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Induction of Immediate-early Genes and the Control of **New COLOGICAL REVIEWS**
 Neurotion of Immediate-early Genes and the Control of
 Neurotransmitter-regulated Gene Expression within

the Nervous System^{*} Harmacology and Experimental Therapeutics
 the Nervous System*

PAUL HUGHES AND MICHAEL DRAGUNOW† **CHECK AND MICHAEL DRAGUNOWS**

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Miller scholar.

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Finally Genes and the Expression
Gene Expression
scription Factors **The I. Immediate-early Genes and Gene Expression**
A. Classes of Transcription Factors
The neuron is the basic unit of the

I. Immediate-early Genes and the Control of
Gene Expression
Classes of Transcription Factors
The neuron is the basic unit of the nervous system.
eurons are often described as being "plastic," because Gene Expression

A. Classes of Transcription Factors

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Neurons are often described as being "plastic," because

they can show short- or long-lasting changes in their A. Classes of Transcription Factors
The neuron is the basic unit of the nervous system.
Neurons are often described as being "plastic," because
they can show short- or long-lasting changes in their
phenotype in response to The neuron is the basic unit of the nervous system.

Neurons are often described as being "plastic," because

they can show short- or long-lasting changes in their

phenotype in response to different stimuli. Neurons are
 of they can show short- or long-lasting changes in the
phenotype in response to different stimuli. Neurons
able to respond to changes in their environment beca
of the existence of universal, stimulus-response infor
tion pr probably phenotype in response to different stimuli. Neurons are
able to respond to changes in their environment because
of the existence of universal, stimulus-response informa-
tion processing mechanisms that can be foun able to respond to changes in their environment because
of the existence of universal, stimulus-response informa-
tion processing mechanisms that can be found within all
living cells.
The responses of the neuron to environ tion processing mechanisms that can be found within all and the associated proteins that, by performing their phys-
living cells.
The responses of the neuron to environmental cues \uparrow Abbreviations: mRNA, messenger ribon

of the existence of universal, stimulus-response information processing mechanisms that can be found within all
living cells.
The responses of the neuron to environmental cues
can be divided into early and late responses. living cells.
Iiving cells.
The responses of the neuron to environmental cues
can be divided into early and late responses. Early re-
sponses occur rapidly after stimulation of the neuron
and last from milliseconds to minu The responses of the neuron to environmental cues
can be divided into early and late responses. Early re-
sponses occur rapidly after stimulation of the neuron
and last from milliseconds to minutes. These early re-
sponses Ine responses of the heuron to environmental caes
can be divided into early and late responses. Early re-
sponses, brought about by interactions of environmental
first-messengers (i.e., neurotransmitters or growth fac-
tor phosphate; CREB, cyclic AMP response element binding protein;

and last from milliseconds to minutes. These early re-

sponses, brought about by interactions of environmental

first-messengers (i.e., neurotransmitters or g and last from immectorus to immutes. These carry re-
sponses, brought about by interactions of environmental
first-messengers (i.e., neurotransmitters or growth fac-
tors) with cell-surface located receptors, occur becaus sponses, brought about by interactions of environmental $\frac{X}{X}$
first-messengers (i.e., neurotransmitters or growth fac-
tors) with cell-surface located receptors, occur because of
activation of second-messenger systems mst-messengers (i.e., neutotransmitters of growth rac-
tors) with cell-surface located receptors, occur because of
activation of second-messenger systems. All of the
known second-messenger systems characterised to date
act bors) with cen-surface located receptors, occur because
activation of second-messenger systems. All of th
known second-messenger systems characterised to da
activate specific protein kinases that in turn active
phosphoryla activation of second-messenger systems. All of the
known second-messenger systems characterised to date
activate specific protein kinases that in turn actively
phosphorylate specific neuronal proteins (Nishizuka,
1988; Ber activate specific protein kinases that in turn actively phosphorylate specific neuronal proteins (Nishizuka, 1988; Berridge, 1993; Pelech and Sanghera, 1992; Garthwaite, 1991; Axelrod et al., 1988; Bronstein et al., 1993; activate specific protein kinases that in turn actively
phosphorylate specific neuronal proteins (Nishizuka,
1988; Berridge, 1993; Pelech and Sanghera, 1992;
Garthwaite, 1991; Axelrod et al., 1988; Bronstein et al.,
1993; phosphorylate specific neuronal proteins (Nishizuka, 1988; Berridge, 1993; Pelech and Sanghera, 1992; Garthwaite, 1991; Axelrod et al., 1988; Bronstein et al., 1993; Nairn et al., 1985). The biological response activated i sistemative, 1991; Axelrod et al., 1988; Bronstein et a
1993; Nairn et al., 1985). The biological response ac
vated in this manner lasts within the limits of the po
sistence of protein phosphorylation, which is often short dat liwalte, 1991, Axenod et al., 1988, Bronstein et al.
1993; Nairn et al., 1985). The biological response activated in this manner lasts within the limits of the per-
sistence of protein phosphorylation, which is often s 1990, Namh et al., 1969). The bloogleaf response actrivated in this manner lasts within the limits of the per-
sistence of protein phosphorylation, which is often short-
lived because of the fine-control of phosphorylation 1992). stence of protein phosphorylation, which is often short-
red because of the fine-control of phosphorylation is
tterns within the neuron by phosphatases (Cohen, $\frac{5}{3}$
92).
The late responses occur within a time frame o lived because of the fine-control of phosphorylation
patterns within the neuron by phosphatases (Cohen,
1992).
The late responses occur within a time frame of hours
to days and in certain circumstances may be rendered
perm

patterns within the heuron by phosphatases (Cohen,
1992).
The late responses occur within a time frame of hours
to days and in certain circumstances may be rendered
permanent within the neuron, and these types of changes
m 1992).
The late responses occur within a time frame of hours
to days and in certain circumstances may be rendered
permanent within the neuron, and these types of changes
may underlie processes such as learning and memory,
 The late responses occur within a time rrame of not
to days and in certain circumstances may be render
permanent within the neuron, and these types of chang
may underlie processes such as learning and memodrug tolerance/se

sion seem necessary for these late responses (Comb et al., 1987; Goelet et al., 1986; Bliss and Collingridge, 1993; 1987; Goelet et al., 1986; Bliss and Collingridge, 1993;
1987; Goelet et al., 1986; Bliss and Collingridge, 1993;
Armstrong and Montminy, 1993). The changes in gene sion seem necessary for these late responses (Comb et al., 1987; Goelet et al., 1986; Bliss and Collingridge, 1993; Armstrong and Montminy, 1993). The changes in gene expression that underlie the late responses of the neur sion seem necessary for these late responses (Comb et al., 1987; Goelet et al., 1986; Bliss and Collingridge, 1993; Armstrong and Montminy, 1993). The changes in gene expression that underlie the late responses of the neur sion seem necessary for these late responses (Colin et al., 1987; Goelet et al., 1986; Bliss and Collingridge, 1993; Armstrong and Montminy, 1993). The changes in gene expression that underlie the late responses of the neu 1967, Goelet et al., 1960, Bliss and Commgridge, 1990,
Armstrong and Montminy, 1993). The changes in gene
expression that underlie the late responses of the neuron
to environmental cues occur because, either directly (for
 Arinstrong and Montinity, 1995). The changes in gene
expression that underlie the late responses of the neuron
to environmental cues occur because, either directly (for
example, steroid-hormone receptor complex) or indirec expression that underne the late responses of the heuron
to environmental cues occur because, either directly (for
example, steroid-hormone receptor complex) or indirectly
(second-messenger-mediated), the information carri we environmental cless occur because, enther urectly (for example, steroid-hormone receptor complex) or indirectly (second-messenger-mediated), the information carried by the first-messenger interacts with the cellular DNA (second-messenger-mediated), the information carried by regulate and change its expression. These changes in gene and the associated proteins that, by performing their phys-
 \ddagger Abbreviations: mRNA, messenger ribonucleic acid; DNA, de-

and the associated proteins that, by performing their phys-
 \ddagger Abbreviations: mRNA, messenger ribonucleic acid; DNA, de-

