACTH and median eminence CRF concentra-
tions 45 minutes postinjection (Haas and George, 1987). tion
Finally, because alterations in CRF neurons have been
effectroconvulsive shock on CRF
depression, the effects of e tions 45 minutes postinjection (Haas and George, 1987).
Finally, because alterations in CRF neurons have been
proposed to play a role in the pathophysiology of major
depression, the effects of electroconvulsive shock on CR Finally, because alterations in CRF neurons have been effect
proposed to play a role in the pathophysiology of major bloot
depression, the effects of electroconvulsive shock on CRF Ove
neurons have been examined in the rat proposed to play a role in the pathophysiology of major
depression, the effects of electroconvulsive shock on CRF
neurons have been examined in the rat (Herman et al.,
1989a). Following seven daily ECT treatments, CRF
mRNA depression, the effects of electroconvulsive shock on CRF
neurons have been examined in the rat (Herman et al.,
1989a). Following seven daily ECT treatments, CRF
mRNA was significantly increased in the PVN, whereas
CRF con neurons have been examined in the rat (Herman et al., 1989a). Following seven daily ECT treatments, CRF mRNA was significantly increased in the PVN, whereas CRF concentrations were decreased. The finding of increased synth 1989a). Following seven daily ECT treatments, CRF emRNA was significantly increased in the PVN, whereas CRF concentrations were decreased. The finding of increased synthesis with decreased tissue concentrations buggests a mRNA was significantly increased in the PVN, whereas
CRF concentrations were decreased. The finding of in-
creased synthesis with decreased tissue concentrations
b suggests an increased activity of the HPA axis following
e CRF concentrations were decreased. The finding of in-
creased synthesis with decreased tissue concentrations be
suggests an increased activity of the HPA axis following the
electroconvulsive treatment. This has not been ob creased synthesis with decreased tissue concenti
suggests an increased activity of the HPA axis fol
electroconvulsive treatment. This has not been ob
in depressed patients in whom measures of HPA a
generally decrease towar **IMMUNE IN THE EXECUTE:**
 IMMUNE FUNCTION
 IMMUNE FUNCTION
 IMMUNE FUNCTION
 INCTENT

generally decrease toward more "normal values.
 IV. Corticotropin-releasing Factor Regulation of
 A. Evidence for Direct Communication between Immune
 Tissues and Corticotropin-releasing Factor-secreting or **TV. Corticotropin-releasing Factor Regulation of**
Immune Function
A. Evidence for Direct Communication between Immune
Tissues and Corticotropin-releasing Factor-secreting or
Corticotropin-releasing Factor-receptive Ne **Corticotropin-releasing Factor-regulation of**
 Corticotropin-releasing Factor-secreting or
 Corticotropin-releasing Factor-secreting or
 Corticotropin-releasing Factor-receptive Neuronal and
 Endocrine Tissues **Example 15 A.**
Evidence for Direct Tissues and Corticotric-
Endocrine Tissues
*L. Effects of cortic 1. Effects of corticotropin-releasing Factor-secreting or inticotropin-releasing Factor-secreting or inticotropin-releasing Factor-receptive Neuronal and adocrine Tissues

1. Effects of corticotropin-releasing factor on t*

mune system. Substantial evidence gained during the past several years has demonstrated that the CNS inter-
past several years has demonstrated that the CNS interexample 1 vearbound that
 Endocrine Tissues

1. Effects of corticotropin-releasing factor on the in

mune system. Substantial evidence gained during th

past several years has demonstrated that the CNS inter-

acts with, 2. Effects of corticotropin-releasing factor on the im-
mune system. Substantial evidence gained during the
past several years has demonstrated that the CNS inter-
acts with, and can modulate the activity of, various
eleme 1. Effects of corticotropin-releasing factor on the im-
mune system. Substantial evidence gained during the
past several years has demonstrated that the CNS inter-
acts with, and can modulate the activity of, various
eleme mune system. Substantial evidence gained during the
past several years has demonstrated that the CNS inter-
acts with, and can modulate the activity of, various
elements of the immune system. This interaction be-
tween th past several years has demonstrated that the CNS inter-
acts with, and can modulate the activity of, various
elements of the immune system. This interaction be-
tween these two major communication systems is likely
involve acts with, and can modulate the activity of, various

elements of the immune system. This interaction be-

tween these two major communication systems is likely

involved in regulating host defense. Much of the interest

i elements of the immune system. This interaction be-
tween these two major communication systems is likely
involved in regulating host defense. Much of the interest
involving CRF and the immune system resulted from the
long tween these two major communication systems is likely
involved in regulating host defense. Much of the interest
involving CRF and the immune system resulted from the
long-standing observations of stress-induced decreases
i involved in regulating host defense. Much of the interest
involving CRF and the immune system resulted from the
long-standing observations of stress-induced decreases
in immune function in animals and humans. Then,
Smith involving CRF and the immune system resulted from the
long-standing observations of stress-induced decreases
in immune function in animals and humans. Then,
Smith et al. (1986) reported that CRF stimulated the
release of long-standing observations of stress-induced decrea
in immune function in animals and humans. Th
Smith et al. (1986) reported that CRF stimulated
release of ACTH and β -endorphin from leukocytes. T
effect was reportedly in immune function in animals and humans. Then,
Smith et al. (1986) reported that CRF stimulated the
release of ACTH and β -endorphin from leukocytes. This
effect was reportedly blocked by the synthetic glucocor-
ticoid Smith et al. (1986) reported that CRF stimulated the release of ACTH and β -endorphin from leukocytes. This effect was reportedly blocked by the synthetic glucocorticoid dexamethasone and suggested that, like pituitary release of ACTH and β -endorphin from leukocytes. This date effect was reportedly blocked by the synthetic glucocor-
ticoid dexamethasone and suggested that, like pituitary HP corticotrophs, the POMC gene may be similar effect was reportedly blocked by the synthetic glucocor-
ticoid dexamethasone and suggested that, like pituitary
corticotrophs, the POMC gene may be similarly ex-
pressed in leukocytes. However, as noted earlier, CRF
recep ticoid dexamethasone and suggested that, like pituitar
corticotrophs, the POMC gene may be similarly ex
pressed in leukocytes. However, as noted earlier, CR
receptors have not been found on lymphocytes. Althoug
CRF recepto corticotrophs, the POMC gene may be similarly expressed in leukocytes. However, as noted earlier, CRF receptors have not been found on lymphocytes. Although CRF receptors have yet to be identified on lymphocytes, our group pressed in leukocytes. However, as noted earlier, CRF whose receptors have not been found on lymphocytes. Although fact CRF receptors have yet to be identified on lymphocytes, every our group (Ritchie et al., 1986) and oth CRF receptors have yet to be identified on lymphocytes,
our group (Ritchie et al., 1986) and others (Stephanou et
al., 1990) have found CRF immunoreactivity and CRF
mRNA in lymphocytes. CRF may be released from lymour group (Ritchie et al., 1986) and others (Stephanou et infra). phocytes to exert local paracrine actions on other im-

phocytes to exert local paracrine actions on other im-
mune system cells or on inflammatory responses (vide
infra).
Irwin and colleagues have repeatedly shown that the
central, but not peripheral, administration of CRF demune system cells or on inflammatory responses (vide not
infra). Creases NK cell cytotoxicity and that this is blocked by
creases NK cell cytotoxicity and that this is blocked by is n
central administration of the CRF ant central, but not peripheral, administration of CRF decreases NK cell cytotoxicity and that this is blocked by central administration of the CRF antagonist, α -helical

NEMEROFF
CRF₉₋₄₁ (Irwin et al., 1987). This action can be observed
10 minutes after i.c.v. injection and persists for ≤ 60 **NEMEROFF**
CRF₉₋₄₁ (Irwin et al., 1987). This action can be observed
10 minutes after i.c.v. injection and persists for <60
minutes following injection, although plasma corticoster-NEMEROFF
CRF₉₋₄₁ (Irwin et al., 1987). This action can be obse
10 minutes after i.c.v. injection and persists for
minutes following injection, although plasma cortico
one concentrations remained elevated for some CRF₉₋₄₁ (Irwin et al., 1987). This action can be observed
10 minutes after i.c.v. injection and persists for ≤ 60
minutes following injection, although plasma corticoster-
one concentrations remained elevated for so 10 minutes after i.c.v. injection and persists for ≤ 60 minutes following injection, although plasma corticosterone concentrations remained elevated for some time (Irwin et al., 1989). This suggests that these actions 10 minutes after i.c.v. injection and persists for \lt minutes following injection, although plasma corticost
one concentrations remained elevated for some tin
(Irwin et al., 1989). This suggests that these actions a
not minutes following injection, although plasma corticoster
one concentrations remained elevated for some tim
(Irwin et al., 1989). This suggests that these actions ar
not mediated by glucocorticoids. Moreover, these reduc
ti one concentrations remained elevated for some (Irwin et al., 1989). This suggests that these action not mediated by glucocorticoids. Moreover, these retions in NK activity are also observed following shock stress and can b (Irwin et al., 1989). This suggests that these actions are
not mediated by glucocorticoids. Moreover, these reduc-
tions in NK activity are also observed following foot-
shock stress and can be blocked by central administr not mediated by glucocorticoids. Moreover, these reductions in NK activity are also observed following footshock stress and can be blocked by central administration of CRF antiserum (Irwin et al., 1990). Finally, this effe tions in NK activity are also observed following footshock stress and can be blocked by central administration of CRF antiserum (Irwin et al., 1990). Finally, this effect of CRF on NK activity is blocked by the ganglionic shock stress and can be blocked by central administration of CRF antiserum (Irwin et al., 1990). Finally, this effect of CRF on NK activity is blocked by the ganglionic blocking agent, chlorisondamine (Irwin et al., 1988). tion of CRF antiserum (Irwin et al., 1990). Finally, this
effect of CRF on NK activity is blocked by the ganglionic
blocking agent, chlorisondamine (Irwin et al., 1988).
Overall, these exciting findings suggest that, under effect of CRF on NK activity is blocked by the ganglionic
blocking agent, chlorisondamine (Irwin et al., 1988).
Overall, these exciting findings suggest that, under cer-
tain stressful conditions, specific CRF neurons, lik blocking agent, chlorisondamine (Irwin et al., 1988).
Overall, these exciting findings suggest that, under certain stressful conditions, specific CRF neurons, likely
extrahypothalamic, activate autonomic outflow to the
spl Overall, these exciting findings suggest that, under certain stressful conditions, specific CRF neurons, likely extrahypothalamic, activate autonomic outflow to the spleen resulting in reductions in the activity of NK cell Irwin et al. (1988, 1990) suggested that this may possibly leen resulting in reductions in the activity of NK cell
win et al. (1988, 1990) suggested that this may possib
e spleen.
Although central CRF systems can decrease NK actival
proposity and possibly lead to a temporary immu

suggests an increased activity of the HPA axis following the spleen.

electroconvulsive treatment. This has not been observed Although central CRF systems can decrease NK activ-

in depressed patients in whom measures of H extrahypothalamic, activate autonomic outflow to the spheen resulting in reductions in the activity of NK cells. Irwin et al. (1988, 1990) suggested that this may possibly be mediated by sympathetic norepinephrine release Irwin et al. (1988, 1990) suggested that this may possibly
be mediated by sympathetic norepinephrine release in
the spleen.
Although central CRF systems can decrease NK active
ity and possibly lead to a temporary immunosup be mediated by sympathetic norepinephrine release in
the spleen.
Although central CRF systems can decrease NK activ-
ity and possibly lead to a temporary immunosuppressive
effect, the inability to mount a proper CRF respon the spleen.
Although central CRF systems can decrease NK act
ity and possibly lead to a temporary immunosuppressi
effect, the inability to mount a proper CRF response m
also lead to potential immune-related problems. Ster
 Although central CRF systems can decrease NK as
ity and possibly lead to a temporary immunosuppres
effect, the inability to mount a proper CRF response
also lead to potential immune-related problems. St
berg et al. (1989a, ity and possibly lead to a temporary immunosuppressive
effect, the inability to mount a proper CRF response may
also lead to potential immune-related problems. Stern-
berg et al. (1989a,b) have evidence that the arthritiseffect, the inability to mount a proper CRF response may
also lead to potential immune-related problems. Stern-
berg et al. (1989a,b) have evidence that the arthritis-
susceptible Lewis strain of rats lack the ability to g also lead to potential immune-related problems. Stern-
berg et al. (1989a,b) have evidence that the arthritis-
susceptible Lewis strain of rats lack the ability to gen-
erate a proper HPA axis response to a given stimulus. berg et al. (1989a,b) have evidence that the arthritis-
susceptible Lewis strain of rats lack the ability to gen-
erate a proper HPA axis response to a given stimulus.
This defect appears to be at the level of CRF gene
exp susceptible Lewis strain of rats lack the ability to generate a proper HPA axis response to a given stimulus.
This defect appears to be at the level of CRF generally expression in the PVN. Their findings suggest that some erate a proper HPA axis response to a given stimul
This defect appears to be at the level of CRF g
expression in the PVN. Their findings suggest that so
diseases characterized by inappropriate or inadequ
immune/inflammator This defect appears to be at the level of CRF gene
expression in the PVN. Their findings suggest that some
diseases characterized by inappropriate or inadequate
immune/inflammatory regulation (e.g., cancer, autoim-
mune di expression in the PVN. Their findings suggest t
diseases characterized by inappropriate or in
immune/inflammatory regulation (e.g., cancer,
mune diseases) may additionally be the result
defects and not immune system defect *2. Actions of cytokinesis of cytokinesis of cytokinesis of cytokines of cytokines on diseases) may additionally be the result of fects and not immune system defects alone.

2. Actions of cytokines on hypothalamic corticot*

immune/inflammatory regulation (e.g., cancer, autoim-
mune diseases) may additionally be the result of CNS
defects and not immune system defects alone.
2. Actions of cytokines on hypothalamic corticotropin-
releasing facto mune diseases) may additionally be the result of CNS
defects and not immune system defects alone.
2. Actions of cytokines on hypothalamic corticotropin-
releasing factor neurons. There is now considerable evi-
dence that e defects and not immune system defects alone.

2. Actions of cytokines on hypothalamic corticotropin-

releasing factor neurons. There is now considerable evi-

dence that elements of the immune system, during times

of str 2. Actions of cytokines on hypothalamic corticotropin-
releasing factor neurons. There is now considerable evi-
dence that elements of the immune system, during times
of stress (e.g., infectious challenge), can stimulate g releasing factor neurons. There is now considerable evi-
dence that elements of the immune system, during times
of stress (e.g., infectious challenge), can stimulate glu-
cocorticoid secretion through activation of the HPA dence that elements of the immune system, during times
of stress (e.g., infectious challenge), can stimulate glu-
cocorticoid secretion through activation of the HPA axis.
This is thought to help provide a means by which t of stress (e.g., infectious challenge), can stimulate glu-
cocorticoid secretion through activation of the HPA axis.
This is thought to help provide a means by which the
body can rapidly activate a stress response to infec cocorticoid secretion through activation of the HPA axis.
This is thought to help provide a means by which the
body can rapidly activate a stress response to infection
as well as modulate immune function. The evidence to
d This is thought to help provide a means by which the
body can rapidly activate a stress response to infection
as well as modulate immune function. The evidence to
date clearly indicates that various lymphokines increase
hy body can ra
as well as m
date clearly
hypothalam
HPA axis.
The earlie well as modulate immune function. The evidence to
the clearly indicates that various lymphokines increase
pothalamic CRF secretion as a means of activating the
PA axis.
The earliest report was that of Woloski et al. (1985)

al., 1990) have found CRF immunoreactivity and CRF stimulation of hypothalamic CRF secretion and not by
mRNA in lymphocytes. CRF may be released from lym-
phocytes to exert local paracrine actions on other im-
et al. (198 date clearly indicates that various lymphokines increase.
hypothalamic CRF secretion as a means of activating the
HPA axis.
The earliest report was that of Woloski et al. (1988)
who reported that both IL-1 and hepatocyte-s hypothalamic CRF secretion as a means of activating th
HPA axis.
The earliest report was that of Woloski et al. (1988
who reported that both IL-1 and hepatocyte-stimulatin
factor stimulated ACTH release from AtT-20 cells. HPA axis.
The earliest report was that of Woloski et al. (1985)
who reported that both IL-1 and hepatocyte-stimulating
factor stimulated ACTH release from AtT-20 cells. How-
ever, in subsequent reports, lymphokine activati The earliest report was that of Woloski et al. (1985)
who reported that both IL-1 and hepatocyte-stimulating
factor stimulated ACTH release from AtT-20 cells. How-
ever, in subsequent reports, lymphokine activation of
plas who reported that both IL-1 and hepatocyte-stimulating
factor stimulated ACTH release from AtT-20 cells. How-
ever, in subsequent reports, lymphokine activation of
plasma HPA axis activity was demonstrated to occur by
stim factor stimulated ACTH release from AtT-20 cells. How-
ever, in subsequent reports, lymphokine activation of
plasma HPA axis activity was demonstrated to occur by
stimulation of hypothalamic CRF secretion and not by
direct ever, in subsequent reports, lymphokine activation of plasma HPA axis activity was demonstrated to occur by stimulation of hypothalamic CRF secretion and not by direct release of adenohypophysial ACTH. Besedovsky et al. (plasma HPA axis activity was demonstrated to occur by
stimulation of hypothalamic CRF secretion and not by
direct release of adenohypophysial ACTH. Besedovsky
et al. (1986) reported that systemic injection of IL-1, but
no stimulation of hypothalamic CRF secretion and not by
direct release of adenohypophysial ACTH. Besedovsky
et al. (1986) reported that systemic injection of IL-1, but
not tumor necrosis factor, IL-2, or γ -interferon, indirect release of adenohypophysial ACTH. Besedovsky
et al. (1986) reported that systemic injection of IL-1, but
not tumor necrosis factor, IL-2, or γ -interferon, in
creased plasma ACTH and glucocorticoid concentrations et al. (1986) reported that systemic injection of IL-1, b
not tumor necrosis factor, IL-2, or γ -interferon, i
creased plasma ACTH and glucocorticoid concentratio
in mice and rats. Rivier et al. (1989) reported that ac
 not tumor necrosis factor, IL-2, or γ -interferon,
creased plasma ACTH and glucocorticoid concentrati
in mice and rats. Rivier et al. (1989) reported that a
vation of the HPA axis by endotoxin (lipopolysacchar
is mediat vation of the HPA axis by endotoxin (lipopolysaccharide) is mediated by activation of IL-1 receptors on hypothalamic CRF cells. A number of different techniques have

CORTICOTROPIN-RELEASING FACTOR 445

CORTICOTROPIN-RE
been used to determine that activation of CRF neurons
is responsible for these actions of lymphokines. Uehara CORTICOTROPIN-REL
been used to determine that activation of CRF neurons
is responsible for these actions of lymphokines. Uehara
et al. (1987) found that IL-1-induced increases in plasma CORTICOTROPIN-REL

is responsible for these actions of lymphokines. Uehara

is responsible for these actions of lymphokines. Uehara

is at al. (1987) found that IL-1-induced increases in plasma

ACTH could be blocked by CR been used to determine that activation of CRF net
is responsible for these actions of lymphokines. U
et al. (1987) found that IL-1-induced increases in pl
ACTH could be blocked by CRF immunoneutraliza
Sapolsky et al. (1987 is responsible for these actions of lymphokines. Uehara
et al. (1987) found that IL-1-induced increases in plasma
ACTH could be blocked by CRF immunoneutralization.
Sapolsky et al. (1987) found similar results with immu-
n et al. (1987) found that IL-1-induced increases in plasma et al. (1987) found that IL-1-induced increases in pla
ACTH could be blocked by CRF immunoneutraliza
Sapolsky et al. (1987) found similar results with im
noneutralization of CRF as well as observing direc
creases in the co ACTH could be blocked by CRF immunoneutralization
Sapolsky et al. (1987) found similar results with immu-
noneutralization of CRF as well as observing direct in-
creases in the concentration of CRF in the hypothala-
mohypo Sapolsky et al. (1987) found similar results with immu-
noneutralization of CRF as well as observing direct in-
creases in the concentration of CRF in the hypothala-
mohypophysial portal vessels after IL-1. Similarly, Bar noneutralization of CRF as well as observing direct in creases in the concentration of CRF in the hypothala mohypophysial portal vessels after IL-1. Similarly, Bar banel et al. (1990), using a push-pull cannula implantee creases in the concentration of CRF in the hypothala-
mohypophysial portal vessels after IL-1. Similarly, Bar-
banel et al. (1990), using a push-pull cannula implanted
in the median eminence, found that intrahypothalamic
 mohypophysial portal vessels after IL-1. Similarly, Bar-
banel et al. (1990), using a push-pull cannula implanted
in the median eminence, found that intrahypothalamic
infusion of IL-1 β directly stimulates release of CR banel et al. (1990), using a push-pull cannula implanted
in the median eminence, found that intrahypothalamic
infusion of IL-1 β directly stimulates release of CRF
Further evidence has recently come from Suda et al
(199 in the median eminence, found that intrahypothalam
infusion of IL-1 β directly stimulates release of CR
Further evidence has recently come from Suda et a
(1990) who also found increases in plasma ACTH co
centrations fol infusion of IL-1 β directly stimulates release of CRF.
Further evidence has recently come from Suda et al.
(1990) who also found increases in plasma ACTH concentrations following injection of IL-1 α or IL-1 β . More-Further evidence has recently come from Suda et al. after (1990) who also found increases in plasma ACTH con-
centrations following injection of IL-1 α or IL-1 β . More-
cular over, concomitant decreases in the content (1990) who also found increases in plasma ACTH concentrations following injection of IL-1 α or IL-1 β . Moreover, concomitant decreases in the content of median eminence CRF and increases in CRF mRNA in the PVN were ob centrations following injection of IL-1 α or IL-1 β . Moreover, concomitant decreases in the content of median eminence CRF and increases in CRF mRNA in the PVN were observed. Finally, a preliminary report of 30 cancer over, concomitant decreases in the content of median
eminence CRF and increases in CRF mRNA in the PVN
were observed. Finally, a preliminary report of 30 cancer
patients receiving immunotherapy with IL-2 or IL-2 plus
lymph eminence CRF and increases in CRF mRNA in the PVN
were observed. Finally, a preliminary report of 30 cancer
patients receiving immunotherapy with IL-2 or IL-2 plus
lymphokine-activated killer cells suggests that IL-2 can
a were observed. Finally, a preliminary report of 30 cancer
patients receiving immunotherapy with IL-2 or IL-2 plus
lymphokine-activated killer cells suggests that IL-2 can
also profoundly activate the HPA axis (Denicoffet a lymphokine-activated killer cells suggests that IL-2 can
also profoundly activate the HPA axis (Denicoffet al.,
1989). Whether this is through stimulation of CRF se-
cretion has yet to be determined.
Although reservations mphokine-activated killer cells suggests that IL-2 can
so profoundly activate the HPA axis (Denicoffet al.,
89). Whether this is through stimulation of CRF se-
etion has yet to be determined.
Although reservations exist re

also profoundly activate the HPA axis (Denicoffet al., p. 1989). Whether this is through stimulation of CRF section has yet to be determined.
Although reservations exist regarding the confidence that can be placed on in v 1989). Whether this is through stimulation of CRF se-
cretion has yet to be determined. The end of the results obtained also
that can be placed on in vitro incubation studies because
of problems of tissue viability, the r cretion has yet to be determined.
Although reservations exist regarding the confidence
that can be placed on in vitro incubation studies because
of problems of tissue viability, the results obtained also
support the hypoth Although reservations exist regarding the confidence
that can be placed on in vitro incubation studies because
of problems of tissue viability, the results obtained also
support the hypothesis that CRF neurons mediate lym that can be placed on in vitro incubation studies because
of problems of tissue viability, the results obtained also
support the hypothesis that CRF neurons mediate lym-
phokine activation of the HPA axis. Tsagarakis et a of problems of tissue viability, the results obtained also
support the hypothesis that CRF neurons mediate lym-
phokine activation of the HPA axis. Tsagarakis et al.
(1989a) reported that both IL-1 α and IL-1 β stimul support the hypothesis that CRF neurons mediate lym-
phokine activation of the HPA axis. Tsagarakis et al.
(1989a) reported that both IL-1 α and IL-1 β stimulated
CRF release from isolated hypothalamic blocks in vitro phokine activation of the HPA axis. Tsagarakis et al.

(1989a) reported that both IL-1 α and IL-1 β stimulated

CRF release from isolated hypothalamic blocks in vitro.

Similar findings were reported by Bernardini et phokine activation of the HPA axis. Isagarakis et al.

(1989a) reported that both IL-1 α and IL-1 β stimulated

CRF release from isolated hypothalamic blocks in vitro.

Similar findings were reported by Bernardini et CRF release from isolated hypothalamic blocks in vitro.

Similar findings were reported by Bernardini et al.

(1990a) who proposed that IL-1's actions were mediated

by arachidonic acid metabolites. In fact, they suggeste Similar findings were reported by Bernardini et al.

(1990a) who proposed that IL-1's actions were mediated

by arachidonic acid metabolites. In fact, they suggested

that arachidonic acid metabolites may be responsible f (1990a) who proposed that IL-1's actions were media
by arachidonic acid metabolites. In fact, they sugges
that arachidonic acid metabolites may be responsible
the actions of a number of neurotransmitters on C
release inclu by arachidonic acid metabolites. In fact, they suggested
that arachidonic acid metabolites may be responsible for
the actions of a number of neurotransmitters on CRF
release including serotonin and acetylcholine (Bernar-
d that arachidonic acid metabolites may be responsible for the actions of a number of neurotransmitters on CR release including serotonin and acetylcholine (Berna dini et al., 1989b). Navarra et al. (1991) reported the both the actions of a number of neurotransmitters on CRF
release including serotonin and acetylcholine (Bernar-
dini et al., 1989b). Navarra et al. (1991) reported that
both IL-1 and IL-6 stimulated CRF release from hypo-
thala release including serotonin and acetylcholine (Bernardini et al., 1989b). Navarra et al. (1991) reported that both IL-1 and IL-6 stimulated CRF release from hypothalamic explants, but not from median eminences alone, in vi dini et al., 1989b). Navarra et al. (1991) reported
both IL-1 and IL-6 stimulated CRF release from h
thalamic explants, but not from median eminences al
in vitro. They found that these actions were antagon
by blockade of t both IL-1 and IL-6 stimulated CRF release from hypo-
thalamic explants, but not from median eminences alone,
in vitro. They found that these actions were antagonized
by blockade of the cyclooxygenase, but not lipooxygen-
 thalamic explants, but not from median eminences alone,
in vitro. They found that these actions were antagonized
by blockade of the cyclooxygenase, but not lipooxygen-
ase, pathway. Neither IL-2, tumor necrosis factor, $\$ in vitro. They found that these actions were antagonized
by blockade of the cyclooxygenase, but not lipooxygen-
ase, pathway. Neither IL-2, tumor necrosis factor, α_2 -
interferon, nor γ -interferon altered CRF or ACT by blockade of the cyclooxygenase, but not lipooxyge
ase, pathway. Neither IL-2, tumor necrosis factor, ϕ
interferon, nor γ -interferon altered CRF or ACTH
lease. In contrast to the above results, Bernardini et
(1990 ase, pathway. Neither IL-2, tumor necrosis factor, α_2 -
interferon, nor γ -interferon altered CRF or ACTH re-
lease. In contrast to the above results, Bernardini et al.
(1990b) reported that tumor necrosis factor doe interferon, nor γ -interferon altered CRF or ACTH re-
lease. In contrast to the above results, Bernardini et al.
(1990b) reported that tumor necrosis factor does stimu-
late CRF release both in vivo and in vitro. In thi lease. In contrast to the above results, Bernardini et al. (1990b) reported that tumor necrosis factor does stimulate CRF release both in vivo and in vitro. In this case, CRF release was inhibited by both cyclooxygenase an (1990b) reported that tumor necrosis factor does stimulate CRF release both in vivo and in vitro. In this case, CRF release was inhibited by both cyclooxygenase and lipooxygenase inhibitors. Finally, platelet-activating f late CRF release both in vivo and in vitro. In this case,
CRF release was inhibited by both cyclooxygenase and
lipooxygenase inhibitors. Finally, platelet-activating fac-
tor has been reported to stimulate CRF release bot CRF release was inhibited by both cyclooxygenase ilpooxygenase inhibitors. Finally, platelet-activating tor has been reported to stimulate CRF release both vivo (Rougeot et al., 1990) and in vitro (Bernardin al., 1989a). R lipooxygenase inhibitors. Finally, platelet-activating factor has been reported to stimulate CRF release both in vivo (Rougeot et al., 1990) and in vitro (Bernardini et al., 1989a). Rougeot et al. (1990) reported that plat tor has been reported to stimulate CR vivo (Rougeot et al., 1990) and in viti
al., 1989a). Rougeot et al. (1990) repor
activating factor acts directly on the r
rather than on perikarya in the PVN.
B. Anglassis and Anti-Inf *B.* Analysis (Rougeot et al., 1990) and in vitro (Bernardini et al., 1989a). Rougeot et al. (1990) reported that platelet-activating factor acts directly on the median eminence rather than on perikarya in the PVN.
B. Ana

Corticotropin-releasing Factor

ther than on perikarya in the PVN. (19

Analgesic and Anti-Inflammatory Properties of minimator

inticotropin-releasing Factor models

Although the mechanism(s) responsible has not been me

termined, Wei and colleagues hav B. Analgesic and Anti-Inflammatory Properties of metastaple control of the control of the control of the method of the metho

LEASING FACTOR
that CRF and related peptides (i.e., sauvagine and uro-
tensin I) possess analgesic and anti-inflammatory prop-LEASING FACTOR
that CRF and related peptides (i.e., sauvagine and ur
tensin I) possess analgesic and anti-inflammatory pro
erties (Wei and Kiang, 1989). Increased exudation 445
that CRF and related peptides (i.e., sauvagine and uro-
tensin I) possess analgesic and anti-inflammatory prop-
erties (Wei and Kiang, 1989). Increased exudation of
plasma proteins into the rat paw produced by antidrom that CRF and related peptides (i.e., sauvagine and urotensin I) possess analgesic and anti-inflammatory properties (Wei and Kiang, 1989). Increased exudation of plasma proteins into the rat paw produced by antidromic stimu that CRF and related peptides (i.e., sauvagine and uro-
tensin I) possess analgesic and anti-inflammatory prop-
erties (Wei and Kiang, 1989). Increased exudation of
plasma proteins into the rat paw produced by antidromic
s tensin I) possess analgesic and anti-inflammatory properties (Wei and Kiang, 1989). Increased exudation of plasma proteins into the rat paw produced by antidromic stimulation of the saphenous nerve has been termed neurogen erties (Wei and Kiang, 1989). Increased exudation of
plasma proteins into the rat paw produced by antidromic
stimulation of the saphenous nerve has been termed
neurogenic plasma extravasation and is inhibited by a
number o plasma proteins into the rat paw produced by antidromic
stimulation of the saphenous nerve has been termed
neurogenic plasma extravasation and is inhibited by a
number of opiate analgesics. CRF inhibited neurogenic
plasma stimulation of the saphenous nerve has been termed
neurogenic plasma extravasation and is inhibited by a
number of opiate analgesics. CRF inhibited neurogenic
plasma extravasation in both hypophysectomized and
adrenalecto neurogenic plasma extravasation and is inhibited b
number of opiate analgesics. CRF inhibited neuroge
plasma extravasation in both hypophysectomized a
adrenalectomized rats, indicating that the effects are
secondary to re number of opiate analgesics. CRF inhibited neurogenic
plasma extravasation in both hypophysectomized and
adrenalectomized rats, indicating that the effects are not
secondary to release of ACTH, β -endorphin, or glucocor plasma extravasation in both hypophysectomized and
adrenalectomized rats, indicating that the effects are not
secondary to release of ACTH, β -endorphin, or glucocor-
ticoids (Wei et al., 1986). These effects were also adrenalectomized rats, indicating that the effects are not secondary to release of ACTH, β -endorphin, or glucocorticoids (Wei et al., 1986). These effects were also seen after local intradermal injection of very small secondary to release of ACTH, β -endorphin, or glucocorticoids (Wei et al., 1986). These effects were also seen after local intradermal injection of very small doses of CRF into the innervated paw. Similarly, increased ticoids (Wei et al., 1986). These effects were also seen
after local intradermal injection of very small doses of
CRF into the innervated paw. Similarly, increased vas-
cular permeability in the trachea following antidromi after local intradermal injection of very small doses of CRF into the innervated paw. Similarly, increased vascular permeability in the trachea following antidromic stimulation of the right vagus nerve or exposure to forma CRF into the innervated paw. Similarly
cular permeability in the trachea follow
stimulation of the right vagus nerve or en
maldahyde vapors is also attenuated by
administration (Wei and Kiang, 1987).
Thermal injury (Kiang lar permeability in the trachea following antidromic
imulation of the right vagus nerve or exposure to for-
aldahyde vapors is also attenuated by peripheral CRF
ministration (Wei and Kiang, 1987).
Thermal injury (Kiang and

stimulation of the right vagus nerve or exposure to for-
maldahyde vapors is also attenuated by peripheral CRF
administration (Wei and Kiang, 1987).
Thermal injury (Kiang and Wei, 1987; Wei et al., 1988)
and exposure to co maldahyde vapors is also attenuated by peripheral CRF
administration (Wei and Kiang, 1987).
Thermal injury (Kiang and Wei, 1987; Wei et al., 1988)
and exposure to concentrated acids (Tian and Wei, 1989)
produce protein ext administration (Wei and Kiang, 1987).
Thermal injury (Kiang and Wei, 1987; Wei et al., 1988)
and exposure to concentrated acids (Tian and Wei, 1989)
produce protein extravasation and edema into the rat
paw as part of the a Thermal injury (Kiang and Wei, 1987; Wei et al., 1988)
and exposure to concentrated acids (Tian and Wei, 1989)
produce protein extravasation and edema into the rat
paw as part of the acute inflammatory response; the
effect and exposure to concentrated acids (Tian and Wei, 19
produce protein extravasation and edema into the
paw as part of the acute inflammatory response;
effects of both noxious agents are attenuated by C
When administered i.v produce protein extravasation and edema into the
paw as part of the acute inflammatory response; if
effects of both noxious agents are attenuated by CI
When administered i.v. in microgram doses or intrad
mally in nanogram paw as part of the acute inflammatory response; the
effects of both noxious agents are attenuated by CRF.
When administered i.v. in microgram doses or intrader-
mally in nanogram doses, CRF is effective when admin-
istered effects of both noxious agents are attenuated by CRF.
When administered i.v. in microgram doses or intrader-
mally in nanogram doses, CRF is effective when admin-
istered up to 4 hours prior to or 20 minutes following
expo When administered i.v. in microgram doses or intradermally in nanogram doses, CRF is effective when administered up to 4 hours prior to or 20 minutes following exposure to the noxious stimuli. These actions of CRF are com mally in nanogram doses, CRF is effective when administered up to 4 hours prior to or 20 minutes following
exposure to the noxious stimuli. These actions of CRF
are completely abolished by administration of the CRF
antago istered up to 4 hours prior to or 20 minutes following
exposure to the noxious stimuli. These actions of CRF
are completely abolished by administration of the CRF
antagonist, α -helical CRF₉₋₄₁. These investigators su exposure to the noxious stimuli. These actions are completely abolished by administration of the antagonist, α -helical CRF₉₋₄₁. These investigato gested that CRF acts directly on endothelial cells the local vascular e completely abolished by administration of the CRF
tagonist, α -helical CRF₉₋₄₁. These investigators sug-
sted that CRF acts directly on endothelial cells lining
e local vascular system near the site of injury.
Becau stimulation of the right vagus nerve or exposure to formal
administration (Wei and Kiang, 1987), and the mail of the significant and Wei, 1988) and exposure to concentrated acids (Tian and Wei, 1988)
Thermal injury (Kiang

antagonist, α -helical CRF₉₋₄₁. These investigators suggested that CRF acts directly on endothelial cells lining
the local vascular system near the site of injury.
Because CRF stimulates the release of β -endorphin
 gested that CRF acts directly on endothelial cells lining
the local vascular system near the site of injury.
Because CRF stimulates the release of β -endorphin
during a stress response, it was hypothesized that CRF
admi the local vascular system near the site of injury.
Because CRF stimulates the release of β -endorphin
during a stress response, it was hypothesized that CRF
administration may possess indirect analgesic properties
throu Because CRF stimulates the release of β -endorphin
during a stress response, it was hypothesized that CRF
administration may possess indirect analgesic properties
through an endogenous peripheral opioid system. In fact, during a stress response, it was hypothesized that C.
administration may possess indirect analgesic propert
through an endogenous peripheral opioid system. In fa
Hargreaves et al. (1987) reported that, in humans
covering f through an endogenous peripheral opioid system. In fact, Hargreaves et al. (1987) reported that, in humans recovering from molar extraction, exogenous CRF administration resulted in significant analgesia compared to placeb Hargreaves et al. (1987) reported that, in humans recovering from molar extraction, exogenous CRF administration resulted in significant analgesia compared to placebo. Moreover, in the rat paw-lick test, CRF produced analg covering from molar extraction, exogenous CRF administration resulted in significant analgesia compared to placebo. Moreover, in the rat paw-lick test, CRF produced analgesia comparable in length and intensity to that of m istration resulted in significant analgesia compared to
placebo. Moreover, in the rat paw-lick test, CRF pro-
duced analgesia comparable in length and intensity to
that of morphine. They later found that the analgesic
prop placebo. Moreover, in the rat paw-lick test, CRF pro-
duced analgesia comparable in length and intensity to
that of morphine. They later found that the analgesic
properties are not attenuated by hypophysectomy or
adrenalec duced analgesia comparable in length and intensity to
that of morphine. They later found that the analgesic
properties are not attenuated by hypophysectomy or
adrenalectomy and are present when injected locally
(Hargreaves that of morphine. They later found that the analgesic
properties are not attenuated by hypophysectomy or
adrenalectomy and are present when injected locally
(Hargreaves et al., 1989). This is in contrast to their
most rece properties are not attenuated by hypophysectomy adrenalectomy and are present when injected local (Hargreaves et al., 1989). This is in contrast to the most recent report (Hargreaves et al., 1990) in which thantinociceptiv adrenalectomy and are present when injected locally (Hargreaves et al., 1989). This is in contrast to their most recent report (Hargreaves et al., 1990) in which the antinociceptive actions of CRF were abolished by hypoph (Hargreaves et al., 1989). This is in contrast to th
most recent report (Hargreaves et al., 1990) in which
antinociceptive actions of CRF were abolished by hyp
physectomy, dexamethasone, naltrexone, naltrexone
methyl brom most recent report (Hargreaves et al., 1990) in which the antinociceptive actions of CRF were abolished by hypophysectomy, dexamethasone, naltrexone, naltrexone methyl bromide, and immunoneutralization of β -endorphin, antinociceptive actions of CRF were abolished by hypo-
physectomy, dexamethasone, naltrexone, naltrexone
methyl bromide, and immunoneutralization of β -endor-
phin, observations that would clearly favor a role for
endog physectomy, dexamethasone, naltrexone, naltrexone
methyl bromide, and immunoneutralization of β -endor-
phin, observations that would clearly favor a role for
endogenous opioids in mediating these analgesic effects.
In methyl bromide, and immunoneutralization of β -endor-
phin, observations that would clearly favor a role for
endogenous opioids in mediating these analgesic effects.
In contrast to these findings, Ayesta and Nikolarakis endogenous opioids in mediating these analgesic effects.
In contrast to these findings, Ayesta and Nikolarakis
(1989) found that the analgesic effects of peripherally
administered CRF were not modified by naloxone ad-
mini endogenous opioids in mediating these analgesic effects.
In contrast to these findings, Ayesta and Nikolarakis
(1989) found that the analgesic effects of peripherally
administered CRF were not modified by naloxone ad-
mini In contrast to these findings, Ayesta and Nikolarakis (1989) found that the analgesic effects of peripherally administered CRF were not modified by naloxone administration nor in rats previously rendered tolerant to morphi (1989) found that the analgesic effects of peripherally administered CRF were not modified by naloxone administration nor in rats previously rendered tolerant to morphine. These findings suggest that opioids do not mediate administered CRF were not modified by naloxone administration nor in rats previously rendered tolerant to morphine. These findings suggest that opioids do not mediate CRF-induced antinociception. In trying to determine the

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que that that, when recording from the spinal trigeminal
reported that, when recording from the spinal trigeminal
nucleus, CRF dose dependently inhibited the evoked owens and networks

nucleus, CRF dose dependently inhibited the evoked

response of these cells following exposure to thermal owend that, when recording from the spinal trigeminal
nucleus, CRF dose dependently inhibited the evoked
response of these cells following exposure to thermal
injury. Again, these responses were unaltered by hyporeported that, when recording from the spinal trigemin
nucleus, CRF dose dependently inhibited the evoke
response of these cells following exposure to thermi
injury. Again, these responses were unaltered by hypo-
physectom reported that, when recording from the spinal trigeminal
nucleus, CRF dose dependently inhibited the evoked
response of these cells following exposure to thermal
injury. Again, these responses were unaltered by hypo-
physe nucleus, CRF dose dependently inhibited the evoked
response of these cells following exposure to thermal
injury. Again, these responses were unaltered by hypo-
physectomy or adrenalectomy. These effects did not oc-
cur fol response of these cells following exposure to therm
injury. Again, these responses were unaltered by hypp
physectomy or adrenalectomy. These effects did not o
cur following i.c.v. administration and were abolished b
periph injury. Again, these responses were unaltered by hypo
physectomy or adrenalectomy. These effects did not oc
cur following i.c.v. administration and were abolished by
peripheral administration of the CRF antagonist. Inter
e cur following i.c.v. administration and were abolished by
peripheral administration of the CRF antagonist. Inter-
estingly, CRF increased the spontaneous firing of cold-
responsive units by 57%, suggesting that CRF selecti peripheral administration of the CRF antagonist. Interripheral administration of the CRF antagonist. Inter-
tingly, CRF increased the spontaneous firing of cold-
sponsive units by 57%, suggesting that CRF selectively
hibits neuronal responses to noxious heat.
In summary, CRF

estingly, CRF increased the spontaneous firing of cold-
responsive units by 57%, suggesting that CRF selectively
inhibits neuronal responses to noxious heat.
In summary, CRF appears to exert anti-inflammatory
and analgesic and analgesic properties that may be partly mediated by
the HPA axis and partly independently. The anti-inflam-
matory properties may result from direct interaction of
CRF with endothelial cells lining blood vessels. As de matory properties may result from direct interaction of In summary, CRF appears to exert anti-inflammatory
and analgesic properties that may be partly mediated by
the HPA axis and partly independently. The anti-inflam-
matory properties may result from direct interaction of
CRF and analgesic properties that may be partly mediated by
the HPA axis and partly independently. The anti-inflam-
matory properties may result from direct interaction of
CRF with endothelial cells lining blood vessels. As de the HPA axis and partly independently. The anti-inflam-
matory properties may result from direct interaction of
CRF with endothelial cells lining blood vessels. As de-
scribed earlier, there was a report of CRF receptors o matory properties may result from direct interaction of CRF with endothelial cells lining blood vessels. As described earlier, there was a report of CRF receptors on aortic endothelial tissues. A second possibility involve CRF with endothelial cells lining blood vessels. As described earlier, there was a report of CRF receptors on aortic endothelial tissues. A second possibility involves the direct interaction of CRF with leukocytes infiltra aortic endothelial tissues. A second possibility involves
the direct interaction of CRF with leukocytes infiltrating
the area of injury. The analgesic effects appear to be the
result of direct alterations of sensory neuron aortic endothelial tissues. A second possibility involves
the direct interaction of CRF with leukocytes infiltrating
the area of injury. The analgesic effects appear to be the
result of direct alterations of sensory neuron the direct interaction of CRF with leukocytes infiltratin
the area of injury. The analgesic effects appear to be th
result of direct alterations of sensory neurons that re
spond to pain. Alternatively, interactions with im the area of injury. The analgesic effects appear to be the
result of direct alterations of sensory neurons that re-
spond to pain. Alternatively, interactions with immune
cells and the reduced local production of various p result of direct alterations of sensory neurons the
spond to pain. Alternatively, interactions with in
cells and the reduced local production of various
mediating chemicals or increases in endogenous
secretion may contribu mediating chemicals or increases in endogenous opioid