oxyribonucleic acid; PKC, protein-kinase C; MAP, mitogen-activated

protein; TCF, ternary comple oxyribonucleic acid; PKC, protein-kinase C; MAP, mitogen-activated
protein; TCF, ternary complex factor; cAMP, cyclic adenosine mono-
phosphate; CREB, cyclic AMP response element binding protein;
IEG, immediate-early gene; protein; TCF, ternary complex factor; cAMP, cyclic adenosine mono-
phosphate; CREB, cyclic AMP response element binding protein;
IEG, immediate-early gene; IEGP, immediate-early gene protein;
ZENK, *zif* 268, egr-1, NGFIA, phosphate; CREB, cyclic AMP response element binding protein;
IEG, immediate-early gene; IEGP, immediate-early gene protein;
IEG, immediate-early gene; IEGP, immediate-early gene protein;
ZENK, zif 268, egr-1, NGFIA, kroxplatelet-derived growth factor; EGF, immediate-early gene protein; ZENK, zif 268, $egr-1$, NGFIA, $krox-24$; CNS, central nervous system; MSV, murine sarcoma virus; NGF, nerve growth factor; PDGF, platelet-derived growth fac ZENK, zif 268, $egr-1$, NGFIA, $kroz-24$; CNS, central nervous system
MSV, murine sarcoma virus; NGF, nerve growth factor; PDGF
platelet-derived growth factor; EGF, epidermal growth factor; TF
transcription factor; RNA, ribo MSV, murine sarcoma virus; NGF, nerve growth factor; PDGF, platelet-derived growth factor; GFF, epidermal growth factor; TF, transcription factor; RNA, ribonucleic acid; cDNA, complementary deoxyribonucleic-acid; G, glycin Vallet derived growth factor; EGF, epidermal growth factor; The transcription factor; RNA, ribonucleic acid; cDNA, complementar deoxyribonucleic-acid; G, glycine; A, adenine; T, thymine; U, uracity CSCC, voltage-sensitive transcription factor; RNA, ribonucleic acid; cDNA, complementary
deoxyribonucleic-acid; G, glycine; A, adenine; T, thymine; U, uracil;
VSCC, voltage-sensitive calcium channel; AP-1, activating protein-1;
TRE, TPA response maturiphonicleic-acid; G, glycine; A, denine; T, thymine; U, uracid
deoxyribonicleic-acid; G, glycine; A, denine; T, thymine; U, uracil
VSCC, voltage-sensitive calcium channel; AP-1, activating protein-1
TRE, TPA response **CREM, CONCORT CONCORTMON CONCORTMENT (CONCORTMENTION** CONCORTER, TPA response element; cAMP, cyclic adenosine monophosphate; CHA, cyclohexyladenosine; CRE, cAMP response element; CREM, CRE binding site modulator protein; TRE, TPA response element; CAMP, cyclic adenosine monophosphate; CHA, cyclohexyladenosine; CRE, cAMP response element; CREM, CRE binding site modulator protein; CaRE/CRE, calcium/cAMP response element; ATF, activating tran Phate; CHA, cyclohexyladenosine; CRE, cAMP response elements; CREM, CRE binding site modulator protein; CaRE/CRE, calcit cAMP response element; ATF, activating transcription factor; Long-term potentiation; HI, hypoxia-isch planuc, CREM, CRE binding site modulator protein; CaRE/CRE, calcium/
cAMP response element; ATF, activating transcription factor; LTP,
long-term potentiation; HI, hypoxia-ischemia; PVN, paraventricular
nucleus; AD, afterdi norepinephrine; i.v., intravenous; i.p. , intraperiton factor; LTP, long-term potentiation; HI, hypoxia-ischemia; PVN, paraventricular nucleus; AD, afterdischarge; SCN, suprachiasmatic nucleus; NE, norepinephrine; i.v., in droxytryptamine; **DOI,** i-(2,5-dimethoxy-4-iodophenyl)-2-aminopromorepinephrine; i.v., intravenous; i.p., intraperitoneal; i.c.v., intracerebroventricular; 6-OHDA, 6-hydroxydopamine; 5-HT, 5-hydroxytryptamine; DOI, 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane; 8-OH-DPAT, 8-hydroxy-2-(d erebroventricular; 6-OHDA, 6-hydroxydopamine; 5-HT, 5-hydroxytryptamine; DOI, 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane; 8-OH-DPAT, 8-hydroxy-2-(di-N-propylamino)tetralin; MDMA, 3,4-methylenedioxymethamphetamine; DARPP convertiments; DOI, 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane; 8-OH-DPAT, 8-hydroxy-2-(di-N-propylamino)tetralin; MDMA, 3,4-methylenedioxymethamphetamine; DARPP-22, dopamine- and cAMP-regulated phosphoprotein; s.c., su cholecystokinin; SE, status epilepticus; LTD, long-term dependency 3.4-methylenedioxymethamphetamine; DARPP-22, dopamine- and CAMP-regulated phosphoprotein; s.c., subcutaneous injection; CCI
cholecystokinin; SE, status epi pursy, our our syncary of the syncatomeric statement of the calibration and cAMP-regulated phosphoprotein; s.c., subcutaneous injection; CCK, cholecystokinin; SE, status epilepticus; LTD, long-term depression; LC, locus co r, a meury brotoury motomany channels, characterized phosphoprotein; s.c., subcutaneous injection; C
cholecystokinin; SE, status epilepticus; LTD, long-term depress
LC, locus coeruleus; PCD, programmed cell death; DND, del rived neurons incomponent, sext, sacceduareous incomponent (choleystokinin; SE, status epilepticus; LTD, long-term depres LC, locus coeruleus; PCD, programmed cell death; DND, del neuronal death; EPS, extrapyramidal side-e ELC, locus coeruleus; PCD, programmed cell death; DND, delayed neuronal death; EPS, extrapyrammed cell death; DND, delayed neuronal death; EPS, extrapyramidal side-effects; BDNF, brain-de-
rived neurotrophic factor; PENK, factor.

PHARMACOLOGICAL REVIEWS

IMMEDIATE-EARLY GENES AN
iological role within the cell, modify the phenotype of the
cell. The genes that code for these proteins can be termed IMMEDIATE-EARLY GENES AT Indianapological role within the cell, modify the phenotype of the the cell. The genes that code for these proteins can be termed krate-response" genes. The challenge in molecular neurobi-MMEDIATE-EARLY GENES AT
iological role within the cell, modify the phenotype of the
cell. The genes that code for these proteins can be termed
"late-response" genes. The challenge in molecular neurobi-
ology has been to id iological role within the cell, modify the phenotype of the this
cell. The genes that code for these proteins can be termed kn
"late-response" genes. The challenge in molecular neurobi-
ology has been to identify the path expression of "late-response" genes. The challenge in molecular neurology has been to identify the pathways and DNA bindeffector molecules (*TFs*) that are involved in controlling expression of "late-response genes" that p "late-response" genes. The challenge in molecular neurology has been to identify the pathways and DNA bineffector molecules (TFs) that are involved in controllinexpression of "late-response genes" that produce phenical ch ology has been to identify the pathways and DNA binding effector molecules (TFs) that are involved in controlling the expression of "late-response genes" that produce phenotypical changes in neurons after activation of se enector molecties (*I Fs*) that are involved in controlling the
expression of "late-response genes" that produce phenotyp-
ical changes in neurons after activation of second-messen-
genes" themselves.
Work over the last de

ical changes in neurons after activation of second-messes ger pathways and indeed to identify the "late-respon genes" themselves.
Work over the last decade has shown that within ce at least three families of signal-regulat ger pathways and indeed to identify the "late-response genes" themselves.

Work over the last decade has shown that within cells,

at least three families of signal-regulated TFs exist (Mitch-

ell and Tjian, 1989; Manniat the work over the last decade has shown that within cells,
at least three families of signal-regulated TFs exist (Mitch-
ell and Tjian, 1989; Manniatis et al., 1987) (fig. 1). The first
type of TF protein is constitutively Work over the last decade has shown that within at least three families of signal-regulated TFs exist (M ell and Tjian, 1989; Manniatis et al., 1987) (fig. 1). The type of TF protein is constitutively expressed within cell at least three lamines of signal-regulated 1 Fs exist (Mitch-
ell and Tjian, 1989; Manniatis et al., 1987) (fig. 1). The first
type of TF protein is constitutively expressed within the
cell. Its transcriptional activity is

AND GENE EXPRESSION 135
threonine amino-acid residues. For this reason, they are
known as *post-translationally activated TFs*.
Second-messenger systems activate protein kinases