**Actions V. Corticotropin-releasing Factor Regulation of Autonomic Function and Other Peripheral
A. Cardiovascular Responses to Central and Peripheral
Administration of Corticotropin-releasing Factor** *Autonomic Function and Other Periphera

Actions

<i>A. Cardiovascular Responses to Central and Periphera*
 Administration of Corticotropin-releasing Factor

In concert with the HPA axis response various s

Actions

Cardiovascular Responses to Central and Peripheral

Iministration of Corticotropin-releasing Factor

In concert with the HPA axis response, various stres

rs elicit rapid alterations in autonomic nervous system A. Cardiovascular Responses to Central and Peripheral beds; and ME, not
Administration of Corticotropin-releasing Factor
In concert with the HPA axis response, various stres-
sors elicit rapid alterations in autonomic nerv A. Carawouscular Responses to Central and Peripheral
Administration of Corticotropin-releasing Factor
In concert with the HPA axis response, various stres-
sors elicit rapid alterations in autonomic nervous system
activity Haministration of Corticotropin-reteasing ractor
In concert with the HPA axis response, various stres-
sors elicit rapid alterations in autonomic nervous system ing
activity readying the body for the "fight or flight" re-
 In concert with the HPA axis response, various stres-
sors elicit rapid alterations in autonomic nervous system ing
activity readying the body for the "fight or flight" re-
adr
sponse and inhibiting vegetative functions. A sors elicit rapid alterations in autonomic nervous system in
activity readying the body for the "fight or flight" re-
sponse and inhibiting vegetative functions. As will be to,
discussed, it appears that CRF neurons in the activity readying the body for the "fight or flight" re-
sponse and inhibiting vegetative functions. As will be
discussed, it appears that CRF neurons in the CNS play
an important role in this response. Although we will ci sponse and inhibiting vegetative functions. As will be discussed, it appears that CRF neurons in the CNS play an important role in this response. Although we will cite a number of studies relevant to this topic, the recent an important role in this response. Although we will cite
a number of studies relevant to this topic, the recent
review by Fisher (1989) is more comprehensive (fig. 5).
Following the availability of synthetic CRF, early st

an important role in this response. Although we will cite
a number of studies relevant to this topic, the recent
review by Fisher (1989) is more comprehensive (fig. 5).
Following the availability of synthetic CRF, early st a number of studies relevant to this topic, the recent by
review by Fisher (1989) is more comprehensive (fig. 5). i.c.
Following the availability of synthetic CRF, early stud-
MA
ies found that relatively high doses of CRF review by Fisher (1989) is more comprehensive (fig. 5). in Following the availability of synthetic CRF, early studies found that relatively high doses of CRF, administered riv., produced vasodilation and hypotension. In do Following the availability of synthetic CRF, early stud-
ies found that relatively high doses of CRF, administered
i.v., produced vasodilation and hypotension. In dogs, a
decrease in MAP was associated with a rebound incre ies found that relatively high doses of CRF, administered ringly, roduced vasodilation and hypotension. In dogs, a to decrease in MAP was associated with a rebound increase phin heart rate that followed an increase in mese i.v., produced vasodilation and hypotension. In dogs, a to decrease in MAP was associated with a rebound increase ph
in heart rate that followed an increase in mesenteric bl
blood flow (Lenz et al., 1985). Similar findings decrease in MAP was associated with a rebound increase
in heart rate that followed an increase in mesenteri
blood flow (Lenz et al., 1985). Similar findings wer
reported in rats (Kiang and Wei, 1985), monkeys (Kali
et al., in heart rate that followed an increase in mesenteric blood flow (Lenz et al., 1985). Similar findings were Fisl
reported in rats (Kiang and Wei, 1985), monkeys (Kalin min
et al., 1983b; Udelsman et al., 1986a), and humans blood flow (Lenz et al., 1985). Similar findings were Fiveported in rats (Kiang and Wei, 1985), monkeys (Kalin
et al., 1983b; Udelsman et al., 1986a), and humans (Her-
et al., 1987). In contrast, Kalin et al. (1983a) did
u reported in rats (Kiang and Wei, 1985), monkeys (Kalinnet al., 1983b; Udelsman et al., 1986a), and humans (Hermus et al., 1987). In contrast, Kalinnet al. (1983a) didnot observe any such effect in sheep when oCRF was leadm et al., 1983b; Udelsman et al., 1986a), and humans (Her-
mus et al., 1987). In contrast, Kalin et al. (1983a) did
not observe any such effect in sheep when oCRF was
administered, although the oCRF did produce a profound
en mus et al., 1987). In contrast, Kalin et al. (1983a) did
not observe any such effect in sheep when oCRF was
administered, although the oCRF did produce a profound
endocrine response. This finding is difficult to explain
b not observe any such effect in sheep when oCRF was
administered, although the oCRF did produce a profound 198
endocrine response. This finding is difficult to explain are
because the hypotensive actions of CRF are hypothe administered, although the oCRF did produce a profound 19

endocrine response. This finding is difficult to explain an

because the hypotensive actions of CRF are hypothesized

to be mediated by increased β -endorphin s endocrine response. This finding is difficult to explain
because the hypotensive actions of CRF are hypothesized
to be mediated by increased β -endorphin secretion, and
this was observed in the sheep. Whether there actu because the hypotensive actions of CRF are hypothesized
to be mediated by increased β -endorphin secretion, and
this was observed in the sheep. Whether there actually
is species selectivity in CRF-induced hypotension or this was observed in the sheep. Whether there actually
is species selectivity in CRF-induced hypotension or
different species-specific responses to oCRF versus rat/
human CRF has not been further studied.

The cells and the reduced local production of various pain-

FIG. 5. Some of the autonomic actions of CRF. When released

mediating chemicals or increases in endogenous opioid

secretion may contribute to the observed acti WE

WE

FIG. 5. Some of the autonomic actions of CRF. When released

within the hypophysiotropic zone, CRF is transported to the pituitary

where it stimulates secretion of ACTH, which in turn elicits glucocor-FIG. 5. Some of the autonomic actions of CRF. When releaseithin the hypophysiotropic zone, CRF is transported to the pituit, where it stimulates secretion of ACTH, which in turn elicits glucocorroricoid (GC) release from t FIG. 5. Some of the autonomic actions of CRF. When release within the hypophysiotropic zone, CRF is transported to the pitu where it stimulates secretion of ACTH, which in turn elicits gluce ticoid (GC) release from the ad FIG. 5. Some of the autonomic actions of CRF. When released
within the hypophysiotropic zone, CRF is transported to the pituitary
where it stimulates secretion of ACTH, which in turn elicits glucocor-
ticoid (GC) release within the hypophysiotropic zone, CRF is transported to the pituitary
where it stimulates secretion of ACTH, which in turn elicits glucocor-
ticoid (GC) release from the adrenal cortex. Anatomical, pharmacolog-
ical, and p where it stimulates secretion of ACTH, which in turn elicits glucoce
ticoid (GC) release from the adrenal cortex. Anatomical, pharmacole
ical, and physiological data support the notion that CRF acts
additional CNS sites to ticoid (GC) release from the adrenal cortex. Anatomical, pharmacolog-
ical, and physiological data support the notion that CRF acts at
additional CNS sites to (a) stimulate sympathetic tone to the adrenal
medulla, resultin ical, and physiological data support the notion that CRF acts at additional CNS sites to (*a*) stimulate sympathetic tone to the adrenal medulla, resulting in epinephrine (epi) secretion; (*b*) stimulate sympathetic noradr medulla, resulting in epinephrine (epi) secretion; (b) stimulate sympthetic noradrenergic outflow to the heart, kidney, and selected vasculated beds; and (c) inhibit cardiac parasympathetic (ACh) nervous activit NE, norepi itic noradrenergic outflow to the heart, kidney, and selected vascula
ls; and (c) inhibit cardiac parasympathetic (ACh) nervous activity
c, norepinephrine. Reprinted with permission from Fisher (1989).
Of considerably grea

beds; and (c) inhibit cardiac parasympathetic (ACh) nervous activity.
NE, norepinephrine. Reprinted with permission from Fisher (1989).
Of considerably greater interest is the repeated find-
ings of increased MAP and heart NE, norepinephrine. Reprinted with permission from Fisher (1989).
Of considerably greater interest is the repeated find-
ings of increased MAP and heart rate following central
administration of the peptide, actions that ar Of considerably greater interest is the repeated find-
ings of increased MAP and heart rate following central
administration of the peptide, actions that are not related
to, and are clearly separate from, activation of th Of considerably greater interest is the repeated find-
ings of increased MAP and heart rate following central
administration of the peptide, actions that are not related
to, and are clearly separate from, activation of the ings of increased MAP and heart rate following central
administration of the peptide, actions that are not related
to, and are clearly separate from, activation of the HPA
axis. Initial work by Brown and colleagues (Brown administration of the peptide, actions that are not related
to, and are clearly separate from, activation of the HPA
axis. Initial work by Brown and colleagues (Brown and
Fisher, 1983; Fisher and Brown, 1984) and subsequen to, and are clearly separate from, activation of the HPA
axis. Initial work by Brown and colleagues (Brown and
Fisher, 1983; Fisher and Brown, 1984) and subsequently
by others (Saunders and Thornhill, 1986) found that
i.c. Fisher, 1983; Fisher and Brown, 1984) and subsequently
by others (Saunders and Thornhill, 1986) found that
i.c.v. administration of CRF resulted in increases in
MAP, heart rate, plasma norepinephrine, and epineph-
rine. Th Fisher, 1983; Fisher and Brown, 1984) and subsequently
by others (Saunders and Thornhill, 1986) found that
i.c.v. administration of CRF resulted in increases in
MAP, heart rate, plasma norepinephrine, and epineph-
rine. Th by others (Saunders and Thornhill, 1986) found that
i.c.v. administration of CRF resulted in increases in
MAP, heart rate, plasma norepinephrine, and epineph-
rine. These effects, consistent with adaptive responses
to thre i.c.v. administration of CRF resulted in increases in MAP, heart rate, plasma norepinephrine, and epinephrine. These effects, consistent with adaptive responses to threatening situations, are not the result of increased ph MAP, heart rate, plasma norepinephrine, and epinephrine. These effects, consistent with adaptive responses to threatening situations, are not the result of increased physical activity (Overton and Fisher, 1989a) and can be rine. These effects, consistent with adaptive responses
to threatening situations, are not the result of increased
physical activity (Overton and Fisher, 1989a) and can be
blocked by chlorisondamine (Brown and Fisher, 198 to threatening situations, are not the result of increased
physical activity (Overton and Fisher, 1989a) and can be
blocked by chlorisondamine (Brown and Fisher, 1983;
Fisher and Brown, 1984; Lenz et al., 1987) or i.c.v a physical activity (Overton and Fisher, 1989a) and can be blocked by chlorisondamine (Brown and Fisher, 1983; Fisher and Brown, 1984; Lenz et al., 1987) or i.c.v administration of the antagonist α -helical CRF₉₋₄₁ (Bro blocked by chlorisondamine (Brown and Fisher, 1983; Fisher and Brown, 1984; Lenz et al., 1987) or i.c.v administration of the antagonist α -helical CRF₉₋₄₁ (Brown et al., 1986). The response can also be somewhat atten Fisher and Brown, 1984; Lenz et al., 1987) or i.c.v administration of the antagonist α -helical CRF₉₋₄₁ (Brown et al., 1986). The response can also be somewhat attenuated by i.c.v. administration of dynorphin₁₋₁₇ an ministration of the antagonist α -helical CRF₉₋₄₁ (Brown
et al., 1986). The response can also be somewhat atten-
uated by i.c.v. administration of dynorphin₁₋₁₇ and se-
lected dynorphin-related peptides (Overton and et al., 1986). The response can also be somewhat atten-
uated by i.c.v. administration of dynorphin₁₋₁₇ and se-
lected dynorphin-related peptides (Overton and Fisher,
1989b). Under normal circumstances, increases in MAP
 uated by i.c.v. administration of dynorphin₁₋₁₇ and se-
lected dynorphin-related peptides (Overton and Fisher,
1989b). Under normal circumstances, increases in MAP
are associated with decreases in heart rate via activat lected dynorphin-related peptides (Overton and Fisher, 1989b). Under normal circumstances, increases in MAP are associated with decreases in heart rate via activation of the baroreceptor reflex. However, under stressful co 1989b). Under normal circumstances, increases in MAP
are associated with decreases in heart rate via activation
of the baroreceptor reflex. However, under stressful con-
ditions the baroreflex function can be altered such are associated with decreases in heart rate via activation
of the baroreceptor reflex. However, under stressful con-
ditions the baroreflex function can be altered such that
simultaneous elevations of arterial pressure and of the baroreceptor reflex. However, under stressful conditions the baroreflex function can be altered such tha
simultaneous elevations of arterial pressure and hear
rate can occur. Central administration of CRF does no
al ditions the baroreflex function can be altered such that
simultaneous elevations of arterial pressure and heart
rate can occur. Central administration of CRF does not
alter baroreceptor sensitivity; rather, it increases sy

CORTICOTROPIN-RELEA
(Fisher, 1988, 1989; Overton et al. 1990). Increases in A
sympathetic outflow are likely responsible for the eleva- that CORTICOTROPIS
(Fisher, 1988, 1989; Overton et al. 1990). Increases
sympathetic outflow are likely responsible for the elev-
tions in plasma catecholamines and increased MA CORTICOTROPIN-R
(Fisher, 1988, 1989; Overton et al. 1990). Increases in
sympathetic outflow are likely responsible for the eleva-
tions in plasma catecholamines and increased MAP,
whereas diminished vagal tone probably rep (Fisher, 1988, 1989; Overton et al. 1990). Increases in Asympathetic outflow are likely responsible for the elevations in plasma catecholamines and increased MAP, actualisments a implement of the tachycardic response and (Fisher, 1988, 1989; Overton et al. 1990). Increases in sympathetic outflow are likely responsible for the elevations in plasma catecholamines and increased MAP, whereas diminished vagal tone probably represents a large co tions in plasma catecholamines and increased MAP, act
whereas diminished vagal tone probably represents a
large component of the tachycardic response and de-
creased baroreceptor reflex. Attempts to localize the isla
anato whereas diminished vagal tone probably represents a in large component of the tachycardic response and de- (let creased baroreceptor reflex. Attempts to localize the is anatomical sites for this action of CRF have not been large component of the tachycardic response and decreased baroreceptor reflex. Attempts to localize the anatomical sites for this action of CRF have not been successful because CRF microinjection into a number of sites hav creased baroreceptor reflex. Attempts to localize the
anatomical sites for this action of CRF have not been
successful because CRF microinjection into a number of
sites have been found to increase sympathetic outflow,
as d anatomical sites for this action of CRF have not been cases successful because CRF microinjection into a number of less sites have been found to increase sympathetic outflow, 20 as determined by increases in plasma cate ch successful because CRF microinjection into a number of leastics have been found to increase sympathetic outflow, 20 as determined by increases in plasma cate cholamine ga concentrations (Brown, 1986). This could either be sites have been found to increase sympathetic outflow,
as determined by increases in plasma catecholamine
concentrations (Brown, 1986). This could either be the
result of diffusion away from the injection site or, as
sugge as determined by increases in plasma catecholamin
concentrations (Brown, 1986). This could either be th
result of diffusion away from the injection site or, a
suggested by Brown, an anatomical redundancy of re
gions sensit concentrations
result of diffusi
suggested by Bi
gions sensitive t
nomic function.
Finally, Saito sult of diffusion away from the injection site or, as releases all redundancy of re-
gested by Brown, an anatomical redundancy of re-
prons sensitive to CRF and capable of modulating auto-
pronic function.
Finally, Saitoh

suggested by Brown, an anatomical redundancy of regions sensitive to CRF and capable of modulating auto
nomic function.
Finally, Saitoh et al. (1990) recently found that CR.
possessed a positive inotropic effect on guinea gions sensitive to CRF and capable of modulating auto-
nomic function. in the
finally, Saitoh et al. (1990) recently found that CRF
plasma
possessed a positive inotropic effect on guinea pig myo-
remem
cardium in vitro. Th nomic function.

Finally, Saitoh et al. (1990) recently found that C

possessed a positive inotropic effect on guinea pig m

cardium in vitro. This was qualitatively different fi

that produced by cardiac glycosides and wa Finally, Saitoh et al. (1990) recently found that CRF possessed a positive inotropic effect on guinea pig myocardium in vitro. This was qualitatively different from that produced by cardiac glycosides and was hypothesized cardium in vitro. This was qualitatively different from
that produced by cardiac glycosides and was hypothe-
sized to result from an increase in the slow inward Ca^{2+}
current. Although CRF receptors or CRF immunoreaccardium in vitro. This was qualitatively different from
that produced by cardiac glycosides and was hypothe-
sized to result from an increase in the slow inward Ca^{2+}
current. Although CRF receptors or CRF immunoreac-
t that produced by cardiac glycosides and was hypothe-
sized to result from an increase in the slow inward Ca^{2+}
current. Although CRF receptors or CRF immunoreac-
tivity have not been previously demonstrated in the heart sized to result from an increase in the slow inward Ca^{2+} studient. Although CRF receptors or CRF immunoreactivity have not been previously demonstrated in the heart for and because CRF in the systemic circulation does current. Although CRF receptors or CRF immunoreac-
tivity have not been previously demonstrated in the heart
and because CRF in the systemic circulation does not
have a definitive physiological role, these actions on the
o and because CRF in the systemic circulation does not have a definitive physiological role, these actions on the heart would be consistent with a role for CRF in an adaptive circulatory response during the fight or flight syndrome.

Administration

B. Metabolic Responses to Corticotropin-releasing Factor
Administration
As discussed previously, CNS administration of CRF
increases sympathetic outflow. In addition to the in-
creases in circulating plasma catecholamine c B. Metabolic Responses to Corticotropin-releasing Fa
Administration
As discussed previously, CNS administration of t
increases sympathetic outflow. In addition to the
creases in circulating plasma catecholamine concer
tion Administration
As discussed previously, CNS administration of CRF
increases sympathetic outflow. In addition to the in-
creases in circulating plasma catecholamine concentra-
tions associated with increased sympathetic act As discussed previously, CNS administration of CRF
increases sympathetic outflow. In addition to the in-
creases in circulating plasma catecholamine concentra-
tions associated with increased sympathetic activity
i.c.v. CR increases sympathetic outflow. In addition to the increases in circulating plasma catecholamine concentra-
tions associated with increased sympathetic activity,
i.c.v. CRF increases physical activity, total oxygen con-
sum creases in circulating plasma catecholamine concentra-
tions associated with increased sympathetic activity,
i.c.v. CRF increases physical activity, total oxygen con-
sumption, plasma glucose, and glucagon concentrations
(i.c.v. CRF increases physical activity, total oxygen con-
i.c.v. CRF increases physical activity, total oxygen con-
sumption, plasma glucose, and glucagon concentrations Fac
(Brown et al., 1982a,b, 1985). As with the abov i.c.v. CRF increases physical activity, total oxygen consumption, plasma glucose, and glucagon concentrations
(Brown et al., 1982a,b, 1985). As with the above changes
in circulatory physiology, these effects are unrelated sumption, plasma glucose, and glucagon concentrations (Brown et al., 1982a,b, 1985). As with the above changes in circulatory physiology, these effects are unrelated to HPA axis activation and are abolished both by the ga (Brown et al., 1982a,b, 1985). As with the above changes In circulatory physiology, these effects are unrelated to dig HPA axis activation and are abolished both by the ganglionic blocker chlorisondamine (Brown et al., 19 HPA axis activation and are abolished both by the ganglionic blocker chlorisondamine (Brown et al., 1982b) and by central administration of the CRF antagonist, α -helical CRF₉₋₄₁. Moreover, the CRF antagonist also blo glionic blocker chlorisondamine (Brown et al., 1982b) in
and by central administration of the CRF antagonist, α -
helical CRF₉₋₄₁. Moreover, the CRF antagonist also pa
blocks stress-induced increases in plasma epineph and by central administration of the CRF antagonist, α -
helical CRF₉₋₄₁. Moreover, the CRF antagonist also p
blocks stress-induced increases in plasma epinephrine seconcentrations by inhibiting sympathetic outflow to helical CRF₉₋₄₁. Moreover, the CRF antagonist also
blocks stress-induced increases in plasma epinephrine
concentrations by inhibiting sympathetic outflow to the
adrenal (Brown et al., 1985). Central administration of
 $\$ blocks stress-induced increases in plasma epinephrine concentrations by inhibiting sympathetic outflow to the adrenal (Brown et al., 1985). Central administration of α -helical CRF₉₋₄₁ also inhibits the increased oxyg concentrations by inhibiting sympathetic outflow to the concentration of player and (Brown et al., 1985). Central administration of player con-

sumption and sympathetic outflow associated with i.e.v. accommentation of th adrenal (Brown et al., 1985). Central administration of p
 α -helical CRF₉₋₄₁ also inhibits the increased oxygen con-

sumption and sympathetic outflow associated with i.c.v. a

administration of the glucocorticoid an α -helical CRF₉₋₄₁ also inhibits the increased oxygen con-
sumption and sympathetic outflow associated with i.c.v.
administration of the glucocorticoid antagonist, RU-486 k
(Hardwick et al., 1989), suggesting that the sumption and sympathetic outflow associated with i.c.v. acided administration of the glucocorticoid antagonist, RU-486 blook (Hardwick et al., 1989), suggesting that these effects of onis RU-486 are secondary to CRF hypers administration of the glucocorticoid antagonist, RU-486 bl

(Hardwick et al., 1989), suggesting that these effects of or

RU-486 are secondary to CRF hypersecretion. Chronic bu

(7 days) i.c.v. administration of CRF, at do (Hardwick et al., 1989), suggesting that these effects RU-486 are secondary to CRF hypersecretion. Chroice (7 days) i.c.v. administration of CRF, at doses that not alter HPA axis activity, has been shown to abolic the exc RU-486 are secondary to CRF hypersecretion. Chronic (7 days) i.c.v. administration of CRF, at doses that do not alter HPA axis activity, has been shown to abolish the excessive weight gain normally observed in genetically (7 days) i.c.v. administration of CRF, at doses that do ity
not alter HPA axis activity, has been shown to abolish coi
the excessive weight gain normally observed in geneti-
rally obese (fa/fa) rats (Rohner-Jeanrenaud et not alter HPA axis activity, has been shown to abolish
the excessive weight gain normally observed in geneti-
cally obese (fa/fa) rats (Rohner-Jeanrenaud et al., 1989).
This was not related to changes in food intake and l the excessive weight gain normally observed in cally obese (fa/fa) rats (Rohner-Jeanrenaud et al This was not related to changes in food intake are represents changes in sympathetic function whe pears to be dysfunctional

tions in plasma catecholamines and increased MAP, activity in brown fat tissue, i.e., in cells that have been
whereas diminished vagal tone probably represents a implicated in thermogenesis and energy mobilization
large co An electrophysiological study recently demonstrated that i.c.v. CRF directly increases sympathetic nervous 447

An electrophysiological study recently demonstrated

that i.c.v. CRF directly increases sympathetic nervous

activity in brown fat tissue, i.e., in cells that have been

implicated in thermogenesis and energy mobiliza An electrophysiological study recently demonstrated
that i.c.v. CRF directly increases sympathetic nervous
activity in brown fat tissue, i.e., in cells that have been
implicated in thermogenesis and energy mobilization
(Eg An electrophysiological study recently demonstrated
that i.c.v. CRF directly increases sympathetic nervous
activity in brown fat tissue, i.e., in cells that have been
implicated in thermogenesis and energy mobilization
(Eg that i.c.v. CRF directly increases sympathetic nervous
activity in brown fat tissue, i.e., in cells that have been
implicated in thermogenesis and energy mobilization
(Egawa et al., 1990). Acute in vitro exposure of pancre activity in brown fat tissue, i.e., in cells that have been
implicated in thermogenesis and energy mobilization
(Egawa et al., 1990). Acute in vitro exposure of pancreatic
islets of Langerhans to CRF resulted in increased implicated in thermogenesis and energy mobilization (Egawa et al., 1990). Acute in vitro exposure of pancreatic islets of Langerhans to CRF resulted in increased glucagon, but not insulin (Moltz and Fawcett, 1985a), releas (Egawa et al., 1990). Acute in vitro exposure of pancreasilets of Langerhans to CRF resulted in increased g cagon, but not insulin (Moltz and Fawcett, 1985a), lease over a small range of CRF concentrations (50 200 pg/ml; a islets of Langerhans to CRF resulted in increased glu-
cagon, but not insulin (Moltz and Fawcett, 1985a), re-
lease over a small range of CRF concentrations (50 to
200 pg/ml; approximately 10 to 40 pM). These investi-
gato cagon, but not insulin (Moltz and Fawcett, 1985a), re-
lease over a small range of CRF concentrations (50 to
200 pg/ml; approximately 10 to 40 pM). These investi-
gators also reported that CRF inhibited insulin release
fro lease over a small range of CRF concentrations (50 to 200 pg/ml; approximately 10 to 40 pM). These investigators also reported that CRF inhibited insulin release from perfused rat pancreas with no effect on glucagon releas 200 pg/ml; approximately 10 to 40 pM). These investigators also reported that CRF inhibited insulin release from perfused rat pancreas with no effect on glucagon release following i.v. CRF administration (Moltz and Fawcett gators also reported that CRF inhibited insulin release
from perfused rat pancreas with no effect on glucagon
release following i.v. CRF administration (Moltz and
Fawcett, 1985b). In contrast, Torres-Aleman et al. (1984)
r from perfused rat pancreas with no effect on glucagon
release following i.v. CRF administration (Moltz and
Fawcett, 1985b). In contrast, Torres-Aleman et al. (1984)
reported that i.v. CRF increased insulin concentrations
i release following i.v. CRF administration (Moltz and Fawcett, 1985b). In contrast, Torres-Aleman et al. (1984) reported that i.v. CRF increased insulin concentrations in the hepatic portal vein of rats without changing pla Fawcett, 1985b). In contrast, Torres-Aleman et al. (1984)
reported that i.v. CRF increased insulin concentrations
in the hepatic portal vein of rats without changing
plasma glucose or glucagon concentrations. It should be
 reported that i.v. CRF increased insulin concentrations
in the hepatic portal vein of rats without changing
plasma glucose or glucagon concentrations. It should be
remembered that it is the central actions of CRF that
appe in the hepatic portal vein of rats without changing
plasma glucose or glucagon concentrations. It should be
remembered that it is the central actions of CRF that
appear to alter autonomic output and not actions at
peripher plasma glucose or glucagon concentrations. It should be
remembered that it is the central actions of CRF that
appear to alter autonomic output and not actions at
peripheral target organs. Also note that, in the numerous
st appear to alter autonomic output and not actions at
peripheral target organs. Also note that, in the numerous
studies in animals and humans, no obvious effect of CRF
on plasma insulin or glucagon concentrations has been found. studies in animals and humans, no obvious effect of CRF

EXECUTE: have a definitive physiological role, these actions on the constrained by a metabolism and energy balance with emphasis on a heart would be consistent with a role for CRF in an potential role for CRF neurons in As discussed previously, CNS administration of CRF
increases sympathetic outflow. In addition to the in-
pervous activity which CRF neurons may help orchesstudies in animals and humans, no obvious effect of CRF
on plasma insulin or glucagon concentrations has been
found.
A brief review by Rothwell (1990) of the effects of CRF
on metabolism and energy balance with emphasis on on plasma insulin or glucagon concentrations has been
found.
A brief review by Rothwell (1990) of the effects of CRF
on metabolism and energy balance with emphasis on a
potential role for CRF neurons in the pathophysiology found.
A brief review by Rothwell (1990) of the effects of CRF
on metabolism and energy balance with emphasis on a
potential role for CRF neurons in the pathophysiology
of obesity and cachexia was recently published. Altho A brief review by Rothwell (1990) of the effects of CRF
on metabolism and energy balance with emphasis on a
potential role for CRF neurons in the pathophysiology
of obesity and cachexia was recently published. Although
any on metabolism and energy balance with emphasis on a
potential role for CRF neurons in the pathophysiology
of obesity and cachexia was recently published. Although
any peripheral extrapituitary physiological actions of
CRF potential role for CRF neurons in the pathophysiology
of obesity and cachexia was recently published. Although
any peripheral extrapituitary physiological actions of
CRF remain to be determined, the evidence strongly
suppo of obesity and cachexia was recently published. Although
any peripheral extrapituitary physiological actions of
CRF remain to be determined, the evidence strongly
supports a role for central CRF neurons in helping to
mobil any peripheral extrapituitary physiological actions of CRF remain to be determined, the evidence strongly supports a role for central CRF neurons in helping to mobilize energy stores during times of stress. These are actio CRF remain to be determined, the evidence stron supports a role for central CRF neurons in helping mobilize energy stores during times of stress. These actions clearly expected from increased sympathe nervous activity whic trate. *C. Gastrointestinal Responses to Corticotropin-releasing*
C. Gastrointestinal Responses to Corticotropin-releasing
Factor Administration Factor Administration
Factor Administration
Factor Administration
During times of stre

ate.

Gastrointestinal Responses to Corticotropin-releasing

actor Administration

During times of stress, vegetative functions such as

gestion are diminished to ensure an adequate blood C. Gastrointestinal Responses to Corticotropin-releasing
Factor Administration
During times of stress, vegetative functions such as
digestion are diminished to ensure an adequate blood
supply to more vital organs. If one a Factor Administration
During times of stress, vegetative functions such as
digestion are diminished to ensure an adequate blood
supply to more vital organs. If one assumes that CRF is
involved in modulating the stress resp Factor Administration

During times of stress, vegetative functions such as

digestion are diminished to ensure an adequate blood

supply to more vital organs. If one assumes that CRF is

involved in modulating the stress During times of stress, vegetative functions such as
digestion are diminished to ensure an adequate blood
supply to more vital organs. If one assumes that CRF is
involved in modulating the stress response, it is plausible
 digestion are diminished to ensure an adequate blood
supply to more vital organs. If one assumes that CRF is
involved in modulating the stress response, it is plausible
that CRF may alter digestive function by decreasing
p supply to more vital organs. If one assumes that CRF is
involved in modulating the stress response, it is plausible
that CRF may alter digestive function by decreasing
parasympathetic outflow in a manner similar to that
se involved in modulating the stress response, it is plausible
that CRF may alter digestive function by decreasing
parasympathetic outflow in a manner similar to that
seen in the circulatory system (vide supra). Tache and
col parasympathetic outflow in a manner similar to that
seen in the circulatory system (vide supra). Tache and
colleagues reported that i.c.v (Garrick et al., 1988; Ste-
phens et al., 1988) or intrahypothalamic (Gunion and
Tac parasympathetic outflow in a manner similar to that
seen in the circulatory system (vide supra). Tache and
colleagues reported that i.c.v (Garrick et al., 1988; Ste-
phens et al., 1988) or intrahypothalamic (Gunion and
Tac seen in the circulatory system (vide supra). Tache and colleagues reported that i.c.v (Garrick et al., 1988; Stephens et al., 1988) or intrahypothalamic (Gunion and Tache, 1987) administration of CRF decreases gastric acid colleagues reported that i.c.v (Garrick et al., 1988; Siphens et al., 1988) or intrahypothalamic (Gunion a Tache, 1987) administration of CRF decreases gast acid secretion and gastric motility. These actions a blocked by c phens et al., 1988) or intrahypothalamic (Gunion and Tache, 1987) administration of CRF decreases gastric acid secretion and gastric motility. These actions are blocked by concurrent administration of an CRF antagonist. Bu Tache, 1987) administration of CRF decreases gast
acid secretion and gastric motility. These actions a
blocked by concurrent administration of an CRF anta
onist. Bueno and Fioramonti (1986) reported that i.c.
but not i.v., acid secretion and gastric motility. These actions are
blocked by concurrent administration of an CRF antag-
onist. Bueno and Fioramonti (1986) reported that i.c.v.,
but not i.v., CRF administration decreased gastric motil blocked by concurrent administration of an CRF antagenist. Bueno and Fioramonti (1986) reported that i.c.v.
but not i.v., CRF administration decreased gastric motility. This was assessed by diminished migrating motor
compl onist. Bueno and Fioramonti (1986) reported that i.c.v.,
but not i.v., CRF administration decreased gastric motil-
ity. This was assessed by diminished migrating motor
complexes which are the rhythmical smooth muscle con-
 but not i.v., CRF administration decreased gastric motility. This was assessed by diminished migrating motor complexes which are the rhythmical smooth muscle contractions originating in the stomach and propagating to the i ity. This was assessed by diminished migrating motor complexes which are the rhythmical smooth muscle contractions originating in the stomach and propagating to the ileum. However, Williams et al. (1987) reported that both complexes which are the rhythmical smooth muscle con-
tractions originating in the stomach and propagating to
the ileum. However, Williams et al. (1987) reported that
both i.c.v. and i.v. CRF administration decreased gastr tractions originating in the stomach and propagating to
the ileum. However, Williams et al. (1987) reported that
both i.c.v. and i.v. CRF administration decreased gastric
emptying and small intestinal motility and increase

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1987) also reported that i.v., but not i.c.v., per

1987) also reported that i.v., but not i.c.v., per (Pappas et al., 1987) also reports and their own previous work, Tache's group
(Pappas et al., 1987) also reported that i.v., but not i.c.v.,
CRF administration inhibited gastric emptying in dogs. OWENS AND

reports and their own previous work, Tache's group

(Pappas et al., 1987) also reported that i.v., but not i.c.v.,

CRF administration inhibited gastric emptying in dogs.

Although these reports appear to be exp The these reports and their own previous work, Tache's group
(Pappas et al., 1987) also reported that i.v., but not i.c.v.,
CRF administration inhibited gastric emptying in dogs.
Although these reports appear to be experim (Pappas et al., 1987) also reported that i.v., but not i.c.v., CRF administration inhibited gastric emptying in dogs.
Although these reports appear to be experimentally sound, the inconsistent findings suggest that conside (Pappas et al., 1987) also reported that i.v., but not i.c.v. CRF administration inhibited gastric emptying in dogs
Although these reports appear to be experimentally
sound, the inconsistent findings suggest that consider
 CRF administration inhibited gastric emptying in dogs. i.c.
Although these reports appear to be experimentally CR
sound, the inconsistent findings suggest that consider-
ior
ably more work is needed before an actual physio Although these reports appear to be experimentally
sound, the inconsistent findings suggest that consider-
ably more work is needed before an actual physiological
role for CRF in altering digestion during stress can be
def sound, the inconsistent findings suggest that consider-
ably more work is needed before an actual physiological dep
role for CRF in altering digestion during stress can be env
definitively established. Nonetheless, decreas ably more work is needed before an actual physiological
role for CRF in altering digestion during stress can be
definitively established. Nonetheless, decreases in gas-
trointestinal function caused by centrally acting CRF role for CRF in altering digestion during stress can be definitively established. Nonetheless, decreases in gas trointestinal function caused by centrally acting CR neurons on parasympathetic activity would be consister wi definitively established. Nonetheless, decre
trointestinal function caused by centrally
neurons on parasympathetic activity would b
with its proposed role in integrating the auto
ous system's response to stressful situatio meurons on parasympathetic activity would be conservative to the in integrating the autonomic ous system's response to stressful situations.
D. Local Gonadal Actions of Corticotropin-releasing Factor

Factor

is system's response to stresstul situations.

Local Gonadal Actions of Corticotropin-releasing

uctor

CRF is present in the testis where it is synthesized

cally. CRF receptors are present on Leydig cells where D. Local Gonadal Actions of Corticotropin-releasing

Factor

CRF is present in the testis where it is synthesized

locally. CRF receptors are present on Leydig cells where bit

it appears to act via a pertussis toxin-insen Example 1 and the test via a perturburier of the central Factor

Factor

CRF is present in the test is synthesized prior a

locally. CRF receptors are present on Leydig cells where blocks

it appears to act via a pertussi protein to inhibit human chorionic gonadotropin-in-CRF is present in the testis where it is synthesized plocally. CRF receptors are present on Leydig cells where it appears to act via a pertussis toxin-insensitive G 1 protein to inhibit human chorionic gonadotropin-in-
du locally. CRF receptors are present on Leydig cells where
it appears to act via a pertussis toxin-insensitive G
protein to inhibit human chorionic gonadotropin-in-
duced cAMP generation and testosterone synthesis (Ul-
isse it appears to act via a pertussis toxin-insensitive G
protein to inhibit human chorionic gonadotropin-in-
duced cAMP generation and testosterone synthesis (UI-
isse et al., 1989, 1990). Although it is still unclear, it
app protein to inhibit human chorionic gonadotropin-in-
duced cAMP generation and testosterone synthesis (Ul-
isse et al., 1989, 1990). Although it is still unclear, it b
appears that human chorionic gonadotropin stimulates to duced cAMP generation and testosterone synthesis (Ulisse et al., 1989, 1990). Although it is still unclear, it appears that human chorionic gonadotropin stimulates the production and release of CRF from populations of Leyd isse et al., 1989, 1990). Although it is still unclear, it bappears that human chorionic gonadotropin stimulates to the production and release of CRF from populations of in Leydig cells. Following release of CRF, CRF recep appears that human chorionic gonadotropin stimulates the production and release of CRF from populations of in Leydig cells. Following release of CRF, CRF receptors the production the same or other Leydig cells inhibit the Leydig cells. Following release of CRF, CRF receptors
on the same or other Leydig cells inhibit the activity
human chorionic gonadotropin has on the production of
testosterone. Thus, this type of feedback ultimately ap-
pe on the same or other Leydig cells inhibit the activity blocked by these drugs and that other behaviors de-
human chorionic gonadotropin has on the production of scribed in the sections that follow are not the result of
tes on the same or other Leydig cells inhibit the activity
human chorionic gonadotropin has on the production of
testosterone. Thus, this type of feedback ultimately ap-
pears to locally inhibit Leydig cell function (Fabbri et human chorionic gonadotropin has on the production
testosterone. Thus, this type of feedback ultimately
pears to locally inhibit Leydig cell function (Fabbri
al., 1990). In addition to these findings, CRF recept
on Leydig testosterone. Thus, this type of feedback ultimately appears to locally inhibit Leydig cell function (Fabbri et al., 1990). In addition to these findings, CRF receptors on Leydig cells stimulate the release of locally syn pears to locally inhibit Leydig cell function (Fabbri et al., 1990). In addition to these findings, CRF receptors on Leydig cells stimulate the release of locally synthe-sized β -endorphin from these cells (Eskeland et al., 1990). In addition to these findings, CRF reception Leydig cells stimulate the release of locally syntl sized β -endorphin from these cells (Eskeland et al., 198
Although these local paracrine actions of CRF are re on Leydig cells stimulate the release of locally synthe-
sized β -endorphin from these cells (Eskeland et al., 1989). anti-
Although these local paracrine actions of CRF are not
fully understood, the findings support ot sized β -endorphin from these cells (Eskeland et al., 1989).

Although these local paracrine actions of CRF are not

fully understood, the findings support other data reveal-

ing decreased reproductive functioning prod Although these local paracrine actions of CRF are not antago
fully understood, the findings support other data revealing
decreased reproductive functioning produced by CRF
at local, neuroendocrine, and behavioral levels, a fully understood, the findings support other data revealing decreased reproductive functioning produced by CRF at local, neuroendocrine, and behavioral levels, actions the all aimed at shifting physiological function away at local, neuroendocrine, and behavioral levels, actions all aimed at shifting physiological function away from vegetative needs to those needs necessary during times of stress. Internal all aimed at shifting physiological function away from

vegetative needs to those needs necessary during times

of stress.