Second-messenger systems and U.S. and they are
second-messenger systems activated TFs.
Second-messenger systems activate protein kinases
KC, calmodulin-dependent kinases I and II, MAP kithreonine amino-acid residues. For this reason, they are
known as *post-translationally activated TFs*.
Second-messenger systems activate protein kinases
(PKC, calmodulin-dependent kinases I and II, MAP ki-
nase) that in t threonine amino-acid residues. For this reason, they
known as *post-translationally activated TFs*.
Second-messenger systems activate protein kina
(PKC, calmodulin-dependent kinases I and II, MAP
nase) that in turn phospho known as *post-translationally activated TFs*.
Second-messenger systems activate protein kinas
(PKC, calmodulin-dependent kinases I and II, MAP h
nase) that in turn phosphorylate the TF. The simult
neous activation of phos Second-messenger systems activate protein kinases
(PKC, calmodulin-dependent kinases I and II, MAP ki-
nase) that in turn phosphorylate the TF. The simulta-
neous activation of phosphatases by second-messenger
systems is a nase) that in turn phosphorylate the TF. The simulta-
neous activation of phosphatases by second-messenger
systems is also important in many cases, because re-
moval of phosphate groups from TFs can also modulate
their tra neous activation of phosphatases by second-messenger
systems is also important in many cases, because re-
moval of phosphate groups from TFs can also modulate
their transcriptional activity. Once activated, the TF
can, alo systems is also important in many cases, because re-
moval of phosphate groups from TFs can also modulate
their transcriptional activity. Once activated, the TF
can, alone or in combination with other TFs, bind to the
(usu moval of phosphate groups from TFs can also modulate
their transcriptional activity. Once activated, the TF
can, alone or in combination with other TFs, bind to the
(usually upstream) regulatory regions of target genes
and their transcriptional activity. Once activated, the TF can, alone or in combination with other TFs, bind to the (usually upstream) regulatory regions of target genes and regulate their expression. An example of this type o n, alone or in combination with other TFs, bind to the sually upstream) regulatory regions of target genes de regulate their expression. An example of this type of Γ is CREB (Montminy et al., 1990); Sheng et al., 1991). (usually upstream) regulatory regions of target genes
and regulate their expression. An example of this type of
TF is CREB (Montminy et al., 1990; Sheng et al., 1991).
The second type of TF is the *ligand-activated TF*.
T

FIG. 1. Signal-regulated transcription factors mediate long-term changes in gene expression within the neuron. The responses of the neuron to its environment may be divided into short and long-term cesponses. Short-term re FIG. 1. Signal-regulated transcription factors mediate long-term changes in gene expression within the neuron. The responses of neuron to its environment may be divided into short and long-term responses. Short-term respon regulated TFs exist. *(1)* Ligand-activated into short and long-term responses. Short-term responses within the neuron last within the limits of the persistence of protein phosphorylation and are produced by activated prot transcriptionally activated TFs, e.g., immediate-early gene family.

regulated TFs exist. (1) Ligand-activated TFs of the steroid hormon

transcriptionally activated TFs, e.g., immediate-early gene family.

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hormones (Evans, 1988). Because the steroid hormones are small, lipid-soluble molecules, they can readily pass HUGHES AND DRAGUNOW
hormones (Evans, 1988). Because the steroid hormones al., 1976).
are small, lipid-soluble molecules, they can readily pass DNA conta
through the outer plasma membrane of the cell by sim-
ple diffusion. plementation. ISO and the steroid hormones al., are small, lipid-soluble molecules, they can readily pass DN
through the outer plasma membrane of the cell by simple diffusion. Once they pass into the cytoplasm, they naite
 hormones (Evans, 1988). Because the steroid hormones
are small, lipid-soluble molecules, they can readily pass
through the outer plasma membrane of the cell by sim-
ple diffusion. Once they pass into the cytoplasm, they
in are small, lipid-soluble molecules, they can readily p
through the outer plasma membrane of the cell by s
ple diffusion. Once they pass into the cytoplasm, t
interact and bind with their corresponding cytoplas
receptor. Th through the outer plasma membrane of the cell by ple diffusion. Once they pass into the cytoplasm, interact and bind with their corresponding cytoplas receptor. The receptor protein undergoes a confortional change and beco ple diffusion. Once they pass into the cytoplasm, they nase t
interact and bind with their corresponding cytoplasmic were i
receptor. The receptor protein undergoes a conforma-viral of
tional change and becomes activated. interact and bind with their corresponding cytoplasmic we
receptor. The receptor protein undergoes a conforma-
tional change and becomes activated. This receptor-li-
gand complex is then able to directly interact with DNA receptor. The receptor protein undergoes a conformational change and becomes activated. This receptor-li-
gand complex is then able to directly interact with DNA
to regulate gene expression. One such receptor is the
glucoc nal change and becomes activated. This receptor-li-
nd complex is then able to directly interact with DNA
regulate gene expression. One such receptor is the
ucocorticoid receptor.
The third type of TF protein regulates gen

gand complex is then able to directly interact with DNA
to regulate gene expression. One such receptor is the
glucocorticoid receptor.
The third type of TF protein regulates gene expression
in an "indirect" way. These TFs w regulate gene expression. One such receptor is the
glucocorticoid receptor.
The third type of TF protein regulates gene expression
in an "indirect" way. These TFs are not usually ex-
pressed constitutively within the cel The third type of TF protein regulates gene expression
in an "indirect" way. These TFs are not usually ex
pressed constitutively within the cell and only regulat
gene expression once they themselves are transcribee
and tra in an "indirect" way. These TFs are not usually expressed constitutively within the cell and only regulate slagene expression once they themselves are transcribed hand translated. For this reason, they are called *transcri* pressed constitutively within the cell and only regulate she
gene expression once they themselves are transcribed ho
and translated. For this reason, they are called *tran-*
scriptionally activated TFs. The genes coding fo gene expression once they themselves are transcribed
and translated. For this reason, they are called *tran-*
scriptionally activated TFs. The genes coding for these
TF proteins are called IEGs (note that not all IEGs are
 and translated. For this reason, they are called *tran-*
scriptionally activated TFs. The genes coding for these
TF proteins are called IEGs (note that not all IEGs are
transcription factors). This family of genes includ scriptionally activated TFs. The genes coding for these
TF proteins are called IEGs (note that not all IEGs are
transcription factors). This family of genes includes c-
fos, fra-1, fra-2, fos-B(Long), fos-B(Short), c-jun, transcription factors). This family of genes includes c-
fos, fra-1, fra-2, fos-B(*Long*), *fos-B*(*Short*), c-*jun, jun-B, jun-D, krox-20*, and *krox-24* (also known as *zif* 268,
NGFI-A, egr-1, or ZENK) (Sheng and Gr transcription factors). This family of genes includes c
fos, fra-1, fra-2, fos-B(Long), fos-B(Short), c-jun, jun-E
jun-D, krox-20, and krox-24 (also known as $zif 268$
MGFI-A, egr-1, or ZENK) (Sheng and Greenberg, 1990
Mor fos, fra-1, fra-2, fos-B(Long), fos-B(Short), c-jun, jun-
jun-D, krox-20, and krox-24 (also known as $zif2(NGFI-A, egr-1, or ZENK)$ (Sheng and Greenberg, 199
Morgan and Curran, 1991b). When a cell is stimulat
the first wave of gene jun-D, krox-20, and krox-24 (also known as $zif 268$, c
NGFI-A, egr-1, or ZENK) (Sheng and Greenberg, 1990; b
Morgan and Curran, 1991b). When a cell is stimulated, t
the first wave of gene transcription involves IEG activa Morgan and Curran, 1991b). When a cell is stimulated, the first wave of gene transcription involves IEG activation. Once translated, the products of these genes (IEGPs) re-enter the nucleus and activate other "late-respons response" genes, resulting in a delayed secondary wave of gene activity.

The first wave of gene transcription involves IEG activa-

(IEGPs) re-enter the nucleus and activate other "late-

response" genes, resulting in a (IEGPs) re-enter the nucleus and activate other "late-
response" genes, resulting in a delayed secondary wave
of gene activity.
This review will document (a) the evidence that sug-

(LEGTS) re-enter the nucleus and activate other hate-
response" genes, resulting in a delayed secondary wave
of gene activity.
This review will document (a) the evidence that sug-
gests that IEGs are important components that
This review will document (*a*) the evidence that sug-
gests that IEGs are important components of the signal-
transduction pathway from receptor to genome in neu-
rons and (*b*) the evidence of a role for IEGs in CNS This review will docur
gests that IEGs are impo
transduction pathway fr
rons and (b) the eviden
plasticity and pathology. *B. Origin as Proto-oncogenes: Oncogenes as*
B. Origin as Proto-oncogenes: Oncogenes as
B. Origin as Proto-oncogenes: Oncogenes as
Components of Signal Transduction Pathways Components and (b) the evidence of a role for IEGs is
plasticity and pathology.
B. Origin as Proto-oncogenes: Oncogenes as
Components of Signal Transduction Pathways
In 1911. Pevton Rous isolated a factor from a

plasticity and pathology.

B. Origin as Proto-oncogenes: Oncogenes as

Components of Signal Transduction Pathways

In 1911, Peyton Rous isolated a factor from a tumour

filtrate that could produce sarcomas when injected in E. Origin as Proto-oncogenes: Oncogenes as

Components of Signal Transduction Pathways

In 1911, Peyton Rous isolated a factor from a tumour

filtrate that could produce sarcomas when injected into

chickens—the Rous sarco B. Origin as Proto-oncogenes: Oncogenes as
Components of Signal Transduction Pathways
In 1911, Peyton Rous isolated a factor from a tumo
filtrate that could produce sarcomas when injected in
chickens—the Rous sarcoma virus In 1911, Peyton Rous isolated a factor from a tumo
filtrate that could produce sarcomas when injected in
chickens—the Rous sarcoma virus (Takeya and Han
fusa, 1983; Wyke, 1983). In 1966, three researcher
Finkel, Biskis and In 1911, Peyton Rous isolated a factor from a tumour
filtrate that could produce sarcomas when injected into
chickens—the Rous sarcoma virus (Takeya and Hana-
fusa, 1983; Wyke, 1983). In 1966, three researchers,
Finkel, Bi mirate that could produce sarcomas when injected
chickens—the Rous sarcoma virus (Takeya and Hafusa, 1983; Wyke, 1983). In 1966, three research
Finkel, Biskis and Jinkin, using essentially sim
methodology as Rous, isolated chickens—the Rous sarcoma virus (Takeya and Hafusa, 1983; Wyke, 1983). In 1966, three researche Finkel, Biskis and Jinkin, using essentially simided of a 260-day of a 260-dold CF1/An 1 mouse. The isolated factor had the ab fusa, 1983; Wyke, 1983). In 1966, three researchers, ro
Finkel, Biskis and Jinkin, using essentially similar sig
methodology as Rous, isolated a factor from an osteosar-
coma found on the ribs and thoracic spine of a 260-d Finkel, Biskis and Jinkin, using essentially sim
methodology as Rous, isolated a factor from an osteos
coma found on the ribs and thoracic spine of a 260-d
old CF1/An 1 mouse. The isolated factor had the abi
to induce bony methodology as Rous, isolated a factor from an osteosar-
coma found on the ribs and thoracic spine of a 260-day-
old CF1/An 1 mouse. The isolated factor had the ability
unit
to induce bony tumour growths when it was admini coma found on the ribs and thoracic spine of a 260-day-

old CF1/An 1 mouse. The isolated factor had the ability

to induce bony tumour growths when it was adminis-

tered to young mice. Investigation of the tumours led to old CF1/An 1 mouse. The isolated factor had the ability
to induce bony tumour growths when it was adminis-
tered to young mice. Investigation of the tumours led to
the identification of viral particles that were designated wirus that was subsequently discovered in a X/GF mouse of the identification of viral particles that were designated FBJ-MSV (Finkel et al., 1966). Another osteosarcoma virus that was subsequently discovered in a X/GF mou the identification of viral particles that were designated pr
FBJ-MSV (Finkel et al., 1966). Another osteosarcoma gu
virus that was subsequently discovered in a X/GF mouse co
after treatment with ⁹⁰Sr was designated FBR FBJ-MSV (Finkel et al., 1966). Another osteosarcom
virus that was subsequently discovered in a X/GF mous
after treatment with ⁹⁰Sr was designated FBR-MSV
Genetic analysis of the Rous sarcoma virus in the lat
1960s identi of the total was subsequently discovered in a AVGF in
after treatment with 90 SF was designated FBR-Mi
Genetic analysis of the Rous sarcoma virus in the 1
1960s identified a gene, v-src, that was present in ac
tion to after treatment with ⁹⁰Sr was designated FBR-MSV.
Genetic analysis of the Rous sarcoma virus in the late
1960s identified a gene, v-src, that was present in addi-
tion to those genes that were required for viral replica-Genetic analysis of the Rous sarcoma virus in the late v-src (1960s identified a gene, v-src, that was present in addi-
tion to those genes that were required for viral replica-
tion (Martin, 1970). It was reasoned that t 1960s identified a gene, v-src, that was presention to those genes that were required for viration (Martin, 1970). It was reasoned that this abled the virus to induce sarcomas in vivo. "oncogene" (cancer-causing gene) was In to those genes that were required for viral replica-
In (Martin, 1970). It was reasoned that this gene encelled the virus to induce sarcomas in vivo. The term was
ncogene" (cancer-causing gene) was coined. Interved that tion (Martin, 1970). It was reasoned that this gene enabled the virus to induce sarcomas in vivo. The term "
"oncogene" (cancer-causing gene) was coined. I
Five years later, it was discovered that this gene could is
be fou

DRAGUNOW
al., 1976). This finding showed that normal cellular
DNA contains counterparts to viral oncogenes (v-oncs). DRAGUNOW
al., 1976). This finding showed that normal cellular
DNA contains counterparts to viral oncogenes (v-oncs).
The viral oncogene was found to encode a tyrosine ki-DRAGUNOW
al., 1976). This finding showed that normal cellular
DNA contains counterparts to viral oncogenes (v-oncs).
The viral oncogene was found to encode a tyrosine ki-
nase termed pp60^{src} (Collett and Erikson, 1978). al., 1976). This finding showed that normal cellular DNA contains counterparts to viral oncogenes (v-oncs). The viral oncogene was found to encode a tyrosine kinase termed pp60^{src} (Collett and Erikson, 1978). As they wer The viral oncogene was found to encode a tyrosine kinase termed pp60^{src} (Collett and Erikson, 1978). As they were initially identified, the cellular counterparts of the nase termed pp60^{src} (Collett and Erikson, 1978). As they were initially identified, the cellular counterparts of the viral oncogenes were termed proto-oncogenes or cellular oncogenes (c-*oncs*). Genetic analysis of FBJ-M mase termed $\rm pp60^{src}$ (Collett and Erikson, 1978). As they were initially identified, the cellular counterparts of the viral oncogenes were termed proto-oncogenes or cellular oncogenes (c-*oncs*). Genetic analysis of FBJ were initially identified, the centual counterparts of this
viral oncogenes (c-oncs). Genetic analysis of FBJ-MSV an
FBR-MSV virus strains identified that both harboure
oncogenes. The product of the FBJ-MSV oncogene (des
i oncogenes (c-oncs). Genetic analysis of FBJ-MSV and FBR-MSV virus strains identified that both harboured oncogenes. The product of the FBJ-MSV oncogene (designated v-fos) was identified as a 55-kD protein (Curran and Teich FBR-MSV virus strains identified that both harboured r BR-MSV virus strains identified that both harboured
oncogenes. The product of the FBJ-MSV oncogene (des-
ignated v-fos) was identified as a 55-kD protein (Curran
and Teich, 1982). The product of the FBR-MSV oncogene
was ignated v-*jos)* was identified as a 55-KD protein (Curran and Teich, 1982). The product of the FBR-MSV oncogene was a 75-kD protein. Genetic and protein analysis showed that both v-*fos* and the FBR-MSV oncogene had homol

was a 75-KD protein. Genetic and protein analysis
showed that both v-*fos* and the FBR-MSV oncogene had
homologous regions (Curran and Verma, 1984).
It became clear that viral oncogenes were derived
from the DNA of vertebr showed that both v-jos and the FBR-MSV oncogene has
homologous regions (Curran and Verma, 1984).
It became clear that viral oncogenes were derive
from the DNA of vertebrate cells (Bishop, 1983; Bishop
1985; Stehelin et al. nomologous regions (Curran and Verma, 1984).
It became clear that viral oncogenes were derived
from the DNA of vertebrate cells (Bishop, 1983; Bishop,
1985; Stehelin et al., 1976). The invading virus "cap-
tures" the gene rrom the DNA of vertebrate cells (Bishop, 1985; Bishop, 1985; Stehelin et al., 1976). The invading virus "captures" the gene from the DNA of infected cells. However, the gene is not always captured as a whole. In normal ce tures" the gene from the DNA of infected cells. However, the gene is not always captured as a whole. In normal cells, these cellular proto-oncogenes do not cause cancer, because they are in a restrictive environment quite tures" the gene from the DNA of infected cells. Howev
the gene is not always captured as a whole. In norn
cells, these cellular proto-oncogenes do not cause canc
because they are in a restrictive environment quite d
tinct the gene is not always captured as a whole. In norm
cells, these cellular proto-oncogenes do not cause cance
because they are in a restrictive environment quite di
tinct from their viral counterparts. However, over-e
press cells, these central proto-oncogenes to not cause cancer,
because they are in a restrictive environment quite dis-
tinct from their viral counterparts. However, over-ex-
pression of viral oncogenes occurs within the unre-
 because they are in a restrictive environment quite unstinct from their viral counterparts. However, over-expression of viral oncogenes occurs within the unrestricted environment of virally infected cells, because v-onc ge tinct from their viral counterparts. However, over-ex-
pression of viral oncogenes occurs within the unre-
stricted environment of virally infected cells, because
v-*onc* gene fragments inserted within the viral DNA are
of pression of viral oncogenes occurs within the unrestricted environment of virally infected cells, because v-onc gene fragments inserted within the viral DNA and often lacking expression-limiting regulatory region that exis stricted environment of virally infected cells, because
v-onc gene fragments inserted within the viral DNA are
often lacking expression-limiting regulatory regions
that exist within the normal proto-oncogene. The over-
exp tumour. at exist within the normal proto-oncogene. The over-
pression of the gene in virally infected cells causes
restricted cell growth and division—the basis of the
mour.
To date, some 50 oncogenes have been identified and
we h It became clear that viral oncogenes were derived
from the DNA of vertebrate cells (Bishop, 1988; Bishelin et al., 1976). The invading virus "cap-
tures" the gene from the DNA of infected cells. However,
tures" the gene i