VI. Corticotropin-releasing Factor Regulation of
 Behavior in Laboratory Animals Behavior in Laboratory Animals
Behavior in Laboratory Animals
Behavior in Laboratory Animals
Soral Responses to Central and Peripher

of stress.
**VI. Corticotropin-releasing Factor Regulational Responses to Central and Peripheral
A. Behavioral Responses to Central and Peripheral
***Administration of Corticotropin-releasing Factor* **Administration Corticotropin-releasing Factor Regulatio**
A. Behavioral Responses to Central and Peripheral
Administration of Corticotropin-releasing Factor
L. Locomotor activation. When administered direction

1. Behavior in Laboratory Animals
 1. Locomotor activation. When administered directly
 1. Locomotor activation. When administered directly

to the brain, CRF produces behaviors similar to those A. Behavioral Responses to Central and Peripheral

Administration of Corticotropin-releasing Factor

1. Locomotor activation. When administered directly

into the brain, CRF produces behaviors similar to those

observed fo A. Behavioral Responses to Central and Peripheral
Administration of Corticotropin-releasing Factor
1. Locomotor activation. When administered directly
into the brain, CRF produces behaviors similar to those
observed follow Administration of Corticotropin-releasing Pactor
1. Locomotor activation. When administered directly
into the brain, CRF produces behaviors similar to those
beserved following exposure to stress. This is consistent
with a 1. Locomotor activation. When administered directly
into the brain, CRF produces behaviors similar to those
observed following exposure to stress. This is consistent
with a proposed role for CRF neurons in mediating
endocr into the brain, CRF produces behaviors similar to those
observed following exposure to stress. This is consistent b
with a proposed role for CRF neurons in mediating C
endocrine, autonomic, and behavioral responses to varobserved following exposure to stress. This is consistent
with a proposed role for CRF neurons in mediating
endocrine, autonomic, and behavioral responses to var-
ious degrees of stress. Following the initial reports
CRF m with a proposed role for CRF neurons in mediating C
endocrine, autonomic, and behavioral responses to var-
ious degrees of stress. Following the initial reports of a
CRF modulation of behavior, a plethora of reports in
eme endocrine, autonomic, and behavioral responses to var-
ious degrees of stress. Following the initial reports of
CRF modulation of behavior, a plethora of reports inh
emerged confirming many of the initial findings. These i ious degrees of stress. Following the initial reports of and CRF modulation of behavior, a plethora of reports in emerged confirming many of the initial findings. These in reports will be cited below. However, we will focu CRF modulation of behavior, a plethora of reports inhibition emerged confirming many of the initial findings. These inductive reports will be cited below. However, we will focus on recent reports we view as most significan emerged confirming many of the initial findings. These
reports will be cited below. However, we will focus on
recent reports we view as most significant. For those
seeking more detailed information, an extensive review
of reports will be cited below. However, we will focus on recent reports we view as most significant. For those seeking more detailed information, an extensive review of the behavioral actions of CRF in laboratory animals by

MEROFF
Because of prior findings with other hypothalamic
ptides, Sutton et al. (1982) examined the effects of NEMEROFF
Because of prior findings with other hypothalamic
peptides, Sutton et al. (1982) examined the effects of
i.c.v. CRF administration in the rat, hypothesizing that NEMEROFF
Because of prior findings with other hypothalamic
peptides, Sutton et al. (1982) examined the effects of
i.c.v. CRF administration in the rat, hypothesizing that
CRF possessed an important role in modulating behav Because of prior findings with other hypothalan
peptides, Sutton et al. (1982) examined the effects
i.c.v. CRF administration in the rat, hypothesizing th
CRF possessed an important role in modulating behav-
ior. These inv Because of prior findings with other hypothalaming peptides, Sutton et al. (1982) examined the effects (i.c.v. CRF administration in the rat, hypothesizing the CRF possessed an important role in modulating behavior. These peptides, Sutton et al. (1982) examined the effects of i.c.v. CRF administration in the rat, hypothesizing that CRF possessed an important role in modulating behavior. These investigators found that CRF produced dose-depen i.c.v. CRF administration in the rat, hypothesizing t
CRF possessed an important role in modulating beh
ior. These investigators found that CRF produced do
dependent increases in locomotor activity in a fami
environment an CRF possessed an important role in modulating behavior. These investigators found that CRF produced dose-
dependent increases in locomotor activity in a familiar
environment and behaviors in open-field testing consist-
ent ior. These investigators found that CRF produced do
dependent increases in locomotor activity in a famile
environment and behaviors in open-field testing consi
ent with what can be termed increased "emotionalit
These effec dependent increases in locomotor activity in a familiar
environment and behaviors in open-field testing consist
ent with what can be termed increased "emotionality."
These effects were not seen following peripheral admin-
 environment and behaviors in open-field testing consist-
ent with what can be termed increased "emotionality."
These effects were not seen following peripheral admin-
istration. Thereafter, a number of investigators con-
f ent with what can be termed increased "emotionality."
These effects were not seen following peripheral administration. Thereafter, a number of investigators con-
firmed these findings (Veldhuis and De Wied, 1984;
Eaves et These effects were not seen following peripheral administration. Thereafter, a number of investigators confirmed these findings (Veldhuis and De Wied, 1984; Eaves et al., 1985; Sherman and Kalin, 1986, 1987; Ehlers and Ch istration. Thereafter, a number of investigators confirmed these findings (Veldhuis and De Wied, 1984; Eaves et al., 1985; Sherman and Kalin, 1986, 1987; Ehlers and Chaplin, 1987). These actions can be blocked by central firmed these findings (Veldhuis and De Wied, 1984;
Eaves et al., 1985; Sherman and Kalin, 1986, 1987; Ehlers
and Chaplin, 1987). These actions can be blocked by
central administration of the CRF antagonist, α -helical
C Eaves et al., 1985; Sherman and Kalin, 1986, 1987; Ehlers
and Chaplin, 1987). These actions can be blocked by
central administration of the CRF antagonist, α -helical
CRF₉₋₄₁ (Britton et al., 1986c), and are not alter and Chaplin, 1987). These actions can be blocked by central administration of the CRF antagonist, α -helical CRF₉₋₄₁ (Britton et al., 1986c), and are not altered by prior administration of dexamethasone at a dose that CRF_{9-41} (Britton et al., 1986c), and are not altered by prior administration of dexamethasone at a dose that blocks pituitary-adrenal activation (Britton et al., 1986a, 1986b). Britton and Indyk (1989) reported that ga prior administration of dexamethasone at a dose that
blocks pituitary-adrenal activation (Britton et al., 1986a,
1986b). Britton and Indyk (1989) reported that gangli-
onic blocking drugs can partially attenuate the locomo prior administration of dexamethasone at a dose that
blocks pituitary-adrenal activation (Britton et al., 1986a,
1986b). Britton and Indyk (1989) reported that gangli-
onic blocking drugs can partially attenuate the locomo blocks pituitary-adrenal activation (Britton et al., 1986a, 1986b). Britton and Indyk (1989) reported that ganglionic blocking drugs can partially attenuate the locomotor effects of i.c.v. CRF, suggesting that some of the 1986b). Britton and Indyk (1989) reported that ganglionic blocking drugs can partially attenuate the locomotor effects of i.c.v. CRF, suggesting that some of the observed behaviors following CRF administration are secondar onic blocking drugs can partially attenuate the locomotor
effects of i.c.v. CRF, suggesting that some of the observed
behaviors following CRF administration are secondary
to increased sympathetic activation and the resulta effects of i.c.v. CRF, suggesting that some of the observed
behaviors following CRF administration are secondary
to increased sympathetic activation and the resultant
increases in MAP and heart rate. However, it is clear
t behaviors following CRF administration are secondary
to increased sympathetic activation and the resultant
increases in MAP and heart rate. However, it is clear
that the locomotor effects of CRF are only partially
blocked to increased sympathetic activation and the resultant
increases in MAP and heart rate. However, it is clear
that the locomotor effects of CRF are only partially
blocked by these drugs and that other behaviors de-
scribed i that the locomotor effects of CRF are only partially blocked by these drugs and that other behaviors described in the sections that follow are not the result of increases in peripheral sympathetic activity. The increases i at the locomotor effects of CRF are only partially
ocked by these drugs and that other behaviors de-
ribed in the sections that follow are not the result of
creases in peripheral sympathetic activity.
The increases in loco

blocked by these drugs and that other behaviors described in the sections that follow are not the result of increases in peripheral sympathetic activity.
The increases in locomotor activity are not altered by destruction o scribed in the sections that follow are not the result of
increases in peripheral sympathetic activity.
The increases in locomotor activity are not altered by
destruction of dopamine nerve terminals (Swerdlow and
Koob, 198 increases in peripheral sympathetic activity.
The increases in locomotor activity are not altered by
destruction of dopamine nerve terminals (Swerdlow and
Koob, 1985) and are blocked only by cataleptic doses of
antipsychot The increases in locomotor activity are not altered by
destruction of dopamine nerve terminals (Swerdlow and
Koob, 1985) and are blocked only by cataleptic doses of
antipsychotic drugs and not at all by the opiate receptor destruction of dopamine nerve terminals (Swerdlow and Koob, 1985) and are blocked only by cataleptic doses of antipsychotic drugs and not at all by the opiate receptor antagonist, naloxone (Koob et al., 1984), suggesting t Koob, 1985) and are blocked only by cataleptic doses of antipsychotic drugs and not at all by the opiate receptor antagonist, naloxone (Koob et al., 1984), suggesting that these effects are independent of both dopamine and antipsychotic drugs and not at all by the opiate receptor
antagonist, naloxone (Koob et al., 1984), suggesting that
these effects are independent of both dopamine and
opioid systems. In addition, Kalivas et al. (1987) foun antagonist, naloxone (Koob et al., 1984), suggesting that
these effects are independent of both dopamine and
opioid systems. In addition, Kalivas et al. (1987) found
that ventral tegmentum injections of CRF did produce
inc these effects are independent of both dopamine and
opioid systems. In addition, Kalivas et al. (1987) found
that ventral tegmentum injections of CRF did produce
increases in activity that are not blocked by dopamine
recept opioid systems. In addition, Kalivas et al. (1987) found
that ventral tegmentum injections of CRF did produce
increases in activity that are not blocked by dopamine
receptor antagonists. In an attempt to determine which
n that ventral tegmentum injections of CRF did pro
increases in activity that are not blocked by dopar
receptor antagonists. In an attempt to determine w
neurotransmitter systems may be involved, Imaki (1987) suggested th increases in activity that are not blocked by dopan
receptor antagonists. In an attempt to determine wh
neurotransmitter systems may be involved, Imaki et
(1987) suggested that CRF may act via α_2 -recep
mediated noradr receptor antagonists. In an attempt to determine which
neurotransmitter systems may be involved, Imaki et al.
(1987) suggested that CRF may act via α_2 -receptor-
mediated noradrenergic activity. Although the pharma-
co (1987) suggested that CRF may act via α_2 -receptor-
mediated noradrenergic activity. Although the pharma-
cological probes used were clearly neither specific nor
sensitive, this observation would be consistent with ele (1987) suggested that CRF may act via α_2 -recept
mediated noradrenergic activity. Although the pharr
cological probes used were clearly neither specific
sensitive, this observation would be consistent with e
trophysiol mediated noradrenergic activity. Although the pharma-
cological probes used were clearly neither specific nor
sensitive, this observation would be consistent with elec-
trophysiological evidence of CRF activation of noradr cological probes used were clearly neither specific nor
sensitive, this observation would be consistent with elec-
trophysiological evidence of CRF activation of noradre-
nergic cells of the locus ceruleus. Sirinathsinghji sensitive, this observation would be consistent with electrophysiological evidence of CRF activation of noradre-
nergic cells of the locus ceruleus. Sirinathsinghji and
Heavens (1989) implicated GABAergic neurons of the
ba trophysiological evidence of CRF activation of noradre-
nergic cells of the locus ceruleus. Sirinathsinghji and
Heavens (1989) implicated GABAergic neurons of the
basal ganglia in the locomotor-activating properties of
CRF nergic cells of the locus ceruleus. Sirinathsinghji and
Heavens (1989) implicated GABA
ergic neurons of the
basal ganglia in the locomotor-activating properties of
CRF. They reported that, using push-pull cannulas, CRF
inc Heavens (1989) implicated GABAergic neurons of the
basal ganglia in the locomotor-activating properties of
CRF. They reported that, using push-pull cannulas, CRF
increased the release of GABA into the caudate nucleus
and g basal ganglia in the locomotor-activating properties (CRF. They reported that, using push-pull cannulas, CR increased the release of GABA into the caudate nucleus and globus pallidus. It is hypothesized that the resultan i CRF. They reported that, using push-pull cannulas, CRF
increased the release of GABA into the caudate nucleus
and globus pallidus. It is hypothesized that the resultant
inhibitory actions of GABA may play a role in CRF-
in increased the release of GABA into the caudate nucleus
and globus pallidus. It is hypothesized that the resultant
inhibitory actions of GABA may play a role in CRF-
induced behaviors. Finally, Britton and Indyk (1990)
rece and globus pallidus. It is hypothesized that the resultant
inhibitory actions of GABA may play a role in CRF-
induced behaviors. Finally, Britton and Indyk (1990)
recently observed that CRF and caffeine have similarities
i inhibitory actions of GABA may play a role in CRF-
induced behaviors. Finally, Britton and Indyk (1990)
recently observed that CRF and caffeine have similarities
in their locomotor activational properties. Thus, both
caffe induced behaviors. Finally, Britton and Indyk (1990)
recently observed that CRF and caffeine have similarities
in their locomotor activational properties. Thus, both
caffeine, which also has anxiogenic actions, and CRF
inc recently observed that CRF and caffeine have similarities
in their locomotor activational properties. Thus, both
caffeine, which also has anxiogenic actions, and CRF
increase activity in nonstressful environments and lower

CORTICOTROPIN-RELE
feine can substitute for the anxiogenic effects of novelty
in altering the actions of CRF on locomotion. Another CORTICOTROPIN-RI
feine can substitute for the anxiogenic effects of novelty
in altering the actions of CRF on locomotion. Another
behavior that may be related to CRF-induced alterations CORTICOTROPIN-R
feine can substitute for the anxiogenic effects of novelty
in altering the actions of CRF on locomotion. Another
behavior that may be related to CRF-induced alterations
in locomotor activity is the decrease feine can substitute for the anxiogenic effects of novelty olin altering the actions of CRF on locomotion. Another subserved the decrease in sleep observed diffeologies in sleep observed diffeologies central CRF administra feine can substitute for the anxiogenic effects of novelty obs
in altering the actions of CRF on locomotion. Another sub-
behavior that may be related to CRF-induced alterations ver
in locomotor activity is the decrease in in altering the actions of CRF on locomotion. Another
behavior that may be related to CRF-induced alterations
in locomotor activity is the decrease in sleep observed
following central CRF administration (Sherman and
Kalin, behavior that may be related to CRF-induced alterations
in locomotor activity is the decrease in sleep observed
following central CRF administration (Sherman and
Kalin, 1986, 1987). However, EEG changes suggest that
decrea in locomotor activity is the decrease in sleep
following central CRF administration (She
Kalin, 1986, 1987). However, EEG changes su
decreases in sleep are separate from increased
activation (Ehlers 1986; Ehlers et al., 19 Kalin, 1986, 1987). However, EEG changes suggest that decreases in sleep are separate from increased locomotor activation (Ehlers 1986; Ehlers et al., 1986).
2. Feeding behavior. The decreased food consumption

Kalin, 1986, 1987). However, EEG changes suggest the decreases in sleep are separate from increased locomot activation (Ehlers 1986; Ehlers et al., 1986).
2. Feeding behavior. The decreased food consumption and associated decreases in sleep are separate from increased locomotor for activation (Ehlers 1986; Ehlers et al., 1986).

2. Feeding behavior. The decreased food consumption in and associated weight loss that is frequently seen followactivation (Ehlers 1986; Ehlers et al., 1986).
2. Feeding behavior. The decreased food consumptio
and associated weight loss that is frequently seen follow
ing stress may be mediated by CRF neurons. Followin
i.c.v. CRF adm 2. Feeding behavior. The decreased food consumption
and associated weight loss that is frequently seen follow-
ing stress may be mediated by CRF neurons. Following
i.c.v. CRF administration, feeding is inhibited in a num-
 and associated weight loss that is frequently seen following stress may be mediated by CRF neurons. Following i.c.v. CRF administration, feeding is inhibited in a number of different experimental paradigms. In a novel envi ing stress may be mediated by CRF neurons. Following mai.c.v. CRF administration, feeding is inhibited in a num-
her of different experimental paradigms. In a novel environment, CRF decreases food intake in food-deprived h i.c.v. CRF administration, feeding is inhibited in a number of different experimental paradigms. In a novel environment, CRF decreases food intake in food-deprived rats (Britton et al., 1982). Similar findings were also se ber of different experimental paradigms. In a novel environment, CRF decreases food intake in food-deprived rats (Britton et al., 1982). Similar findings were also seen in familiar environments (Britton et al., 1982, 1986b vironment, CRF decreases food intake in food-deprived
rats (Britton et al., 1982). Similar findings were also seen
in familiar environments (Britton et al., 1982, 1986b).
Additionally, Gosnell et al. (1983) observed identi rats (Britton et al., 1982). Similar findings were also seen
in familiar environments (Britton et al., 1982, 1986b). S
Additionally, Gosnell et al. (1983) observed identical b
findings in rats with unlimited access to food in familiar environments (Britton et al., 1982, 1986b).
Additionally, Gosnell et al. (1983) observed identical l
findings in rats with unlimited access to food. In sheep,
50% decreases in food intake could be induced by do Additionally, Gosnell et al. (1983) observed identical ble
findings in rats with unlimited access to food. In sheep, ot
50% decreases in food intake could be induced by doses of
of CRF as low as 60 ng/kg i.c.v. (Ruckebusc findings in rats with unlimited access to food. In sheep, ot 50% decreases in food intake could be induced by doses of of CRF as low as 60 ng/kg i.c.v. (Ruckebusch and Malfindert, 1986). In addition, decreases in food inta 50% decreases in food intake could be induced by dose
of CRF as low as 60 ng/kg i.c.v. (Ruckebusch and Mal
bert, 1986). In addition, decreases in food intake wer
still observed even in rats pretreated with drugs knowi
to i of CRF as low as 60 ng/kg i.c.v. (Ruckebusch and I
bert, 1986). In addition, decreases in food intake v
still observed even in rats pretreated with drugs kn
to increase food consumption. These agents include n
cimol, norep bert, 1986). In addition, decreases in food intake were m
still observed even in rats pretreated with drugs known wito
increase food consumption. These agents include mus-
cimol, norepinephrine, dynorphin, ethylketocyclazo still observed even in rats pretreated with drugs know
to increase food consumption. These agents include mus
cimol, norepinephrine, dynorphin, ethylketocyclazocine
and insulin (Levine et al., 1983; Morley et al., 1985). A to increase food consumption. These agents include mus-
cimol, norepinephrine, dynorphin, ethylketocyclazocine,
and insulin (Levine et al., 1983; Morley et al., 1985). As
with the locomotor actions described above, these a cimol, norepinephrine, dynorphin, ethylketocyclazocine,
and insulin (Levine et al., 1983; Morley et al., 1985). As
with the locomotor actions described above, these anxi-
induced illness are not the result of CRF-induced i and insulin (Levine et al., 1983; Morley et al., 1985). As
with the locomotor actions described above, these anxi-
ogenic actions are not the result of increased HPA axis
activity, nor are they the result of CRF-induced il with the locomotor actions described above, these anxi-
ogenic actions are not the result of increased HPA axis
activity, nor are they the result of CRF-induced illness
or lassitude in the rats. As with other CRF-induced
b ogenic actions are not the result of increased HPA axis ulat
activity, nor are they the result of CRF-induced illness decr
or lassitude in the rats. As with other CRF-induced decr
behaviors, the decreases in food intake fo activity, nor are they the result of CRF-induced illness decreases or lassitude in the rats. As with other CRF-induced decreases behaviors, the decreases in food intake following centrally administered CRF can be blocked b or lassitude in the rats. As with other CRF-induced dependencies, the decreases in food intake following centrally administered CRF can be blocked by the CRF dantagonist (Krahn et al., 1986). Moreover, the CRF of antagonis behaviors, the decreases in food intake following centrally administered CRF can be blocked by the CRF antagonist (Krahn et al., 1986). Moreover, the CRF antagonist partially reversed the decreases in food intake observed antagonist (Krahn et al., 1986). Moreover, the CRF antagonist partially reversed the decreases in food intake observed following restraint stress, suggesting that endogenous CRF neurons may play a role in stress-induced an antagonist partially reversed the decreases in food intake
observed following restraint stress, suggesting that en-
dogenous CRF neurons may play a role in stress-induced
anorexia. In an attempt to localize the neuroanatom antagonist partially reversed the decreases in food intake
observed following restraint stress, suggesting that en-
dogenous CRF neurons may play a role in stress-induced
anorexia. In an attempt to localize the neuroanatom observed following restraint stress, suggesting that energy dependence CRF neurons may play a role in stress-induced dependence
anorexia. In an attempt to localize the neuroanatomical the site of action of CRF on food inta dogenous CRF neurons may play a role in stress-induced deal w
anorexia. In an attempt to localize the neuroanatomical the ar
site of action of CRF on food intake, Krahn et al. (1988) from
microinjected CRF into several bra anorexia. In an attempt to localize the neuroanatomic
site of action of CRF on food intake, Krahn et al. (198
microinjected CRF into several brain regions. CRF on
decreased food intake when microinjected into the PV
but no site of action of CRF on food intake, Krahn et al. (1988) f
microinjected CRF into several brain regions. CRF only
decreased food intake when microinjected into the PVN
but not when injected into the lateral hypothalamus, decreased food intake when microinjected into the PVN tial impetus for many clinical studies examining a role
but not when injected into the lateral hypothalamus, for CRF in the pathophysiology of affective and anxiety
ven decreased food intake when microinjected into the PVN tiput not when injected into the lateral hypothalamus, for ventromedial hypothalamus, globus pallidus, or caudate different of rats. Interestingly, PVN CRF injections a but not when injected into the lateral hypothalamus,
ventromedial hypothalamus, globus pallidus, or caudate
of rats. Interestingly, PVN CRF injections also increased
grooming behaviors similarly to that observed following
 ventromedial hypothalamus, globus pallidus, or caudate disof rats. Interestingly, PVN CRF injections also increased grooming behaviors similarly to that observed following in i.c.v. injections. The mechanisms by which thes of rats. Interestingly, PVN CRF injections also increased
grooming behaviors similarly to that observed following
i.c.v. injections. The mechanisms by which these changes
in food intake occur are unknown but plausibly coul i.c.v. injections. The mechanisms by which these changes
in food intake occur are unknown but plausibly could
involve monoamine systems within the hypothalamus
and/or PVN control of autonomic nervous system activ-
ity.
In ity. involve monoamine systems within the hypothalamus
and/or PVN control of autonomic nervous system activ-
ity.
In a recent chronic study in which CRF was continu-
ously infused into the third ventricle for 7 days, CRF involve monoamine systems within the hypothalamus the
and/or PVN control of autonomic nervous system activ-
ity. Spe
In a recent chronic study in which CRF was continu-
ously infused into the third ventricle for 7 days, CR

and/or PVN control of autonomic nervous system activity.
In a recent chronic study in which CRF was continu-
ously infused into the third ventricle for 7 days, CRF
reduced body weight and increased sympathetic activity,
as ity.
In a recent chronic study in which CRF was continu-
ously infused into the third ventricle for 7 days, CRF
reduced body weight and increased sympathetic activity,
as measured by brown fat thermogenesis, but did not
pr In a recent chronic study in which CRF was continu-
ously infused into the third ventricle for 7 days, CRF
reduced body weight and increased sympathetic activity, re
as measured by brown fat thermogenesis, but did not
prod ously infused into the third ventricle for 7 days, CRF reduced body weight and increased sympathetic activity, as measured by brown fat thermogenesis, but did not produce any consistent decreases in food intake (Arase et a reduced body weight and increased sympathetic activity,
as measured by brown fat thermogenesis, but did not
produce any consistent decreases in food intake (Arase
et al., 1988). In a related, but less physiologically relev as measured by brown fat thermogenesis, but did not wh
produce any consistent decreases in food intake (Arase sti
et al., 1988). In a related, but less physiologically relevant per
experiment, Krahn et al. (1990) administe

LEASING FACTOR 449

observed that the anorectic effect of CRF decreased

substantially over time. Weight gain was slowed only at LEASING FACTOR 449
observed that the anorectic effect of CRF decreased
substantially over time. Weight gain was slowed only at
very high doses. The results of these two studies are 449

very dependence that the anderectic effect of CRF decreased

substantially over time. Weight gain was slowed only at

very high doses. The results of these two studies are

difficult to interpret. However, the finding observed that the anorectic effect of CRF decreased
substantially over time. Weight gain was slowed only at
very high doses. The results of these two studies are
difficult to interpret. However, the findings suggest the
po substantially over time. Weight gain was slowed only at
very high doses. The results of these two studies are
difficult to interpret. However, the findings suggest the
possibility of tolerance to the anorexic actions of CR substantially over time. Weight gain was slowed only at
very high doses. The results of these two studies are
difficult to interpret. However, the findings suggest the
possibility of tolerance to the anorexic actions of CR very high doses. The results of these tweefificult to interpret. However, the finding possibility of tolerance to the anorexic advision which may have implications for the hyperfor CRF in anorexia nervosa (vide infra).
3. fficult to interpret. However, the findings suggest the sasibility of tolerance to the anorexic actions of CRF nich may have implications for the hypothesized role r CRF in anorexia nervosa (vide infra).
3. Sexual behavior

possibility of tolerance to the anorexic actions of CRF
which may have implications for the hypothesized role
for CRF in anorexia nervosa (vide infra).
3. Sexual behavior. Although it has not been studied
in great detail, which may have implications for the hypothesized role
for CRF in anorexia nervosa (vide infra).
3. Sexual behavior. Although it has not been studied
in great detail, both male and female sexual behavior is
potently inhibit for CRF in anorexia nervosa (vide infra).

3. Sexual behavior. Although it has not been studied

in great detail, both male and female sexual behavior is

potently inhibited by central administration of CRF in a

manner s 3. Sexual behavior. Although it has not been stud
in great detail, both male and female sexual behavio
potently inhibited by central administration of CRF i
manner similar to that seen in stressed animals. S
nathsinghij et in great detail, both male and female sexual behavior is
potently inhibited by central administration of CRF in a
manner similar to that seen in stressed animals. Siri-
nathsinghji et al. (1983) initially reported that mic potently inhibited by central administration of CRF in a
manner similar to that seen in stressed animals. Siri-
nathsinghji et al. (1983) initially reported that microin-
jection of CRF into the arcuate-ventromedial area o manner similar to that seen in stressed animals. Sirinathsinghji et al. (1983) initially reported that microin-
jection of CRF into the arcuate-ventromedial area of the
hypothalamus or the mesencephalic central gray area
p nathsinghji et al. (1983) initially reported that microin-
jection of CRF into the arcuate-ventromedial area of the
hypothalamus or the mesencephalic central gray area
potently suppressed sexual receptivity in female rats. jection of CRF into the arcuate-ventromedial area of t
hypothalamus or the mesencephalic central gray are
potently suppressed sexual receptivity in female ra
Similar findings were observed in male rats and could
blocked by hypothalamus or the mesencephalic central gray area
potently suppressed sexual receptivity in female rats.
Similar findings were observed in male rats and could be
blocked by naloxone infusion or microinfusion of gonad-
ot potently suppressed sexual receptivity in female rats.
Similar findings were observed in male rats and could be
blocked by naloxone infusion or microinfusion of gonad-
otropin-releasing hormone into the medial preoptic are Similar findings were observed in male rats and could be
blocked by naloxone infusion or microinfusion of gonad-
otropin-releasing hormone into the medial preoptic area
of the hypothalamus (Sirinathsinghji, 1986, 1987). Th blocked by naloxone infusion or microinfusion of gonad-
otropin-releasing hormone into the medial preoptic area
of the hypothalamus (Sirinathsinghji, 1986, 1987). These
findings suggest that CRF may exert its effects throu otropin-releasing hormone into the medial preoptic area
of the hypothalamus (Sirinathsinghji, 1986, 1987). These
findings suggest that CRF may exert its effects through
mechanisms that involve activation of opioid pathways of the hypothalamus (Sirinathsinghji, 1986, 1987). These
findings suggest that CRF may exert its effects through
mechanisms that involve activation of opioid pathways
which can result in decreased LHRH release. It is not
c findings suggest that CRF may exert its effects through
mechanisms that involve activation of opioid pathways
which can result in decreased LHRH release. It is not
clear whether decreased LHRH release into the portal
plexu mechanisms that involve activation of opioid pathways
which can result in decreased LHRH release. It is no
clear whether decreased LHRH release into the porta
plexus or into other CNS regions or both is responsible
for the which can result in decreased LHRH release. It is
clear whether decreased LHRH release into the p
plexus or into other CNS regions or both is respon
for the decreased sexual behavior. Although specula
it may be that decrea clear whether decreased LHRH release into the porta
plexus or into other CNS regions or both is responsible
for the decreased sexual behavior. Although speculative
it may be that decreased pituitary LH and follicle-stim
ul plexus or into other CNS regions or both is responsible
for the decreased sexual behavior. Although speculative,
it may be that decreased pituitary LH and follicle-stim-
ulating hormone release may result in a physiologica for the decreased sexual behavior. Although speculative,
it may be that decreased pituitary LH and follicle-stim-
ulating hormone release may result in a physiological
decrease of testicular and ovarian function and that
d it may be that decreased pituitary LH and follicle-stim-
ulating hormone release may result in a physiological
decrease of testicular and ovarian function and that
decreased central release of LHRH may diminish sexual
desi ulating hormone release may result in a physiological
decrease of testicular and ovarian function and that
decreased central release of LHRH may diminish sexual
desire or pleasure. Nevertheless, CRF neurons may me-
diate s decrease of testicular and ovarian function
decreased central release of LHRH may dimin
desire or pleasure. Nevertheless, CRF neuron
diate some of the previously described deleteri
of various stressors on reproductive func creased central release of LHRH may diminish sexu
sire or pleasure. Nevertheless, CRF neurons may m
ate some of the previously described deleterious effec
various stressors on reproductive function.
4. Animal models of anx

desire or pleasure. Nevertheless, CRF neurons may mediate some of the previously described deleterious effects
of various stressors on reproductive function.
4. Animal models of anxiety and depression. The great-
est numbe diate some of the previously described deleterious effects
of various stressors on reproductive function.
4. Animal models of anxiety and depression. The great-
est number of studies examining the actions of i.c.v. CRF
dea of various stressors on reproductive function.
4. Animal models of anxiety and depression. The great-
est number of studies examining the actions of i.c.v. CRF
deal with the hypothesis that CRF may mediate many of
the anxi 4. Animal models of anxiety and depression. The greatest number of studies examining the actions of i.c.v. CRF deal with the hypothesis that CRF may mediate many of the anxiogenic and fear-related aspects of stress. Data f deal with the hypothesis that CRF may mediate many of the anxiogenic and fear-related aspects of stress. Data from a wide array of behavioral tests support this hypothesis. These preclinical studies have also been a pardeal with the hypothesis that CRF may mediate many of
the anxiogenic and fear-related aspects of stress. Data
from a wide array of behavioral tests support this hy-
pothesis. These preclinical studies have also been a parthe anxiogenic and fear-related aspects of stress. Data
from a wide array of behavioral tests support this hy-
pothesis. These preclinical studies have also been a par-
tial impetus for many clinical studies examining a ro disorders. thesis. These preclinical studies have also been a par-
al impetus for many clinical studies examining a role
r CRF in the pathophysiology of affective and anxiety
sorders.
It has been suggested that the effects of CRF exa

in in means for many clinical studies examining a role
for CRF in the pathophysiology of affective and anxiety
disorders.
It has been suggested that the effects of CRF examined
in a novel environment can provide informatio for CRF in the pathophysiology of affective and anxi
disorders.
It has been suggested that the effects of CRF exami
in a novel environment can provide information ab
the effects of the peptide in a stressful, aversive envi disorders.
It has been suggested that the effects of CRF examined
in a novel environment can provide information about
the effects of the peptide in a stressful, aversive environ-
ment. CRF, when administered to rats i.c.v It has been suggested that the effects of CRF examined
in a novel environment can provide information about
the effects of the peptide in a stressful, aversive environ-
ment. CRF, when administered to rats i.c.v., increase in a novel environment can provide information about
the effects of the peptide in a stressful, aversive environ-
ment. CRF, when administered to rats i.c.v., increases
the frequency of those behaviors normally expressed i the effects of the peptide in a stressful, aversive environ-
ment. CRF, when administered to rats i.c.v., increases
the frequency of those behaviors normally expressed in
response to a novel environment (Britton et al., 19 ment. CRF, when administered to rats i.c.v., increases
the frequency of those behaviors normally expressed in
response to a novel environment (Britton et al., 1982).
Specifically, CRF increases grooming and freezing be-
ha the frequency of those behaviors normally expressed in
response to a novel environment (Britton et al., 1982).
Specifically, CRF increases grooming and freezing be-
haviors and decreases rearing and the number of ap-
proac Specifically, CRF increases grooming and freezing behaviors and decreases rearing and the number of approaches to a food pellet. Similar findings have been reported in mice (Berridge and Dunn, 1986, 1987) in which reduced Specifically, CRF increases grooming and freezing behaviors and decreases rearing and the number of approaches to a food pellet. Similar findings have been reported in mice (Berridge and Dunn, 1986, 1987) in which reduced haviors and decreases rearing and the number of approaches to a food pellet. Similar findings have been reported in mice (Berridge and Dunn, 1986, 1987) in which reduced time was spent in contact with novel stimuli and res proaches to a food pellet. Similar findings have been
reported in mice (Berridge and Dunn, 1986, 1987) in
which reduced time was spent in contact with novel
stimuli and resembled behaviors observed following a
period of r reported in mice (Berridge and Dunn, 1986, 1987) in which reduced time was spent in contact with novel stimuli and resembled behaviors observed following a period of restraint stress. These effects could be blocked by the which reduced time was spent in contact with novel
stimuli and resembled behaviors observed following a
period of restraint stress. These effects could be blocked
by the CRF antagonist, α -helical CRF₉₋₄₁, and by nal-

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ability of opiate antagonists to block these actions of si

Ability of opiate antagonists to block these actions of si

CRF have not been replicated nor has any further evi-OWENS AN

ability of opiate antagonists to block these actions of

CRF have not been replicated nor has any further evi-

dence for an opioidergic role in CRF's actions been owend a owen a owen a owen the dence for an opioidergic role in CRF's actions of side of the dence for an opioidergic role in CRF's actions been streported. In fact, Dunn and Berridge (1987) reported inj ability of opiate antagonists to block these actions of si
CRF have not been replicated nor has any further evi-
dence for an opioidergic role in CRF's actions been st
reported. In fact, Dunn and Berridge (1987) reported i ability of opiate antagonists to block these action
CRF have not been replicated nor has any further
dence for an opioidergic role in CRF's actions
reported. In fact, Dunn and Berridge (1987) repo
that naloxone failed to a CRF have not been replicated nor has any further evidence for an opioidergic role in CRF's actions been
reported. In fact, Dunn and Berridge (1987) reported
that naloxone failed to alter the increases in noradrener-
gic me dence for an opioidergic role in CRF's action
reported. In fact, Dunn and Berridge (1987)
that naloxone failed to alter the increases in nor
gic metabolism produced by i.c.v. CRF in the p.
cortex, hypothalamus, and brainst

that naloxone failed to alter the increases in noradrener-
gic metabolism produced by i.c.v. CRF in the prefrontal
cortex, hypothalamus, and brainstem of mice.
Another test of anxiogenic activity is the conflict test
strin gic metabolism produced by i.c.v. CRF in the prefrontal
cortex, hypothalamus, and brainstem of mice.
Another test of anxiogenic activity is the conflict test
in which CRF produces a suppression of punished and
nonpunished cortex, hypothalamus, and brainstem of mice.

Another test of anxiogenic activity is the conflict to

in which CRF produces a suppression of punished a

nonpunished responding. The effects on punished

sponding are not med Another test of anxiogenic activity is the conflict test stre
in which CRF produces a suppression of punished and
nonpunished responding. The effects on punished re-
ical
sponding are not mediated by pituitary-adrenal act in which CRF produces a suppression of punished and
nonpunished responding. The effects on punished re-
sponding are not mediated by pituitary-adrenal activa-
tion (Britton et al., 1986a) and are blocked by the CRF firi
a nonpunished responding. The effects on punished re-
sponding are not mediated by pituitary-adrenal activa-
tion (Britton et al., 1986a) and are blocked by the CRF firi
antagonist, α -helical CRF₉₋₄₁ (Britton et al., 1 sponding are not mediated by pituitary-adrenal activa-
tion (Britton et al., 1986a) and are blocked by the CRF firit
antagonist, α -helical CRF₉₋₄₁ (Britton et al., 1986c), and esta
are attenuated by ethanol (Britton tion (Britton et al., 1986a) and are blocked by the CRF fir
antagonist, α -helical CRF₉₋₄₁ (Britton et al., 1986c), and est
are attenuated by ethanol (Britton and Koob, 1986) and mi
chlordiazepoxide (Britton et al., 1 antagonist, α -helical CRF₉₋₄₁ (Britton et al., 1986c), and est
are attenuated by ethanol (Britton and Koob, 1986) and mis
chlordiazepoxide (Britton et al., 1985). These last two we
results suggest that one potential are attenuated by ethanol (Britton and Koob, 1986) and
chlordiazepoxide (Britton et al., 1985). These last two
results suggest that one potential mechanism for the
anxiolytic properties of ethanol and benzodiazepines may
b chlordiazepoxide (Britton et al., 1985). T
results suggest that one potential mecha
anxiolytic properties of ethanol and benzodi
be through alterations in brain CRF neuro
al., 1989, 1991d; Grigoriadis et al., 1989a).
A wid sults suggest that one potential mechanism for the CR
xiolytic properties of ethanol and benzodiazepines may oge
through alterations in brain CRF neurons (Owens et fiel
, 1989, 1991d; Grigoriadis et al., 1989a). non
A wide

anxiolytic properties of ethanol and benzodiazepines may
be through alterations in brain CRF neurons (Owens et
al., 1989, 1991d; Grigoriadis et al., 1989a).
A wide variety of other behavioral tests have also
linked CRF to be through alterations in brain CRF neurons (Owens et al., 1989, 1991d; Grigoriadis et al., 1989a).
A wide variety of other behavioral tests have also linked CRF to anxiety and other stress-related behaviors including depr al., 1989, 1991d; Grigoriadis et al., 1989a). nor
A wide variety of other behavioral tests have also to
linked CRF to anxiety and other stress-related behaviors inc
including depression. Central administration of CRF po-
t A wide variety of other behavioral tests have also
linked CRF to anxiety and other stress-related behaviors
including depression. Central administration of CRF po-
tentiates acoustic startle in rats, the effects of which c linked CRF to anxiety and other stress-related behaviors
including depression. Central administration of CRF po-
tentiates acoustic startle in rats, the effects of which can
be blocked by the CRF antagonist (Swerdlow et al including depression. Central administration of CRF potentiates acoustic startle in rats, the effects of which ca
be blocked by the CRF antagonist (Swerdlow et al., 1986)
or the anxiolytic benzodiazepine, chlordiazepoxic
(tentiates acoustic startle in rats, the effects of which can
be blocked by the CRF antagonist (Swerdlow et al., 1989) squ
or the anxiolytic benzodiazepine, chlordiazepoxide ior
(Swerdlow et al., 1986). CRF also decreases s be blocked by the CRF antagonist (Swerdlow et al., 1989)
or the anxiolytic benzodiazepine, chlordiazepoxide
(Swerdlow et al., 1986). CRF also decreases social inter-
action in rats without decreasing locomotion (Dunn and
F or the anxiolytic benzodiazepine, chlordiazepoxide
(Swerdlow et al., 1986). CRF also decreases social inter-
action in rats without decreasing locomotion (Dunn and
File, 1987). This is considered evidence of anxiogenesis
a (Swerdlow et al., 1986). CRF also decreases social inter-
action in rats without decreasing locomotion (Dunn and
File, 1987). This is considered evidence of anxiogenesis
and is reversed by the CRF antagonist. CRF facilita action in rats without decreasing locomotion (Dunn and File, 1987). This is considered evidence of anxiogenesis and is reversed by the CRF antagonist. CRF facilitates stress-induced fighting induced by inescapable foot sh File, 1987). This is considered evidence of anxiogenesis
and is reversed by the CRF antagonist. CRF facilitates
stress-induced fighting induced by inescapable foot shock
(Tazi et al., 1987). Moreover, α -helical CRF₉₋₄ and is reversed by the CRF antagonist. CRF facilitates
stress-induced fighting induced by inescapable foot shock
(Tazi et al., 1987). Moreover, α -helical CRF₉₋₄₁ blocks
this and the fighting induced by higher levels stress-induced fighting induced by inescapable foot shock

(Tazi et al., 1987). Moreover, α -helical CRF₉₋₄₁ blocks

this and the fighting induced by higher levels of stress

alone. Following exposure to odors associa this and the fighting induced by higher levels of stress
alone. Following exposure to odors associated with fear-
induced urination and defecation from a different set of
rats, α -helical CRF₉₋₄₁ reduces the level of alone. Following exposure to odors associated with fear-
induced urination and defecation from a different set of
rats, α -helical CRF₉₋₄₁ reduces the level of anxiety and
hesitation observed in previously "unstressed induced urination and defecation from a different set of
rats, α -helical CRF₉₋₄₁ reduces the level of anxiety and
hesitation observed in previously "unstressed" rats (Tak-
ahashi et al., 1990). Kalin and colleagues h induced urination and defecation from a different set
rats, α -helical CRF₉₋₄₁ reduces the level of anxiety a
hesitation observed in previously "unstressed" rats (Te
ahashi et al., 1990). Kalin and colleagues have sho rats, α -helical CRF₉₋₄₁ reduces the level of anxiety and hesitation observed in previously "unstressed" rats (Tak-
ahashi et al., 1990). Kalin and colleagues have shown
that i.c.v. CRF increases stress-induced freezi hesitation observed in previously "unstressed" rats (Takahashi et al., 1990). Kalin and colleagues have shown that i.c.v. CRF increases stress-induced freezing behaviors elicited by electric shock (Sherman and Kalin, 1988) ahashi et al., 1990). Kalin and colleagues have shown
that i.c.v. CRF increases stress-induced freezing behav-
iors elicited by electric shock (Sherman and Kalin, 1988).
These stress-induced freezing behaviors are conside that i.c.v. CRF increases stress-induced freezing behav-
iors elicited by electric shock (Sherman and Kalin, 1988).
These stress-induced freezing behaviors are considered
an index of a rat's level of fear. Like many of th iors elicited by electric shock (Sherman and Kalin, 198
These stress-induced freezing behaviors are consider
an index of a rat's level of fear. Like many of t
behaviors and tests described previously, α -helic
CRF₉₋₄₁ These stress-induced freezing behaviors are considered
an index of a rat's level of fear. Like many of the
behaviors and tests described previously, α -helical
CRF₉₋₄₁ blocks the effects of CRF-induced and shock-
indu an index of a rat's level of fear. Like many of the
behaviors and tests described previously, α -helical
CRF₉₋₄₁ blocks the effects of CRF-induced and shock-
induced freezing behaviors when given 20, but not 40,
minut behaviors and tests described previously, α -helical CRF₉₋₄₁ blocks the effects of CRF-induced and shock-
induced freezing behaviors when given 20, but not 40,
minutes prior to foot shock (Kalin et al., 1988; Kalin an induced freezing behaviors when given 20, but not 40, minutes prior to foot shock (Kalin et al., 1988; Kalin and Takahashi, 1990). This group has also studied the effects of i.c.v. CRF on primate infants (Kalin et al., 198 induced freezing behaviors when given 20, but not
minutes prior to foot shock (Kalin et al., 1988; Kalin a
Takahashi, 1990). This group has also studied the effe
of i.c.v. CRF on primate infants (Kalin et al., 198
Infant r minutes prior to foot shock (Kalin et al., 1988; Kalin and Takahashi, 1990). This group has also studied the effects of i.c.v. CRF on primate infants (Kalin et al., 1989). Infant rhesus monkeys emit frequent distress voca Takahashi, 1990). This group has also studied the effects
of i.c.v. CRF on primate infants (Kalin et al., 1989).
Infant rhesus monkeys emit frequent distress vocaliza-
tions ("coos") and alter their activity levels when b of i.c.v. CRF on primate infants (Kalin et al., 1989).
Infant rhesus monkeys emit frequent distress vocaliza-
tions ("coos") and alter their activity levels when briefly
separated from their mothers. CRF, at doses $>10 \mu$ Infant rhesus monkeys emit frequent distress vocaliza-
tions ("coos") and alter their activity levels when briefly
separated from their mothers. CRF, at doses >10 μ g
i.c.v., inhibited this behavior without affecting di tions ("coos") and alter their activity levels when briefly
separated from their mothers. CRF, at doses >10 μ g
i.c.v., inhibited this behavior without affecting distress
vocalizations. Moreover, relatively large doses separated from their mothers. CRF, at doses >10 μ g
i.c.v., inhibited this behavior without affecting distress
vocalizations. Moreover, relatively large doses of CRF
administered i.c.v. to adult rhesus monkeys produced
 vocalizations. Moreover, relatively large doses of CRF administered i.c.v. to adult rhesus monkeys produced symptoms of behavioral despair similar to that induced by long-term separation (Kalin et al., 1983c; Kalin, 1990). administered i.c.v. to adult rhesus monkeys produced during a 15-min test period 45 min following infusion of CRF into the

that naloxone failed to alter the increases in noradrener-

gic metabolism produced by i.c.v. CRF in the prefrontal

cortex, hypothalamus, and brainstem of mice.