expression of the gene in virally infected cells causes
unrestricted cell growth and division—the basis of the
tumour.
To date, some 50 oncogenes have been identified and
have had their proto-oncogene counterparts cloned.
 unrestricted cell growth and division—the basis of the
tumour.
To date, some 50 oncogenes have been identified and
have had their proto-oncogene counterparts cloned.
High conservation of nucleotide sequence of cellular and tumour.
To date, some 50 oncogenes have been identified and
have had their proto-oncogene counterparts cloned.
High conservation of nucleotide sequence of cellular and
viral oncogenes between species suggests that these
ge To date, some 50 oncogenes nave been identified and
have had their proto-oncogene counterparts cloned.
High conservation of nucleotide sequence of cellular and
viral oncogenes between species suggests that these
genes may mave had their proto-oncogene counterparts cloned.

High conservation of nucleotide sequence of cellular and

viral oncogenes between species suggests that these

genes may have some important role to play in the

functio High conservation of nucleotide sequence of cellular ε viral oncogenes between species suggests that the genes may have some important role to play in functioning of the cell (Bishop, 1983). Indeed, it is necognised t viral oncogenes between species suggests that the
genes may have some important role to play in t
functioning of the cell (Bishop, 1983). Indeed, it is no
recognised that many of the viral oncogenes are neopla
tic, because genes may have some important role to play in the
functioning of the cell (Bishop, 1983). Indeed, it is not
recognised that many of the viral oncogenes are neoplas
tic, because they encode proteins that have fundamentat
ro signal transduction mechanisms from the cell mem-
recognised that many of the viral oncogenes are neoplas-
tic, because they encode proteins that have fundamental
roles in intercellular communication and intracellular
sign tic, because they encode proteins that have fundamenta
roles in intercellular communication and intracellula
signal transduction mechanisms from the cell mem
brane to the nucleus (Macara, 1989; Storms and Bose
1989). For e signal transduction mechanisms from the cell mem-
brane to the nucleus (Macara, 1989; Storms and Bose,
1989). For example, the oncogene v-sis codes for a sub-
unit of the growth factor PDGF, whereas the v-erbB
oncogene enc brane to the nucleus (Macara, 1989; Storms and Bose, 1989). For example, the oncogene v-sis codes for a sub-
unit of the growth factor PDGF, whereas the v-erbB
oncogene encodes for an analog of the receptor for EGF.
The v-1989). For example, the oncogene v-sis codes for a sub-
unit of the growth factor PDGF, whereas the v-erbB
oncogene encodes for an analog of the receptor for EGF.
The v-ras oncogene protein shares homology with G-
protein oncogene encodes for an analog of the receptor for EGF.
The v-ras oncogene protein shares homology with G-
proteins, binds guanine nucleotides, and has intrinsic
guanosine triphosphatase activity. Oncogenes that en-
code c oncogene encodes for an analog of the receptor for EGF.
The v-ras oncogene protein shares homology with G-
proteins, binds guanine nucleotides, and has intrinsic
guanosine triphosphatase activity. Oncogenes that en-
code The *v-ras* oncogene protem snares nonloogy with G-
proteins, binds guanine nucleotides, and has intrinsic
guanosine triphosphatase activity. Oncogenes that en-
code cytoplasmic proteins involved in cellular signal
transdu guanosine triphosphatase activity. Oncogenes that encode cytoplasmic proteins involved in cellular signal transduction include v- raf (serine/threonine kinase) and v- src (tyrosine kinase). The v- $erbA$ oncogene codes for t

cransauction include v-raj (serine/threonine kinase) and v-src (tyrosine kinase). The v-erbA oncogene codes for
the intracellular thyroid hormone receptor.
Over-expression of these proteins in virally infect
cells leads to the intracellular thyroid hormone receptor.

Over-expression of these proteins in virally infected

cells leads to tumour formation, because signal path-

ways specifying growth and division become overstimu-

lated (Carbo Over-expression of these proteins in virally infected
cells leads to tumour formation, because signal path-
ways specifying growth and division become overstimu-
lated (Carbone and Levine, 1990). Some of the oncogenes
iden cells leads to tumour formation, because signal pathways specifying growth and division become overstimulated (Carbone and Levine, 1990). Some of the oncogenes identified were found to have a *nuclear localisation*. One of

PHARMACOLOGICAL REVIEWS

AND GENE EXPRESSION 137
 fos-B(L) (Nakabeppu and Nathans, 1991; Mumberg et

al., 1991).

Because these genes were activated by competence

the avian myelocytomatosis virus (MC29).

C. Induction of Immediate-early Genes in Cultured

C. Induction of Immediate-early Genes in Cultured

Cells

C 137
Because these genes were activated by competence,
tors and had a nuclear localisation and could bind to
tors and had a nuclear localisation and could bind to fos-B(L) (Nakabeppu and Nathans, 1991; Mumberg et al., 1991).
Because these genes were activated by competence factors and had a nuclear localisation and could bind to DNA, it was postulated that they could act as TFs t al., 1991).
Because these genes were activated by competence
factors and had a nuclear localisation and could bind to
DNA, it was postulated that they could act as TFs to
control DNA replication by regulating the activatio because these genes were activated by competence
factors and had a nuclear localisation and could bind to
DNA, it was postulated that they could act as TFs to
control DNA replication by regulating the activation of
target-Figures and had a nuclear localisation and codd bind to
DNA, it was postulated that they could act as TFs to
control DNA replication by regulating the activation of
target-genes expressed later in the growth response
(King DINA, It was posturated that they comd act as IFS to
control DNA replication by regulating the activation of
target-genes expressed later in the growth response
(Kingston et al., 1985; Sambucetti and Curran, 1986).
Althoug target-genes expressed later in the growth response (Kingston et al., 1985; Sambucetti and Curran, 1986) Although experiments designed to test these ideas dem onstrated that expression of c -*fos* or c -*myc* alone was (Kingston et al., 1960; Sambucetti and Curran, 1960).
Although experiments designed to test these ideas demonstrated that expression of c -*fos* or c -*myc* alone was not sufficient to initiate the cellular growth respo Although experiments designed to test these ideas demonstrated that expression of c-fos or c-myc alone was not sufficient to initiate the cellular growth response, antisense experiments demonstrated that expression of c-fo onstrated that expression of c-*jos* or c-*jnyc* afone was he sufficient to initiate the cellular growth response, ant sense experiments demonstrated that expression of c-*f* and c-*myc* was essential for the optimum mitog suncent to initiate the centuar growth response, anti-
sense experiments demonstrated that expression of c-fos
and c-myc was essential for the optimum mitogenic re-
sponse of cells to growth factors and lymphocyte mito-
ge and c-myc was essential for the optimum imtogenic response of cells to growth factors and lymphocyte mitogens (Heikkila et al., 1987; Holt et al., 1986; Nishikura and Murray, 1987), suggesting that in some way, these genes ns (Heikkila et al., 1987; Holt et al., 1986; Nishikura
id Murray, 1987), suggesting that in some way, these
nes were involved in the processes controlling cell
owth (Rollins and Stiles, 1988).
In addition, these early stu