Another test of anxiogenic activity is the conflict test st NEMEROFF
sickness or sedation and is likely linked to increased
fearfulness. Finally, it has been shown that prior re-NEMEROFF
sickness or sedation and is likely linked to increased
fearfulness. Finally, it has been shown that prior re-
straint stress enhances locomotor responses to saline owens and nemerors
actions of sickness or sedation and is likely linked to increased
urther evi-
fearfulness. Finally, it has been shown that prior re-
tions been straint stress enhances locomotor responses to saline
() re included to increased
sickness or sedation and is likely linked to increased
fearfulness. Finally, it has been shown that prior re-
straint stress enhances locomotor responses to saline
injections and the intensity of ster sickness or sedation and is likely linked to increased
fearfulness. Finally, it has been shown that prior re-
straint stress enhances locomotor responses to saline
injections and the intensity of stereotypic behaviors to
a fearfulness. Finally, it has been shown that prior
straint stress enhances locomotor responses to si
injections and the intensity of stereotypic behavior
amphetamine in rats. These sensitizing effects of p
exposure to stre straint stress enhances locomotor responses to saline
injections and the intensity of stereotypic behaviors to
amphetamine in rats. These sensitizing effects of prior
exposure to stress can be attenuated by i.c.v. administ injections and the intensity
amphetamine in rats. These
exposure to stress can be atte
tion of the CRF antagonist
stressor (Cole et al., 1990).
We and others have attem nphetamine in rats. These sensitizing effects of prosure to stress can be attenuated by i.c.v. administ
on of the CRF antagonist at the time of the initessor (Cole et al., 1990).
We and others have attempted to localize th

exposure to stress can be attenuated by i.c.v. administra-
tion of the CRF antagonist at the time of the initial
stressor (Cole et al., 1990).
We and others have attempted to localize the anatom-
ical site of action for ma tion of the CRF antagonist at the time of the initial
stressor (Cole et al., 1990).
We and others have attempted to localize the anatom-
ical site of action for many of these behaviors. Because
CRF is known to directly inc stressor (Cole et al., 1990).
We and others have attempted to localize the anatom
ical site of action for many of these behaviors. Because
CRF is known to directly increase noradrenergic cel
firing in the locus ceruleus an We and others have attempted to localize the ana
ical site of action for many of these behaviors. Bec
CRF is known to directly increase noradrenergic
firing in the locus ceruleus and because of the
established hypothesis l ical site of action for many of these behaviors. Because CRF is known to directly increase noradrenergic cell
firing in the locus ceruleus and because of the well-
established hypothesis linking noradrenergic neurotrans-
m CRF is known to directly increase noradrenergic cell
firing in the locus ceruleus and because of the well-
established hypothesis linking noradrenergic neurotrans-
mission with stress, anxiety, and depressive disorders,
we firing in the locus ceruleus and because of the welestablished hypothesis linking noradrenergic neurotran mission with stress, anxiety, and depressive disorder we examined the behavioral effects of microinfusion (CRF into established hypothesis linking noradrenergic neurotrans-
mission with stress, anxiety, and depressive disorders,
we examined the behavioral effects of microinfusion of
CRF into the locus ceruleus (Butler et al., 1990). Anx mission with stress, anxiety, and depressive disorders,
we examined the behavioral effects of microinfusion of
CRF into the locus ceruleus (Butler et al., 1990). Anxi-
ogenic activity was assessed in rats placed in an open we examined the behavioral effects of microinfusion of CRF into the locus certure all, 1990). Anxi-

ogenic activity was assessed in rats placed in an open

field containing a small, darkened compartment that was

nonthre CRF into the locus ceruleus (Butler et al., 1990). Anxi-
ogenic activity was assessed in rats placed in an open
field containing a small, darkened compartment that was
nonthreatening to the rats. Bilateral infusion of CRF nonthreatening to the rats. Bilateral infusion of CRF (1 to 100 ng) into the locus ceruleus dose dependently increased the time spent in the darkened compartment and decreased the amount of time spent exploring the outside field containing a small, darkened compartment that was
nonthreatening to the rats. Bilateral infusion of CRF (1
to 100 ng) into the locus ceruleus dose dependently
increased the time spent in the darkened compartment
and nonthreatening to the rats. Bilateral infusion of CRF (1 to 100 ng) into the locus ceruleus dose dependently increased the time spent in the darkened compartment and decreased the amount of time spent exploring the outside to 100 ng) into the locus ceruleus dose dependen
increased the time spent in the darkened compartme
and decreased the amount of time spent exploring t
outside of the compartment or venturing into the inr
squares of the ope and decreased the amount of time spent exploring the outside of the compartment or venturing into the inner squares of the open field, all indices of anxiogenic behavior (fig. 6). In addition, significant increases in the centration of the norepinephrine metabolite 3,4-dihyoutside of the compartment or venturing into the inner
squares of the open field, all indices of anxiogenic behav-
ior (fig. 6). In addition, significant increases in the con-
centration of the norepinephrine metabolite 3, squares of the open field, all indices of anxiogenic behavior (fig. 6). In addition, significant increases in the concentration of the norepinephrine metabolite 3,4-dihy-
droxyphenylglycol was seen in forebrain projection ior (fig. 6). In addition, significant increases in the concentration of the norepinephrine metabolite 3,4-dihy-
droxyphenylglycol was seen in forebrain projection areas.
These data suggested that CRF produces its anxiogen centration of the norepinephrine metabolite 3,4-dihy-
droxyphenylglycol was seen in forebrain projection areas.
These data suggested that CRF produces its anxiogenic
effects, at least in part, by increasing the activity of droxyphenylglycol was seen in forebrain projection areas.
These data suggested that CRF produces its anxiogenic
effects, at least in part, by increasing the activity of locus
ceruleus noradrenergic neurons. In support of These data suggested that CRF produces its anxiogenic
effects, at least in part, by increasing the activity of locus
ceruleus noradrenergic neurons. In support of this hy-
pothesis are the findings of Cole and Koob (1988) effects, at least in part, by increasing the activity of locus
ceruleus noradrenergic neurons. In support of this hy-
pothesis are the findings of Cole and Koob (1988) who
observed that the β -adrenergic blocker propran ceruleus noradrenergic neurons. In support of this hypothesis are the findings of Cole and Koob (1988) who observed that the β -adrenergic blocker propranolol blocked the reduction in punished responding produced by i.c pothesis are the findings of Cole and Koob (1988) who observed that the β -adrenergic blocker propranolol blocked the reduction in punished responding produced by i.c.v. CRF administration in the conflict test. In contr by i.c.v. CRF administration in the conflict test. In

cerebral aqueduct or locus ceruleus. The number of animals per group
during a 15-min test period 45 min following infusion of CRF into the
cerebral aqueduct or locus ceruleus. The number of animals per group
is indicated a FIG. 6. Time spent withdrawn in a small darkened compartment
during a 15-min test period 45 min following infusion of CRF into the
cerebral aqueduct or locus ceruleus. The number of animals per group
is indicated at each FIG. 6. Time spent withdrawn in a small darkened compartme
during a 15-min test period 45 min following infusion of CRF into t
cerebral aqueduct or locus ceruleus. The number of animals per gro
is indicated at each data p during a 15-min test period 45 min following infusion of CRF into the cerebral aqueduct or locus ceruleus. The number of animals per group is indicated at each data point. Significantly different from controls using Dunne

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 $\begin{array}{c} \text{corricorr} \\ \text{benzodiazepine inverse agonist FG 7142, which is it} \\ \text{anxiogenic. These results are most likely due to posts} \\ \text{aptic } \beta\text{-receptor blockade in forebrain terminal fields} \end{array}$ CORTICOTROPIN-RELI
benzodiazepine inverse agonist FG 7142, which is itself in
anxiogenic. These results are most likely due to postsyn-
aptic β -receptor blockade in forebrain terminal fields of p:
the locus ceruleus an benzodiazepine inverse agonist FG 7142, which is itself in anxiogenic. These results are most likely due to postsyn-
aptic β -receptor blockade in forebrain terminal fields of picked to be the result of ir
the locus cer benzodiazepine inverse agonist FG 7142, which is itself anxiogenic. These results are most likely due to postsynaptic β -receptor blockade in forebrain terminal fields of the locus ceruleus and are not thought to be the anxiogenic. These results are most likely due to postsynaptic β -receptor blockade in forebrain terminal fields of the locus ceruleus and are not thought to be the result of 5-HT antagonism or local anesthetic propertie aptic β -receptor blockade in forebrain terminal fields of problem the locus ceruleus and are not thought to be the result of in 5-HT antagonism or local anesthetic properties of pro-
5-HT antagonism or local anesthetic the locus ceruleus and are not thought to be the result of ir
5-HT antagonism or local anesthetic properties of pro-
pranolol. Although central administration of CRF, stress,
or administration of the α_2 antagonist, id 5-HT antagonism or local anesthetic properties of pro-
pranolol. Although central administration of CRF, stress,
or administration of the α_2 antagonist, idazoxan, elicited
decreases in exploratory behavior, presumably pranolol. Although central administration of CRF, stress,
or administration of the α_2 antagonist, idazoxan, elicited
decreases in exploratory behavior, presumably through
increased locus ceruleus noradrenergic activit or administration of the α_2 antagonist, idazoxan, elicited
decreases in exploratory behavior, presumably through
increased locus ceruleus noradrenergic activity, Berridge
and Dunn (1989) suggested that it is noradrene decreases in exploratory behavior, presumably through
increased locus ceruleus noradrenergic activity, Berridge A. S
and Dunn (1989) suggested that it is noradrenergic ac-
tivation of CRF release in the CNS, rather than th increased locus ceruleus noradrenergic activity, Berridge
and Dunn (1989) suggested that it is noradrenergic ac-
tivation of CRF release in the CNS, rather than the
reverse, that is responsible for the changes observed in
 and Dunn (1989) suggested that it is noradrenergic activation of CRF release in the CNS, rather than the to lefter reverse, that is responsible for the changes observed in effectness-induced exploratory behavior. Although tivation of CRF release in the CNS, rather than the reverse, that is responsible for the changes observed stress-induced exploratory behavior. Although it is nonconceivable that certain noradrenergic receptors maregulate t reverse, that is responsible for the changes observed in ef
stress-induced exploratory behavior. Although it is not
inconceivable that certain noradrenergic receptors may
regulate the activity of CRF neurons, it does not d effects. inconceivable that certain noradrenergic receptors may
regulate the activity of CRF neurons, it does not deter-
mine the anatomical site at which CRF produces its
effects.
In summary, we believe that the available data sup

regulate the activity of CRF neurons, it does not deter-
mine the anatomical site at which CRF produces its
effects.
In summary, we believe that the available data support
a role for endogenous CRF neurons in increasing l mine the anatomical site at which CRF produces its
effects. (
In summary, we believe that the available data support
in
a role for endogenous CRF neurons in increasing locus
free cruleus activity as a probable mechanism f effects.

In summary, we believe that the available data support

in

a role for endogenous CRF neurons in increasing locus

ceruleus activity as a probable mechanism for some of

the observed behaviors and anxiogenic eff In summary, we believe that the available data support
a role for endogenous CRF neurons in increasing locus
ceruleus activity as a probable mechanism for some of
the observed behaviors and anxiogenic effects produced
by s and anxiogeni
is has potenti
TABLE 1
d symptoms of ma

y stress. As such, this has potentially vital clinical
suppression (DSM varial and symptoms of major depression (DSM Sourial and the behavioral effects of centrally administered CRF to elected and the behavioral effects of Similarities between signs and symptoms of major depression (DSM

DSM III-R major depression	Effects of centrally administered CRF
Depressed mood (irritable mood	Mimics the behavioral de-
in children and adolescents)	spair syndrome observed
most of day, nearly every day,	after maternal separation
as indicated either by subjec-	in rhesus monkey infants
tive account or observations by others	
Markedly diminished interest or	Diminishes sexual behavior
pleasure in all or almost all ac- tivities most of day, nearly every day	in male and female rats
Significant weight loss or weight gain when not dieting or de- crease or increase in appetite nearly every day	Decreases food consumption in rats
Insomnia or hypersomnia nearly every day	Disrupts normal sleep pat- terns with concomitant EEG changes
Psychomotor agitation or retar- dation nearly every day	Increases locomotor activity in a familiar environment and produces "stress-like" alterations in locomotion in a novel environment
Fatigue or loss of energy nearly every day	No data
Feelings of worthlessness or ex- cessive or inappropriate guilt nearly every day	No data
Diminished ability to think or concentrate or indecisiveness nearly every day	No data
Recurrent thoughts of death, re- current suicidal ideation or a suicide attempt	No data

CORTICOTROPIN-RELEASING FACTOR **451**

benzodiazepine inverse agonist FG 7142, which is itself implications in the pathogenesis of a variety of anxiety

anxiogenic. These results are most likely due to postsyn- and depressi LEASING FACTOR
implications in the pathogenesis of a variety of anxiety
and depressive disorders. Indeed, many of the effects LEASING FACTOR 451
implications in the pathogenesis of a variety of anxiety
and depressive disorders. Indeed, many of the effects
produced by centrally administered CRF are highly rem-451
implications in the pathogenesis of a variety of anxiety
and depressive disorders. Indeed, many of the effect:
produced by centrally administered CRF are highly rem
iniscent of the signs and symptoms of major depressio implications in the pathogenesis of a variety of anxiety
and depressive disorders. Indeed, many of the effects
produced by centrally administered CRF are highly rem-
iniscent of the signs and symptoms of major depression
(implications
and depress
produced by
iniscent of t
(table 1).
VII **Example 2018 Set all substance in the set all specified CRF** are highly rem-
the of the signs and symptoms of major depression
1).
VII. Electrophysiological Responses to
Corticotropin-releasing Factor

Corticotropin-releasing Factor (table 1).
VII. Electrophysiological Responses to
Corticotropin-releasing Factor
A. Single-Unit Recordings

II-R criteria) and the behavioral effects of centrally administered CRF and Nemetor Similarities between signs and symptoms of major depression (DSM Souza and Nemetoff, 1990), three chapters are devoted in laboratory ani VII. Electrophysiological Responses to

Corticotropin-releasing Factor

Single-Unit Recordings

One of the criteria that must be fulfilled for a substance

be considered a neurotransmitter is demonstration of **Corticotropin-releasing Factor**
A. Single-Unit Recordings
One of the criteria that must be fulfilled for a substance
to be considered a neurotransmitter is demonstration of
effects of the substance on the electrical activ A. Single-Unit Recordings
One of the criteria that must be fulfilled for a substance
to be considered a neurotransmitter is demonstration of
effects of the substance on the electrical activity of
neurons. Toward this end, A. Single-Unit necoraings

One of the criteria that must be fulfilled for a substance

to be considered a neurotransmitter is demonstration of

effects of the substance on the electrical activity of

neurons. Toward this e One of the criteria that must be fulfilled for a substance
to be considered a neurotransmitter is demonstration of
effects of the substance on the electrical activity of
neurons. Toward this end, CRF has been used in a
num to be considered a neurotransmitter is demonstration of effects of the substance on the electrical activity of neurons. Toward this end, CRF has been used in a number of studies in which the peptide has been shown to alter effects of the substance on the electrical activity of neurons. Toward this end, CRF has been used in a number of studies in which the peptide has been shown to alter the electrical activity of various neurons. These elect neurons. Toward this end, CRF has been used in a
number of studies in which the peptide has been shown
to alter the electrical activity of various neurons. These
electrophysiological studies are generally of three types:
(number of studies in which the peptide has been shown
to alter the electrical activity of various neurons. These
electrophysiological studies are generally of three types:
(*a*) single-unit recordings from brain slice prep to alter the electrical activity of various neurons. These
electrophysiological studies are generally of three types:
(a) single-unit recordings from brain slice preparations
in vitro, (b) single-unit recordings from anes electrophysiological studies are generally of three type (a) single-unit recordings from brain slice preparation in vitro, (b) single-unit recordings from anesthetized of reely moving rats in vivo, and (c) EEG recordin (a) single-unit recordings from brain slice preparations
in vitro, (b) single-unit recordings from anesthetized or
freely moving rats in vivo, and (c) EEG recordings from
rats. Although there is a paucity of electrophysio in vitro, (b) single-unit recordings from anesthetized or
freely moving rats in vivo, and (c) EEG recordings from
rats. Although there is a paucity of electrophysiological
studies to date, the findings summarized below freely moving rats in vivo, and (c) EEG recordings from
rats. Although there is a paucity of electrophysiological
studies to date, the findings summarized below clearly
support a role for CRF as a neurotransmitter in a wid rats. Although there is a paucity of electrophysiological
studies to date, the findings summarized below clearly
support a role for CRF as a neurotransmitter in a wide
variety of brain areas. For interested readers, in the studies to date, the findings summarized below clearly
support a role for CRF as a neurotransmitter in a wide
variety of brain areas. For interested readers, in the first
comprehensive book published concerning CRF (De
Sou support a role for
variety of brain ar
comprehensive b
Souza and Nemer
to electrophysiolo
Several studies riety of brain areas. For interested readers, in the first
mprehensive book published concerning CRF (De
vuza and Nemeroff, 1990), three chapters are devoted
electrophysiology.
Several studies of the effects of CRF on the

comprehensive book published concerning CRF (De
Souza and Nemeroff, 1990), three chapters are devoted
to electrophysiology.
Several studies of the effects of CRF on the activity of
various CNS neurons indicate that the pep Souza and Nemeroff, 1990), three chapters are devoted
to electrophysiology.
Several studies of the effects of CRF on the activity of
various CNS neurons indicate that the peptide exerts
predominantly excitatory actions in to electrophysiology.

Several studies of the effects of CRF on the activity of

various CNS neurons indicate that the peptide exerts

predominantly excitatory actions in the locus ceruleus

(fig. 7) (Valentino et al., 198 Several studies of the effects of CRF on the activity of
various CNS neurons indicate that the peptide exerts
predominantly excitatory actions in the locus ceruleus
(fig. 7) (Valentino et al., 1983), cerebral cortex and so various CNS neurons indicate that the peptide exerts
predominantly excitatory actions in the locus ceruleus
(fig. 7) (Valentino et al., 1983), cerebral cortex and some
regions of the hypothalamus (Eberly et al., 1983), hip predominantly excitatory actions in the locus ceruleus
(fig. 7) (Valentino et al., 1983), cerebral cortex and some
regions of the hypothalamus (Eberly et al., 1983), hip-
pocampus (Aldenhoff et al., 1983), and lumbar spina (fig. 7) (Valentino et al., 1983), cerebral cortex and sor
regions of the hypothalamus (Eberly et al., 1983), hi
pocampus (Aldenhoff et al., 1983), and lumbar spin
cord motor neurons (Bell and De Souza, 1989). Howeve
sever regions of the hypothalamus (Eberly et al., 1983), hip-
pocampus (Aldenhoff et al., 1983), and lumbar spinal
cord motor neurons (Bell and De Souza, 1989). However
several studies have also indicated predominantly inhib-
it pocampus (Aldenhoff et al., 1983), and lumbar spinal
cord motor neurons (Bell and De Souza, 1989). However,
several studies have also indicated predominantly inhib-
itory actions of CRF in the lateral septum, thalamus,
and cord motor neurons (Bell and De Souza, 1989). However,
several studies have also indicated predominantly inhib-
itory actions of CRF in the lateral septum, thalamus,
and hypothalamic PVN (Eberly et al., 1983). Many brain
r

FIG. 7. Effect of pressure application of CRF to different neurons.
CRF was directly applied to neurons of the locus ceruleus (LC), cerebellar Purkinje cells (CB), neurons of the mesencephalic nucleus of the trigeminus (MV FIG. 7. Effect of pressure application of CRF to different neurons.
CRF was directly applied to neurons of the locus ceruleus (LC),
cerebellar Purkinje cells (CB), neurons of the mesencephalic nucleus
of the trigeminus (MV CRF was directly applied to neurons of the locus ceruleus (LC), cerebellar Purkinje cells (CB), neurons of the mesencephalic nucleus of the trigeminus (MV), or parabrachial cells (PB) for the time period indicated by bars of the trigeminus (MV), or parabrachial cells (PB) for the time period indicated by bars above the records. Numbers above the bars, amount of pressure in pounds per inch that was applied to the CRF-containing micropipette. of the the same as that used on LC cells. Numbers above the bars, amount
of pressure in pounds per inch that was applied to the CRF-containing
micropipette. For CB and MV cells, the pipette used to administer CRF
was the s of pressure in pounds per inch that was applied to the CRF-containing
micropipette. For CB and MV cells, the pipette used to administer CRF
was the same as that used on LC cells in the corresponding records in
the top pane micropipette. For CB and MV cells, the pip
was the same as that used on LC cells in
the top panel. Although CRF was excitate
PB neuron, it had no effect on CB or
permission from Valentino et al. (1983).

effects of CRF determined. At least as far as the hipp
campus is concerned, the increased electrical activi owens and networks
effects of CRF determined. At least as far as the hippo-
campus is concerned, the increased electrical activity
appears to result from diminished afterhyperpolarization ac owens al
effects of CRF determined. At least as far as the hippo
campus is concerned, the increased electrical activity
appears to result from diminished afterhyperpolarization
following bursts of firings (Aldenhoff et al. effects of CRF determined. At least as far as the hippo-
campus is concerned, the increased electrical activity
appears to result from diminished afterhyperpolarization
following bursts of firings (Aldenhoff et al., 1983; 1990).

appears to result from diminished afterhyperpolarization act
following bursts of firings (Aldenhoff et al., 1983; Siggins, be
1990).
De Souza's group (Sharkey et al., 1989) examined the On
effects of i.c.v. CRF on glucose following bursts of firings (Aldenhoff et al., 1983; Siggins, 1990).

De Souza's group (Sharkey et al., 1989) examined the

effects of i.c.v. CRF on glucose utilization, a method used

to assess neuronal activity, using 1990). De Souza's group (Sharkey et al., 1989) examined the effects of i.c.v. CRF on glucose utilization, a method used to assess neuronal activity, using $[^{14}C]2$ -deoxyglucose uptake in rat brain. Evidence of increased De Souza's group (Sharkey et al., 1989) examined the O
effects of i.c.v. CRF on glucose utilization, a method used
to assess neuronal activity, using $[^{14}C]2$ -deoxyglucose in
uptake in rat brain. Evidence of increased n effects of i.c.v. CRF on glucose utilization, a method u
to assess neuronal activity, using $[^{14}C]2$ -deoxygluc
uptake in rat brain. Evidence of increased neuro
activity (evidenced by increased glucose utilization)
observ to assess neuronal activity, using [¹⁴C]2-deoxyglucose
uptake in rat brain. Evidence of increased neuronal
activity (evidenced by increased glucose utilization) was
observed in the median eminence and lateral hypothal-
a uptake in rat brain. Evidence of increased neuronal of identity (evidenced by increased glucose utilization) was tive observed in the median eminence and lateral hypothal-
amus consistent with its known hypophysiotropic ac activity (evidenced by increased glucose utilization) was
observed in the median eminence and lateral hypothal-
amus consistent with its known hypophysiotropic ac-
tions. Moreover, CRF also increased glucose uptake in
regi observed in the median eminence and lateral hypothal-
amus consistent with its known hypophysiotropic ac-
tions. Moreover, CRF also increased glucose uptake in
regions implicated in mediating the stress response, in-
cludi amus consistent with its known hypophysiotropic ac-
tions. Moreover, CRF also increased glucose uptake in
regions implicated in mediating the stress response, in-
cluding the locus ceruleus and raphe nucleus. Increases
wer tions. Moreover, CRF also increased glucose uptake in regions implicated in mediating the stress response, including the locus ceruleus and raphe nucleus. Increases were also observed in several thalamic nuclei, localized regions implicated in mediating the stress response, including the locus ceruleus and raphe nucleus. Increases
were also observed in several thalamic nuclei, localized
areas of the cerebellum, the red nucleus, and inferior cluding the locus ceruleus and raphe nucleus. Increa
were also observed in several thalamic nuclei, locali:
areas of the cerebellum, the red nucleus, and infer
olive. Reductions in activity were observed in the p
frontal c tum. eas of the cerebellum, the red nucleus, and infive. Reductions in activity were observed in the bontal cortex, nucleus accumbens, and dorsal tegn
m.
The brain region most closely scrutinized electrophysically as a target f

frontal cortex, nucleus accumbens, and dorsal tegmentum.

The brain region most closely scrutinized electrophys-

iologically as a target for the actions of CRF is the locus

ceruleus. The locus ceruleus contains the norad tum.

The brain region most closely scrutinized electrophys-

iologically as a target for the actions of CRF is the locus

ceruleus. The locus ceruleus contains the noradrenergic

perikarya that project >70% of the norepin The brain region most closely scrutinized electrophysiologically as a target for the actions of CRF is the locus ceruleus. The locus ceruleus contains the noradrenergic perikarya that project >70% of the norepinephrine fib iologically as a target for the actions of CRF is the locus
ceruleus. The locus ceruleus contains the noradrenergic
perikarya that project >70% of the norepinephrine fibers
for the forebrain. As noted previously, CRF-cont ceruleus. The locus ceruleus contains the noradrenergic
perikarya that project >70% of the norepinephrine fibers
to the forebrain. As noted previously, CRF-containing
nerve terminals have been visualized in both rat and
pr to the forebrain. As noted previously, CRF-containing and primate locus ceruleus. The origin of these fibers is, endowever, unknown. Activation of the locus ceruleus and subsequent release of norepinephrine in its project nerve terminals have been visualized in both rat and
primate locus ceruleus. The origin of these fibers is,
however, unknown. Activation of the locus ceruleus and
subsequent release of norepinephrine in its projection
area primate locus ceruleus. The origin of these fibers is,
however, unknown. Activation of the locus ceruleus and 198
subsequent release of norepinephrine in its projection cha
areas have been implicated in arousal and vigilan however, unknown. Activation of the locus ceruleus and
subsequent release of norepinephrine in its projection
areas have been implicated in arousal and vigilance re-
sponses, as well as in the pathophysiology of anxiety an areas have been implicated in arousal and vigilance re-
sponses, as well as in the pathophysiology of anxiety and
depression. Briefly, excitation of the locus ceruleus is
thought to notify the CNS that incoming sensory inf areas have been implicated in arousal and vigilance responses, as well as in the pathophysiology of anxiety and depression. Briefly, excitation of the locus ceruleus is thought to notify the CNS that incoming sensory infor sponses, as well as in the pathophysiology of anxiety and
depression. Briefly, excitation of the locus ceruleus is
thought to notify the CNS that incoming sensory infor-
mation should be attended to. This is a functionally depression. Briefly, excitation of the locus ceruleus is thought to notify the CNS that incoming sensory information should be attended to. This is a functionally antagor useful adaptive response, particularly in stressful thought to notify the CNS that incoming sensory infor-
mation should be attended to. This is a functionally anta-
useful adaptive response, particularly in stressful or life-
threatening situations (Bloom, 1979; Redmond, 1 mation should be attended to. This is a functionally useful adaptive response, particularly in stressful or life-
threatening situations (Bloom, 1979; Redmond, 1987). A role for CRF in integrating an organism's response to useful adaptive response, parthreatening situations (Bloor
role for CRF in integrating
stress would, therefore, fit
effects in the locus ceruleus.
As alluded to above, i.c.v. reatening situations (Bloom, 1979; Redmond, 1987)
le for CRF in integrating an organism's response
ress would, therefore, fit nicely with its activation
fects in the locus ceruleus.
As alluded to above, i.c.v. CRF increase

role for CRF in integrating an organism's response t
stress would, therefore, fit nicely with its activations
effects in the locus ceruleus.
As alluded to above, i.c.v. CRF increases the spontar
neous discharge rate of the stress would, therefore, fit nicely with its activational
effects in the locus ceruleus.
As alluded to above, i.c.v. CRF increases the sponta-
neous discharge rate of the locus ceruleus in both anes-
thetized and unanesthe effects in the locus ceruleus.

As alluded to above, i.c.v. CRF increases the sponta-

neous discharge rate of the locus ceruleus in both anes-

thetized and unanesthetized rats (Valentino et al., 1983;

Valentino and Foot As alluded to above, i.c.v. CRF increases the sponta-
neous discharge rate of the locus ceruleus in both anes-
thetized and unanesthetized rats (Valentino et al., 1983;
Valentino and Foote, 1987; Valentino, 1990). Followin neous discharge rate of the locus ceruleus in both anes-
thetized and unanesthetized rats (Valentino et al., 1983;
Valentino and Foote, 1987; Valentino, 1990). Following
confirmation of this finding, these investigators st thetized and unanesthetized rats (Valentino et al., 1983; behaviolentino and Foote, 1987; Valentino, 1990). Following dose
confirmation of this finding, these investigators studied activitie action of CRF on evoked dischar the action of CRF on evoked discharges from the locus
ceruleus. Various sensory and noxious stimuli result in
immediate locus ceruleus discharge for approximately 8
to 100 ms after the stimulus. This is followed by a perio ceruleus. Various sensory and noxious stimuli result
immediate locus ceruleus discharge for approximately
to 100 ms after the stimulus. This is followed by a peri
during which relatively few discharges are observed (p
tact immediate locus ceruleus discharge for approximately 80
to 100 ms after the stimulus. This is followed by a period
during which relatively few discharges are observed (pos-
tactivational inhibition). I.C.V. CRF, although i to 100 ms after the stimulus. This is followed by a period
during which relatively few discharges are observed (pos-
tactivational inhibition). I.C.V. CRF, although increas-
ing unstimulated discharge activity as described during which relatively few discharges are observed (postactivational inhibition). I.C.V. CRF, although increasing unstimulated discharge activity as described above, decreases evoked activity and results in more discharg tactivational inhibition). I.C.V. CRF, although increas-
ing unstimulated discharge activity as described above, decreases evoked activity and results in more discharges the
during the postactivational phase (Valentino an ing unstimulated discharge activity as described above, dec
decreases evoked activity and results in more discharges the
during the postactivational phase (Valentino and Foote, glue
1988). The overall effect of CRF (1.0 t decreases evoked activity and results in more discharges
during the postactivational phase (Valentino and Foote,
1988). The overall effect of CRF (1.0 to 3.0 μ g) is to
decrease the signal to noise ratio between evoked

campus is concerned, the increased electrical activity ceruleus activation. This is thought to allow for the
appears to result from diminished afterhyperpolarization actions of other neurotransmitters in the target areas NEMEROFF
neurons is generally decreased or unaffected by locus
ceruleus activation. This is thought to allow for the NEMEROFF
neurons is generally decreased or unaffected by locus
ceruleus activation. This is thought to allow for the
actions of other neurotransmitters in the target areas to NEMEROFF
neurons is generally decreased or unaffected by locus
ceruleus activation. This is thought to allow for the
actions of other neurotransmitters in the target areas to
be increased. Therefore, the signal to noise ac meurons is generally decreased or unaffected by locus
ceruleus activation. This is thought to allow for the
actions of other neurotransmitters in the target areas to
be increased. Therefore, the signal to noise activity of neurons is generally decreased or unaffected by locus
ceruleus activation. This is thought to allow for the
actions of other neurotransmitters in the target areas to
be increased. Therefore, the signal to noise activity of ceruleus activation. This is thought to allow for the actions of other neurotransmitters in the target areas to be increased. Therefore, the signal to noise activity of target neurons is increased when the locus ceruleus f actions of other neurotransmitters in the target areas to
be increased. Therefore, the signal to noise activity of
target neurons is increased when the locus ceruleus fires.
One hypothesis suggests that this biases target be increased. Therefore, the signal to noise activity of target neurons is increased when the locus ceruleus fires.
One hypothesis suggests that this biases target neurons to a more sensitive deliniation of sensory input. target neurons is increased when the locus ceruleus fire
One hypothesis suggests that this biases target neuror
to a more sensitive deliniation of sensory input. Th
initial hypothesis that CRF would enhance the respons
of to a more sensitive deliniation of sensory input. The initial hypothesis that CRF would enhance the response of locus ceruleus neurons to sensory stimuli as an adaptive response to a potentially stressful environment does to a more sensitive deliniation of sensory input. The initial hypothesis that CRF would enhance the response of locus ceruleus neurons to sensory stimuli as an adaptive response to a potentially stressful environment does initial hypothesis that CRF would enhance the response
of locus ceruleus neurons to sensory stimuli as an adap-
tive response to a potentially stressful environment does
not fit with the observed data to date. In contrast, not fit with the observed data to date. In contrast, CRF, at the doses so far studied, decreases the signal to noise ratio by increasing tonic discharge rates. Perhaps CRF-mediated activation of locus ceruleus activity res not fit with the observed data to date. In contrast, CRF,
at the doses so far studied, decreases the signal to noise
ratio by increasing tonic discharge rates. Perhaps CRF-
mediated activation of locus ceruleus activity re at the doses so far studied, decreases the signal to noise
ratio by increasing tonic discharge rates. Perhaps CRF-
mediated activation of locus ceruleus activity results in
persistent norepinephrine release in target regio information. ediated activation of locus ceruleus activity results in
rsistent norepinephrine release in target regions and
rsistent arousal of target neurons to incoming sensory
formation.
Because central CRF administration increases persistent norepinephrine release in target regions and
persistent arousal of target neurons to incoming sensory
information.
Because central CRF administration increases blood
pressure and because activation of the locus

frontal cortex, nucleus accumbens, and dorsal tegmen-

increases sympathetic outflow, Valentino et al., (1986)

The brain region most closely scrutinized electrophys-

iologically as a target for the actions of CRF is the to the forebrain. As noted previously, CRF-containing anesthetized rats. However, both i.c.v. CRF or the stress
nerve terminals have been visualized in both rat and of nitroprusside-induced hypotension produced identical
p mediated activation of locus ceruleus activity results in
persistent norepineprime release in target regions and
persistent arousal of target neurons to incoming sensory
information.
Hecause central CRF administration inc persistent arousal of target neurons to incoming sensory
information.
Because central CRF administration increases blood
pressure and because activation of the locus ceruleus
increases sympathetic outflow, Valentino et al. information.
Because central CRF administration increases blood
pressure and because activation of the locus ceruleus
increases sympathetic outflow, Valentino et al., (1986)
sought to determine whether CRF activation of th Because central CRF administration increases blood
pressure and because activation of the locus ceruleus
increases sympathetic outflow, Valentino et al., (1986)
sought to determine whether CRF activation of the locus
cerul pressure and because activation of the locus ceruleus
increases sympathetic outflow, Valentino et al., (1986)
sought to determine whether CRF activation of the locus
ceruleus was responsible for the previously observed inincreases sympathetic outflow, Valentino et al., (1986)
sought to determine whether CRF activation of the locus
ceruleus was responsible for the previously observed in-
creases in blood pressure. Although CRF did increase
 sought to determine whether CRF activation of the locus
ceruleus was responsible for the previously observed in-
creases in blood pressure. Although CRF did increase
locus ceruleus activity, it did not alter blood pressure ceruleus was responsible for the previously observed increases in blood pressure. Although CRF did increase
locus ceruleus activity, it did not alter blood pressure in
anesthetized rats. However, both i.c.v. CRF or the str creases in blood pressure. Although CRF did increase
locus ceruleus activity, it did not alter blood pressure in
anesthetized rats. However, both i.c.v. CRF or the stress
of nitroprusside-induced hypotension produced ident locus ceruleus activity, it did not alter blood pressure in
anesthetized rats. However, both i.c.v. CRF or the stress
of nitroprusside-induced hypotension produced identical
effects on locus ceruleus activity (Valentino an anesthetized rats. However, both i.c.v. CRF or the stress
of nitroprusside-induced hypotension produced identical
effects on locus ceruleus activity (Valentino and Wehby,
1988). Thus, both perturbations increased tonic dis of nitroprusside-induced hypotension produced identical
effects on locus ceruleus activity (Valentino and Wehby,
1988). Thus, both perturbations increased tonic dis-
charge rates and disrupted locus ceruleus discharge
evok effects on locus ceruleus activity (Valentino and Wehby, 1988). Thus, both perturbations increased tonic discharge rates and disrupted locus ceruleus discharge evoked by sensory stimuli such that stimuli were less effectiv 1988). Thus, both perturbations increased tonic discharge rates and disrupted locus ceruleus discharge evoked by sensory stimuli such that stimuli were less effective in producing phasic increases in locus ceruleus dischar charge rates and disrupted locus ceruleus discharge evoked by sensory stimuli such that stimuli were less effective in producing phasic increases in locus ceruleus discharge. The neuronal effects of nitroprusside infusion evoked by sensory stimuli such that stimuli were leffective in producing phasic increases in locus cerule
discharge. The neuronal effects of nitroprusside infusionstress were abolished by prior administration of the CF
ant effective in producing phasic increases in locus ceruleus
discharge. The neuronal effects of nitroprusside infusion
stress were abolished by prior administration of the CRF
antagonist administered i.c.v. but not dexamethas stress were abolished by prior administration of the CRF
antagonist administered i.c.v. but not dexamethasone.
Results of this study suggest that the stress produced by
nitroprusside-induced hypotension activates locus cer antagonist administered i.c.v. but not dexamethasone.
Results of this study suggest that the stress produced by
nitroprusside-induced hypotension activates locus ceru-
leus activity via release of CRF from CRF neurons.
B. Results of this study suggest that the stress produced by
nitroprusside-induced hypotension activates locus ceru-
leus activity via release of CRF from CRF neurons.
B. Electroencephalographic and Convulsive Studies
EEG s troprusside-induced hypotension activates locus cerus
activity via release of CRF from CRF neurons.
Electroencephalographic and Convulsive Studies
EEG studies of the effects of CRF were recently com
ehensively reviewed by

confirmation of this finding, these investigators studied
the action of CRF on evoked discharges from the locus
decreases in slow wave sleep EEG activity compared to
ceruleus. Various sensory and noxious stimuli result in
 the action of CRF on evoked discharges from the locus

ceruleus. Various sensory and noxious stimuli result in

saline-injected controls (Ehlers, 1986; Ehlers et al.,

immediate locus ceruleus discharge for approximately 8 leus activity via release of CRF from CRF neurons.

B. Electroencephalographic and Convulsive Studies

EEG studies of the effects of CRF were recently com-

prehensively reviewed by Ehlers (1990). Briefly, i.c.v.

CRF resu B. Electroencephalographic and Convulsive Studies
EEG studies of the effects of CRF were recently com-
prehensively reviewed by Ehlers (1990). Briefly, i.c.v.
CRF results in EEG activation associated with increased
behavio B. Electroencephalographic and Convulsive Studies
EEG studies of the effects of CRF were recently com-
prehensively reviewed by Ehlers (1990). Briefly, i.c.v.
CRF results in EEG activation associated with increased
behavio EEG studies of the effects of CRF were recently comprehensively reviewed by Ehlers (1990). Briefly, i.c.
CRF results in EEG activation associated with increase
behavioral activity and decreased sleep time. In fact,
doses t prehensively reviewed by Ehlers (1990). Briefly, i.c.v.
CRF results in EEG activation associated with increased
behavioral activity and decreased sleep time. In fact, at
doses too low to alter locomotor or pituitary-adrena CRF results in EEG activation associated with increased
behavioral activity and decreased sleep time. In fact, at
doses too low to alter locomotor or pituitary-adrenal
activity, rats remained awake and vigilant and display doses too low to alter locomotor or pituitary-adrenal doses too low to alter locomotor or pituitary-adrenal
activity, rats remained awake and vigilant and displayed
decreases in slow wave sleep EEG activity compared to
saline-injected controls (Ehlers, 1986; Ehlers et al.,
19 1986). In contrast to these findings in rats following i.c.v.
CRF administration that are thought to be independent
of pituitary-adrenal activation, Holsboer et al. (1988)
reported that i.v. CRF administration in humans al decreases in slow wave sleep EEG activity compared to
saline-injected controls (Ehlers, 1986; Ehlers et al.,
1986). In contrast to these findings in rats following i.c.v.
CRF administration that are thought to be independe reporting intertal controls (Ehlers, 1986; Ehlers et al., 1986). In contrast to these findings in rats following i.c.v. CRF administration that are thought to be independent of pituitary-adrenal activation, Holsboer et al. 1986). In contrast to these findings in rats following i.c.v.
CRF administration that are thought to be independent
of pituitary-adrenal activation, Holsboer et al. (1988)
reported that i.v. CRF administration in humans al CRF administration that are thought to be independent
of pituitary-adrenal activation, Holsboer et al. (1988)
reported that i.v. CRF administration in humans also
decreased slow wave sleep. Whether these changes were
the r of pituitary-adrenal activation, Holsboer et al. (1988)
reported that i.v. CRF administration in humans also
decreased slow wave sleep. Whether these changes were
the result of large CRF-induced increases in circulating
gl reported that i.v. CRF administration in humans also
decreased slow wave sleep. Whether these changes were
the result of large CRF-induced increases in circulating
glucocorticoids prior to falling asleep is unclear. In rat decreased slow wave sleep. Whether these changes were
the result of large CRF-induced increases in circulating
glucocorticoids prior to falling asleep is unclear. In rats,
as the CRF dose is increased, paroxysmal EEG activ the result of large CRF-induced increases in circulating
glucocorticoids prior to falling asleep is unclear. In rats,
as the CRF dose is increased, paroxysmal EEG activity
is observed after a delay of several hours. There

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CORTICOTROPIN-RELE
then spread to the hippocampus and cerebral cortex
(Ehlers, 1990); seizure activity then follows. It is after
ity CORTICOTROPIN-REI

(Ehlers, 1990); seizure activity then follows. It is after

the spread of EEG seizure activity to the cortex that CORTICOTROPIN-RE
then spread to the hippocampus and cerebral cortex
(Ehlers, 1990); seizure activity then follows. It is after
the spread of EEG seizure activity to the cortex that
physical signs of seizure activity are ob then spread to the hippocampus and cerebral cortex (Ehlers, 1990); seizure activity then follows. It is after the spread of EEG seizure activity to the cortex that physical signs of seizure activity are observed. Of specia (Ehlers, 1990); seizure activity then follows. It is after the spread of EEG seizure activity to the cortex than physical signs of seizure activity are observed. Of special interest is the fact that the EEG activity devel the spread of EEG seizure activity to the cortex that physical signs of seizure activity are observed. Of special conterest is the fact that the EEG activity develops in a tunanner indistinguishable from seizures produced physical signs of seizure activity are observed. Of special
interest is the fact that the EEG activity develops in a
manner indistinguishable from seizures produced by elec-
trical kindling of the amygdala (Ehlers et al., interest is the fact that the EEG activity develops in a
manner indistinguishable from seizures produced by elec-
trical kindling of the amygdala (Ehlers et al., 1983; Weiss
et al., 1986). Weiss et al. (1986) also noted th trical kindling of the amygdala (Ehlers et al., 1983; Weiss
et al., 1986). Weiss et al. (1986) also noted that i.c.v.
CRF sensitized the amygdala to electrical kindling, i.e.,
a reduced number of electrical stimulations we trical kindling of the amygdala (Ehlers et al., 1983; Weiss
et al., 1986). Weiss et al. (1986) also noted that i.c.v. in
CRF sensitized the amygdala to electrical kindling, i.e., co
a reduced number of electrical stimulati et al., 1986). Weiss et al. (1986) also noted that i.c.v. in CRF sensitized the amygdala to electrical kindling, i.e., con a reduced number of electrical stimulations were necessary to produce kindling. In contrast, electr CRF sensitized the amygdala to electrical kindling, i.e.,
a reduced number of electrical stimulations were neces-
sary to produce kindling. In contrast, electrically kindled
rats were less sensitive to CRF-induced seizures a reduced number of electrical stimulations were necessary to produce kindling. In contrast, electrically kindled D
rats were less sensitive to CRF-induced seizures than st
were saline-treated controls. Moreover, tolerance sary to produce kindling. In contrast, electrically kindled Devents were less sensitive to CRF-induced seizures than strewer saline-treated controls. Moreover, tolerance develops to the seizure-inducing actions of i.c.v. C rats were less sensitive to CRF-induced seizures than
were saline-treated controls. Moreover, tolerance devel-
ops to the seizure-inducing actions of i.c.v. CRF. These
results suggest that electrically kindled seizures and were saline-treated c
ops to the seizure-in
results suggest that
CRF-induced seizure
biologically distinct.
Relevant to the re is to the seizure-inducing actions of i.c.v. CRF. T
sults suggest that electrically kindled seizures
RF-induced seizures, although somewhat similar
plogically distinct.
Relevant to the reported alterations in polysom
phy p

results suggest that electrically kindled seizures a
CRF-induced seizures, although somewhat similar,
biologically distinct.
Relevant to the reported alterations in polysomn
raphy produced by CRF (vide supra), centrally ad biologically distinct. The reported alterations in polysomnog-

raphy produced by CRF (vide supra), centrally adminis-

tered CRF significantly shortens the narcosis induced by

pentobarbital (Imaki et al., 1986). These e Relevant to the reported alterations in polysomnog-
raphy produced by CRF (vide supra), centrally adminis-
tered CRF significantly shortens the narcosis induced by
pentobarbital (Imaki et al., 1986). These effects are
blo raphy produced by CRF (vide supra), centrally administered CRF significantly shortens the narcosis induced by reg
pentobarbital (Imaki et al., 1986). These effects are ret
blocked by α -helical CRF₉₋₄₁ and further sug tered CRF significantly shortens the i
pentobarbital (Imaki et al., 1986).
blocked by α -helical CRF₉₋₄₁ and ft
CRF may alter normal sleep mechan
possess intrinsic analeptic properties
CRF clearly alters the firing ra ntobarbital (Imaki et al., 1986). These effects are retrocked by α -helical CRF₉₋₄₁ and further suggest that the RF may alter normal sleep mechanisms and may even Thissess intrinsic analeptic properties. CRF clearly a

blocked by α -helical CRF₉₋₄₁ and further suggest that the CRF may alter normal sleep mechanisms and may even T possess intrinsic analeptic properties.
CRF clearly alters the firing rate of various CNS denotions at lo CRF may alter normal sleep mechanisms and may even
possess intrinsic analeptic properties. $\begin{array}{c}$ et a
CRF clearly alters the firing rate of various CNS
neurons at low doses. Unfortunately, there is a paucity
of data r possess intrinsic analeptic properties.
CRF clearly alters the firing rate of various CNS
neurons at low doses. Unfortunately, there is a paucity
of data regarding the electrophysiological effects of CRF
throughout the CNS CRF clearly alters the firing rate of various CNS denotes an example in the increase of data regarding the electrophysiological effects of CRF throughout the CNS. The major difficulty we have noticed is the inability, to neurons at low doses. Unfortunately, there is a paucity
of data regarding the electrophysiological effects of CRF
throughout the CNS. The major difficulty we have no-
ticed is the inability, to date, to identify a CRF neur of data regarding the electrophysiological effects of CRF
throughout the CNS. The major difficulty we have no-
irciced is the inability, to date, to identify a CRF neuron
in by its electrical signature. Whereas the effect throughout the CNS. The major difficulty we have no-
ticed is the inability, to date, to identify a CRF neuron
by its electrical signature. Whereas the effects of various
environmental and pharmacological manipulations of by its electrical signature. Whereas the effects of variation individual and pharmacological manipulation individual monoamine-containing neurons are measuble, this is not the case with CRF nor is it with majority of other **VIII. Responses of Nonhypophysiotrophysiotropic Server Algeberry CRF** nor is it ity of other putative neuropeptide transm
 VIII. Responses of Nonhypophysiotro
 VIII. Responses of Nonhypophysiotro
 Corticotropin-relea

this is not the case with CRF nor is it with the
prity of other putative neuropeptide transmitters.
VIII. Responses of Nonhypophysiotropic
Corticotropin-releasing Factor Neurons to
Pharmacological and Environmental majority of other putative neuropeptide transmitters.
 PHI. Responses of Nonhypophysiotropic
 **Corticotropin-releasing Factor Neurons to

Pharmacological and Environmental Perturbation A. Primary and Secondary Effects of Stress on Nonendocription A. Primary and Secondary Effects of Stress on**
A. Primary and Secondary Effects of Stress on
**Nonendocrine Corticotropin-releasing Factor Neuron Pharmacological and Environmental
Perturbation**
A. Primary and Secondary Effects of Stress on
Nonendocrine Corticotropin-releasing Factor Neurons
1. Effects of stress on corticotropin-releasing factor neu-

1. Primary and Secondary Effects of Stress on
 Nonendocrine Corticotropin-releasing Factor Neurons
 1. Effects of stress on corticotropin-releasing factor neu-
 rons. Because the data reviewed previously clearly su Friends that Secondary Effects of Stress on
Nonendocrine Corticotropin-releasing Factor Neurons
1. Effects of stress on corticotropin-releasing factor neu-
rons. Because the data reviewed previously clearly sug-
gest that The regulate that regulate that regulate that regulate that regulate pituitary-adrenal axis activity, also in the mediate the autonomic and behavioral responses of an conduction and behavioral responses of an conduction of 1. Effects of stress on corticotropin-releasing factor neu-
rons. Because the data reviewed previously clearly sug-
gest that CRF neurons, apart from, but in concert with, con-
those that regulate pituitary-adrenal axis a rons. Because the data reviewed previously clearly sug-
gest that CRF neurons, apart from, but in concert with, cont
those that regulate pituitary-adrenal axis activity, also in the
mediate the autonomic and behavioral res gest that CRF neurons, apart from, but in concert with,
those that regulate pituitary-adrenal axis activity, also
mediate the autonomic and behavioral responses of an
organism to stress, it is of general scientific interes those that regulate pituitary-adrenal axis activity, also in the adjacent locus ceruleus. Indeed, the increased CRF mediate the autonomic and behavioral responses of an concentrations observed in the locus ceruleus followi organism to stress, it is of general scientific interest to organism to stress, it is of general scientific interest to
study the function and regulation of these nonendocrine
CRF neurons. Moreover, because a vast clinical literature
indicates that CRF neurons likely are dysfunctio study the function and regulation of these nonendocrine
CRF neurons. Moreover, because a vast clinical literature
indicates that CRF neurons likely are dysfunctional in
certain psychiatric illnesses, study of CRF neuronal modalities. certain psychiatric illnesses, study of CRF neuronal sys-
tems may provide yet untapped and novel treatment rec
modalities. reg
We (Chappell et al., 1986) previously reported that in t
both acute immobilization stress at

We (Chappell et al., 1986) previously reported that both acute immobilization stress at 4° C for 3 hours and tems may provide yet untapped and novel treatment
modalities.
We (Chappell et al., 1986) previously reported that
both acute immobilization stress at 4°C for 3 hours and
chronic (14 day) exposure to a series of unpredictab

then spread to the hippocampus and cerebral cortex stressors alter the concentration of CRF immunoreactive
(Ehlers, 1990); seizure activity then follows. It is after ity in various microdissected brain regions of the rat. CRF-induced seizures, although somewhat similar, are
biologically distinct.
nons. Although stress increased dopamine utilization in
Relevant to the reported alterations in polysomnog-
raphy produced by CRF (vide supra), ce LEASING FACTOR
stressors alter the concentration of CRF immunore
ity in various microdissected brain regions of the 1 **in the STAR CEASING FACTOR**
ity in various microdissected brain regions of the rat. Of
particular interest is the finding that both acute and 453
stressors alter the concentration of CRF immunoreactiv-
ity in various microdissected brain regions of the rat. Of
particular interest is the finding that both acute and
chronic stress resulted in a 2-fold increase in stressors alter the concentration of CRF immunoreact
ity in various microdissected brain regions of the rat.
particular interest is the finding that both acute a
chronic stress resulted in a 2-fold increase in the concentr stressors alter the concentration of CRF immunoreactiv-
ity in various microdissected brain regions of the rat. Of
particular interest is the finding that both acute and
chronic stress resulted in a 2-fold increase in the be electrophysiobogically responsive to applied CRF. In chronic stress resulted in a 2-fold increase in the concentrations of CRF in the locus ceruleus, an area known to be electrophysiologically responsive to applied CRF. In addition, chronic stress decreased CRF concentration chronic stress resulted in a 2-fold increase in the concentrations of CRF in the locus ceruleus, an area known to be electrophysiologically responsive to applied CRF. In addition, chronic stress decreased CRF concentration trations of CRF in the locus ceruleus, an area known to
be electrophysiologically responsive to applied CRF. In
addition, chronic stress decreased CRF concentrations
in the dorsal vagal complex. The dorsal vagal complex
co addition, chronic stress decreased CRF concentrations
in the dorsal vagal complex. The dorsal vagal complex
contains various nuclei that are CRF responsive and
regulate autonomic function. In a related experiment,
Deutch e addition, chronic stress decreased CRF concentrations
in the dorsal vagal complex. The dorsal vagal complex
contains various nuclei that are CRF responsive and
regulate autonomic function. In a related experiment,
Deutch e in the dorsal vagal complex. The dorsal vagal complex
contains various nuclei that are CRF responsive and
regulate autonomic function. In a related experiment,
Deutch et al. (1987) determined whether mild foot-shock
stress contains various nuclei that are CRF responsive and
regulate autonomic function. In a related experiment,
Deutch et al. (1987) determined whether mild foot-shock
stress altered CRF concentrations in mesotelencephalic
dopam regulate autonomic function. In a related experiment,
Deutch et al. (1987) determined whether mild foot-shock
stress altered CRF concentrations in mesotelencephalic
dopamine system regions. Because exposure to mild
stresso Deutch et al. (1987) determined whether mild foot-shock
stress altered CRF concentrations in mesotelencephalic
dopamine system regions. Because exposure to mild
stressors is known to activate mesocortical dopamine
neurons, stress altered CRF concentrations in mesotelencephalic
dopamine system regions. Because exposure to mild
stressors is known to activate mesocortical dopamine
neurons, it was plausible to hypothesize that this acti-
vation dopamine system regions. Because exposure to mild
stressors is known to activate mesocortical dopamine
neurons, it was plausible to hypothesize that this acti-
vation might occur through interactions with CRF neu-
rons. Al stressors is known to activate mesocortical dopamine
neurons, it was plausible to hypothesize that this acti-
vation might occur through interactions with CRF neu-
rons. Although stress increased dopamine utilization in
th neurons, it was plausible to hypothesize that this activation might occur through interactions with CRF neurons. Although stress increased dopamine utilization in the prefrontal cortex and ventral tegmentum, CRF concentrat vation might occur through interactions with CRF neu-
rons. Although stress increased dopamine utilization in
the prefrontal cortex and ventral tegmentum, CRF con-
centrations were unchanged in the dopamine cell body
regio rons. Although stress increased dopamine utilization in
the prefrontal cortex and ventral tegmentum, CRF con-
centrations were unchanged in the dopamine cell body
regions of the ventral tegmentum, substantia nigra, and
ret the prefrontal cortex and ventral tegmentum, CRF concentrations were unchanged in the dopamine cell body regions of the ventral tegmentum, substantia nigra, and retrorubral field and in the dopamine projection areas of the centrations were unchanged in the dopamine cell body
regions of the ventral tegmentum, substantia nigra, and
retrorubral field and in the dopamine projection areas of
the prefrontal cortex, striatum, and nucleus accumbens. regions of the ventral tegmentum, substantia nigra, and
retrorubral field and in the dopamine projection areas of
the prefrontal cortex, striatum, and nucleus accumbens.
This is in agreement with our earlier findings (Chap retrorubral field and in the dopamine projection areas of
the prefrontal cortex, striatum, and nucleus accumbens.
This is in agreement with our earlier findings (Chappell
et al., 1986) and suggests that stress-related chan tinct. is is in agreement with our earlier findings (Chappell
al., 1986) and suggests that stress-related changes in
pamine and CRF systems are neurochemically dis-
ict.
The protooncogene c-*fos* is expressed in many tissues
resp

et al., 1986) and suggests that stress-related changes in dopamine and CRF systems are neurochemically distinct.
The protooncogene c-fos is expressed in many tissues
in response to growth factor stimulation. It appears tha dopamine and CRF systems are neurochemically dis-
tinct.
The protooncogene c-*fos* is expressed in many tissues
in response to growth factor stimulation. It appears that
induction of the c-*fos* gene may be important in th tinct.
The protooncogene c-*fos* is expressed in many tissues
in response to growth factor stimulation. It appears that
induction of the c-*fos* gene may be important in the
establishment of long-term functional changes in The protooncogene c-*fos* is expressed in many tissues
in response to growth factor stimulation. It appears that
induction of the c-*fos* gene may be important in the
establishment of long-term functional changes in neu-
 in response to growth factor stimulation. It appears that
induction of the c-*fos* gene may be important in the
establishment of long-term functional changes in neu-
rons. Recently, Ceccatelli et al. (1989b) examined the
i induction of the c-fos gene may be important in the
stablishment of long-term functional changes in net
rons. Recently, Ceccatelli et al. (1989b) examined th
induction of c-fos immunoreactivity following exposure
of rats t establishment of long-term functional changes in neu-
rons. Recently, Ceccatelli et al. (1989b) examined the
induction of c-*fos* immunoreactivity following exposure
of rats to various stressors. As expected, many CRF-
con rons. Recently, Ceccatelli et al. (1989b) examined the induction of c-*fos* immunoreactivity following exposure of rats to various stressors. As expected, many CRF-containing neurons in the PVN stained positively for c-*fo* induction of c-*fos* immunoreactivity following exposure
of rats to various stressors. As expected, many CRF-
containing neurons in the PVN stained positively for c-
fos immunoreactivity. Of interest to this discussion, containing neurons in the PVN stained positively for c-
fos immunoreactivity. Of interest to this discussion, c-
fos immunoreactivity was also induced in cells of the
locus ceruleus, the ventrolateral medulla, and the nucl fos immunoreactivity. Of interest to this discussion, cfos immunoreactivity was also induced in cells of the locus ceruleus, the ventrolateral medulla, and the nucleus of the solitary tract in the dorsal vagal complex. Although many of the cells in the locus ceruleus were undo fos immunoreactivity was also induced in cells of the
locus ceruleus, the ventrolateral medulla, and the nucleus
of the solitary tract in the dorsal vagal complex. Although
many of the cells in the locus ceruleus were undo locus ceruleus, the ventrolateral medulla, and the nucleus
of the solitary tract in the dorsal vagal complex. Although
many of the cells in the locus ceruleus were undoubtedly
noradrenergic, a number of cells, such as thos many of the cells in the locus ceruleus were undoubtedly noradrenergic, a number of cells, such as those in the parabrachial nucleus proximal to the locus ceruleus, are not. Anatomical studies have previously shown that it many of the cells in the locus ceruleus were undoubtedly
noradrenergic, a number of cells, such as those in the
parabrachial nucleus proximal to the locus ceruleus, are
not. Anatomical studies have previously shown that it noradrenergic, a number of cells, such as those in the
parabrachial nucleus proximal to the locus ceruleus, are
not. Anatomical studies have previously shown that it is
possible that those cells in the parabrachial nucleus parabrachial nucleus proximal to the locus ceruleus, are
not. Anatomical studies have previously shown that it is
possible that those cells in the parabrachial nucleus that
contain CRF could easily innervate noradrenergic not. Anatomical studies have previously shown that it is
possible that those cells in the parabrachial nucleus that
contain CRF could easily innervate noradrenergic cells
in the adjacent locus ceruleus. Indeed, the increas contain CRF could easily innervate noradrenergic cells contain CRF could easily innervate noradrenergic cells
in the adjacent locus ceruleus. Indeed, the increased CRF
concentrations observed in the locus ceruleus following
stress could possibly emanate from parabrachial CRF
n in the adjacent locus ceruleus. Indeed, the increased CRF concentrations observed in the locus ceruleus following
stress could possibly emanate from parabrachial CRF
neurons, although this has not been determined. Finally, concentrations observed in the locus ceruleus following
stress could possibly emanate from parabrachial CRF
neurons, although this has not been determined. Finally,
Hauger et al. (1988) studied the effect of a single pro-
 stress could possibly emanate from parabrachial CRF
neurons, although this has not been determined. Finally,
Hauger et al. (1988) studied the effect of a single pro-
longed immobilization stress (0.25 to 48 hours) on CRF
r neurons, although this has not been determined. Final
Hauger et al. (1988) studied the effect of a single pi
longed immobilization stress (0.25 to 48 hours) on CI
receptor binding. As noted earlier, anterior pituitary CI
r Hauger et al. (1988) studied the effect of a single pro-
longed immobilization stress (0.25 to 48 hours) on CRF
receptor binding. As noted earlier, anterior pituitary CRF
receptors were significantly reduced in density (do longed immobilization stress (0.25 to 48 hours) on CR
receptor binding. As noted earlier, anterior pituitary CR
receptors were significantly reduced in density (down
regulated); however, CRF receptor density was unaltere
i receptor binding. As noted earlificantly requilated); however, CRF reception the frontoparietal cortex, olf-
amygdala, and lateral septum.
2. Secondary effects of stress *2. Ferry effects of streeptor* density was unaltered
in the frontoparietal cortex, olfactory bulb, hippocampus,
amygdala, and lateral septum.
2. Secondary effects of stress. Although manipulation

OWENS AND NEM
of the HPA axis and its effects on hypothalamic CRF beh
neurons was examined in section III, little mention was inte owens and the HPA axis and its effects on hypothalamic CRF be
neurons was examined in section III, little mention was in
made at that time regarding the effects of these manip- in owens
of the HPA axis and its effects on hypothalamic Cl
neurons was examined in section III, little mention w
made at that time regarding the effects of these man
ulations on extrahypothalamic CRF neurons. First, the of the HPA axis and its effects on hypothalamic CRF be
neurons was examined in section III, little mention was
imade at that time regarding the effects of these manip-
ulations on extrahypothalamic CRF neurons. First, ther of the HPA axis and its effects on hypothalamic CRF
neurons was examined in section III, little mention was
made at that time regarding the effects of these manip-
ulations on extrahypothalamic CRF neurons. First, there
is neurons was examined in section III, little mention was
made at that time regarding the effects of these manip-
inditions on extrahypothalamic CRF neurons. First, there
is a significant circadian variation in the concentra made at that time regarding the effects of these manipulations on extrahypothalamic CRF neurons. First, there is a significant circadian variation in the concentration of CRF in a number of extrahypothalamic brain regions ulations on extrahypothalamic CRF neurons. First, there is a significant circadian variation in the concentration
of CRF in a number of extrahypothalamic brain regions
(Owens et al., 1990a). These include several cortical, is a significant circadian variation in the concentration
of CRF in a number of extrahypothalamic brain regions
(Owens et al., 1990a). These include several cortical,
limbic, and brainstem regions. These findings are not
s of CRF in a number of extrahypothalamic brain regions
(Owens et al., 1990a). These include several cortical,
limbic, and brainstem regions. These findings are not
surprising because a number of neuronal systems exhibit
rh (Owens et al., 1990a). These include several cortical,
limbic, and brainstem regions. These findings are not
surprising because a number of neuronal systems exhibit
rhythmical and/or oscillating firing patterns during the limbic, and brainstem regions. These findings are not
surprising because a number of neuronal systems exhibit
rhythmical and/or oscillating firing patterns during the
course of the day (Llinas, 1989). Moreover, the majori surprising because a number of neuronal systems exh
rhythmical and/or oscillating firing patterns during
course of the day (Llinas, 1989). Moreover, the majo:
of these diurnal changes are insensitive to circulat
glucocorti rhythmical and/
course of the day
of these diurnal
glucocorticoids a
docrine activity.
Several invest urse of the day (Llinas, 1989). Moreover, the majority
these diurnal changes are insensitive to circulating
accoorticoids and appear not to be linked to neuroen-
crine activity.
Several investigators have examined the eff

of these diurnal changes are insensitive to circula
glucocorticoids and appear not to be linked to neuro-
docrine activity.
Several investigators have examined the effect
exogenous glucocorticoid administration on extrah_i glucocorticoids and appear not to be linked to neuroen-
docrine activity.
Several investigators have examined the effects of
exogenous glucocorticoid administration on extrahypo-
thalamic CRF neurons. Beyer et al. (1988) f docrine activity.

Several investigators have examined the effects of advised exogenous glucocorticoid administration on extrahypoture

thalamic CRF neurons. Beyer et al. (1988) found no

effect of high-dose dexamethasone Several investigators have examined the effects of exogenous glucocorticoid administration on extrahypothalamic CRF neurons. Beyer et al. (1988) found no tieffect of high-dose dexamethasone on CRF mRNA in either the centr exogenous glucocorticoid administration on extrahypothalamic CRF neurons. Beyer et al. (1988) found no effect of high-dose dexamethasone on CRF mRNA in either the central nucleus of the amygdala, BNST, or supraoptic nucleu thalamic CRF neurons. Beyer et al. (1988) found
effect of high-dose dexamethasone on CRF mRN.
either the central nucleus of the amygdala, BNST
suppraoptic nucleus. Our group (Owens et al., 19
recently reported that 7-day c effect of high-dose dexamethasone on CRF mRNA in
either the central nucleus of the amygdala, BNST, or
supraoptic nucleus. Our group (Owens et al., 1990a)
recently reported that 7-day corticosterone supplemen-
tation to rat either the central nucleus of the amygdala, BNST,
supraoptic nucleus. Our group (Owens et al., 199
recently reported that 7-day corticosterone supplem
tation to rats with intact adrenal glands was with
effect on CRF concen supraoptic nucleus. Our group (Owens et al., 1990a)
recently reported that 7-day corticosterone supplemen-
tation to rats with intact adrenal glands was without
effect on CRF concentrations in all of the 13 extrahy-
pothal recently reported that 7-day corticosterone supplementation to rats with intact adrenal glands was without effect on CRF concentrations in all of the 13 extrahypothalamic brain regions examined, although glucocor-
ticoid s tation to rats with intact adrenal glands was with
effect on CRF concentrations in all of the 13 extra
pothalamic brain regions examined, although glucoo
ticoid supplementation altered the diurnal rhythm
CRF concentrations effect on CRF concentrations in all of the 13 extrahy-
pothalamic brain regions examined, although glucocor-
ticoid supplementation altered the diurnal rhythm of
CRF concentrations in several brain regions. Further-
more, pothalamic brain regions examined, although gluce
ticoid supplementation altered the diurnal rhythr
CRF concentrations in several brain regions. Furt
more, Hauger et al. (1987) reported that subchroni
to 4 days) administra ticoid supplementation altered the diurnal rhythm of and ipsapirone, increased CRF concentrations in those
CRF concentrations in several brain regions. Further-
more, Hauger et al. (1987) reported that subchronic (1 hippo CRF concentrations in several brain regions. Furthemore, Hauger et al. (1987) reported that subchronic (to 4 days) administration of corticosterone supplementation did not alter CRF receptor number or affinity is the corte more, Haug
to 4 days) a
tation did r
the cortex,
tory bulb.
In addition 4 days) administration of corticosterone supplemention did not alter CRF receptor number or affinity in e cortex, hippocampus, amygdala, septum, and olfacty bulb.
In addition to a study of the effects of administered accoo

tation did not alter CRF receptor number or affinity
the cortex, hippocampus, amygdala, septum, and olfa
tory bulb.
In addition to a study of the effects of administer
glucocorticoids, the effects of adrenalectomy on extr
 the cortex, hippocampus, amygdala, septum, and olfactory bulb.
In addition to a study of the effects of administered
glucocorticoids, the effects of adrenalectomy on extra-
hypothalamic CRF neurons have also been investiga tory bulb.

In addition to a study of the effects of administered

glucocorticoids, the effects of adrenalectomy on extra-

hypothalamic CRF neurons have also been investigated.

It is of paramount importance to note that In addition to a study of the effects of administered
glucocorticoids, the effects of adrenalectomy on extra-
hypothalamic CRF neurons have also been investigated.
It is of paramount importance to note that associated
with glucocorticoids, the effects of adrenalectomy on extra-
hypothalamic CRF neurons have also been investigated.
It is of paramount importance to note that associated alte
with glucocorticoid deficiency are a number of other hypothalamic CRF neurons have also been investigated.
It is of paramount importance to note that associated
with glucocorticoid deficiency are a number of other
effects including hyperactivity of paraventricular CRF
neuron It is of paramount importance to note that associated
with glucocorticoid deficiency are a number of other
effects including hyperactivity of paraventricular CRF
neurons. Beyer et al. (1988) reported that adrenalectomy
did with glucocorticoid deficiency are a number of other
effects including hyperactivity of paraventricular CRF
neurons. Beyer et al. (1988) reported that adrenalectomy
did not alter CRF mRNA in the amygdala, BNST, or
supraopt effects including hyperactivity of paraventricular CRF pre
neurons. Beyer et al. (1988) reported that adrenalectomy tex
did not alter CRF mRNA in the amygdala, BNST, or can
supraoptic nucleus as determined by Northern blot neurons. Beyer et al. (1988) reported that adrenalectomy te did not alter CRF mRNA in the amygdala, BNST, or casupraoptic nucleus as determined by Northern blot (C analysis, nor did it alter CRF receptor density in any bra did not alter CRF mRNA in the amygdala, BNST, or
supraoptic nucleus as determined by Northern blot
analysis, nor did it alter CRF receptor density in any
brain region as determined by autoradiography (Wynn
et al., 1984). S supraoptic nucleus as determined by Northern t
analysis, nor did it alter CRF receptor density in a
brain region as determined by autoradiography (W₃
et al., 1984). Sawchenko (1987a) reported in one stu
but not in anothe analysis, nor did it alter CRF receptor density in any
brain region as determined by autoradiography (Wynn
et al., 1984). Sawchenko (1987a) reported in one study,
but not in another (Swanson et al., 1983), that adrenal-
ec brain region as determined by autoradiography (Wynn use tal., 1984). Sawchenko (1987a) reported in one study, oblut not in another (Swanson et al., 1983), that adrenal-
ectomy increased the number of CRF cell bodies in the et al., 1984). Sawchenko (1987a) reported in one study, obesity
but not in another (Swanson et al., 1983), that adrenal-
ectomy increased the number of CRF cell bodies in the
perirhinal area of the cortex, the central nucl but not in another (Swanson et al., 1983), that adrenal-
ectomy increased the number of CRF cell bodies in the
perirhinal area of the cortex, the central nucleus of the
amygdala, and the BNST. Whether this results from
inc ectomy increased the number of CRF cell be
perirhinal area of the cortex, the central numygdala, and the BNST. Whether this
increased synthesis or the expression of (
previously not expressing CRF is unknown.
In summary, n rirhinal area of the cortex, the central nucleus of the nygdala, and the BNST. Whether this results from creased synthesis or the expression of CRF in cells eviously not expressing CRF is unknown.
In summary, neither adren amygdala, and the BNST. Whether this results from
increased synthesis or the expression of CRF in cells
previously not expressing CRF is unknown.
In summary, neither adrenalectomy nor increased cir-
culating concentrations

increased synthesis or the expression of CRF in cells
previously not expressing CRF is unknown.
In summary, neither adrenalectomy nor increased cir-
culating concentrations of glucocorticoids appears to af-
fect CRF neuron hypothalamus. *B. Responses of glueocorticoids appears to affect CRF neurons, except for those in the PVN of the hypothalamus.*
 B. Responses of Extrahypothalamic Corticotropin-
 Responses of Extrahypothalamic Corticotropin-
 Respo fect CRF neurons, except for those in the PVN of the

Manipulation

Because of the data suggesting that extrahypothalamic

NEMEROFF
behavioral responses of an organism to stress, it is of
interest to characterize which neurotransmitter systems NEMEROFF
behavioral responses of an organism to stress, it is of
interest to characterize which neurotransmitter systems
interact with these neurons. It should be reiterated at NEMEROFF
behavioral responses of an organism to stress, it is of
interest to characterize which neurotransmitter systems
interact with these neurons. It should be reiterated at
the outset that the paucity of neuroanatomica behavioral responses of an organism to stress, it is dinterest to characterize which neurotransmitter system
interact with these neurons. It should be reiterated \imath
the outset that the paucity of neuroanatomical and phy behavioral responses of an organism to stress, it is o
interest to characterize which neurotransmitter systems
interact with these neurons. It should be reiterated a
the outset that the paucity of neuroanatomical and phys
 interest to characterize which neurotransmitter system
interact with these neurons. It should be reiterated at
the outset that the paucity of neuroanatomical and phys
iological information concerning specific extrahypotha
 interact with these neurons. It should be reiterated at
the outset that the paucity of neuroanatomical and phys-
iological information concerning specific extrahypotha-
lamic CRF pathways renders interpretation of drug-
in iological information concerning specific extrahypotha-
lamic CRF pathways renders interpretation of drug-
induced changes in CRF concentrations difficult. For
example, many studies of regional brain CRF concentra-
tions d iological information concerning specific extrahypotha-
lamic CRF pathways renders interpretation of drug-
induced changes in CRF concentrations difficult. For
example, many studies of regional brain CRF concentra-
tions d lamic CRF pathways renders interpretation of drug-
induced changes in CRF concentrations difficult. For
example, many studies of regional brain CRF concentra-
tions do not distinguish between changes in release,
synthesis, induced changes in CRF concentrations difficult. For
example, many studies of regional brain CRF concentra-
tions do not distinguish between changes in release,
synthesis, storage, or degradation. Nonetheless, any
drug-ind example, many studies of regional brain CRF concentra-
tions do not distinguish between changes in release,
synthesis, storage, or degradation. Nonetheless, any
drug-induced changes in CRF concentrations likely de-
note al tions do not distinguish between changes in release,
synthesis, storage, or degradation. Nonetheless, any
drug-induced changes in CRF concentrations likely de-
note alterations in the activity of CRF neurons. One
would do synthesis, storage, or degradation. Nonetheless, any
drug-induced changes in CRF concentrations likely de-
note alterations in the activity of CRF neurons. One
would do well to remember that, prior to the advent of
advance drug-induced changes in CRF concentrations likely
note alterations in the activity of CRF neurons.
would do well to remember that, prior to the adver
advanced neurochemical techniques for measuring
turnover of monoamines, note alterations in the activity of CRF neurons.
would do well to remember that, prior to the adver
advanced neurochemical techniques for measuring
turnover of monoamines, measurement of the concer
tions of various neurotr would do well to remember that, prior to the advent of
advanced neurochemical techniques for measuring the
turnover of monoamines, measurement of the concentra-
tions of various neurotransmitters (5-HT, norepineph-
rine, d advanced neurochemical techniques for measuring the
turnover of monoamines, measurement of the concentra-
tions of various neurotransmitters (5-HT, norepineph-
rine, dopamine, etc.) in discrete brain regions following
expe turnover of monoamines, measurement of the conc
tions of various neurotransmitters (5-HT, norepi
rine, dopamine, etc.) in discrete brain regions foll
experimental perturbation were considered importa
gauging alterations in tions of various
rine, dopamine,
experimental per
gauging alteratic
taining neurons.
While studyin

turnover of monoamines, measurement of the concentra-
tions of various neurotransmitters (5-HT, norepineph-
rine, dopamine, etc.) in discrete brain regions following
experimental perturbation were considered important for experimental perturbation were considered important for
gauging alterations in the activity of monoamine-con-
taining neurons.
While studying serotonergic regulation of the HPA
axis, we observed that chronic (21 days) admi gauging alterations in the activity of monoamine-
taining neurons.
While studying serotonergic regulation of the I
axis, we observed that chronic (21 days) administra
of the 5-HT_{1A} agonists, 8-hydroxydipropylaminotetr
an taining neurons.

While studying serotonergic regulation of the HPA

axis, we observed that chronic (21 days) administration

of the 5-HT_{1A} agonists, 8-hydroxydipropylaminotetralin

and ipsapirone, increased CRF concent While studying serotonergic regulation of the HPA
axis, we observed that chronic (21 days) administration
of the 5-HT_{1A} agonists, 8-hydroxydipropylaminotetralin
and ipsapirone, increased CRF concentrations in those
area axis, we observed that chronic (21 days) administration
of the 5-HT_{1A} agonists, 8-hydroxydipropylaminotetralin
and ipsapirone, increased CRF concentrations in those
areas preferentially enriched with 5-HT_{1A} receptors of the 5-HT_{1A} agonists, 8-hydroxydipropylaminotetralin
and ipsapirone, increased CRF concentrations in those
areas preferentially enriched with 5-HT_{1A} receptors (i.e.,
hippocampus, entorhinal cortex, and piriform cort and ipsapirone, increased CRF concentrations in those
areas preferentially enriched with 5-HT_{1A} receptors (i.e.,
hippocampus, entorhinal cortex, and piriform cortex).
Another area with somewhat lower 5-HT_{1A} receptor d centrations. During the course of similar studies of the $5-\text{HT}_2$ receptor subtype, neither acute nor chronic adhippocampus, entorhinal cortex, and piriform cortex).
Another area with somewhat lower $5\text{-}HT_{1A}$ receptor densities, the amygdala, also exhibited increased CRF concentrations. During the course of similar studies of th Another area with somewhat lower $5\text{-}HT_{1A}$ receptor densities, the amygdala, also exhibited increased CRF concentrations. During the course of similar studies of the $5\text{-}HT_2$ receptor subtype, neither acute nor chron (\pm) -1-(2,5-dimethoxy-4-bromophenyl)-2-aminopropane, centrations. During the course of similar studies of the 5-HT₂ receptor subtype, neither acute nor chronic administration of the potent $5-HT_2$ and $5-HT_{1C}$ agonist, (\pm) -1-(2,5-dimethoxy-4-bromophenyl)-2-aminopropane 5-HT₂ receptor subtype, neither acute nor chronic a
ministration of the potent 5-HT₂ and 5-HT_{1C} agonis
(\pm)-1-(2,5-dimethoxy-4-bromophenyl)-2-aminopropan
altered CRF concentrations in any of 13 brain region
studie ministration of the potent 5-HT₂ and 5-HT_{1c} agonist,
 (\pm) -1-(2,5-dimethoxy-4-bromophenyl)-2-aminopropane,
altered CRF concentrations in any of 13 brain regions
studied, including the median eminence, hypothalamus,
pr (\pm) -1-(2,5-dimethoxy-4-bromophenyl)-2-aminopropan
altered CRF concentrations in any of 13 brain regio
studied, including the median eminence, hypothalam
prefrontal cortex, frontal/parietal cortex, cingulate co
tex, sept studied, including the median eminence, hypothalamus, prefrontal cortex, frontal/parietal cortex, cingulate cortex, septum, BNST, piriform cortex, amygdala, hippocampus, raphe nuclei, locus ceruleus, and cerebellum (Owens tex, septum, BNST, piriform cortex, amygdala, hippoefrontal cortex, frontal/parietal cortex, cingulate cor-
x, septum, BNST, piriform cortex, amygdala, hippo-
mpus, raphe nuclei, locus ceruleus, and cerebellum
wens et al., 1990b, 1991a).
Fenfluramine is an amphetamine deri

B. Responses of Extrahypothalamic Corticotropin-

releasing Factor Neurons to Pharmacological and plasma corticosterone correlated with brain fenflur-

Manipulation

Manipulation

CRF neurons mediate many of the physiologi tex, septum, BNST, piriform cortex, amygdala, hippo-
campus, raphe nuclei, locus ceruleus, and cerebellum
(Owens et al., 1990b, 1991a).
Fenfluramine is an amphetamine derivative that is
used as a weight-reducing agent in t campus, raphe nuclei, locus ceruleus, and cerebellum
(Owens et al., 1990b, 1991a).
Fenfluramine is an amphetamine derivative that is
used as a weight-reducing agent in the treatment of
obesity. It has been postulated that (Owens et al., 1990b, 1991a).
Fenfluramine is an amphetamine derivative that is
used as a weight-reducing agent in the treatment of
obesity. It has been postulated that fenfluramine in-
creases central serotonergic neurotr Fenfluramine is an amphetamine derivative that is
used as a weight-reducing agent in the treatment of
obesity. It has been postulated that fenfluramine in-
creases central serotonergic neurotransmission resulting
in decre used as a weight-reducing agent in the treatment cobesity. It has been postulated that fenfluramine in creases central serotonergic neurotransmission resultin in decreased food intake and altered autonomic outflow
which, i obesity. It has been postulated that fenfluramine
creases central serotonergic neurotransmission resulti
in decreased food intake and altered autonomic outfl
which, in turn, increases metabolism (Rowland and Ca
ton, 1986). creases central serotonergic neurotransmission resulting
in decreased food intake and altered autonomic outflow
which, in turn, increases metabolism (Rowland and Carl-
ton, 1986). As we have noted previously, central admin in decreased food intake and altered autonomic outflow
which, in turn, increases metabolism (Rowland and Carl-
ton, 1986). As we have noted previously, central admin-
istration of CRF produces similar effects on weight and which, in turn, increases metabolism (Rowland and Carl-
ton, 1986). As we have noted previously, central admin-
istration of CRF produces similar effects on weight and
autonomic activity. We (Appel et al., 1991) observed i ton, 1986). As we have noted previously, central adm
istration of CRF produces similar effects on weight a
autonomic activity. We (Appel et al., 1991) observed
rats that chronic fenfluramine treatment resulted
dose-depende istration of CRF produces similar effects on weight
autonomic activity. We (Appel et al., 1991) observe
rats that chronic fenfluramine treatment resulte
dose-dependent decreases in hypothalamic CRF con
trations and recipro rats that chronic fenfluramine treatment resulted in dose-dependent decreases in hypothalamic CRF concentrations and reciprocal increases in plasma corticoster-
one concentrations. These changes in hypothalamic CRF dose-dependent decreases in hypothalamic CRF concendose-dependent decreases in hypothalamic CRF concentrations and reciprocal increases in plasma corticoster-
one concentrations. These changes in hypothalamic CRF
and plasma corticosterone correlated with brain fenflur-
ami trations and reciprocal increases in plasma corticoster-
one concentrations. These changes in hypothalamic CRF
and plasma corticosterone correlated with brain fenflur-
amine concentrations. In addition to these changes in
 one concentrations. These changes in hypothalamic CRF
and plasma corticosterone correlated with brain fenflur-
amine concentrations. In addition to these changes in
hypophysiotropic function, fenfluramine treatment sig-
ni and plasma corticosterone correlated with brain fenfluramine concentrations. In addition to these changes in hypophysiotropic function, fenfluramine treatment significantly increased hippocampal, midbrain, and spinal cord

cortex, caudate/putamen, thalamus, pons/medulla, and
cerebellum were unaffected. Because serotonin is a po-
tent CRF secretagogue, it is hypothesized that the la CORTICOTROPIN-RELE

cortex, caudate/putamen, thalamus, pons/medulla, and

cerebellum were unaffected. Because serotonin is a po-

tent CRF secretagogue, it is hypothesized that the

weight-reducing effects of fenfluramine cortex, caudate/putamen, thalamus, pons/medulla, and
cerebellum were unaffected. Because serotonin is a po-
tent CRF secretagogue, it is hypothesized that the
weight-reducing effects of fenfluramine may be mediated,
in par cortex, caudate/putamen, thalamus, po
cerebellum were unaffected. Because s
tent CRF secretagogue, it is hypoth
weight-reducing effects of fenfluramine
in part, through altered CRF secretion.
While studying regulation of H rebellum were unaffected. Because serotonin is a po-
nt CRF secretagogue, it is hypothesized that the
eight-reducing effects of fenfluramine may be mediated,
part, through altered CRF secretion.
While studying regulation o

tent CRF secretagogue, it is hypothesized that the weight-reducing effects of fenfluramine may be mediated in part, through altered CRF secretion.
While studying regulation of HPA axis function, othe groups have also exami weight-reducing effects of fenfluramine may be media
in part, through altered CRF secretion.
While studying regulation of HPA axis function, o
groups have also examined the effects of various c
pounds on CRF concentrations in part, through altered CRF secretion. street while studying regulation of HPA axis function, other compounds have also examined the effects of various compounds on CRF concentrations outside the hypothala-
mus. Haas and While studying regulation of HPA axis function, other
groups have also examined the effects of various com-
pounds on CRF concentrations outside the hypothala-
mus. Haas and George (1987) did not observe any
changes in CRF groups have also examined the effects of various com-
pounds on CRF concentrations outside the hypothala-
mus. Haas and George (1987) did not observe any obs
changes in CRF immunoreactivity in the frontal cortex, stre
hipp pounds on CRF concentrations outside the hypothala-
mus. Haas and George (1987) did not observe any
changes in CRF immunoreactivity in the frontal cortex,
hippocampus, medulla-pons, midbrain-thalamus, and
cerebellum follow mus. Haas and George (1987) did not observe any o
changes in CRF immunoreactivity in the frontal cortex, si
hippocampus, medulla-pons, midbrain-thalamus, and the
cerebellum following i.c.v. doses of neuropeptide Y that n
i changes in CRF immunoreactivity in the frontal cortex,
hippocampus, medulla-pons, midbrain-thalamus, and
cerebellum following i.c.v. doses of neuropeptide Y that
increased plasma ACTH concentrations (i.e., increased
median hippocampus, medulla-pons, midbrain-thalamus,
cerebellum following i.c.v. doses of neuropeptide Y
increased plasma ACTH concentrations (i.e., increa
median eminence CRF release). Similarly, Tizabi e
(1985) did not find any cerebellum following i.c.v. doses of neuropeptide Y that
increased plasma ACTH concentrations (i.e., increased ti
median eminence CRF release). Similarly, Tizabi et al.
(1985) did not find any alterations in CRF concentraincreased plasma ACTH concentrations (i.e., increased
median eminence CRF release). Similarly, Tizabi et al.
(1985) did not find any alterations in CRF concentra-
tions in the dorsal or ventral BNST, central nucleus of
the median eminence CRF release). Similarly, Tizabi et al.
(1985) did not find any alterations in CRF concentra-
tions in the dorsal or ventral BNST, central nucleus of
the amygdala, or a variety of hypothalamic nuclei, ex-
cl (1985) did not find any alterations in CRF concentrations in the dorsal or ventral BNST, central nucleus of the amygdala, or a variety of hypothalamic nuclei, excluding the PVN, following the administration of either the m the amygdala, or a variety of hypothalamic nuclei, ex-
cluding the PVN, following the administration of either
the monoamine-depleting agent, reserpine, or the tricy-
clic antidepressant, desipramine, an norepinephrine reuptake inhibitor. cluding the PVN, following the administration of either
the monoamine-depleting agent, reserpine, or the tricy-
clic antidepressant, desipramine, an norepinephrine pressants abolishes stress-induced changes in CRF neu-
reu

the monoamine-depleting agent, reserpine, or the tricy-
clic antidepressant, desipramine, an norepinephrine
reuptake inhibitor.
Some of the most interesting pharmacological studies
to date pertain to the possibility that c clic antidepressant, desipramine, an norepinephrine pre

reuptake inhibitor.