and Murray, 1567), suggesting that in some way, these
genes were involved in the processes controlling cell
growth (Rollins and Stiles, 1988).
In addition, these early studies also identified several
features of the induct growth (Kolinis and Stiles, 1966).
In addition, these early studies also identified several
features of the induction of the cellular proto-oncogenes.
The first characteristic identified was that induction
occurred rapidly features of the induction of the cellular proto-oncogenes.
The first characteristic identified was that induction
occurred rapidly within the cell. Secondly, it was iden-
tified that induction was transient, and thirdly th The first characteristic identified was that induct
occurred rapidly within the cell. Secondly, it was identified that induction was transient, and thirdly t
induction was protein-synthesis-independent. Indeed
the presence occurred rapidly within the cell. Secondly, it was identified that induction was transient, and thirdly that induction was protein-synthesis-independent. Indeed, in the presence of protein-synthesis inhibitors (cycloheximi tified that induction was transient, and thirdly that
induction was protein-synthesis-independent. Indeed, in
the presence of protein-synthesis inhibitors (cyclohexi-
mide/anisomycin), induction of c-*fos* mRNA by mitogens induction was protein-synthesis-independent. Indeed, in
the presence of protein-synthesis inhibitors (cyclohexi-
mide/anisomycin), induction of c-*fos* mRNA by mitogens
was super-induced, maximal levels of c-*fos* mRNA wer the presence of protein-synthesis inhibitors (cyclohexi-
mide/anisomycin), induction of c-*fos* mRNA by mitogens
was super-induced, maximal levels of c-*fos* mRNA were
increased, and the persistence of c-*fos* mRNA within mide/anisomycin), induction of c-*fos* mRNA by mitogens
was super-induced, maximal levels of c-*fos* mRNA were
increased, and the persistence of c-*fos* mRNA within the
cell was prolonged (Cochran et al., 1984; Greenberg e was super-induced, maximal levels of c-*jos* mixtyle were
increased, and the persistence of c-*fos* mRNA within the
cell was prolonged (Cochran et al., 1984; Greenberg et
al., 1986). The effect of protein-synthesis inhibit cent was protonged (Cochran et al., 1964; Greenberg et al., 1986). The effect of protein-synthesis inhibition suggested that factors responsible for initiating transcription preexisted within the cell (i.e., were constitut gested that factors responsible for findually transcribe
tion preexisted within the cell (i.e., were constitutiv
present) and were activated by posttranslational mo
fication. Induction of c-fos transcription by proteins ti tion preexisted within the centry, were constitutively
present) and were activated by posttranslational modi-
fication. Induction of *c-fos* transcription by proteins that
only require posttranslational modification for ac fication. Induction of c-*fos* transcription by proteins that only require posttranslational modification for active tion (i.e., phosphorylation), would explain how induction of c-*fos* mRNA can be produced within minutes only require posttranslational modification for activation (i.e., phosphorylation), would explain how induction of c-fos mRNA can be produced within minutes, after mitogen stimulation of the cell. In addition, the transien tion (i.e., phosphorylation), would explain how induct
of c-fos mRNA can be produced within minutes, at
mitogen stimulation of the cell. In addition, the tr-
sient nature of c-fos mRNA induction by mitogens ε
the super of c-fos mRNA can be produced within minutes, a
mitogen stimulation of the cell. In addition, the tr
sient nature of c-fos mRNA induction by mitogens a
the super-induction of c-fos mRNA produced by prot
synthesis inhibitio mitogen stimulation of the cell. In addition, the transient nature of c-fos mRNA induction by mitogens and the super-induction of c-fos mRNA produced by proteinsient nature of *c-fos* mRNA induction by mitogens and
the super-induction of *c-fos* mRNA produced by protein-
synthesis inhibition suggested that a *de-novo* synthe-
sised, mitogen-induced protein, was required for shutsynthesis inhibition suggested that a de-*hooo* synthesised, mitogen-induced protein, was required for shut-of of c-fos transcription (Sassone-Corsi et al., 1988b; Auwerx and Sassone-Corsi, 1991; Lucibello et al., 1989; Wi of c-*fos* transcription (Sassone-Corsi et al., 1988b; Auw-
erx and Sassone-Corsi, 1991; Lucibello et al., 1989; Wil-
son and Treisman, 1988).
The newly synthesised protein responsible for tran-
scriptional shut-off of the

The zinc finger-containing genes *krox*-20 and *krox*-24 al., 1990; Lucibello et al., 1989). Such a negative-feed-
emaire et al., 1988), also termed *zif* 268 (Christy et al. back mechanism (*trans*-repression) occurred on erx and Sassone-Corsi, 1991; Lucibello et al., 1989; Wilson and Treisman, 1988).

The newly synthesised protein responsible for transcriptional shut-off of the c-fos gene was identified as its

protein product, Fos (Sasson son and Treisman, 1988).
The newly synthesised protein responsible for
scriptional shut-off of the c-*fos* gene was identified
protein product, Fos (Sassone-Corsi et al., 1988b; G
al., 1990; Lucibello et al., 1989). Such a The newly synthesised protein responsible for tran-
scriptional shut-off of the c-*fos* gene was identified as its
protein product, Fos (Sassone-Corsi et al., 1988b; Gius et
al., 1990; Lucibello et al., 1989). Such a negat *c-fos* gene was identified as
protein product, Fos (Sassone-Corsi et al., 1988b; Gius
al., 1990; Lucibello et al., 1989). Such a negative-fee
back mechanism (*trans*-repression) occurred only wh
c-*fos* transcription was protem product, ros (Sassone-Corsi et al., 1966), Gius et al., 1990; Lucibello et al., 1989). Such a negative-feed-
back mechanism (*trans*-repression) occurred only when
c-fos transcription was induced by mitogens and, co back mechanism (*trans*-repression) occurred only when c-*fos* transcription was induced by mitogens and, consequently, only c-*fos* serum-inducible promoter elements (i.e., the SRE) are molecular targets of repression (se c-*jos* transcription was induced by mitogens and, consequently, only c-*fos* serum-inducible promoter elements (i.e., the SRE) are molecular targets of repression (see next section.) In vitro binding studies suggest that (i.e., the SRE) are molecular targets of repression (sext section.) In vitro binding studies suggest that F os protein directly interacts with the transcription complex that dictates the mitogen response. Two region of t

IMMEDIATE-EARLY GENES
1986). Other nuclear oncogenes included *v-jun* and *v-*
myc; *v-jun* is the oncogene of avian sarcoma virus 17 *myc; v-jun* is the oncogenes included *v-jun* and *v-fos-myc; v-jun* is the oncogene of avian sarcoma virus 17 al., (Vogt and Bos, 1990), whereas *v-myc* is the oncogene of I the avian myelocytomatosis virus (MC29). fact 1986). Other nuclear oncogenes included myc ; $v\text{-}jun$ is the oncogene of avian sarco:
(Vogt and Bos, 1990), whereas $v\text{-}myc$ is the the avian myelocytomatosis virus (MC29). *C. Induction of Immediate-early Genes in Cultured*
C. Induction of Immediate-early Genes in Cultured
C. Induction of Immediate-early Genes in Cultured
Cells

Cells

C. Induction of Immediate-early Genes in Cultured
Cells
Induction of c-fos in cultured cells was first iden
in experiments that aimed to identify growth-fa
responsive genes that might control the re-entry Cells

Induction of c-fos in cultured cells was first identified

in experiments that aimed to identify growth-factor-

responsive genes that might control the re-entry of G_0

resting cells into the cell cycle. Growth Induction of c-fos in cultured cells was first identified
in experiments that aimed to identify growth-factor-
responsive genes that might control the re-entry of G_0
resting cells into the cell cycle. Growth factors ha resting cells into the cell cycle. Growth factors have been
characterised according to their effects on BALB/c 3T3
for example, PDGF renders cells competent sponse of cells to growth factors and lymphocyte mito-
for exampl to begin the cell cycle. Thus, PDGF is characterised as a responsive genes that might control the re-entry of G_0 suff
resting cells into the cell cycle. Growth factors have been
characterised according to their effects on BALB/c 3T3
fibroblasts. For example, PDGF renders cell resting cells into the cell cycle. Growth factors have been
characterised according to their effects on BALB/c 3T3
fibroblasts. For example, PDGF renders cells competent
to begin the cell cycle. Thus, PDGF is characterised characterised according to their effects on BALB/c 3T3
fibroblasts. For example, PDGF renders cells competent
to begin the cell cycle. Thus, PDGF is characterised as a
"competence factor." The competence factor does not
ha fibroblasts. For example, PDGF renders cells competent
to begin the cell cycle. Thus, PDGF is characterised as a
"competence factor." The competence factor does not
have to be continuously present (Pledger et al., 1978).
C to begin the cell cycle. Thus, PDGF is characterised as a g
"competence factor." The competence factor does not a
have to be continuously present (Pledger et al., 1978). g
Competent cells then require a second mitogen suc "competence factor." The competence factor does not have to be continuously present (Pledger et al., 1978). Competent cells then require a second mitogen such as EGF to fully initiate a cycle of cell division. EGF is thus have to be continuously present (Pledger et al., 1978).
Competent cells then require a second mitogen such as
EGF to fully initiate a cycle of cell division. EGF is thus
characterised as a "progression factor." Progressio EGF to fully initiate a cycle of cell division. EGF is thus
characterised as a "progression factor." Progression fac-
tors must be present throughout the G_1 phase (Stiles et
al., 1979). It was postulated that changes i sign might underlie the long-lasting ability of cells to

the might underlie the long-lasting ability of cells to

respond to progression factors such as EGF and insulin-

like growth factor-1 after brief application of c tors must be present throughout the G_1 phase (Stiles et al., 1979). It was postulated that changes in gene expression might underlie the long-lasting ability of cells to respond to progression factors such as EGF and i al., 1979). It was postula
sion might underlie the
respond to progression i
like growth factor-1 afte
factors such as PDGF.
Experiments were in on might underlie the long-lasting ability of cells to spond to progression factors such as EGF and insulin-
ee growth factor-1 after brief application of competence
ctors such as PDGF.
Experiments were initiated to find a

these extend to progression ractors such as EGT and insumi-
like growth factor-1 after brief application of competence
factors such as PDGF.
Experiments were initiated to find and characterise
these "competence genes." I michted but the setter is experiments were initiated to find and characterise
these "competence genes." In the very first studies, the
c-fos and c-myc proto-oncogenes were identified as genes
whose rapid but transient tran Experiments were initiated to find and characterise
these "competence genes." In the very first studies, the
c-fos and c-myc proto-oncogenes were identified as genes
whose rapid but transient transcription was activated in these "competence genes." In the very first studies, the
c-fos and c-myc proto-oncogenes were identified as genes
cell was prolonged (Cochran et al., 1984; Greenberg et
whose rapid but transient transcription was activated c-*fos* and c-*myc* proto-oncogenes were identified as ger
whose rapid but transient transcription was activated
response to brief exposure of cells to mitogens (Rolli
and Stiles, 1988), specifically PDGF (Kelly et al., 19 whose rapid but transient transcription was activated in response to brief exposure of cells to mitogens (Rollins and Stiles, 1988), specifically PDGF (Kelly et al., 1983). Kruijer et al., 1984; Cochran et al., 1984), seru response to brief exposure of cens to imtogens (found
and Stiles, 1988), specifically PDGF (Kelly et al., 198
Kruijer et al., 1984; Cochran et al., 1984), serum (Green
berg and Ziff, 1984), and EGF (Bravo et al., 1985). Su berg and Ziff, 1984), and EGF (Bravo et al., 1985). Sub-

fication. Induction of c-fos transcription by proteins that

sequently, c-jun was also found to be induced by mito-

only require posttranslational modification fo Example Fe al., 1564, Cochran et al., 1564), serum (Green-
berg and Ziff, 1984), and EGF (Bravo et al., 1985). Sub-
sequently, c-jun was also found to be induced by mito-
only 1
gens (Lamph et al., 1988). This finding was sequently, c-jun was also found to be induced by mitogens (Lamph et al., 1988). This finding was followed closely by the identification of several more putative "competence genes" by screening serum-inducible cDNA librarie gens (Lamph et al., 1988). This finding was followed tion
closely by the identification of several more putative of c
"competence genes" by screening serum-inducible cDNA mit
libraries for clones related in sequence to cclosely by the identification of several more putative of α "competence genes" by screening serum-inducible cDNA mit
libraries for clones related in sequence to c-*fos* and c-*jun*. sien
In this way, *fra*-1 (Cohen and "competence genes" by screening serum-inducible cDNA
libraries for clones related in sequence to c-*fos* and c-*jun*.
In this way, *fra*-1 (Cohen and Curran, 1988), *jun*-B
(clone 465; Lau and Nathans, 1987; later identif libraries for clones related in sequence to c-fos and c-ju
In this way, fra-1 (Cohen and Curran, 1988), jun
(clone 465; Lau and Nathans, 1987; later identified as
c-jun-related gene; Ryder et al., 1988), fos-B (Zerial
al. In this way, $fra-1$ (Cohen and Curran, 1988), $jun-1$
(clone 465; Lau and Nathans, 1987; later identified as
c- jun -related gene; Ryder et al., 1988), fos -B (Zerial ϵ
al., 1989), and $fra-2$ (Nishina et al., 1990) were ident (clone 465; Lau and Nathans, 1987; later identified as a synthesis inhibition suggested that a *de-novo* synthe-
c-jun-related gene; Ryder et al., 1988), *fos-B* (Zerial et sised, mitogen-induced protein, was required for al., 1989), and $fra-2$ (Nishina et al., 1990) were identi-
field. Although jun -D expression was not markedly stim-
field. Although jun -D expression was not markedly stim-
ulated by serum, its high constitutive expression i fied. Although jun-D expression was not markedly stim-1989). c-jun-related gene family (Hirai et al., 1989; Ryder et al., 1989).
The zinc finger-containing genes $krox-20$ and $krox-24$
(Lemaire et al., 1988), also termed zif 268 (Christy et al.
1988), *NGFI*-A (Milbrandt, 1987), or *e*

c-jun-related gene family (Hirai et al., 1989; Ryder et al., 1989).
1989).
The zinc finger-containing genes *krox*-20 and *krox*-24
(Lemaire et al., 1988), also termed *zif* 268 (Christy et al.
1988), *NGFI*-A (Milbrandt, 1989). The zinc finger-containing genes $krox-20$ and $krox-2$
(Lemaire et al., 1988), also termed *zif* 268 (Christy et a
1988), *NGFI*-A (Milbrandt, 1987), or *egr*-1 (Sukhatme e
al., 1988) were also activated rapidly after The zinc finger-containing genes $krox-20$ and $krox-24$ al., (Lemaire et al., 1988), also termed zif 268 (Christy et al. bad 1988), *NGFI*-A (Milbrandt, 1987), or *egr*-1 (Sukhatme et c-fc al., 1988) were also activated rapi Lemare et an., 1966), also termed 2t/206 (Cirristy et al. back
1988), *NGFI*-A (Milbrandt, 1987), or *egr*-1 (Sukhatme et c-fos
al., 1988) were also activated rapidly after serum stim-
ulation of 3T3 cells, suggesting that all, 1966) were also activated rapidly after serum sum-
ulation of 3T3 cells, suggesting that these genes may
also be involved in the generation of cell competence.
More recently, an alternatively spliced variant of *fos*-

 $\begin{minipage}{0.9\linewidth} \hline \texttt{138} & \texttt{HUGHE:} \\\\ \texttt{a region that encompasses the SRE and the AP-1/T:} \\\\ \texttt{like site, and a sequence located between base-pairs-} \end{minipage}$ HUGHES AND DRA
a region that encompasses the SRE and the AP-1/TRE-
like site, and a sequence located between base-pairs -283 et
and -213 that has regions of homology with the human syr HUGHES AND DI
a region that encompasses the SRE and the AP-1/TRE-
like site, and a sequence located between base-pairs -283
et and -213 that has regions of homology with the human
HSP70 promotor (Sassone-Corsi et al., 1988 a region that encompasses the SRE and the AP
like site, and a sequence located between base-pa
and -213 that has regions of homology with the
HSP70 promotor (Sassone-Corsi et al., 1988b).
Replacement of Fos peptide sequenc region that encompasses the SRE and the AP-1/TRE-
induce site, and a sequence located between base-pairs -283 et a
id -213 that has regions of homology with the human syn:
SP70 promotor (Sassone-Corsi et al., 1988b). is cl