Some of the most interesting pharmacological studies

to date pertain to the possibility that clinically efficacious (Ginatidepressants and/or reuptake inhibitor.
Some of the most interesting pharmacological studies
to date pertain to the possibility that clinically efficacious
antidepressants and/or anxiolytics may interact with
central CRF neurons. Because prec Some of the most interesting pharmacological studies
to date pertain to the possibility that clinically efficacious (G)
antidepressants and/or anxiolytics may interact with
central CRF neurons. Because preclinical and cli to date pertain to the possibility that clinically efficacion
antidepressants and/or anxiolytics may interact wicentral CRF neurons. Because preclinical and clinic
studies suggest that CRF neurons of hypothalamic a
extrahy central CRF neurons. Because preclinical and clinical
studies suggest that CRF neurons of hypothalamic and
extrahypothalamic origin may be involved in the patho-
physiology of anxiety and depressive disorders, we ex-
amine studies suggest that CRF neurons of hypothalamic and studies suggest that CRF neurons of hypothalamic and
extrahypothalamic origin may be involved in the patho-
physiology of anxiety and depressive disorders, we ex-
amined the actions of a single acute injection of imipra-
m extrahypothalamic origin may be involved in the patho-
physiology of anxiety and depressive disorders, we ex-
amined the actions of a single acute injection of imipra-
mine, alprazolam, or adinazolam on CRF concentrations
 physiology of anxiety and depressive disorders, we ex-
amined the actions of a single acute injection of imipra-
mine, alprazolam, or adinazolam on CRF concentrations
in 18 rat brain regions (Owens et al., 1989). Imipramin amined the actions of a single acute injection of imipra-

in 18 rat brain regions (Owens et al., 1989). Imipramine

is a prototypical tricyclic antidepressant that, along with

its active metabolite, desipramine, inhibits mine, alprazolam, or adinazolam on CRF concentrations
in 18 rat brain regions (Owens et al., 1989). Imipramine
is a prototypical tricyclic antidepressant that, along with
its active metabolite, desipramine, inhibits both 5 in 18 rat brain regions (Owens et al., 1989). Imipram
is a prototypical tricyclic antidepressant that, along w
its active metabolite, desipramine, inhibits both 5-
and norepinephrine reuptake. Alprazolam and its
methylamin is a prototypical tricyclic antidepressant that, along with
its active metabolite, desipramine, inhibits both 5-HT
and norepinephrine reuptake. Alprazolam and its di-
methylamino analog, adinazolam, are atypical triazolobits active metabolite, desipramine, inhibits both 5-HT and norepinephrine reuptake. Alprazolam and its dimethylamino analog, adinazolam, are atypical triazoloberizodiazepines (Hester et al., 1971, 1980; Hester and Voigtlan and norepinephrine reuptake. Alprazolam and its dimethylamino analog, adinazolam, are atypical triazolobenzodiazepines (Hester et al., 1971, 1980; Hester and Voigtlander, 1979; Lahti et al., 1983) that possess both anxioly methylamino analog, adinazolam, are atypical triazolob-
enzodiazepines (Hester et al., 1971, 1980; Hester and
Voigtlander, 1979; Lahti et al., 1983) that possess both
anxiolytic properties typical of benzodiazepines and ha enzodiazepines (Hester et al., 1971, 1980; Hester an
Voigtlander, 1979; Lahti et al., 1983) that possess bot
anxiolytic properties typical of benzodiazepines and hav
also been reported to possess clinical antidepressant an Voigtlander, 1979; Lahti et al., 1983) that possess both
anxiolytic properties typical of benzodiazepines and have
also been reported to possess clinical antidepressant and
antipanic activity unique to these benzodiazepine anxiolytic properties typical of benzodiazepines and have
also been reported to possess clinical antidepressant and
antipanic activity unique to these benzodiazepines (Am-
sterdam et al., 1986; Dunner et al., 1987; Fawcett also been reported to possess clinical antidepressant and
antipanic activity unique to these benzodiazepines (Am-
sterdam et al., 1986; Dunner et al., 1987; Fawcett et al.,
1987; Feighner et al., 1983; Rickels et al., 1987 antipanic activity unique to these benzodiazepines (Amsterdam et al., 1986; Dunner et al., 1987; Fawcett et al., 1987; Feighner et al., 1983; Rickels et al., 1987). One hour following an acute injection, CRF concentration sterdam et al., 1986; Dunner et al., 1987; Fawcett et al., 59
1987; Feighner et al., 1983; Rickels et al., 1987). One
hour following an acute injection, CRF concentrations
were decreased in the locus ceruleus, amygdala, pi 1987; Feighner et al., 1983; Rickels et al., 1987). One
hour following an acute injection, CRF concentrations
were decreased in the locus ceruleus, amygdala, piriform
cortex, and cingulate cortex in both alprazolam- and
ad hour following an acute injection, CRF concentrations
were decreased in the locus ceruleus, amygdala, piriform
cortex, and cingulate cortex in both alprazolam- and
adinazolam-treated rats. Imipramine treatment was
without were decreased in the locus ceruleus, amygdala, piriform
cortex, and cingulate cortex in both alprazolam- and
adinazolam-treated rats. Imipramine treatment was
without effect on CRF concentrations in all brain regions
stud cortex, and cingulate cortex in both alprazolam- and
adinazolam-treated rats. Imipramine treatment was
without effect on CRF concentrations in all brain regions
studied. In a second study, the time course of these effects
 adinazolam-treated rats. Imipramine treatment was
without effect on CRF concentrations in all brain regions
studied. In a second study, the time course of these effects
were studied in which alprazolam decreased CRF con-
c without effect on CRF concentrations in all brain regions
studied. In a second study, the time course of these effects
were studied in which alprazolam decreased CRF con-
centrations in the locus ceruleus 30 to 180 minutes studied. In a second study, the time course of these effects
were studied in which alprazolam decreased CRF con-
centrations in the locus ceruleus 30 to 180 minutes
postinjection (Owens et al., 1991d). The 180-minute time
 were studied in which alprazolam decreased CRF contrations in the locus ceruleus 30 to 180 minupostinjection (Owens et al., 1991d). The 180-minute ticourse corresponds very closely with the bioavailabile and metabolism of centrations in the locus ceruleus 30 to 180 minutes
postinjection (Owens et al., 1991d). The 180-minute time
course corresponds very closely with the bioavailability
and metabolism of alprazolam. Moreover, CRF concen-
tra postinjection (Owens et al., 1991d). The 180-minute time
course corresponds very closely with the bioavailability
and metabolism of alprazolam. Moreover, CRF concen-
trations in the locus ceruleus remained decreased during course corresponds very closely with the bioavailability FIG. 8. Effects of alprazolam and stress on CRF concentrations in
and metabolism of alprazolam. Moreover, CRF concen-
trations in the locus ceruleus remained decrea

CORTICOTROPIN-RELEASING FACTOR

cortex, caudate/putamen, thalamus, pons/medulla, and addition, CRF concentrations in the dorsal vagal com-

cerebellum were unaffected. Because serotonin is a po- plex were decreased 24 hour corricorropin-releasing factors

ons/medulla, and addition, CRF concentrations in the dorsal vagal com-

erotonin is a po- plex were decreased 24 hours following abrupt alprazo-LEASING FACTOR
addition, CRF concentrations in the dorsal vagal co
plex were decreased 24 hours following abrupt alpra
lam withdrawal. These changes during drug withdrav 455
addition, CRF concentrations in the dorsal vagal com-
plex were decreased 24 hours following abrupt alprazo-
lam withdrawal. These changes during drug withdrawal
are, not surprisingly, similar to those observed followi addition, CRF concentrations in the dorsal vagal complex were decreased 24 hours following abrupt alprazolam withdrawal. These changes during drug withdrawal are, not surprisingly, similar to those observed following stres addition, CRF concentrations
plex were decreased 24 hours
lam withdrawal. These change
are, not surprisingly, similar to
stress (Chappell et al., 1986).
Of particular interest is the ex were decreased 24 hours following abrupt alprazom
m withdrawal. These changes during drug withdrawal
e, not surprisingly, similar to those observed following
ress (Chappell et al., 1986).
Of particular interest is the f

lam withdrawal. These changes during drug withdrawal
are, not surprisingly, similar to those observed following
stress (Chappell et al., 1986).
Of particular interest is the finding of decreased CRF
concentrations in the l are, not surprisingly, similar to those observed following
stress (Chappell et al., 1986).
Of particular interest is the finding of decreased CRF
concentrations in the locus ceruleus following acute or
chronic alprazolam t stress (Chappell et al., 1986).

Of particular interest is the finding of decreased CRF

concentrations in the locus ceruleus following acute or

chronic alprazolam treatment, which is opposite to that

observed following Of particular interest is the finding of decreased CRF
concentrations in the locus ceruleus following acute or
chronic alprazolam treatment, which is opposite to that
observed following exposure to either acute or chronic
 concentrations in the locus ceruleus following acute or
chronic alprazolam treatment, which is opposite to that
observed following exposure to either acute or chronic
stress (fig. 8). As noted previously, CRF has been show chronic alprazolam treatment, which is opposite to that
observed following exposure to either acute or chronic
stress (fig. 8). As noted previously, CRF has been shown
to increase the firing rate of noradrenergic locus cer observed following exposure to either acute or chro
stress (fig. 8). As noted previously, CRF has been sho
to increase the firing rate of noradrenergic locus cerule
neurons. Thus, CRF may intrinsically modulate the
tivity stress (fig. 8). As noted previously, CRF has been shot to increase the firing rate of noradrenergic locus cerule neurons. Thus, CRF may intrinsically modulate the ativity of the major CNS noradrenergic cell body popution, to increase the firing rate of noradrenergic locus ceruleus
neurons. Thus, CRF may intrinsically modulate the ac-
tivity of the major CNS noradrenergic cell body popula-
tion, one that has long been implicated in the patho neurons. Thus, CRF may intrinsically modulate the activity of the major CNS noradrenergic cell body population, one that has long been implicated in the pathophysiology of stress, anxiety, and depression (Bloom, 1979; Klei tivity of the major CNS noradrenergic cell body population, one that has long been implicated in the patho-
physiology of stress, anxiety, and depression (Bloom,
1979; Klein, 1987; Redmond, 1987). It is unclear at
present tion, one that has long been implicated in the paphysiology of stress, anxiety, and depression (Bl 1979; Klein, 1987; Redmond, 1987). It is unclear present whether classical benzodiazepines (diaze chlordiazepoxide, etc.) a physiology of stress, anxiety, and depression (Bloc
1979; Klein, 1987; Redmond, 1987). It is unclear
present whether classical benzodiazepines (diazepa
chlordiazepoxide, etc.) alter regional CRF immunore
tivity or whether 1979; Klein, 1987; Redmond, 1987). It is unclear at present whether classical benzodiazepines (diazepam chlordiazepoxide, etc.) alter regional CRF immunoreactivity or whether treatment with anxiolytics or antidepressants a

A complementary study from De Souza's laboratory tivity or whether treatment with anxiolytics or antide-
pressants abolishes stress-induced changes in CRF neu-
rons.
A complementary study from De Souza's laboratory
(Grigoriadis et al., 1989a) examined the effects of chro pressants abolishes stress-induced changes in CRF neurons.
A complementary study from De Souza's laboratory
(Grigoriadis et al., 1989a) examined the effects of chronic
tricyclic antidepressant or benzodiazepine treatment o rons.

A complementary study from De Souza's laboratory

(Grigoriadis et al., 1989a) examined the effects of chronic

tricyclic antidepressant or benzodiazepine treatment on

CRF receptor kinetics in a variety of rat brain A complementary study from De Souza's laboratory
(Grigoriadis et al., 1989a) examined the effects of chronic
tricyclic antidepressant or benzodiazepine treatment on
CRF receptor kinetics in a variety of rat brain regions.
 (Grigoriadis et al., 1989a) examined the effects of chronic
tricyclic antidepressant or benzodiazepine treatment or
CRF receptor kinetics in a variety of rat brain regions
They reported that, although there were trends tow tricyclic antidepressant or benzodiazepine treatment on CRF receptor kinetics in a variety of rat brain regions.
They reported that, although there were trends toward
increased CRF binding in the brain stem, cerebellum,
hy CRF receptor kinetics in a variety of rat brain regions.
They reported that, although there were trends toward
increased CRF binding in the brain stem, cerebellum,
hypothalamus, and frontal cortex following imipramine
trea They reported that, although there were trends toward
increased CRF binding in the brain stem, cerebellum,
hypothalamus, and frontal cortex following imipramine
treatment, the changes were only statistically significant
in increased CRF binding in the brain stem, cerebell
hypothalamus, and frontal cortex following imipran
treatment, the changes were only statistically signific
in the brainstem. CRF receptor-binding density was
nificantly dec hypothalamus, and frontal cortex following imipramine
treatment, the changes were only statistically significant
in the brainstem. CRF receptor-binding density was sig-
nificantly decreased in the frontal cortex and hippoc treatment, the changes were only statistically significant
in the brainstem. CRF receptor-binding density was sig-
nificantly decreased in the frontal cortex and hippocam-
pus following chronic treatment with either alpraz in the brainstem. CRF receptor-binding density was significantly decreased in the frontal cortex and hippocampus following chronic treatment with either alprazolam, adinazolam, or diazepam. The authors accurately point out nificantly decreased in the frontal cortex and hippocampus following chronic treatment with either alprazolam,
adinazolam, or diazepam. The authors accurately point
out that the relatively small effects of these drugs on
C pus following chronic treatment with either alprazolam,
adinazolam, or diazepam. The authors accurately point
out that the relatively small effects of these drugs on
CRF receptor binding do not necessarily imply a lack of

ACUTE CHRONIC 24 HOUR ACUTE CHRONIC
ALPRAZOLAM ALPRAZOLAM WITHDRAWAL STRESS STRESS
FIG. 8. Effects of alprazolam and stress on CRF concentrations in
the locus ceruleus. The anxiolytic/antidepressant triazolobenzodiaze-
pin those of acute or chronic stress but not alprazolam withdrawal. * P < FIG. 8. Effects of alprazolam and stress on CRF concentrations in
the locus ceruleus. The anxiolytic/antidepressant triazolobenzodiaze-
pine, alprazolam, produces effects in the locus ceruleus opposite to
those of acute or the locus ceruleus. The anxiolytic/antidepressant triazolobe
pine, alprazolam, produces effects in the locus ceruleus of
those of acute or chronic stress but not alprazolam withdra
0.05, ** $P < 0.01$, *** $P < 0.001$ compare

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relatively small effects on CRF synthesis and release in incurate basal state. Because of the inability at present to its The basal state. Because of the inability at present to its
directly measure CRF release in extrahypothalamic brain
directly measure CRF release in extrahypothalamic brain directly small effects on CRF synthesis and release in inthe basal state. Because of the inability at present to its directly measure CRF release in extrahypothalamic brain nu regions, experiments aimed at measuring CRF co relatively small effects on CRF synthesis and release
the basal state. Because of the inability at present
directly measure CRF release in extrahypothalamic bra
regions, experiments aimed at measuring CRF conce
trations, C relatively small effects on CRF synthesis and release in
the basal state. Because of the inability at present to
directly measure CRF release in extrahypothalamic brain
regions, experiments aimed at measuring CRF concen-
t the basal state. Because of the inability at present to idirectly measure CRF release in extrahypothalamic brain regions, experiments aimed at measuring CRF concentrations, CRF receptors, and CRF mRNA during basal states a directly measure CRF release in extrahypothalamic brain nu
regions, experiments aimed at measuring CRF concen-
trations, CRF receptors, and CRF mRNA during basal wis
states and during exposure to stress or in animal models needed. states and during exposure to stress or in animal models
that mimic anxious or depressive human states are sorely
needed.
Based upon their previous electrophysiological exper-
iments, Valentino et al. (1990) examined the e

states and during exposure to stress or in animal models
that mimic anxious or depressive human states are sorely
needed.
Based upon their previous electrophysiological exper-
iments, Valentino et al. (1990) examined the that mimic anxious or depressive human states are sore needed.
Based upon their previous electrophysiological experiments, Valentino et al. (1990) examined the effects acute and chronic antidepressant treatment on noratene renergied.

Rased upon their previous electrophysiological experiments, Valentino et al. (1990) examined the effects of acute and chronic antidepressant treatment on norad-

renergic neurons of the locus ceruleus. They fou Based upon their previous electrophysiological experiments, Valentino et al. (1990) examined the effects of acute and chronic antidepressant treatment on norad-
renergic neurons of the locus ceruleus. They found that
chron iments, Valentino et al. (1990) examined the effects of Cor
acute and chronic antidepressant treatment on norad-
renergic neurons of the locus ceruleus. They found that
chronic (21 days) treatment with desipramine attenua acute and chronic antidepressant treatment on norad-
renergic neurons of the locus ceruleus. They found that
chronic (21 days) treatment with desipramine attenuated
locus ceruleus activation following hypotensive stress, renergic neurons of the locus ceruleus. They found that

chronic (21 days) treatment with desipramine attenuated for

locus ceruleus activation following hypotensive stress, an

effect thought to require CRF release (Vale chronic (21 days) treatment with desipramine attenuated
locus ceruleus activation following hypotensive stress, an
effect thought to require CRF release (Valentino and
Wehby, 1988). Locus ceruleus activation by i.c.v. CRF
 locus ceruleus activation following hypotensive stress, an
effect thought to require CRF release (Valentino and
Wehby, 1988). Locus ceruleus activation by i.c.v. CRF
was not altered in desipramine-treated rats. In contras effect thought to require CRF release (Valentino and Wehby, 1988). Locus ceruleus activation by i.c.v. CRF was not altered in desipramine-treated rats. In contrast to the effects of desipramine, chronic administration of t Wehby, 1988). Locus ceruleus activation by i.c.v. CRF was not altered in desipramine-treated rats. In contrast to the effects of desipramine, chronic administration of the serotonergic reuptake inhibitor, sertraline, did n was not altered in desipramine-treated rats. In contrast
to the effects of desipramine, chronic administration of
the serotonergic reuptake inhibitor, sertraline, did not
alter locus ceruleus activity by either stress or the serotonergic reuptake inhibitor, sertraline, did not
alter locus ceruleus activity by either stress or i.c.v. CRF.
However, the response of the cells to repeated sciatic
nerve stimulation was opposite to that produced alter locus ceruleus activity by either stress or i.c.v. CRF. alter locus ceruleus activity by either stress or i.c.v. CRF.
However, the response of the cells to repeated sciatic preve stimulation was opposite to that produced by CRF.
They suggested from these data that certain antid However, the response of the cells to repeated sciatic nerve stimulation was opposite to that produced by CRF.
They suggested from these data that certain antidepres-
sants may interfere with the effects of CRF in the loc nerve stimulation was opposite to that produced by CRF.
They suggested from these data that certain antidepressants may interfere with the effects of CRF in the locus
ceruleus as a possible mechanism of action. This may
oc They suggested from these data that certain antidepressants may interfere with the effects of CRF in the locus ceruleus as a possible mechanism of action. This may occur via noradrenergic reuptake inhibitors attenuating st requires Sants may interfere with the effects of CRF in the locus

ceruleus as a possible mechanism of action. This may

occur via noradrenergic reuptake inhibitors attenuating

stress-induced locus ceruleus activation, an ceruleus as a possible mechanism of action. This may
occur via noradrenergic reuptake inhibitors attenuating
stress-induced locus ceruleus activation, an action that
requires CRF release, possibly by inhibiting local CRF
r requires CRF release, possibly by inhibiting local CRF release. In contrast to desipramine, sertraline and other serotonin reuptake inhibitors may functionally antagostress-induced locus ceruleus activation, an action that
requires CRF release, possibly by inhibiting local CRF
release. In contrast to desipramine, sertraline and other
serotonin reuptake inhibitors may functionally antag requires CRF release, possibly by inhibiting local CRF
release. In contrast to desipramine, sertraline and other
serotonin reuptake inhibitors may functionally antago-
nize the actions of CRF by producing opposing effects
 release. In contrast to desipramine, sertraline and other
serotonin reuptake inhibitors may functionally antagonize the actions of CRF by producing opposing effects
on the locus ceruleus. Although their conclusions are
ba serotonin reuptake inhibitors may functionally antagonize the actions of CRF by producing opposing effects on the locus ceruleus. Although their conclusions are based on limited data, the findings clearly do not provide a nize the actions of CRF by producing opposing effect
on the locus ceruleus. Although their conclusions ar
based on limited data, the findings clearly do not provid
any evidence to preclude the hypothesis that the CRI
inner on the locus ceruleus. Although
based on limited data, the findin
any evidence to preclude the h
innervation of the locus ceruleu
apeutic actions of antidepressant
Clinical studies (section IX) h any evidence to preclude the hypothesis that the CRF
innervation of the locus ceruleus is involved in the ther-
apeutic actions of antidepressants.
Clinical studies (section IX) have implicated both neu-

any evidence to preclude the hypothesis that the CRF
innervation of the locus ceruleus is involved in the ther-
apeutic actions of antidepressants.
Clinical studies (section IX) have implicated both neu-
ronal degeneratio innervation of the locus ceruleus is involved in the ther-
apeutic actions of antidepressants.
Clinical studies (section IX) have implicated both neu-
ronal degeneration of CRF and cholinergic neurons in
Alzheimer's disea apeutic actions of antidepressants. Clinical studies (section IX) have implicated both neuronal degeneration of CRF and cholinergic neurons in Alzheimer's disease. To mimic the purported cholinergic bel deficit observed in Clinical studies (section IX) have implicated both no
ronal degeneration of CRF and cholinergic neurons
Alzheimer's disease. To mimic the purported choliner
deficit observed in Alzheimer's disease, De Souza a
Battaglia (19 Alzheimer's disease. To mimic the purported cholinergic deficit observed in Alzheimer's disease, De Souza and Battaglia (1986) examined the effects of chronic muscarinic receptor blockade (by continuous atropine infusion) Alzheimer's disease. To mimic the purported cholinergic
deficit observed in Alzheimer's disease, De Souza and
Battaglia (1986) examined the effects of chronic musca-
rinic receptor blockade (by continuous atropine infusion deficit observed in Alzheimer's disease, De Souza and
Battaglia (1986) examined the effects of chronic musca-
rinic receptor blockade (by continuous atropine infusion)
on CRF receptor kinetics in rat brain. They found that Battaglia (1986) examined the effects of chronic muscarinic receptor blockade (by continuous atropine infusion) pon CRF receptor kinetics in rat brain. They found that CRF receptors increased in the frontal/parietal corte rinic receptor blockade (by continuous atropine infusion)
on CRF receptor kinetics in rat brain. They found that
CRF receptors increased in the frontal/parietal cortex, a
finding similar to that in Alzheimer's disease repo on CRF receptor kinetics in rat brain. They found that $\frac{1}{11}$ CRF receptors increased in the frontal/parietal cortex, a sifinding similar to that in Alzheimer's disease reported by De Souza et al. (1986), but receptor CRF receptors increased in the frontal/parietal cortex, a
finding similar to that in Alzheimer's disease reported
by De Souza et al. (1986), but receptor number did not
change in the olfactory bulb, cerebellum, striatum, o finding similar to that in Alzheimer's disease reported
by De Souza et al. (1986), but receptor number did not
change in the olfactory bulb, cerebellum, striatum, or
hippocampus. However, the increases in CRF receptors
in by De Souza et al. (1986), but receptor number did not ral change in the olfactory bulb, cerebellum, striatum, or the hippocampus. However, the increases in CRF receptors rig in the cortex do not appear to be functional as change in the olfactory bulb, cerebellum, striatum, or
hippocampus. However, the increases in CRF receptors
in the cortex do not appear to be functional as assessed
by second messenger generation. These increases are
thoug hippocampus. However, the increases in CRF receptors right-to-left manner. Left-to-right stimulation of the left
in the cortex do not appear to be functional as assessed eve increased evoked activity in the contralateral i in the cortex do not appear to be functional as assessed
by second messenger generation. These increases are
thought to represent either spare receptors, alternate
second messenger systems (i.e., they are not coupled to
ad by second messenger generation. These increases are olitiously to represent either spare receptors, alternate the second messenger systems (i.e., they are not coupled to headenylate cyclase), or incomplete coupling to G pr second messenger systems (i.e., they are not coupled to adenylate cyclase), or incomplete coupling to G proteins.
In a subsequent experiment in which CRF receptors were examined in dissociated fetal rat cortex cell culture adenylate cyclase), or incomplete coupling to G proteins. than 10-fold after 144 hours. These increases then de-
In a subsequent experiment in which CRF receptors were clined to control values 30 hours following completion

NEMEROFF
incubation with the cells decreased the concentration of
its own receptor by 36%, atropine did not alter the NEMEROFF
incubation with the cells decreased the concentration of
its own receptor by 36%, atropine did not alter the
number of CRF receptors. Again the lack of data regard-NEMEROFF
incubation with the cells decreased the concentration
its own receptor by 36%, atropine did not alter t
number of CRF receptors. Again the lack of data regar
ing CRF anatomical pathways and synaptic interaction owens and nemerors

incubation with the cells decreased the concentration of

present to its own receptor by 36%, atropine did not alter the

amic brain number of CRF receptors. Again the lack of data regard-

RF concen- i incubation with the cells decreased the concentration
its own receptor by 36%, atropine did not alter
number of CRF receptors. Again the lack of data rega
ing CRF anatomical pathways and synaptic interaction
with other tra its own receptor by 36%, atropine did not alter the
number of CRF receptors. Again the lack of data regard-
ing CRF anatomical pathways and synaptic interactions
with other transmitter systems renders any firm hypoth-
esis number of CRF receptors. Again the lack of data regarding CRF anatomical pathways and synaptic interactions with other transmitter systems renders any firm hypothesis regarding CRF involvement in the etiology of Alzheimer' ing CRF anatomi
with other transnesis regarding Cl
heimer's disease,
system, tenuous.
C. Miscellaneous. *C. Miscellaneous Changes in Extrahypothalamical strates any timesis regarding CRF involvement in the etiolog*
C. Miscellaneous Changes in Extrahypothalamic
C. Miscellaneous Changes in Extrahypothalamic
Corticotropincortingalesigness

We studied rats from the FSL which have been bred for differences in sensitivity to cholinergic agonists (Owens et al., 1991c). The FSL rats have been proposed as a genetic animal model of depression because, like some C. Miscellaneous Changes in Extrahypothalamic
Corticotropin-releasing Factor Neurons
We studied rats from the FSL which have been bred
for differences in sensitivity to cholinergic agonists (Ow-
ens et al., 1991c). The FSL Corticotropin-releasing Factor Neurons
We studied rats from the FSL which have been bred
for differences in sensitivity to cholinergic agonists (Ow-
ens et al., 1991c). The FSL rats have been proposed as a
genetic animal m We studied rats from the FSL which have been bred
for differences in sensitivity to cholinergic agonists (Ow-
ens et al., 1991c). The FSL rats have been proposed as a
genetic animal model of depression because, like some
d for differences in sensitivity to cholinergic agonists (Ovens et al., 1991c). The FSL rats have been proposed as genetic animal model of depression because, like sor depressed patients, they are more sensitive to cholinerg ens et al., 1991c). The FSL rats have been proposed a genetic animal model of depression because, like sometic
depressed patients, they are more sensitive to choliner
agonists, are less active, exhibit higher rapid eye mom genetic animal model of depression because, like some
depressed patients, they are more sensitive to cholinergic
agonists, are less active, exhibit higher rapid eye move-
ment density, and "respond" to classical antidepres depressed patients, they are more sensitive to choline
agonists, are less active, exhibit higher rapid eye m
ment density, and "respond" to classical antidepressa
In addition, these rats exhibit increased concentrat
of mus agonists, are less active, exhibit higher rapid eye move-
ment density, and "respond" to classical antidepressants.
In addition, these rats exhibit increased concentrations
of muscarinic receptors in the striatum and hippo ment density, and "respond" to classical antidepressants.
In addition, these rats exhibit increased concentrations
of muscarinic receptors in the striatum and hippocam-
pus. We observed in two studies that FSL rats had
dec In addition, these rats exhibit increased concentrations
of muscarinic receptors in the striatum and hippocam-
pus. We observed in two studies that FSL rats had
decreased concentrations of CRF in the locus ceruleus,
prefro of muscarinic receptors in the striatum
pus. We observed in two studies tha
decreased concentrations of CRF in th
prefrontal cortex, and median eminenc
CRF receptors in the anterior pituitary.
Hashimoto et al. (1985) measu is. We observed in two studies that FSL rats had
creased concentrations of CRF in the locus ceruleus,
efrontal cortex, and median eminence and decreased
RF receptors in the anterior pituitary.
Hashimoto et al. (1985) measu

decreased concentrations of CRF in the locus ceruleus,
prefrontal cortex, and median eminence and decreased
CRF receptors in the anterior pituitary.
Hashimoto et al. (1985) measured the regional brain
CRF concentration of prefrontal cortex, and median eminence and decreased
CRF receptors in the anterior pituitary.
Hashimoto et al. (1985) measured the regional brain
CRF concentration of SHR and reported that CRF im-
munoreactivity was signif CRF receptors in the anterior pituitary.

Hashimoto et al. (1985) measured the regional brain

CRF concentration of SHR and reported that CRF im-

munoreactivity was significantly reduced in midbrain,

medulla, cortex, and Hashimoto et al. (1985) measured the regional bra
CRF concentration of SHR and reported that CRF is
munoreactivity was significantly reduced in midbrai
medulla, cortex, and hypothalamus. It was suggested th
the CRF differe CRF concentration of SHR and reported that CRF im-
munoreactivity was significantly reduced in midbrain,
medulla, cortex, and hypothalamus. It was suggested that
the CRF differences may be responsible for the abnor-
maliti munoreactivity was significantly reduced in midbrain,
medulla, cortex, and hypothalamus. It was suggested that
the CRF differences may be responsible for the abnor-
malities in the pituitary-adrenal axis, autonomic re-
spo medulla, cortex, and hypothalamus. It was suggested the CRF differences may be responsible for the abnomilaties in the pituitary-adrenal axis, autonomic is sponses, and behaviors of SHR, although the large sis of the brain the CRF differences may be responsible for the abnormalities in the pituitary-adrenal axis, autonomic responses, and behaviors of SHR, although the large size of the brain regions studied severely limits any conclusions th malities in the pituitary-adrenal axis, autonomic responses, and behaviors of SHR, although the large size of the brain regions studied severely limits any conclusions that can be drawn. Again, the lack of anatomical and p sponses, and behaviors of SHR, although the large size
of the brain regions studied severely limits any conclu-
sions that can be drawn. Again, the lack of anatomical
and physiological knowledge surrounding extrahypotha-
l data. and physiological knowledge surrounding extrahypotha-
lamic CRF neurons hinders the interpretation of these
data.
Considerably more useful and increasingly more often
utilized is the measurement of CRF mRNA concentra-
tion

Considerably more useful and increasingly more often utilized is the measurement of CRF mRNA concentralamic CRF neurons hinders the interpretation of these
data.
Considerably more useful and increasingly more often
utilized is the measurement of CRF mRNA concentra-
tions following various experimental paradigms with the
be data.
Considerably more useful and increasingly more often
utilized is the measurement of CRF mRNA concentra-
tions following various experimental paradigms with the
belief that increases or decreases in mRNA levels reflec Considerably more useful and increasingly more often
utilized is the measurement of CRF mRNA concentra-
tions following various experimental paradigms with the
belief that increases or decreases in mRNA levels reflect
incr utilized is the measurement of CRF mRNA concentra-
tions following various experimental paradigms with the
belief that increases or decreases in mRNA levels reflect
increases or decreases in the neuronal rate of peptide
sy tions following various experimental paradigms with the belief that increases or decreases in mRNA levels reflect increases or decreases in the neuronal rate of peptide synthesis due to changes in secretion rate. As mentio belief that increases or decreases in mRNA levels reflect
increases or decreases in the neuronal rate of peptide
synthesis due to changes in secretion rate. As mentioned
previously, these studies have proven particularly u increases or decreases in the neuronal rate of peptide
synthesis due to changes in secretion rate. As mentioned
previously, these studies have proven particularly useful
in studying PVN CRF neuronal regulation. The only
st previously, these studies have proven particularly useful
in studying PVN CRF neuronal regulation. The only
study to date examining extrahypothalamic CRF neu-
rons is that of Barmack and Young (1990) who placed
rabbits in previously, these studies have proven particularly useful
in studying PVN CRF neuronal regulation. The only
study to date examining extrahypothalamic CRF neu-
rons is that of Barmack and Young (1990) who placed
rabbits in in studying PVN CRF neuronal regulation. The only
study to date examining extrahypothalamic CRF neu-
rons is that of Barmack and Young (1990) who placed
rabbits in a rotating drum which essentially stimulated
the animals f study to date examining extrahypothalamic CRF neu-
rons is that of Barmack and Young (1990) who placed
rabbits in a rotating drum which essentially stimulated
the animals field of vision in a constant left-to-right or
righ rons is that of Barmack and Young (1990) who placed
rabbits in a rotating drum which essentially stimulated
the animals field of vision in a constant left-to-right or
right-to-left manner. Left-to-right stimulation of the rabbits in a rotating drum which essentially stimulated
the animals field of vision in a constant left-to-right or
right-to-left manner. Left-to-right stimulation of the left
eye increased evoked activity in the contralate the animals field of vision in a constant left-to-right or
right-to-left manner. Left-to-right stimulation of the left
eye increased evoked activity in the contralateral inferior
olive neurons in the right caudal cap. The that CRF mRNA levels increased 4- to 7-fold after 48 eye increased evoked activity in the contralateral inferior
olive neurons in the right caudal cap. The authors found
that CRF mRNA levels increased 4- to 7-fold after 48
hours of optokinetic (rotation) stimulation and by m olive neurons in the right caudal cap. The authors found
that CRF mRNA levels increased 4- to 7-fold after 48
hours of optokinetic (rotation) stimulation and by more
than 10-fold after 144 hours. These increases then de-
c hours of optokinetic (rotation) stimulation and by more hours of optokinetic (rotation) stimulation and by more
than 10-fold after 144 hours. These increases then de-
clined to control values 30 hours following completion of
the experiment. These observations specifically impli

PHARMACOLOGICAL REVIEWS

CORTICOTROPIN-RE
system which may predominantly involve fine control of
eye movement. Of greater significance may be the fact
that this study validates the use mRNA quantitation as CORTICOTROPIN-RELE
system which may predominantly involve fine control of
eye movement. Of greater significance may be the fact
that this study validates the use mRNA quantitation as
a tool to study the effects of various system which may predominantly involve fine control of
eye movement. Of greater significance may be the fact
that this study validates the use mRNA quantitation as
a tool to study the effects of various experimental per-
t system which may predominantly involve fine con-
eye movement. Of greater significance may be that this study validates the use mRNA quantita
a tool to study the effects of various experiment
turbations on changes in CRF n e movement. Of greater significance may be the fact
at this study validates the use mRNA quantitation as
tool to study the effects of various experimental per-
phations on changes in CRF neuronal activity.
At the present t

that this study validates the use mRNA quantitation as
a tool to study the effects of various experimental per-
turbations on changes in CRF neuronal activity.
At the present time, it would appear that the most
accurate m a tool to study the effects of various experimental per-
turbations on changes in CRF neuronal activity. et a
At the present time, it would appear that the most (198
accurate methods used to study changes in CRF neuronal turbations on changes in CRF neuronal activity.
At the present time, it would appear that the mo
accurate methods used to study changes in CRF neuron
function require the combined measurement of (*a*) CF
concentrations in At the present time, it would appear that the most (19)
accurate methods used to study changes in CRF neuronal Cl
function require the combined measurement of (a) CRF (1
concentrations in discrete brain regions, (b) CRF accurate methods used to study changes in CRF neuronal C
function require the combined measurement of (a) CRF (
concentrations in discrete brain regions, (b) CRF recep-
for number and affinity and CRF-stimulated second function require the combined measurement of (a) CRF (1 μ g concentrations in discrete brain regions, (b) CRF reception field tor number and affinity and CRF-stimulated second Using messenger generation in the same brai concentrations in discrete brain regions, (b) CRF receptor number and affinity and CRF-stimulated secon messenger generation in the same brain regions, and (CRF mRNA concentrations. Note that CRF mRN. measurement is mo tor number and affinity and CRF-stimulated second Unessenger generation in the same brain regions, and (c) (CRF mRNA concentrations. Note that CRF mRNA fields measurement is most useful when the anatomical path-
way from CRF mRNA concentrations. Note that CRF mRNA measurement is most useful when the anatomical pathway from cell body (location of mRNA) to terminal fields (location of CRF peptide in vesicles and CRF receptors CRF mRNA concentrations. Note that CRF mRNA
measurement is most useful when the anatomical path-
way from cell body (location of mRNA) to terminal fields
(location of CRF peptide in vesicles and CRF receptors
at the synaps measurement is most useful when the anatomical path-
way from cell body (location of mRNA) to terminal fields
a pe
(location of CRF peptide in vesicles and CRF receptors
at the synapse) is known. Future techniques being de way from cell body (location of mRNA) to terminal fields (location of CRF peptide in vesicles and CRF receptors at the synapse) is known. Future techniques being developed include microdialysis to measure CRF release in vi (location of CRF peptide in vesicles and CRF receptors trated the synapse) is known. Future techniques being de-
veloped include microdialysis to measure CRF release in canceling
vivo, electrophysiological identification o veloped include microdialysis to measure CRF release in
vivo, electrophysiological identification of CRF neurons,
and peptidase inhibitors to alter degradation of CRF
following secretion into the synaptic cleft.
IX. Clinic electrophysiological identification of CRF neurons
peptidase inhibitors to alter degradation of CRI
wing secretion into the synaptic cleft.
IX. Clinical Studies implicating a Role for
ticotropin-releasing Factor Hypersec

Collowing secretion into the synaptic cleft. The collowing secretion into the synaptic cleft. The change of the corticotropin-releasing Factor Hypersecretion in the Pathophysiology of Psychiatric Illness Chream **the Pathophysiology of Psychiatric Illness IX. Clinical Studies implicating a Ro**
Corticotropin-releasing Factor Hypersective Pathophysiology of Psychiatric I
A. Major Depression and Anxiety Disorders
1 Corticotropin-releasing factor stimulation

**1. Corticotropin-releasing Factor Hypersecretion i

1. Corticotropin-releasing** factor stimulation test. Pre-
 1. Corticotropin-releasing factor stimulation test. Pre-
 1. Corticotropin-releasing factor stimulation t origin in orchestrating an organism's response to stress. A. *Indijor Depression and Arixiety Disorders*
1. Corticotropin-releasing factor stimulation test. Pre-
clinical studies clearly support a prominent role for CRF
neurons of both hypothalamic and extrahypothalamic
origin in 1. Corticotropin-releasing factor stimulation test. Pre-
clinical studies clearly support a prominent role for CRF
neurons of both hypothalamic and extrahypothalamic
origin in orchestrating an organism's response to stress clinical studies clearly support a prominent role for CRF
neurons of both hypothalamic and extrahypothalamic
origin in orchestrating an organism's response to stress.
Moreover, stress has been implicated in precipitating
d meurons of both hypothalamic and extrahypothalamic

origin in orchestrating an organism's response to stress.

Moreover, stress has been implicated in precipitating

depressive episodes in genetically vulnerable individual origin in orchestrating an organism's response to stress.
Moreover, stress has been implicated in precipitating
depressive episodes in genetically vulnerable individuals
(Anisman and Zacharko, 1982). Therefore, the possibi Moreover, stress has been implicated in precipitating
depressive episodes in genetically vulnerable individuals
(Anisman and Zacharko, 1982). Therefore, the possibility
exists that CRF neuronal dysregulation could contribu depressive episodes in genetically vulnerable individuals

(Anisman and Zacharko, 1982). Therefore, the possibility

exists that CRF neuronal dysregulation could contribute

from human illness. With this in mind, one of th (Anisman and Zacharko, 1982). Therefore, the possibiexists that CRF neuronal dysregulation could contrit
to human illness. With this in mind, one of the m
reproducible findings in biological psychiatry is
hyperactivity of exists that CRF neuronal dysregulation could contribute
to human illness. With this in mind, one of the most
reproducible findings in biological psychiatry is the
hyperactivity of the HPA axis as evidenced by hypercor-
tis to human illness. With this in mind, one of the most
reproducible findings in biological psychiatry is the
hyperactivity of the HPA axis as evidenced by hypercor-
tisolemia and dexamethasone nonsuppression in patients
with reproducible findings in biological psychiatry is the
hyperactivity of the HPA axis as evidenced by hypercor-
tisolemia and dexamethasone nonsuppression in patients
with endogenous depression. A number of investigators
the hyperactivity of the HPA axis as evidenced by hypercortisolemia and dexamethasone nonsuppression in patients with endogenous depression. A number of investigators thave attempted to study the mechanism(s) that result in th tisolemia and dexamethasone nonsuppression in patients
with endogenous depression. A number of investigators
have attempted to study the mechanism(s) that result ir
this hypercortisolemia. Although there is some evidence
f with endogenous depression. A number of investigators that the mechanism(s) that result in supplemential this hypercortisolemia. Although there is some evidence in the CNS for enhanced cortisol responses to ACTH in depress have attempted to study the mechanism(s) that result in
this hypercortisolemia. Although there is some evidence
for enhanced cortisol responses to ACTH in depression, four
most evidence points to a primary alteration in th for enhanced cortisol responses to ACTH in depression,
most evidence points to a primary alteration in the CNS
that leads to hyperactivity of the HPA axis, with CRF
neuronal hyperactivity the most plausible candidate.
The r enhanced cortisol responses to ACTH in depression,
ost evidence points to a primary alteration in the CNS
at leads to hyperactivity of the HPA axis, with CRF
uronal hyperactivity the most plausible candidate.
The most wi most evidence points to a primary alteration in the CNS
that leads to hyperactivity of the HPA axis, with CRF
neuronal hyperactivity the most plausible candidate.
The most widely studied, and perhaps least direct,
method t

that leads to hyperactivity of the HPA axis, with CRF com-
neuronal hyperactivity the most plausible candidate. The most widely studied, and perhaps least direct, tion
method to elucidate the pathophysiology of the HPA axi neuronal hyperactivity the most plausible candidate. The most widely studied, and perhaps least direct, tion
method to elucidate the pathophysiology of the HPA axis an
is the measurement of the neuroendocrine response to The most widely studied, and perhaps least direct method to elucidate the pathophysiology of the HPA ax
is the measurement of the neuroendocrine response
exogenously administered CRF. Both rat/human CR
and oCRF produce ro is the measurement of the neuroendocrine response to exogenously administered CRF. Both rat/human CRF and oCRF produce robust ACTH, β -endorphin, β -lipotropin, and cortisol responses following i.v. or subcuta-neous a is the measurement of the neuroendocrine response to exogenously administered CRF. Both rat/human CRF and oCRF produce robust ACTH, β -endorphin, β -lipotropin, and cortisol responses following i.v. or subcutaneous ad exogenously administered CRF. Both rat/human CRF
and oCRF produce robust ACTH, β -endorphin, β -lipo-
tropin, and cortisol responses following i.v. or subcuta-
neous administration in normal subjects (Hermus et al., d and oCRF produce robust ACTH, β -endorphin, β -lipo-
tropin, and cortisol responses following i.v. or subcuta-
neous administration in normal subjects (Hermus et al., depi
1984; DeBold et al., 1985; Watson et al., 198 tropin, and cortisol responses following i.v. or subcuta-
neous administration in normal subjects (Hermus et al.,
1984; DeBold et al., 1985; Watson et al., 1986). Although
there is a diminished sensitivity of ACTH secretio meous administration in normal subjects (Hermus et al., 1984; DeBold et al., 1985; Watson et al., 1986). Although there is a diminished sensitivity of ACTH secretion to negative feedback regulation by glucocorticoids in ol 1984; DeBold et al., 1985; Watson et al.
there is a diminished sensitivity of AC
negative feedback regulation by glucoce
men, the ACTH response to exogenou
decline with age (Pavlov et al., 1986).

CORTICOTROPIN-RELEASING FACTOR **457**
system which may predominantly involve fine control of Pharmacokinetic studies have shown that, when ad-
eye movement. Of greater significance may be the fact ministered i.v., CRF has a CORTICOTROPIN-RELEASING FACTOR
ve fine control of Pharmacokinetic studies have shown that, when ad-LEASING FACTOR
Pharmacokinetic studies have shown that, when a
ministered i.v., CRF has an apparent volume of dist
bution equal to that of plasma volume and a final elin 45

Bution FACTOR

Pharmacokinetic studies have shown that, when a

ministered i.v., CRF has an apparent volume of distr

bution equal to that of plasma volume and a final elim

nation half-life ranging from 45 to 180 minu Pharmacokinetic studies have shown that, when administered i.v., CRF has an apparent volume of distribution equal to that of plasma volume and a final elimination half-life ranging from 45 to 180 minutes (Schulte et al., 1 Pharmacokinetic studies have shown that, when administered i.v., CRF has an apparent volume of distribution equal to that of plasma volume and a final elimination half-life ranging from 45 to 180 minutes (Schulte et al., 1 ministered i.v., CRF has an apparent volume of distribution equal to that of plasma volume and a final elimination half-life ranging from 45 to 180 minutes (Schulte et al., 1982, 1984; Tsukada et al., 1984). Schulte et al. bution equal to that of plasma volume and a final elimination half-life ranging from 45 to 180 minutes (Schulte et al., 1982, 1984; Tsukada et al., 1984). Schulte et al. (1985) studied pituitary desensitization to prolong nation half-life ranging from 45 to 180 minutes (Schulte et al., 1982, 1984; Tsukada et al., 1984). Schulte et al. (1985) studied pituitary desensitization to prolonged CRF infusion and found that following infusion of CR et al., 1982, 1984; Tsukada et al., 1984). Schulte et al.
(1985) studied pituitary desensitization to prolonged
CRF infusion and found that following infusion of CRF
(1 μ g/kg/hour) for 24 hours, a bolus dose of 1 μ g (1985) studied pituitary desensitization to prolonged CRF infusion and found that following infusion of CRF (1 μ g/kg/hour) for 24 hours, a bolus dose of 1 μ g/kg failed to produce any response immediately afterward. CRF infusion and found that following infusion of CRF (1 μ g/kg/hour) for 24 hours, a bolus dose of 1 μ g/kg failed to produce any response immediately afterward. Using a less sound experimental design, Désir et al. ((1 μ g/kg/hour) for 24 hours, a bolus dose of 1 μ g/kg
failed to produce any response immediately afterward.
Using a less sound experimental design, Désir et al.
(1986) still found a vigorous ACTH and cortisol respons failed to produce any response immediately afterward.
Using a less sound experimental design, Désir et al.
(1986) still found a vigorous ACTH and cortisol response
following repeated CRF injections (0.3 to 0.4 μ g/kg ev Using a less sound experimental design, Désir et (1986) still found a vigorous ACTH and cortisol respond following repeated CRF injections (0.3 to 0.4 μ g/kg evant 4 hours for 72 hours). Of interest, both groups still f (1986) still found a vigorous ACTH and cortisol response following repeated CRF injections (0.3 to 0.4 μ g/kg every 4 hours for 72 hours). Of interest, both groups still found a persistent diurnal variation in plasma AC following repeated CRF injections (0.3 to 0.4 μ g/kg every
4 hours for 72 hours). Of interest, both groups still found
a persistent diurnal variation in plasma ACTH concen-
trations in the presence of a continuous CRF i 4 hours for 72 hours). Of interest, both groups still found
a persistent diurnal variation in plasma ACTH concen-
trations in the presence of a continuous CRF infusion.
This suggests that the circadian periodicity of ACTH
 secretion. ations in the presence of a continuous CRF infusion.

is suggests that the circadian periodicity of ACTH

nnot be explained solely by median eminence CRF

cretion.

Administering CRF i.v. in what is commonly termed

e CRF

Corticotropin-releasing Factor Hypersecretion in

the Pathophysiology of Psychiatric Illness

A. Major Depression and Anxiety Disorders

1. Corticotropin-releasing factor stimulation test. Pre-

1. Corticotropin-releasing This suggests that the circadian periodicity of ACTH
cannot be explained solely by median eminence CRF
secretion.
Administering CRF i.v. in what is commonly termed
the CRF stimulation test, a number of investigators have
o cannot be explained solely by median eminence CRF
secretion.
Administering CRF i.v. in what is commonly termed
the CRF stimulation test, a number of investigators have
observed a blunted ACTH response with a normal total
c secretion.

Administering CRF i.v. in what is commonly terme

the CRF stimulation test, a number of investigators hav

observed a blunted ACTH response with a normal tota

cortisol response in patients with major depressio Administering CRF i.v. in what is commonly termed
the CRF stimulation test, a number of investigators have
observed a blunted ACTH response with a normal total
cortisol response in patients with major depression com-
pared the CRF stimulation test, a number of investigators have
observed a blunted ACTH response with a normal total
cortisol response in patients with major depression com-
pared with controls (Holsboer et al., 1984a,b; Gold and observed a blunted ACTH response with a normal tot cortisol response in patients with major depression con pared with controls (Holsboer et al., 1984a,b; Gold an Chrousos, 1985; Gold et al., 1984, 1986b; Amsterdam al., 198 cortisol response in patients with major depression compared with controls (Holsboer et al., 1984a,b; Gold and Chrousos, 1985; Gold et al., 1984, 1986b; Amsterdam et al., 1987; Lesch et al., 1988b; Kathol et al., 1989; Kri pared with controls (Holsboer et al., 1984a,b; Gold and
Chrousos, 1985; Gold et al., 1984, 1986b; Amsterdam et
al., 1987; Lesch et al., 1988b; Kathol et al., 1989; Krish-
nan et al., 1991). Rupprecht et al. (1989) observed Chrousos, 1985; Gold et al., 1984, 1986b; Amsterdam et al., 1987; Lesch et al., 1988b; Kathol et al., 1989; Krishnan et al., 1991). Rupprecht et al. (1989) observed blunted ACTH, but normal β -endorphin, responses in de al., 1987; Lesch et al., 1988b; Kathol et al., 1989; I
nan et al., 1991). Rupprecht et al. (1989) obs
blunted ACTH, but normal β -endorphin, respons
depressed individuals. In contrast to these fin
Young et al. (1990) ob nan et al., 1991). Rupprecht et al. (1989) observed
blunted ACTH, but normal β -endorphin, responses in
depressed individuals. In contrast to these findings,
Young et al. (1990) observed blunted β -endorphin/ β -
lip blunted ACTH, but normal β -endorphin, responses in
depressed individuals. In contrast to these findings,
Young et al. (1990) observed blunted β -endorphin/ β -
lipotropin responses to relatively low doses of CRF in
 depressed individuals. In contrast to these findings,
Young et al. (1990) observed blunted β -endorphin/ β -
lipotropin responses to relatively low doses of CRF in
depressed patients. Their blunted responses appear to
 Young et al. (1990) observed blunted β -endorphin/ β -
lipotropin responses to relatively low doses of CRF in
depressed patients. Their blunted responses appear to
represent a shortened length of pituitary stimulation
 lipotropin responses to 1
depressed patients. Thei
represent a shortened le
from CRF rather than a c
POMC-derived peptides.
In a single, recent study pressed patients. Their blunted responses appear to
present a shortened length of pituitary stimulation
om CRF rather than a decreased initial release of these
OMC-derived peptides.
In a single, recent study, Amsterdam et

represent a shortened length of pituitary stimulation
from CRF rather than a decreased initial release of these
POMC-derived peptides.
In a single, recent study, Amsterdam et al. (1988) found
that depressed, patients exhib from CRF rather than a decreased initial release of these
POMC-derived peptides.
In a single, recent study, Amsterdam et al. (1988) found
that depressed, patients exhibited a normal ACTH re-
sponse to CRF following clinica POMC-derived peptides.
In a single, recent study, Amsterdam et al. (1988) found
that depressed, patients exhibited a normal ACTH response to CRF following clinical recovery suggesting tha
the blunted ACTH response, like de In a single, recent study, Amsterdam et al. (1988) for that depressed, patients exhibited a normal ACTH sponse to CRF following clinical recovery suggesting the blunted ACTH response, like dexamethasone resuppression, may at depressed, patients exhibited a normal ACTH re-
onse to CRF following clinical recovery suggesting that
e blunted ACTH response, like dexamethasone non-
ppression, may be a "state" marker for depression.
In contrast to

sponse to CRF following clinical recovery suggesting that
the blunted ACTH response, like dexamethasone non-
suppression, may be a "state" marker for depression.
In contrast to all of these findings, Leake et al. (1989)
fo suppression, may be a "state" marker for depression.
In contrast to all of these findings, Leake et al. (1989)
found no evidence for a blunted ACTH response in
depressed individuals. Moreover, when ambient cortisol suppression, may be a "state" marker for depression.
In contrast to all of these findings, Leake et al. (1989)
found no evidence for a blunted ACTH response in
depressed individuals. Moreover, when ambient cortisol
concent In contrast to all of these findings, Leake et al. (1)
found no evidence for a blunted ACTH response
depressed individuals. Moreover, when ambient cor
concentrations in depressed and normal individuals w
neutralized (i.e., found no evidence for a blunted ACTH response in
depressed individuals. Moreover, when ambient cortiso
concentrations in depressed and normal individuals wer
neutralized (i.e., equally suppressed to low concentrations)
usi depressed individuals. Moreover, when ambient cortisol
concentrations in depressed and normal individuals were
neutralized (i.e., equally suppressed to low concentra-
tions) using the steroid synthesis inhibitor metyrapone concentrations in depressed and normal individue
neutralized (i.e., equally suppressed to low c
tions) using the steroid synthesis inhibitor me
an augmented response to CRF was observ
depressed population (Lisansky et al., utralized (i.e., equally suppressed to low concentra-
ons) using the steroid synthesis inhibitor metyrapone,
a augmented response to CRF was observed in the
pressed population (Lisansky et al., 1989).
The CRF stimulation t tions) using the steroid synthesis inhibitor metyrapone,
an augmented response to CRF was observed in the
depressed population (Lisansky et al., 1989).
The CRF stimulation test has also been used to study
other pituitary h

an augmented response to CRF was observed in the
depressed population (Lisansky et al., 1989).
The CRF stimulation test has also been used to study
other pituitary hormone responses. For example, whereas
controls exhibit n depressed population (Lisansky et al., 1989).
The CRF stimulation test has also been used to study
other pituitary hormone responses. For example, whereas
controls exhibit no growth hormone response to CRF,
depressed patie The CRF stimulation test has also been used to study
other pituitary hormone responses. For example, whereas
controls exhibit no growth hormone response to CRF,
depressed patients exhibit a significant net increase in
grow other pituitary hormone responses. For example, whereas controls exhibit no growth hormone response to CRF, depressed patients exhibit a significant net increase in growth hormone secretion (Lesch et al., 1988a). In addit controls exhibit no growth hormone response to CRF,
depressed patients exhibit a significant net increase in
growth hormone secretion (Lesch et al., 1988a). In ad-
dition, whereas control subjects exhibit a slight increase depressed patients exhibit a significant net increase in growth hormone secretion (Lesch et al., 1988a). In addition, whereas control subjects exhibit a slight increase in plasma δ sleep-inducing peptide concentrations, growth hormone secretion (Lesch et dition, whereas control subjects exhibin plasma δ sleep-inducing peptide c
pressed patients show a marked decre
administration (Lesch et al., 1988b).

458 OWENS AND NEMEROFF
The CRF stimulation test has been applied to patients trations th
with other psychiatric diagnoses. Smith et al. (1989) tion (i.e., d 458 OWENS AND 1
The CRF stimulation test has been applied to patients
with other psychiatric diagnoses. Smith et al. (1989)
reported that CRF administration $(1 \mu g/kg \text{ i.v.})$ produces reported that CRF administration (1 tg/kg i.v.) produces The CRF stimulation test has been applied to patients
with other psychiatric diagnoses. Smith et al. (1989)
reported that CRF administration $(1 \mu g/kg i.v.)$ produces
a blunted ACTH response in patients with posttraumatic
stre The CRF stimulation test has been applied to patients
with other psychiatric diagnoses. Smith et al. (1989) t
reported that CRF administration $(1 \mu g/kg \text{ i.v.})$ produces
a blunted ACTH response in patients with posttraumati with other psychiatric diagnoses. Smith et al. (1989)
reported that CRF administration $(1 \mu g/kg \text{ i.v.})$ produces
a blunted ACTH response in patients with posttraumatic
stress disorder, some of whom also fulfilled the crite a blunted ACTH response in patients with posttraumatic
stress disorder, some of whom also fulfilled the criteria
for major depression defined in *Diagnostic and Statistical*
Manual of Mental Disorders, ed. 3. Blunted ACT for major depression defined in *Diagnostic and Statistical*
Manual of Mental Disorders, ed. 3. Blunted ACTH responses are also observed following short-term (12 to 72
hours) abstinence in chronic alcoholics (Heuser et al. Manual of Mental Disorders, ed. 3. Blunted ACTH responses are also observed following short-term (12 to 72 hours) abstinence in chronic alcoholics (Heuser et al., 1988). Similar results were observed by Adinoff et al. (199 sponses are also observed following short-term (12 to 72 reports) abstinence in chronic alcoholics (Heuser et al., approximately 1988). Similar results were observed by Adinoff et al. (1990) at 1 and 3 weeks of abstinence hours) abstinence in chronic alcoholics (Heuser et al., agness). Similar results were observed by Adinoff et al. ence (1990) at 1 and 3 weeks of abstinence but not at longer no 1 periods of time. Roy-Byrne et al. (1986) re 1988). Similar results were observed by Adinoff et al. (1990) at 1 and 3 weeks of abstinence but not at longer periods of time. Roy-Byrne et al. (1986) reported blunted ACTH responses to administered CRF in patients with (1990) at 1 and 3 weeks of abstinence but not at longer
periods of time. Roy-Byrne et al. (1986) reported blunted
ACTH responses to administered CRF in patients with
panic disorder. In contrast to the report of Roy-Byrne periods of time. Roy-Byrne et al. (1986) reported blunte
ACTH responses to administered CRF in patients with panic disorder. In contrast to the report of Roy-Byrne
al. (1986), Rapaport et al. (1989) observed no difference CTH responses to administered CRF in patients w
nic disorder. In contrast to the report of Roy-Byrne
(1986), Rapaport et al. (1989) observed no difference
the ACTH response to low-dose CRF (0.03 μ g/kg).
Of interest is

panic disorder. In contrast to the report of Roy-Byrne et al. (1986), Rapaport et al. (1989) observed no differences certin the ACTH response to low-dose CRF $(0.03 \mu g/kg)$. Of interest is the work of Sapolsky (1989) who ad al. (1986), Rapaport et al. (1989) observed no differences cent
in the ACTH response to low-dose CRF (0.03 μ g/kg). Synt
of interest is the work of Sapolsky (1989) who admin-
istered the CRF stimulation test to wild bab in the ACTH response to low-dose CRF $(0.03 \mu g/kg)$.
Of interest is the work of Sapolsky (1989) who admin-
istered the CRF stimulation test to wild baboons living
freely in East Africa. He previously showed that, in
baboons Of interest is the work of Sapolsky (1989) who administered the CRF stimulation test to wild baboons living
freely in East Africa. He previously showed that, in
baboons that live in a stable dominance hierarchy, so-
ciall istered the CRF stimulation test to wild baboons living
freely in East Africa. He previously showed that, in
baboons that live in a stable dominance hierarchy, so-
cially subordinate males are hypercortisolemic relative
to freely in East Africa. He previously showed that, in
baboons that live in a stable dominance hierarchy, so-
cially subordinate males are hypercortisolemic relative
to dominant animals. These subordinate males that are
und baboons that live in a stable dominance hierarchy, scially subordinate males are hypercortisolemic relation.
to dominant animals. These subordinate males that a under long-term stress, both social and physical, she blunted to dominant animals. These subordinate males that are under long-term stress, both social and physical, show blunted ACTH responses following CRF administration. It is unclear whether the stressors experienced by sub-ordin to dominant animals. These subordinate males that are
under long-term stress, both social and physical, show
blunted ACTH responses following CRF administration.
It is unclear whether the stressors experienced by sub-
ordi under long-term stress, both social and physical, show
blunted ACTH responses following CRF administration.
It is unclear whether the stressors experienced by sub-
ordinate animals produce chronic CRF hypersecretion
that blunted ACTH responses following CRF administration.

It is unclear whether the stressors experienced by sub-

ordinate animals produce chronic CRF hypersecretion

that then results in a blunted ACTH response to CRF

(vid It is unclear whether the stressors experienced by sub-
ordinate animals produce chronic CRF hypersecretion
that then results in a blunted ACTH response to CRF
(vide infra). Alternatively, the author previously showed
that ordinate animals produce chronic CRF hypersecret
that then results in a blunted ACTH response to C
(vide infra). Alternatively, the author previously show
that those animals that become subordinates on
social hierarchical that then results in a blunted ACTH response to CRF

(vide infra). Alternatively, the author previously showed

that those animals that become subordinates on the

social hierarchical scale may possess somewhat dysfunc-

t (vide infra). Alternatively, the author previously showe
that those animals that become subordinates on th
social hierarchical scale may possess somewhat dysfunc
tional or maladaptive sex and stress hormone axes t
begin wi that those animals that become subordinates on the
social hierarchical scale may possess somewhat dysfunc-
tional or maladaptive sex and stress hormone axes to
begin with. Nonetheless, his studies suggest that inap-
propri social hierarchical scale may possess somewhat dysfunctional or maladaptive sex and stress hormone axes to
begin with. Nonetheless, his studies suggest that inappropriate HPA axis activity (CRF neuronal activity?) is
asso tional or maladaptive sex and stress hormone axes to
begin with. Nonetheless, his studies suggest that inap-
propriate HPA axis activity (CRF neuronal activity?) is
associated with poor outcome (i.e., decreased ability to
 begin with. Nonetheless, his studies suggest that inappropriate HPA axis activity (CRF neuronal activity?) is
associated with poor outcome (i.e., decreased ability to
find a mate and continue the gene pool) in a natural
ha propriate HPA axis activity (CRF neuronal activity?)
associated with poor outcome (i.e., decreased ability find a mate and continue the gene pool) in a natur
habitat. These findings have implications for huma
disorders suc associated with poor outcome (i.e.
find a mate and continue the ge
habitat. These findings have im
disorders such as depression, gene
der, and chronic stress syndromes
Several hypotheses have been nd a mate and continue the gene pool) in a natural
bitat. These findings have implications for human
sorders such as depression, generalized anxiety disor-
r, and chronic stress syndromes.
Several hypotheses have been intr

habitat. These findings have implications for human
disorders such as depression, generalized anxiety disor-
der, and chronic stress syndromes.
Several hypotheses have been introduced to explain
the mechanism of this blunt disorders such as depression, generalized anxiety disor-
der, and chronic stress syndromes.
Several hypotheses have been introduced to explain
the mechanism of this blunted ACTH response to ad-
ministered CRF. One hypothes der, and chronic stress syndromes.

Several hypotheses have been introduced to explainthe mechanism of this blunted ACTH response to a

ministered CRF. One hypothesis is that the blunte

ACTH responses result primarily fro Several hypotheses have been introduced to explain 1980,
the mechanism of this blunted ACTH response to ad-
ministered CRF. One hypothesis is that the blunted provi
ACTH responses result primarily from decreased pitui-
wer the mechanism of this blunted ACTH response to ad-
ministered CRF. One hypothesis is that the blunted pro
ACTH responses result primarily from decreased pitui-
tary responsiveness to CRF in the face of long-term Gan-
hyper ministered CRF. One hypothesis is that the blunt
ACTH responses result primarily from decreased pitt
tary responsiveness to CRF in the face of long-ter
hypersecretion of CRF from the median eminence as
the resultant down-r ACTH responses result primarily from decreased pituitary responsiveness to CRF in the face of long-term hypersecretion of CRF from the median eminence and the resultant down-regulation of pituitary CRF receptors. The data, tary responsiveness to CRF in the face of long-term Garrick et al. (1987) reported that CSF CRF concentra-
hypersecretion of CRF from the median eminence and tions were not positively correlated with CSF cortisol
the resul hypersecretion of CRF from the median eminence and
the resultant down-regulation of pituitary CRF recep-
tors. The data, when scrutinized, support this hypothesis
more strongly than an alternative hypothesis suggesting
alt the resultant down-regulation of pituitary CRF recep-
tors. The data, when scrutinized, support this hypothesis p
more strongly than an alternative hypothesis suggesting h
altered sensitivity of the pituitary to glucocort tors. The data, when scrutinized, support this hypothesis P-
more strongly than an alternative hypothesis suggesting h
altered sensitivity of the pituitary to glucocorticoid neg-
ative feedback, although this may play some ative feedback, although this may play some role. This related); it is similarly dysynchronous with plasma
has not yet been tested directly by measurement of ACTH concentrations. Kalin et al. (1987) also reported
anterior ative feedback, although this may play some role. This
has not yet been tested directly by measurement of
anterior pituitary CRF receptors or CRF mRNA in the
PVN in postmortem tissue from depressed patients. In
fact, two r has not yet been tested directly by measurement of A
anterior pituitary CRF receptors or CRF mRNA in the
PVN in postmortem tissue from depressed patients. In
fact, two recent studies (von Bardeleben and Holsboer, th
1989; anterior pituitary CRF receptors or CRF mRNA in the
PVN in postmortem tissue from depressed patients. In
fact, two recent studies (von Bardeleben and Holsboer,
1989; Krishnan et al., 1991) indicated that following
dexameth 1989; Krishnan et al., 1991) indicated that following dexamethasone pretreatment depressed patients exhibit greater increases in plasma ACTH and cortisol concen-

stress disorder, some of whom also fulfilled the criteria CRF observed in depressed patients are not due to hy-
for major depression defined in *Diagnostic and Statistical* percortisolemic negative feedback. Although most for major depression defined in *Diagnostic and Statistical* percortisolemic negative feedback. Although most stud-
Manual of Mental Disorders, ed. 3. Blunted ACTH re-
sponses are also observed following short-term (12 NEMEROFF
trations than normal persons following CRF admini
tion (i.e., depressed patients escape from dexametha NEMEROFF
trations than normal persons following CRF administra-
tion (i.e., depressed patients escape from dexamethasone
suppression). These results further suggest that the NEMEROFF
trations than normal persons following CRF administra-
tion (i.e., depressed patients escape from dexamethasone
suppression). These results further suggest that the
blunted ACTH responses to exogenously administer trations than normal persons following CRF administration (i.e., depressed patients escape from dexamethasone suppression). These results further suggest that the blunted ACTH responses to exogenously administered CRF obse trations than normal persons following CRF administra-
tion (i.e., depressed patients escape from dexamethasone
suppression). These results further suggest that the
blunted ACTH responses to exogenously administered
CRF ob suppression). These results further suggest that the suppression). These results further suggest that the blunted ACTH responses to exogenously administered CRF observed in depressed patients are not due to hypercortisolemic negative feedback. Although most studies are conco blunted ACTH responses to exogenously administer
CRF observed in depressed patients are not due to h
percortisolemic negative feedback. Although most stu
ies are concordant, differences exist and are likely t
result of pat CRF observed in depressed patients are not due to h
percortisolemic negative feedback. Although most stu
ies are concordant, differences exist and are likely t
result of patient population (depression severity, misc
agnosi percortisolemic negative feedback. Although most studies are concordant, differences exist and are likely the result of patient population (depression severity, misdiagnosis, etc.) and/or ACTH assay methodological differen ies are concordant, differences exist and are likely the
result of patient population (depression severity, misdi-
agnosis, etc.) and/or ACTH assay methodological differ-
ences. In any case, further studies are needed. How result of patient population (depression severity, misdiagnosis, etc.) and/or ACTH assay methodological differences. In any case, further studies are needed. However, no matter the number of studies, these neuroendocrine s agnosis, etc.) and/or ACTH assay methodologica
ences. In any case, further studies are needed. H
no matter the number of studies, these neuroen
studies purported to be a "window of the bra
always be a secondary measure of *2. Cerebrospinal fluid corticotes are needed. However,* α matter the number of studies, these neuroendocrine udies purported to be a "window of the brain" will ways be a secondary measure of CNS activity.
2. Cerebrospi

no matter the number of studies, these neuroendocrine
studies purported to be a "window of the brain" will
always be a secondary measure of CNS activity.
2. Cerebrospinal fluid corticotropin-releasing factor con-
centratio always be a secondary measure of CNS activity.
2. Cerebrospinal fluid corticotropin-releasing factor concentrations. To directly test the hypothesis that the
synaptic availability of CRF is increased in depression,
and pos always be a secondary measure of CNS activity.
2. Cerebrospinal fluid corticotropin-releasing factor con-
centrations. To directly test the hypothesis that the
synaptic availability of CRF is increased in depression,
and p 2. Cerebrospinal fluid corticotropin-releasing factor concentrations. To directly test the hypothesis that the synaptic availability of CRF is increased in depression, and possibly other psychiatric illnesses, we and other centrations. To directly test the hypothesis that the
synaptic availability of CRF is increased in depression,
and possibly other psychiatric illnesses, we and others
have measured the concentration of CRF in CSF. Post
et synaptic availability of CRF is increased in depression,
and possibly other psychiatric illnesses, we and others
have measured the concentration of CRF in CSF. Post
et al. (1982) showed that, for neuropeptides found in
bot and possibly other psychiatric illnesses, we and others
have measured the concentration of CRF in CSF. Post
et al. (1982) showed that, for neuropeptides found in
both CSF and plasma, there is a marked CSF-plasma
dissociati et al. (1982) showed that, for neuropeptides found in both CSF and plasma, there is a marked CSF-plasma dissociation indicating that neuropeptides are secreted directly into CSF from brain tissue and that CSF neu-ropeptide et al. (1982) showed that, for neuropeptides found in both CSF and plasma, there is a marked CSF-plasma dissociation indicating that neuropeptides are secreted directly into CSF from brain tissue and that CSF neuropeptide both CSF and plasma, there is a marked CSF-plasma
dissociation indicating that neuropeptides are secreted
directly into CSF from brain tissue and that CSF neu-
ropeptide concentrations are not derived from the sys-
temic c dissociation indicating that neuropeptides are secret
directly into CSF from brain tissue and that CSF ne
ropeptide concentrations are not derived from the sy
temic circulation due to the presence of the blood-bra
barrier. directly into CSF from brain tissue and that CSF ne
ropeptide concentrations are not derived from the sy
temic circulation due to the presence of the blood-bra
barrier. Thus, plasma CRF concentrations likely repi
sent secr ropeptide concentrations are not derived from the systemic circulation due to the presence of the blood-brain
barrier. Thus, plasma CRF concentrations likely represent secretion from hypothalamic CRF neurons termi-
nating temic circulation due to the presence of the blood-brain
barrier. Thus, plasma CRF concentrations likely repre-
sent secretion from hypothalamic CRF neurons termi-
nating in the median eminence and from other peripheral
so barrier. Thus, plasma CRF concentrations likely represent secretion from hypothalamic CRF neurons terminating in the median eminence and from other peripheral sources, whereas CSF CRF concentrations likely reflect the acti nt secretion from hypothalamic CRF neurons termi-
ting in the median eminence and from other peripheral
urces, whereas CSF CRF concentrations likely reflect
e activity of extrahypothalamic CRF neurons.
Following the first

altered sensitivity of the pituitary to glucocorticoid neg-
ative feedback, although this may play some role. This related); it is similarly dysynchronous with plasma
has not yet been tested directly by measurement of ACTH nating in the median eminence and from other peripheral
sources, whereas CSF CRF concentrations likely reflect
the activity of extrahypothalamic CRF neurons.
Following the first report demonstrating the existence
of CRF in sources, whereas CSF CRF concentrations likely reflect
the activity of extrahypothalamic CRF neurons.
Following the first report demonstrating the existence
of CRF in human CSF (Suda et al., 1983), a number of
basic and cl the activity of extrahypothalamic CRF neurons.
Following the first report demonstrating the existence
of CRF in human CSF (Suda et al., 1983), a number of
basic and clinical studies were conducted. CRF was found
to be clea of CRF in human CSF (Suda et al., 1983), a number of basic and clinical studies were conducted. CRF was found to be cleared from CSF in adult rhesus monkeys more rapidly than can be accounted for by bulk flow, suggestof CRF in human CSF (Suda et al., 1983), a number of basic and clinical studies were conducted. CRF was found to be cleared from CSF in adult rhesus monkeys more rapidly than can be accounted for by bulk flow, suggesting t basic and clinical studies were conducted. CRF was found
to be cleared from CSF in adult rhesus monkeys more
rapidly than can be accounted for by bulk flow, suggest-
ing that a transport system exists for the active remova to be cleared from CSF in adult rhesus monkeys more
rapidly than can be accounted for by bulk flow, suggest-
ing that a transport system exists for the active removal
of CRF from CSF; however a mechanism for how this
would rapidly than can be accounted for by bulk flow, suggest-
ing that a transport system exists for the active removal
of CRF from CSF; however a mechanism for how this
would function has not been described (Oldfield et al.,
1 ing that a transport system exists for the active removal
of CRF from CSF; however a mechanism for how this
would function has not been described (Oldfield et al.,
1985). Further evidence that CSF CRF concentrations
are de of CRF from CSF; however a mechanism for how this
would function has not been described (Oldfield et al.,
1985). Further evidence that CSF CRF concentrations
are derived from nonhypophysiotropic CRF have been
provided from would function has not been described (Oldfield et al., 1985). Further evidence that CSF CRF concentrations are derived from nonhypophysiotropic CRF have been provided from studies in which CSF CRF concentrations were repe 1985). Further evidence that CSF CRF concentrat
are derived from nonhypophysiotropic CRF have b
provided from studies in which CSF CRF concentrat
were repeatedly measured during the course of the
Garrick et al. (1987) repo are derived from nonhypophysiotropic CRF have been
provided from studies in which CSF CRF concentrations
were repeatedly measured during the course of the day.
Garrick et al. (1987) reported that CSF CRF concentra-
tions w provided from studies in which CSF CRF concentrations
were repeatedly measured during the course of the day.
Garrick et al. (1987) reported that CSF CRF concentra-
tions were not positively correlated with CSF cortisol
con were repeatedly measured during the course of the day.
Garrick et al. (1987) reported that CSF CRF concentra-
tions were not positively correlated with CSF cortisol
concentrations in rhesus monkeys, which directly reflect
 Garrick et al. (1987) reported that CSF CRF concentra-
tions were not positively correlated with CSF cortisol
concentrations in rhesus monkeys, which directly reflect
plasma cortisol concentrations. In fact, CSF CRF ex-
hi tions were not positively correlated with CSF cortisol
concentrations in rhesus monkeys, which directly reflect
plasma cortisol concentrations. In fact, CSF CRF ex-
hibits peak concentrations that precede those of CSF
cort concentrations in rhesus monkeys, which directly reflect
plasma cortisol concentrations. In fact, CSF CRF ex-
hibits peak concentrations that precede those of CSF
cortisol by approximately 14 hours (almost inversely
relate plasma cortisol concentrations. In fact, CSF CRF exhibits peak concentrations that precede those of CSF cortisol by approximately 14 hours (almost inversely related); it is similarly dysynchronous with plasma ACTH concentr hibits peak concentrations that precede those of CSF
cortisol by approximately 14 hours (almost inversely
related); it is similarly dysynchronous with plasma
ACTH concentrations. Kalin et al. (1987) also reported
that CSF cortisol by approximately 14 hours (almost inversely related); it is similarly dysynchronous with plasma ACTH concentrations. Kalin et al. (1987) also reported that CSF CRF concentrations in rhesus monkeys are not entraine related); it is similarly dysynchronous with plasma
ACTH concentrations. Kalin et al. (1987) also reported
that CSF CRF concentrations in rhesus monkeys are not
entrained with pituitary-adrenal activity. It is evident
that ACTH concentrations. Kalin et al. (1987) also reported
that CSF CRF concentrations in rhesus monkeys are not
entrained with pituitary-adrenal activity. It is evident
that CSF CRF is not merely a reflection of median
eminen that CSF CRF concentrations in rhesus monkeys are not
entrained with pituitary-adrenal activity. It is evident
that CSF CRF is not merely a reflection of median
eminence CRF release. Although the source of CSF CRF
remains entrained with pituitary-adrenal activity. It is evident
that CSF CRF is not merely a reflection of median
eminence CRF release. Although the source of CSF CRF
remains unknown, CRF neurons in cortical, limbic, and
brainste

U- U I

CORTICOTROPIN-RELEA
tricular system and may all contribute to the CSF CRF pool.

CORTICOTROPIN-RELEA

In a developmental study of pediatric patients, CSF $\overline{\xi}$

RF concentrations were highest in the immediate posttricular system and may all contribute to the CSF CR
pool.
In a developmental study of pediatric patients, CS
CRF concentrations were highest in the immediate post-
natal period (Hedner et al., 1989). CSF CRF concentra In a developmental study of pediatric patients, CSF CRF concentrations were highest in the immediate postnatal period (Hedner et al., 1989). CSF CRF concentrations decreased significantly during the first postnatal pool.
In a developmental study of pediatric patients, CSF
CRF concentrations were highest in the immediate post-
natal period (Hedner et al., 1989). CSF CRF concentra-
tions decreased significantly during the first postnat In a developmental study of pediatric patients, CSF
CRF concentrations were highest in the immediate post-
natal period (Hedner et al., 1989). CSF CRF concentra-
tions decreased significantly during the first postnatal
ye CRF concentrations were highest in the immediate post-
natal period (Hedner et al., 1989). CSF CRF concentra-
tions decreased significantly during the first postnatal
year compared with the immediate postnatal period and
b tal period (Hedner et al., 1989). CSF CRF concer
ons decreased significantly during the first postr
ar compared with the immediate postnatal period
 $/1$ year of age were similar to that observed in adu
We showed in a serie

tions decreased significantly during the first postnatal
year compared with the immediate postnatal period and
by 1 year of age were similar to that observed in adults.
We showed in a series of studies that CRF concentra-
 year compared with the immediate postnatal period and
by 1 year of age were similar to that observed in adults.
We showed in a series of studies that CRF concentra-
tions are significantly elevated in the CSF of drug-free
 by 1 year of age were similar to that observed in adults.
We showed in a series of studies that CRF concentra-
tions are significantly elevated in the CSF of drug-free
patients with major depression (Nemeroff et al., 1984; We showed in a series of studies that CRF concentra-
tions are significantly elevated in the CSF of drug-free
patients with major depression (Nemeroff et al., 1984;
Arató et al., 1986; Banki et al., 1987; France et al., 1 tions are significantly elevated in the CSF of drug-free
patients with major depression (Nemeroff et al., 1984;
Arató et al., 1986; Banki et al., 1987; France et al., 1988;
Widerlöv et al., 1988; Risch et al., 1991) or fol patients with major depression (Nemeroff et al., 1984; \leq 1
Arató et al., 1986; Banki et al., 1987; France et al., 1988;
Widerlöv et al., 1988; Risch et al., 1991) or following
completion of suicide (Arató et al., 1989 Arató et al., 1986; Banki et al., 1987; France et al., Widerlöv et al., 1988; Risch et al., 1991) or follo completion of suicide (Arató et al., 1989). In our study, we measured the CSF concentration of CRF normal controls, Widerlöv et al., 1988; Risch et al., 1991) or following
completion of suicide (Arató et al., 1989). In our first
study, we measured the CSF concentration of CRF in 10
normal controls, 23 depressed patients. 11 schizophrenstudy, we measured the CSF concentration of CRF in 10
normal controls, 23 depressed patients, 11 schizophren-
ics, and 29 demented patients. The CSF concentration
of CRF was elevated in the depressed patients compared
to a study, we measured the CSF concentration of CRF in 10
normal controls, 23 depressed patients, 11 schizophren-
ics, and 29 demented patients. The CSF concentration
of CRF was elevated in the depressed patients compared
to a normal controls, 23 depressed patients, 11 schizophrenics, and 29 demented patients. The CSF concentration
of CRF was elevated in the depressed patients compared
to all of the other groups; 11 of the 23 depressed patients
 ics, and 29 demented patients. The CSF concentration
of CRF was elevated in the depressed patients compared
to all of the other groups; 11 of the 23 depressed patients
had CSF CRF concentrations higher than the highest
no of CRF was elevated in the depressed patients compared
to all of the other groups; 11 of the 23 depressed patients
had CSF CRF concentrations higher than the highest
normal controls (Nemeroff et al., 1984). In our second
 to all of the other groups; 11 of the 23 depressed patientied CSF CRF concentrations higher than the high normal controls (Nemeroff et al., 1984). In our secostudy, we measured the CSF concentration of CRF in depressed pat had CSF CRF concentrations higher than the highest
normal controls (Nemeroff et al., 1984). In our second
study, we measured the CSF concentration of CRF in 54
depressed patients, 138 neurological controls, 23 schizo-
phr normal controls (Nemeroff et al., 1984). In our second
study, we measured the CSF concentration of CRF in 54
depressed patients, 138 neurological controls, 23 schizo-
phrenic patients, and 6 manic patients (fig. 9). The
de study, we measured the CSF concentration of CRF in 54
depressed patients, 138 neurological controls, 23 schizo-
phrenic patients, and 6 manic patients (fig. 9). The
depressed patients exhibited a marked 2-fold elevation
i depressed patients, 138 neurological controls, 23 schizo-
phrenic patients, and 6 manic patients (fig. 9). The
depressed patients exhibited a marked 2-fold elevation
in CSF CRF concentrations (Banki et al., 1987). In a
thi phrenic patients, and 6 manic patients (fig. 9). The depressed patients exhibited a marked 2-fold elevation in CSF CRF concentrations (Banki et al., 1987). In a third study, we found that patients with major depression had depressed patients exhibited a marked 2-fold elevation
in CSF CRF concentrations (Banki et al., 1987). In a
third study, we found that patients with major depression
had higher CSF CRF levels than patients with chronic
pai in CSF CRF concentrations (Banki et al., 1987). In
third study, we found that patients with major depressi
had higher CSF CRF levels than patients with chro
pain (France et al., 1988). Our fourth study, conduc
in Budapest, third study, we found that patients with major depression
had higher CSF CRF levels than patients with chronic
pain (France et al., 1988). Our fourth study, conducted
in Budapest, also indicated increased CSF CRF concen-
t had higher CSF CRF levels than patients with chronic
pain (France et al., 1988). Our fourth study, conducted
in Budapest, also indicated increased CSF CRF concen-
trations in depressed patients (Arató et al., 1986). Fi-
n pain (France et al., 1988). Our fourth study, conducted
in Budapest, also indicated increased CSF CRF concen-
trations in depressed patients (Arató et al., 1986). Fi-
nally, a fifth study was conducted in which we measure in Budapest, also indicated increased CSF CRF concentrations in depressed patients (Arató et al., 1986). Finally, a fifth study was conducted in which we measured phromassured CSF CRF concentrations collected postmortem f trations in depressed patients (Arató et al., 1986).
nally, a fifth study was conducted in which we meas
CSF CRF concentrations collected postmortem from
intracisternal space in depressed suicide victims
"sudden death" con nally, a fifth study was conducted in which we measured CSF CRF concentrations collected postmortem from the intracisternal space in depressed suicide victims and "sudden death" controls. Again, CSF CRF concentrations were CSF CRF concentrations collected postmortem from the
intracisternal space in depressed suicide victims and
"sudden death" controls. Again, CSF CRF concentra-
tions were elevated in the depressed group (Arató et al., (New
 intracisternal space in depressed suicide victims and 2 pat "sudden death" controls. Again, CSF CRF concentra-
tions were elevated in the depressed group (Arató et al., (Ne
1989). Although as a total group, Roy et al. "sudden death" controls. Again, CSF CRF concentra
tions were elevated in the depressed group (Arató et al.
1989). Although as a total group, Roy et al. (1987) did
not find any difference between depressed patients and
cont tions were elevated in the depressed group (Arató et al., (New 1989). Although as a total group, Roy et al. (1987) did in the not find any difference between depressed patients and controls, those patients who were dexame 1989). Although as a total group, Roy et and find any difference between depressed controls, those patients who were dexame suppressors exhibited higher concentrations.
than depressed dexamethasone suppressors To determin it find any difference between depressed patients
ntrols, those patients who were dexamethasone ippressors exhibited higher concentrations of CSF (
an depressed dexamethasone suppressors.
To determine whether elevated CSF

controls, those patients who were dexamethasone non-
suppressors exhibited higher concentrations of CSF CRF
than depressed dexamethasone suppressors.
To determine whether elevated CSF CRF concentra-
tions in depression rep suppressors exhibited higher concentrations of CSF (
than depressed dexamethasone suppressors.
To determine whether elevated CSF CRF concer
tions in depression represent a state or trait marker
(Nemeroff et al., 1991) meas than depressed dexamethasone suppressors. To determine whether elevated CSF CRF concentrations in depression represent a state or trait marker, we as (Nemeroff et al., 1991) measured CSF CRF concentrations in depressed pat To determine whether elevated CSF CRF concentra-
tions in depression represent a state or trait marker, we
(Nemeroff et al., 1991) measured CSF CRF concentra-
tions in depressed patients before and after a course of
ECT. B tions in depression represent a state or trait marker, we
(Nemeroff et al., 1991) measured CSF CRF concentra-
tions in depressed patients before and after a course of
ECT. Before ECT, depressed patients exhibited elevated
 (Nemeroff et al., 1991) measured CSF CRF concentra-
tions in depressed patients before and after a course of
ECT. Before ECT, depressed patients exhibited elevated
CSF CRF concentrations compared with controls.
Twenty-four tions in depressed patients before and after a course of

ECT. Before ECT, depressed patients exhibited elevated

CSF CRF concentrations compared with controls.

Twenty-four hours after their final ECT, a significant

dec ECT. Before ECT, depressed patients exhibited elevated nu
CSF CRF concentrations compared with controls. tis
Twenty-four hours after their final ECT, a significant me
decrease in CSF CRF concentrations was observed. This t CSF CRF concentrations compared with controls.
Twenty-four hours after their final ECT, a significant
decrease in CSF CRF concentrations was observed. This
finding indicates that CSF CRF concentrations, like
hypercortisole finding indicates that CSF CRF concentrations, like
hypercortisolemia, represent a state, rather than a trait,
marker. Moreover, these findings are not discordant with
the hypothesis that CRF neuronal hyperactivity contrib finding indicates that CSF CRF concentrations,
hypercortisolemia, represent a state, rather than a t
marker. Moreover, these findings are not discordant
the hypothesis that CRF neuronal hyperactivity con
utes to the signs *3. percortisolemia, represent a state, rather than a traker. Moreover, these findings are not discordant ve hypothesis that CRF neuronal hyperactivity contes to the signs and symptoms of major depression.

<i>3. Corticotrop* marker. Moreover, these findings are not discordant with
the hypothesis that CRF neuronal hyperactivity contrib-
these to the signs and symptoms of major depression.
2. Corticotropin-releasing factor receptors in postmor-

Periode Controls Schizophrenia Major Male Controls

Dopression

N = 73 N = 23 N = 54 N = 65

FIG. 9. CSF CRF-like immunoreactivity in patients with schizo-

phrenia [as defined in *Diagnostic and Statistical Manual of Me* Disorders M¹
 Disorders, N¹

FIG. 9. CSF CRF-like immunoreactivity in patients with schizo-

phrenia [as defined in *Diagnostic and Statistical Manual of Menta*,
 Disorders, ed. 3 (DSM-III)], patients with DSM-III FIG. 9. CSF CRF-like immunoreactivity in patients with schizo-
phrenia [as defined in *Diagnostic and Statistical Manual of Mental*
Disorders, ed. 3 (DSM-III)], patients with DSM-III major depression,
and control subject FIG. 9. CSF CRF-like immunoreactivity in patients with schizo-
phrenia [as defined in *Diagnostic and Statistical Manual of Mental*
Disorders, ed. 3 (DSM-III)], patients with DSM-III major depression,
and control subject phrenia [as defined in *Diagnostic and Statistical Manual of Mental Disorders*, ed. 3 (DSM-III)], patients with DSM-III major depression, and control subjects with various peripheral neurological diseases. Patients with D Disorders, ed. 3 (DSM-III)], patients with DSM-III major depression,
and control subjects with various peripheral neurological diseases.
Patients with DSM-III major depression exhibited a markedly higher
(almost 2-fold) CS and control subjects with various peripheral neurological diseases.
Patients with DSM-III major depression exhibited a markedly higher (almost 2-fold) CSF CRF concentration than the control subjects (Newman-Keuls test, P Patients with DSM-III major depression exhibited a markedly higher (almost 2-fold) CSF CRF concentration than the control subjects (Newman-Keuls test, $P < 0.001$). The mean CSF CRF concentration in the depressed group was (almost 2-fold) CSF CRF concentration than the control subjects (Newman-Keuls test, $P < 0.001$). The mean CSF CRF concentration in the depressed group was also significantly higher than that of the schizophrenic group (Ne (Newman-Keuls test, $P < 0.001$). The mean CSF CRF concentration
in the depressed group was also significantly higher than that of the
schizophrenic group (Newman-Keuls test, $P < 0.05$). Six (26%) of the
23 schizophrenic p in the depressed group was also significantly higher than that of the schizophrenic group (Newman-Keuls test, $P < 0.05$). Six (26%) of the 23 schizophrenic patients and 24 (44%) of the 54 depressed patients had higher CSF schizophrenic
23 schizophre
had higher CS
sex-matched c
et al. (1987). schizophrenic group (Newman-Keuls test, $P < 0.05$). Six (26%) of the 23 schizophrenic patients and 24 (44%) of the 54 depressed patients had higher CSF CRF concentrations than the highest value among the sex-matched contr had higher CSF CRF concentrations than the highest value among the
sex-matched control subjects. Reprinted with permission from Banki
et al. (1987).
(Van Praag, 1985) and >50% of completed suicides are
accomplished by pati

decrease in CSF CRF concentrations was observed. This the frontal cortex of 26 suicide victims and 28 control
finding indicates that CSF CRF concentrations, like subjects (Nemeroff et al., 1988). The suicide group ex-
hype sex-matched control subjects. Reprinted with permission from Ba
et al. (1987).
(Van Praag, 1985) and >50% of completed suicides a
accomplished by patients with major depression. I
therefore hypothesized that, if CRF is chr et al. (1987).
(Van Praag, 1985) and >50% of completed suicides an
accomplished by patients with major depression. W
therefore hypothesized that, if CRF is chronically hype
secreted in major depression, a reduced (down-reg (Van Praag, 1985) and $>50\%$ of completed suicides are accomplished by patients with major depression. We therefore hypothesized that, if CRF is chronically hypersecreted in major depression, a reduced (down-regulated) n accomplished by patients with major depression. We
therefore hypothesized that, if CRF is chronically hyper-
secreted in major depression, a reduced (down-regulated)
number of CRF receptors may be present in the brain
tiss therefore hypothesized that, if CRF is chronically hyper-
secreted in major depression, a reduced (down-regulated)
number of CRF receptors may be present in the brain
tissue of suicide victims. To test this hypothesis, we
 secreted in major depression, a reduced (down-regulated)
number of CRF receptors may be present in the brain
tissue of suicide victims. To test this hypothesis, we
measured the number and affinity of CRF receptors in
the f number of CRF receptors may be present in the brain
tissue of suicide victims. To test this hypothesis, we
measured the number and affinity of CRF receptors in
the frontal cortex of 26 suicide victims and 28 control
subjec tissue of suicide victims. To test this hypothesis, we
measured the number and affinity of CRF receptors in
the frontal cortex of 26 suicide victims and 28 control
subjects (Nemeroff et al., 1988). The suicide group ex-
hi the frontal cortex of 26 suicide victims and 28 control subjects (Nemeroff et al., 1988). The suicide group exhibited a 23% reduction in the number of CRF-binding sites compared with controls (fig. 10). This finding further suggests that CRF is hypersecreted in the CNS of patie subjects (Nemeroff et al., 1988). The suicide group ex-
hibited a 23% reduction in the number of CRF-binding
sites compared with controls (fig. 10). This finding fur-
ther suggests that CRF is hypersecreted in the CNS of
p hibited a 23% reduction in the number of CRF-binding
sites compared with controls (fig. 10). This finding fur-
ther suggests that CRF is hypersecreted in the CNS of
patients with major depression. Clearly, further studies
 sites compared with controls (fig. 10). This finding further suggests that CRF is hypersecreted in the CNS of patients with major depression. Clearly, further studies examining CRF receptors and CRF mRNA in other brain reg

 $\frac{200}{140}$ and $\frac{200}{140}$ and $\frac{200}{140}$ and $\frac{200}{140}$ and $\frac{200}{140}$. Composite Scatchard analysis utilizing each individual frontal cortical sample. Points, means (bars, \pm SE) for all samples from suic frontal cortical sample. Points, means (bars, \pm SE) for all samples from suicides (\bullet) and controls (\circ). Reprinted with permission from Nemeroff et al. (1988).

B. Anorexia Nervosa

patients with anorexia nervosa share the hypercortisodepression and also exhibit depressive symptoms. These B. Anorexia Ivervosa
1. Endocrine and cerebrospinal fluid studies. Many
patients with anorexia nervosa share the hypercortiso-
lemia observed in the majority of patients with major
depression and also exhibit depressive sy 1. Endocrine and cerebrospinal fluid studies. Many
patients with anorexia nervosa share the hypercortiso-
lemia observed in the majority of patients with major
depression and also exhibit depressive symptoms. These
finding patients with anorexia nervosa share the hypercortis
lemia observed in the majority of patients with maj
depression and also exhibit depressive symptoms. The
findings, together with preclinical studies, suggest th
CRF hype lemia observed in the majority of patients with major
depression and also exhibit depressive symptoms. These
findings, together with preclinical studies, suggest that
CRF hypersecretion may also play a role in the patho-
p depression and also exhibit depressive symptoms. These findings, together with preclinical studies, suggest that CRF hypersecretion may also play a role in the patho-
physiology of this disease. For example, there is evide findings, together with preclinical studies, suggest that CRF hypersecretion may also play a role in the patho-
physiology of this disease. For example, there is evidence
that fenfluramine-induced anorexia in laboratory an CRF hypersecretion may also play a role in the path
physiology of this disease. For example, there is evider
that fenfluramine-induced anorexia in laboratory as
mals may be secondary to increased CRF activity (App
et al., physiology of this disease. For example, there is evidence
that fenfluramine-induced anorexia in laboratory ani-
mals may be secondary to increased CRF activity (Appel
et al., 1991). As observed in major depression, underthat fenfluramine-induced anorexia in laboratory ani-
mals may be secondary to increased CRF activity (Appel
et al., 1991). As observed in major depression, under-
weight patients with anorexia nervosa exhibit blunted
ACTH mals may be secondary to increased CRF activity (Appel
et al., 1991). As observed in major depression, under-
weight patients with anorexia nervosa exhibit blunted
ACTH responses after i.v. CRF administration (Gold et
al., et al., 1991). As observed in major depression, underweight patients with anorexia nervosa exhibit blunted
ACTH responses after i.v. CRF administration (Gold et
al., 1986a; Hotta et al., 1986). Gold and colleagues (1986a)
 weight patients with anorexia nervosa exhibit blunted
ACTH responses after i.v. CRF administration (Gold et
al., 1986a; Hotta et al., 1986). Gold and colleagues (1986a)
reported that the patients' responses to CRF normaliz ACTH responses after i.v. CRF administration (Gold et al., 1986a; Hotta et al., 1986). Gold and colleagues (1986a) reported that the patients' responses to CRF normalized 6 months, but not immediately, after correction of al., 1986a; Hotta et al., 1986). Gold and colleagues (1986a)
reported that the patients' responses to CRF normalized
6 months, but not immediately, after correction of weight
loss. In contrast, Hotta et al. (1986) reported reported that
6 months, but
loss. In contra
responses to
weight gain.
In CSF stud months, but not immediately, after correction of weight
ss. In contrast, Hotta et al. (1986) reported that ACTH
sponses to CRF normalized immediately following
ight gain.
In CSF studies, both Hotta et al. (1986) and Kaye e

loss. In contrast, Hotta et al. (1986) reported that ACTH
responses to CRF normalized immediately following
weight gain.
In CSF studies, both Hotta et al. (1986) and Kaye et
al. (1987) found elevated CSF CRF concentrations weight gain.
In CSF studies, both Hotta et al. (1986) and Kaye et al. (1987) found elevated CSF CRF concentrations in these patients. As with the ECT study described in the previous section, the increase in CSF CRF concent weight gain.
In CSF studies, both Hotta et al. (1986) and Kay
al. (1987) found elevated CSF CRF concentration
these patients. As with the ECT study described in
previous section, the increase in CSF CRF concentions appears In CSF studies, both Hotta et al. (1986) and Kaye et al. (1987) found elevated CSF CRF concentrations in these patients. As with the ECT study described in the previous section, the increase in CSF CRF concentrations appea al. (1987) found elevated CSF CRF concentrations
these patients. As with the ECT study described in
previous section, the increase in CSF CRF concentions
appears to be a state-dependent marker beca
Kaye and colleagues repo these patients. As with the ECT study described in the
previous section, the increase in CSF CRF concentra-
tions appears to be a state-dependent marker because
Kaye and colleagues reported both normalized pituitary-
adren previous section, the increase in CSF CRF concentra-
tions appears to be a state-dependent marker because
Kaye and colleagues reported both normalized pituitary-
adrenal function and CSF CRF concentrations after
weight rec tions appears to be a state-dependent marker because
Kaye and colleagues reported both normalized pituitary-
adrenal function and CSF CRF concentrations after
weight recovery. Moreover, these authors reported that
CSF CRF Kaye and colleagues reported both normalized pituitary-
adrenal function and CSF CRF concentrations after
weight recovery. Moreover, these authors reported that
CSF CRF concentrations were significantly correlated
with dep patients. *C. C. Alzheimer's Disease*
C. Alzheimer's Disease
L. Alzheimer's Disease
L. Alterations in regione i the depression severity ratings in the weight-corrected
 1. Alzheimer's Disease
 1. Alterations in regional brain corticotropin-releasing
 1. Alterations in regional brain corticotropin-releasing
 itor concentra

NEMEROFF
is a neurodegenerative disease characterized by a pro-
gressively worsening dementia, pathologically by the ap-NEMEROFF
is a neurodegenerative disease characterized by a pro-
gressively worsening dementia, pathologically by the ap-
pearance of neurofibrillary tangles and plaques in partic-NEMEROFF
is a neurodegenerative disease characterized by a p
gressively worsening dementia, pathologically by the a
pearance of neurofibrillary tangles and plaques in part
ular areas of the CNS, and biochemically by degene Examples of the Machimar areas of the conservative disease characterized by a progressively worsening dementia, pathologically by the appearance of neurofibrillary tangles and plaques in particular areas of the CNS, and bi is a neurodegenerative disease characterized by a progressively worsening dementia, pathologically by the appearance of neurofibrillary tangles and plaques in particular areas of the CNS, and biochemically by degeneration gressively worsening dementia, pathologically by the appearance of neurofibrillary tangles and plaques in particular areas of the CNS, and biochemically by degeneration of cholinergic neurons in the substantia innominata, pearance of neurofibrillary tangles and plaques in particular areas of the CNS, and biochemically by degeneration
of cholinergic neurons in the substantia innominata, as
well as a number of other neurotransmitter alteratio ular areas of the CNS, and biochemically by degeneration
of cholinergic neurons in the substantia innominata, as
well as a number of other neurotransmitter alterations
(McDonald and Nemeroff, 1991). Bissette et al. (1985) of cholinergic neurons in the substantia innominata, as
well as a number of other neurotransmitter alterations
(McDonald and Nemeroff, 1991). Bissette et al. (1985)
reported a marked reduction in CRF concentrations in
the well as a number of other neurotransmitter alterations (McDonald and Nemeroff, 1991). Bissette et al. (1985) reported a marked reduction in CRF concentrations in the frontal and temporal cortex ($\approx 50\%$) as well as in t (McDonald and Nemeroff, 1991). Bissette et al. (1985)
reported a marked reduction in CRF concentrations in
the frontal and temporal cortex ($\approx 50\%$) as well as in the
caudate nucleus ($\approx 70\%$) from postmortem Alzheime reported a marked reduction in CRF concentrations in
the frontal and temporal cortex $(\approx 50\%)$ as well as in the
caudate nucleus $(\approx 70\%)$ from postmortem Alzheimer's
disease brain tissue. These findings were confirmed an the frontal and temporal cortex $(\approx 50\%)$ as well as in the caudate nucleus $(\approx 70\%)$ from postmortem Alzheimer's disease brain tissue. These findings were confirmed and extended by De Souza et al. (1986) who observed dec disease brain tissue. These findings were confirmed and extended by De Souza et al. (1986) who observed decreased CRF concentrations in the frontal, temporal, and occipital cortex in patients with Alzheimer's disease and r (fig. 11). In addition, immunocytochemical studies have extended by De Souza et al. (1986) who observed decreased CRF concentrations in the frontal, temporal, and occipital cortex in patients with Alzheimer's disease and reciprocal increases (up-regulation) of CRF receptors (fi creased CRF concentrations in the frontal, temporal, and
occipital cortex in patients with Alzheimer's disease and
reciprocal increases (up-regulation) of CRF receptors
(fig. 11). In addition, immunocytochemical studies ha occipital cortex in patients with Alzheimer's disease and
reciprocal increases (up-regulation) of CRF receptors
(fig. 11). In addition, immunocytochemical studies have
demonstrated abnormal CRF-immunoreactive neurons
in th reciprocal increases (up-regula)

(fig. 11). In addition, immunoc

demonstrated abnormal CRF-

in the amygdala, some of w

plaques (Powers et al., 1987).

2. Cerebrospinal fluid studies. g. 11). In addition, immunocytochemical studies have
monstrated abnormal CRF-immunoreactive neurons
the amygdala, some of which contained amyloid
aques (Powers et al., 1987).
2. Cerebrospinal fluid studies. Along with the

eroff et al. (1988). CRF have been reported to be decreased in severe end-
 B. Anorexia Nervosa
 1. Endocrine and cerebrospinal fluid studies. Many

patients with anorexia nervosa share the hypercortiso-

lemia observe demonstrated abnormal CRF-immunoreactive neurons
in the amygdala, some of which contained amyloid
plaques (Powers et al., 1987).
2. Cerebrospinal fluid studies. Along with the reduction
of cortical CRF concentrations, CSF in the amygdala, some of which contained amyloic
plaques (Powers et al., 1987).
2. Cerebrospinal fluid studies. Along with the reduction
of cortical CRF concentrations, CSF concentrations of
CRF have been reported to be de plaques (Powers et al., 1987).

2. Cerebrospinal fluid studies. Along with the reduc

of cortical CRF concentrations, CSF concentration

CRF have been reported to be decreased in severe

stage Alzheimer's disease. Decrease 2. Cerebrospinal fluid studies. Along with the reductor of cortical CRF concentrations, CSF concentration CRF have been reported to be decreased in severe exage Alzheimer's disease. Decreases in CRF concentions have been r

patients.
 factor concentrations and receptors. Alzheimer's disease and controls. Columns, means (bars, \pm SE). The number of
 factor concentrations and receptors. Alzheimer's disease and $\frac{1}{2}$ and $\frac{1}{2}$ and TEMPORAL FRONTAL OCCIPITAL CINQULATE

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FIG. 11. CRF-like immunoreactivity (a) and CRF receptor binding

(b) in discrete regions of the cerebral cortex of patients with Alzheimer's

disease and c CORTEX CORTEX CORTEX CORTEX CORTEX

FIG. 11. CRF-like immunoreactivity (a) and CRF receptor binding

(b) in discrete regions of the cerebral cortex of patients with Alzheimer's

disease and controls. Columns, means (bars, FIG. 11. CRF-like immunoreactivity (a) and CRF receptor bin(b) in discrete regions of the cerebral cortex of patients with Alzheim disease and controls. Columns, means (bars, \pm SE). The numbe patients in each group is g (b) in discrete regions of the cerebral cortex of patients with Alzheimer's disease and controls. Columns, means (bars, \pm SE). The number of patients in each group is given at the bottom of each histogram. Data were ana disease and controls. Columns, means (bars, \pm SE). The patients in each group is given at the bottom of each his were analyzed for differences using a Student's t test. * P 0.025, *** P < 0.005 compared with control g

CORTICOTROPIN-RI
adrenal dysfunction (May et al., 1987) or without direct
correlation with disease severity or decreased cognitive CORTICOTROPIN-REI
adrenal dysfunction (May et al., 1987) or without direct
correlation with disease severity or decreased cognitive
functioning (Mouradian et al., 1986). In contrast to the CORTICOTROPIN-RELE
adrenal dysfunction (May et al., 1987) or without direct (the
correlation with disease severity or decreased cognitive un
functioning (Mouradian et al., 1986). In contrast to the with
findings of Mouradi adrenal dysfunction (May et al., 1987) or without direct
correlation with disease severity or decreased cognitive
functioning (Mouradian et al., 1986). In contrast to the
findings of Mouradian et al. (1986), Pomara et al. adrenal dysfunction (May et al., 1987) or without di
correlation with disease severity or decreased cogni
functioning (Mouradian et al., 1986). In contrast to
findings of Mouradian et al. (1986), Pomara et al. (19
found a correlation with disease severity or decreased cognitive
functioning (Mouradian et al., 1986). In contrast to the
findings of Mouradian et al. (1986), Pomara et al. (1989)
found a significant correlation between global neu functioning (Mouradian et al., 1986). In contrast to the will
findings of Mouradian et al. (1986), Pomara et al. (1989) sion
found a significant correlation between global neuropsy-
chological impairment ratings and lower findings of Mouradian et al. (1986), Pomara et al. (1989)
found a significant correlation between global neuropsy-
chological impairment ratings and lower CSF CRF con-
centrations without significant overall decreases in C found a significant correlation between global neuropsy-
chological impairment ratings and lower CSF CRF con-
centrations without significant overall decreases in CSF
CRF concentrations in the Alzheimer's group as a whole, dementia. **EXECUTE CONSUMIST CONSUMIDED CONSUMING CONSUMING CONSUMING A**
CRF concentrations in the Alzheimer's group as a
although the patients studied had only mild to modementia.
D. Other Psychiatric and Neurological Illnesse

though the patients studied had only mild to moderate

mentia.

Other Psychiatric and Neurological Illnesses

Reductions in CRF concentrations have been observed

the cerebral cortex from patients with Parkinson's

is dementia.

D. Other Psychiatric and Neurological Illnesses

Reductions in CRF concentrations have been observed

in the cerebral cortex from patients with Parkinson's

disease and progressive supranuclear palsy (Whitehouse D. Other Psychiatric and Neurological Illnesses
Reductions in CRF concentrations have been observed
in the cerebral cortex from patients with Parkinson's
disease and progressive supranuclear palsy (Whitehouse
et al., 1987) D. Uther Psychiatric and Neurological Illnesses
Reductions in CRF concentrations have been obse
in the cerebral cortex from patients with Parkins
disease and progressive supranuclear palsy (Whiteh
et al., 1987). As in Alzh Reductions in CRF concentrations have been obser
in the cerebral cortex from patients with Parkinse
disease and progressive supranuclear palsy (Whiteher al., 1987). As in Alzheimer's disease, CRF concentions are decreased in the cerebral cortex from patients with Parkinson's

disease and progressive supranuclear palsy (Whitehouse

et al., 1987). As in Alzheimer's disease, CRF concentra-

tions are decreased in the caudate/putamen in Huntin disease and progressive supranuclear palsy (Whitehouse
et al., 1987). As in Alzheimer's disease, CRF concentra-
tions are decreased in the caudate/putamen in Hunting-
ton's disease (De Souza et al., 1987). However, unlike et al., 1987). As in Alzheimer's disease, CRF concentra-
tions are decreased in the caudate/putamen in Hunting-
ton's disease (De Souza et al., 1987). However, unlike in
Alzheimer's disease, CRF concentrations were un-
cha tions are decreased in the caudate/putamen in Huntington's disease (De Souza et al., 1987). However, unlike in Alzheimer's disease, CRF concentrations were unchanged in various cortical regions. Finally, CSF CRF concentrat changed in various cortical regions. Finally, CSF CRF concentrations have been reported to be decreased approximately 50% in patients with amyotrophic lateral sclerosis (Klimek et al., 1986). Alzheimer's disease, CRF concentrations were unoximately 50% in patients with amyotrophic lateral
erosis (Klimek et al., 1986).
 X. Conclusions and Future Directions

From the considerable evidence described in this mon-

Traph, it is clear that CRF integrates the ov

x. Conclusions and Future Directions

sclerosis (Klimek et al., 1986).
 X. Conclusions and Future Directions

From the considerable evidence described in this monograph, it is clear that CRF integrates the overall physiological and behavioral responses of an Mom **X. Conclusions and Future Directions**

From the considerable evidence described in this mon-

ograph, it is clear that CRF integrates the overall phys-

iological and behavioral responses of an organism to the

stress A. Conclusions and **Future Directions**
From the considerable evidence described in this mon-
ograph, it is clear that CRF integrates the overall phys-
iological and behavioral responses of an organism to
stress. The neuroe From the considerable evidence described in this mon-
ograph, it is clear that CRF integrates the overall phys-
iological and behavioral responses of an organism to the
stress. The neuroendocrine response to stress is prim ograph, it is clear that CRF integrates the overall physiological and behavioral responses of an organism to stress. The neuroendocrine response to stress is primarily controlled by CRF neurons whose perikarya originate in iological and behavioral responses of an organism to the stress. The neuroendocrine response to stress is primarily montrolled by CRF neurons whose perikarya originate in aide PVN of the hypothalamus, although vasopressine stress. The neuroendocrine response to stress is primarily controlled by CRF neurons whose perikarya originate in the PVN of the hypothalamus, although vasopressinergic neurons likely contribute to some extent. It is not k the PVN of the hypothalamus, although vasopressinergic
neurons likely contribute to some extent. It is not known
which CRF neurons are responsible for the behavioral
and autonomic responses accompanying stress. However,
CR which CRF neurons are responsible for the behavioral
and autonomic responses accompanying stress. However,
CRF neurons in the cerebral cortex and limbic system
and CRF neurons of the medulla and pons are logical
candidates which CRF neurons are responsible for the behavioral gree
and autonomic responses accompanying stress. However,
CRF neurons in the cerebral cortex and limbic system
and CRF neurons of the medulla and pons are logical
candi and autonomic responses accompa
CRF neurons in the cerebral cor
and CRF neurons of the medulla
candidates for regulation of many
autonomic responses, respectively
Because of the vast array of fun RF neurons in the cerebral cortex and limbic system

id CRF neurons of the medulla and pons are logical

mdidates for regulation of many of the behavioral and

moutonomic responses, respectively.

Because of the vast arra

candidates for regulation of many of the behavioral and
autonomic responses, respectively.
Because of the vast array of functions over which CRF
may exert a modulatory influence, it is plausible, and the
clinical evidence autonomic responses, respectively.

Because of the vast array of functions over which CRF

may exert a modulatory influence, it is plausible, and the

clinical evidence quite convincing, that inappropriate

regulation of C Because of the vast array of functions over which CRF
may exert a modulatory influence, it is plausible, and the
clinical evidence quite convincing, that inappropriate
regulation of CRF neurons may contribute to human
ill may exert a modulatory influence, it is plausible, and the clinical evidence quite convincing, that inappropriate regulation of CRF neurons may contribute to human illness. To date, CRF dysregulation appears to occur in a clinical evidence quite convincing, that inappropriate regulation of CRF neurons may contribute to human illness. To date, CRF dysregulation appears to occur in a number of psychiatric disorders, including major depression order. mess. To date, CRF dysregulation appears to occur in
number of psychiatric disorders, including major
pression, posttraumatic stress disorder, and panic dis-
der.
Although the number of papers dealing with the study
variou

a number of psychiatric disorders, including major
depression, posttraumatic stress disorder, and panic dis-
order.
Although the number of papers dealing with the study
of various aspects of CRF neurobiology has increased depression, posttraumatic stress disorder, and panic dis-

order.

Although the number of papers dealing with the study

of various aspects of CRF neurobiology has increased

being the past several years, much has yet to
 order.

Although the number of papers dealing with the stu

of various aspects of CRF neurobiology has increas

exponentially in the past several years, much has yet

be learned regarding the detailed description of the me Although the number of papers dealing with the study
of various aspects of CRF neurobiology has increased
exponentially in the past several years, much has yet to
be learned regarding the detailed description of the mech-
 exponentially in the past several years, much has yet to
be learned regarding the detailed description of the mech-
anisms by which CRF alters behavior and autonomic
activity. As additional neuroanatomical studies are un-
 exponentially in the past several years, much has y
be learned regarding the detailed description of the m
anisms by which CRF alters behavior and auton-
activity. As additional neuroanatomical studies are
dertaken, the gr be learned regarding the detailed description of the mechanisms by which CRF alters behavior and autonomic telucidativity. As additional neuroanatomical studies are understanding of CRF neurocircuity gained will undoubtedl anisms by which CRF alters behavior and autonomic
activity. As additional neuroanatomical studies are un-
dertaken, the greater understanding of CRF neurocircui-
try gained will undoubtedly result in elucidation of which
s activity. As additional neuroanatomical studies are understanding of CRF neurocircuity gained will undoubtedly result in elucidation of which the specific CRF neuronal populations mediate the various pactions of CRF. As mo dertaken, the greater understanding of CRF neurocircuity gained will undoubtedly result in elucidation of which specific CRF neuronal populations mediate the various lactions of CRF. As more is learned about the regulatory

LEASING FACTOR 461
(there is no a priori reason that the CRF gene should be
under the same regulation throughout the brain), there LEASING FACTOR 461

(there is no a priori reason that the CRF gene should be

under the same regulation throughout the brain), there

will be better understanding of normal CRF gene expres-LEASING FACTOR
(there is no a priori reason that the CRF gene should
under the same regulation throughout the brain), th
will be better understanding of normal CRF gene expr
sion and function. Indeed, manipulation of the r (there is no a priori reason that the CRF gene should be under the same regulation throughout the brain), there will be better understanding of normal CRF gene expression and function. Indeed, manipulation of the regulator (there is no a priori reason that the CRF gene should be
under the same regulation throughout the brain), there
will be better understanding of normal CRF gene expres-
sion and function. Indeed, manipulation of the regulat under the same regulation throughout the brain
will be better understanding of normal CRF gene
sion and function. Indeed, manipulation of the reg
elements may provide an avenue for future tre
strategies aimed at altering C Il be better understanding of normal CRF gene expres-
on and function. Indeed, manipulation of the regulatory
ements may provide an avenue for future treatment
rategies aimed at altering CRF gene expression.
Although there elements may provide an avenue for future treatment
strategies aimed at altering CRF gene expression.
Although there is limited evidence at present, it is

elements may provide an avenue for future treatment
strategies aimed at altering CRF gene expression.
Although there is limited evidence at present, it is
plausible that some anxiolytic and antidepressant drugs
may exert a strategies aimed at altering CRF gene expression.
Although there is limited evidence at present, it
plausible that some anxiolytic and antidepressant dr
may exert a portion of their efficacy through alteration
in CRF neuro Although there is limited evidence at present, it
plausible that some anxiolytic and antidepressant dru
may exert a portion of their efficacy through alteratic
in CRF neuronal functioning. Although tricyclic antid
pressant may exert a portion of their efficacy through alterations
in CRF neuronal functioning. Although tricyclic antide-
pressants alter serotonergic and noradrenergic neuro-
transmission acutely and chronically, and benzodiazein CRF neuronal functioning. Although tricyclic antidein CRF neuronal functioning. Although tricyclic antide-
pressants alter serotonergic and noradrenergic neuro-
transmission acutely and chronically, and benzodiaze-
pine anxiolytics potentiate GABA-stimulated Cl⁻ flux, it pressants alter serotonergic and noradrenergic neuro-
transmission acutely and chronically, and benzodiaze-
pine anxiolytics potentiate GABA-stimulated Cl⁻ flux, it
is still unclear how these actions result in their clin transmission acutely and chronically, and benzodiaze-
pine anxiolytics potentiate GABA-stimulated Cl⁻ flux, it
is still unclear how these actions result in their clinical
efficacy. As we have noted previously, future tec is still unclear how these actions result in their clinical
efficacy. As we have noted previously, future techniques
including the use of microdialysis probes to measure CRF
release in vivo, the possibility of electrophysi peptidases and peptidase inhibitors, in addition to the present techniques that can be used to measure CRF including the use of microdialysis probes to measure CRF
release in vivo, the possibility of electrophysiological
identification of CRF neurons, and the use of specific
peptidases and peptidase inhibitors, in addition to t release in vivo, the possibility of electrophysiological
identification of CRF neurons, and the use of specific
peptidases and peptidase inhibitors, in addition to the
present techniques that can be used to measure CRF
pep identification of CRF neurons, and the use of specification to the present techniques that can be used to measure CR peptide, CRF receptors, and CRF mRNA, will greatly increase our ability to understand CRF neurobiology. M peptidases and peptidase inhibitors, in addition to the present techniques that can be used to measure CRF peptide, CRF receptors, and CRF mRNA, will greatly increase our ability to understand CRF neurobiology. Moreover, i present techniques that can be used to measure CRF
peptide, CRF receptors, and CRF mRNA, will greatly
increase our ability to understand CRF neurobiology.
Moreover, it is important to determine whether the re-
cently descr increase our ability to understand CRF neurobiology.
Moreover, it is important to determine whether the recently described CRF-binding protein actively controls
the synaptic availability of CRF.

the PVN of the hypothalamus, although vasopressinergic lems, the recent cloning of the CRF-binding protein and
neurons likely contribute to some extent. It is not known the eagerly awaited cloning of the CRF receptor will
 candidates for regulation of many of the behavioral and
autonomic responses, respectively.
Because of the vast array of functions over which CRF
may exert a modulatory influence, it is plausible, and the
clinical evidence Clearly, one of the most exciting areas of research is the possibility of using a CRF antagonist for the treatment of depression and/or anxiety. Although computercently described CRF-binding protein actively cont
the synaptic availability of CRF.
Clearly, one of the most exciting areas of researc
the possibility of using a CRF antagonist for the tr
ment of depression and/or anxiety the synaptic availability of CRF.
Clearly, one of the most exciting areas of research
the possibility of using a CRF antagonist for the trea
ment of depression and/or anxiety. Although compute
aided drug design of such a l Clearly, one of the most exciting areas of research is
the possibility of using a CRF antagonist for the treat-
ment of depression and/or anxiety. Although computer-
aided drug design of such a large peptide presents probthe possibility of using a CRF antagonist for the treat-
ment of depression and/or anxiety. Although computer-
aided drug design of such a large peptide presents prob-
lems, the recent cloning of the CRF-binding protein an ment of depression and/or anxiety. Although computer-
aided drug design of such a large peptide presents prob-
lems, the recent cloning of the CRF-binding protein and
the eagerly awaited cloning of the CRF receptor will
gr greatly aid in the elucidation of the active portion of the lems, the recent cloning of the CRF-binding protein and
the eagerly awaited cloning of the CRF receptor will
greatly aid in the elucidation of the active portion of the
peptide or the active site on the receptor. These dis the eagerly awaited cloning of the CRF receptor will greatly aid in the elucidation of the active portion of the peptide or the active site on the receptor. These discoveries may lead to the rational design of lipophillic greatly aid in the elucidation of the active portion of the
peptide or the active site on the receptor. These discov-
eries may lead to the rational design of lipophillic drugs
which may possess clinical utility. Moreover, peptide or the active site on the receptor. These discoveries may lead to the rational design of lipophillic drugs which may possess clinical utility. Moreover, these compounds could lead to useful ligands for positron emi eries may lead to the rational design of lipophillic drugs
which may possess clinical utility. Moreover, these com-
pounds could lead to useful ligands for positron emission
tomography or single photon emission computerize which may possess clinical utility. Moreover, these com-
pounds could lead to useful ligands for positron emission
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mography neuroimaging studies. Another possible means pounds could lead to useful ligands for positron emission
tomography or single photon emission computerized to-
mography neuroimaging studies. Another possible means
of producing potentially useful compounds would depend
u tomography or single photon emission computerized to
mography neuroimaging studies. Another possible mean
of producing potentially useful compounds would depen
upon the synthesis of peptidase-resistant CRF analog
having th ography neuroimaging studies. Another possible means
producing potentially useful compounds would depend
oon the synthesis of peptidase-resistant CRF analogs
wing the ability to permeate the blood-brain barrier.
Although t of producing potentially useful compounds would depend
upon the synthesis of peptidase-resistant CRF analogs
having the ability to permeate the blood-brain barrier.
Although the scientific design of CRF-active drugs
may pr

upon the synthesis of peptidase-resistant CRF analogs
having the ability to permeate the blood-brain barrier.
Although the scientific design of CRF-active drugs
may prove difficult in the near future, the one tried and
tru having the ability to permeate the blood-brain barrier.

Although the scientific design of CRF-active drugs

may prove difficult in the near future, the one tried and

true method of drug discovery, serendipity, may prove Although the scientific design of CRF-active drugs
may prove difficult in the near future, the one tried and
true method of drug discovery, serendipity, may prove
fruitful. Indeed, a CRF receptor-binding assay is now
being true method of drug discovery, serendipity, may prove
fruitful. Indeed, a CRF receptor-binding assay is now
being used in new drug-screening processes at many
pharmaceutical companies.
Considering that CRF was first isolat ie method of drug discovery, serendipity, may provality. Indeed, a CRF receptor-binding assay is not ing used in new drug-screening processes at maximaceutical companies.
Considering that CRF was first isolated and characi

fruitful. Indeed, a CRF receptor-binding assay is now
being used in new drug-screening processes at many
pharmaceutical companies.
Considering that CRF was first isolated and charac-
terized barely 10 years ago, one marvel being used in new drug-screening processes at many
pharmaceutical companies.
Considering that CRF was first isolated and charac-
terized barely 10 years ago, one marvels at the wealth of
knowledge that has been gathered to pharmaceutical companies.
Considering that CRF was first isolated and characterized barely 10 years ago, one marvels at the wealth of
knowledge that has been gathered to date. We believe
that in the next decade many of the Considering that CRF was first isolated and characterized barely 10 years ago, one marvels at the wealth of knowledge that has been gathered to date. We believe that in the next decade many of the experiments and technique terized barely 10 years ago, one marvels at the wealth of knowledge that has been gathered to date. We believe that in the next decade many of the experiments and techniques mentioned above will come to fruition and provid knowledge that has been gathered to date. We believe
that in the next decade many of the experiments and
techniques mentioned above will come to fruition and
provide a wealth of detailed information regarding basic
CRF phy that in the next decade many of the experiments and
techniques mentioned above will come to fruition and
provide a wealth of detailed information regarding basic
CRF physiology. Even more exciting to us are the pos-
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PHARMACOLOGICAL REVIEWS

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ropeptides in general, and CRF in particular, may find $\frac{u}{n}$

usefulness in the therapy of human mental illness. USE OWER

1992 Usefulness in the therapy of human mental illness.

1993 Usefulness in the therapy of human mental illness.

1994 Usefulness Weare grateful to Scott T. Cain Garth Big peptides in general, and CRF in particular, may find efulness in the therapy of human mental illness.
Acknowledgments. We are grateful to Scott T. Cain, Garth Bissette
d David L Knight for helpful discussions and to Nancy

Experience in general, and David II pursually lines.

B Acknowledgments. We are grateful to Scott T. Cain, Garth Bissette,

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assistance with manuscript pre assiumess in the therapy of human assumes the manuscript preparation.

and David L Knight for helpful discusses the manuscript preparation.

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assistance with manuscript preparation.
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