like site, and a sequence located between base-pairs -2
and -213 that has regions of homology with the hum:
HSP70 promotor (Sassone-Corsi et al., 1988b).
Replacement of Fos peptide sequences C-terminal
amino acid 337 block and -213 that has regions of homology with the human
HSP70 promotor (Sassone-Corsi et al., 1988b).
Replacement of Fos peptide sequences C-terminal to
amino acid 337 blocks down-regulation of c-fos tran-
scription by Fos p HSP70 promotor (Sassone-Corsi et al., 1988b).
Replacement of Fos peptide sequences C-terminal to
amino acid 337 blocks down-regulation of c-fos trans-
scription by Fos protein, suggesting that these regions
are involved in Replacement of Fos peptide sequences C-terminal to hamino acid 337 blocks down-regulation of c-fos transcription by Fos protein, suggesting that these regions are involved in *trans*-repression (Wilson and Treisman, 1988). amino-acid 337 blocks down-regulation of c-fos trans-
scription by Fos protein, suggesting that these regions and
are involved in *trans*-repression (Wilson and Treisman,
1988). In addition, mutant Fos proteins lacking th scription by Fos protein, suggesting that these regions
are involved in *trans*-repression (Wilson and Treisman,
1988). In addition, mutant Fos proteins lacking the basic
amino-acid DNA binding domains used to bind to the
 1988). In addition, mutant Fos proteins lacking the basic fos amino-acid DNA binding domains used to bind to the and AP-1 site do not lose the ability to *trans*-repress (Gius et tha al., 1990; Lucibello et al., 1989), su amino-acid DNA binding domains used to bind to tl
AP-1 site do not lose the ability to *trans*-repress (Gius
al., 1990; Lucibello et al., 1989), suggesting that diffe
ent mechanisms are involved in *trans*-repression an
c AP-1 site do not lose the ability to *trans*-repress (Gius et tha al., 1990; Lucibello et al., 1989), suggesting that different mechanisms are involved in *trans*-repression and cell *cis*-activation of genes by Fos. Fos al., 1990; Lucibello et al., 1989), suggesting that differ-
ent mechanisms are involved in *trans*-repression and ce
cis-activation of genes by Fos. Fos is also able to down-
regulate Krox-24 protein by interaction with th ent mechanisms are involved in *trans*-repression ε *cis*-activation of genes by Fos. Fos is also able to dovergulate Krox-24 protein by interaction with the SRE the regulatory region of this gene (Gius et al., 1990). cis-activation of genes by Fos. Fos is also able to down-had
regulate Krox-24 protein by interaction with the SRE in dela
the regulatory region of this gene (Gius et al., 1990). (See base
next section.) Other mechanisms, regulate Krox-24 protein by interaction with the SRE in due regulatory region of this gene (Gius et al., 1990). (See bark free nect section.) Other mechanisms, in addition to prevention of transcriptional shut-off, may als the regulatory region of this gene (Gius et al., 1990). (See bandward state in the prevention of transcriptional shut-off, may also contribute to c-
the superinduction effect, such as enhancement of limRNA stability (Lemai next section.) Other mechanisms, in addition to prevention of transcriptional shut-off, may also contribute to the superinduction effect, such as enhancement of mRNA stability (Lemaire et al., 1988), the prevention of new tion of transcriptional shut-off, may also contribute to c-J
the superinduction effect, such as enhancement of life
mRNA stability (Lemaire et al., 1988), the prevention of and
new synthesis of labile degradation enzymes, the superinduction effect, such as enhancement mRNA stability (Lemaire et al., 1988), the preventine are synthesis of labile degradation enzymes, or offects of protein-synthesis inhibitors (Mahadevan Edwards, 1991; Edwards RNA stability (Lemaire et al., 1988), the prevention of an expandisor and the synthesis of labile degradation enzymes, or other stifects of protein-synthesis inhibitors (Mahadevan and sequands, 1991; Edwards and Mahadevan

new synthesis of labile degradation enzymes, or other steffects of protein-synthesis inhibitors (Mahadevan and sedwards, 1991; Edwards and Mahadevan, 1992). In addition to *trans*-repression by its own product, the the ind effects of protein-synthesis inhibitors (Mahadevan and Edwards, 1991; Edwards and Mahadevan, 1992). In addition to *trans*-repression by its own product, the thin duction of c-*fos* mRNA is rendered transient because of Ju In addition to *trans*-repression by its own product, the
induction of c-*fos* mRNA is rendered transient because of Ju
untranslated AT-rich sequences found within the 3' re-
gion of the transcript. This 67-nucleotide reg induction of c-fos mRNA is rendered transient because of Juntranslated AT-rich sequences found within the 3' region of the transcript. This 67-nucleotide region, located some 500 nucleotides down-stream from the end of th untranslated AT-rich sequences found within the 3' region of the transcript. This 67-nucleotide region, located some 500 nucleotides down-stream from the end of the coding domain and about 120 nucleotides upstream of the p gion of the transcript. This o_f-hucleotide region, located
some 500 nucleotides down-stream from the end of the
coding domain and about 120 nucleotides upstream of
the poly(A) addition signal sequence, influences the st some 500 nucleotides down-stream from the end of the
coding domain and about 120 nucleotides upstream of the
the poly(A) addition signal sequence, influences the sta-
bility of c-fos mRNA (Blanchard et al., 1988). Removal the poly(A) addition signal sequence, influences the stability of c-fos mRNA (Blanchard et al., 1988). Removal of this noncoding region results in a ten-fold increase in the amount of Fos protein translated and confers tra 1987). is noncoding region results in a ten-fold increase in the
nount of Fos protein translated and confers transform-
g potential on the mutant gene (Verma and Graham,
87).
The occurrence of such AU/AT-rich sequences in most
an

amount of Fos protein translated and confers transform-
ing potential on the mutant gene (Verma and Graham, lon
1987).
The occurrence of such AU/AT-rich sequences in most
transiently expressed mRNAs suggests the presence ing potential on the mutant gene (Verma and Graham, lost 1987).

The occurrence of such AU/AT-rich sequences in most D .

transiently expressed mRNAs suggests the presence of a

common system of degradation (Caput et al. 1987). The occurrence of such AU/AT-rich sequences in most $D.1$
transiently expressed mRNAs suggests the presence of a T
common system of degradation (Caput et al., 1986). The use
induction of c-*jun* mRNA expression als The occurrence of such AU/AT-rich sequences in most
transiently expressed mRNAs suggests the presence of a
common system of degradation (Caput et al., 1986). The
induction of c-jun mRNA expression also rises rapidly in
cel transiently expressed mRNAs suggests the presence of a
common system of degradation (Caput et al., 1986). The
induction of c -*jun* mRNA expression also rises rapidly in celli
cells stimulated by mitogen (Almendral et al common system of degradation (Caput et al., 1986). The used to study the mechanisms of action of NGF. PC12 induction of *c-jun* mRNA expression also rises rapidly in cells are the tumour counterparts of adrenal chromaffin induction of c-jun mRNA expression also rises rapidly in cells stimulated by mitogen (Almendral et al., 1988; Lamph et al., 1988; Rauscher et al., 1988). However, in contrast to the *trans*-repression of c-fos gene by Fos cells stimulated by mitogen (Almendral et al., 1988; celamph et al., 1988; Rauscher et al., 1988). However, in quentirast to the *trans*-repression of c-*fos* gene by Fos ph protein, the c-jun proto-oncogene is positively Lamph et al., 1988; Rauscher et al., 1988). However, contrast to the *trans*-repression of c-*fos* gene by I protein, the c-*jun* proto-oncogene is positively autore_{ lated by its product c-Jun (Angel et al., 1988). The contrast to the *trans*-repression of c-*fos* gene by Fos
protein, the c-*jun* proto-oncogene is positively autoregu-
lated by its product c-Jun (Angel et al., 1988). The c-Jun
protein binds to a high-affinity AP-1-like si protein, the c-*jun* proto-oncogene is positively autoregulated by its product c-Jun (Angel et al., 1988). The c-Jun eprotein binds to a high-affinity AP-1-like site (*GTGA*-t CATCAT) within its promoter and further stimul lated by its product c-Jun (Angel et al., 1988). The c-Jun
protein binds to a high-affinity AP-1-like site (GTGA-
CATCAT) within its promoter and further stimulates
c-jun transcription. Because the c-Jun protein positively protein binds to a high-affinity AP-1-like site (GTGA-
CATCAT) within its promoter and further stimulates scri-
c-jun transcription. Because the c-Jun protein positively 198-
autoregulates the expression of its own gene, CATCAT) within its promoter and further stimulates sc-jun transcription. Because the c-Jun protein positively 19 autoregulates the expression of its own gene, powerful to negative mechanisms of regulation must also exist *c-jun* transcription. Because the c-Jun protein positively 1:
autoregulates the expression of its own gene, powerful the
negative mechanisms of regulation must also exist to M
control c-jun mRNA levels, inasmuch as induct megative mechanisms of regulation must also exist to Morgan, 1985).

control c-*jun* mRNA levels, inasmuch as induction of These results were in agreement with the growth fac-

c-*jun* mRNA, such as that of c-*fos*, occur negative mechanisms of regulation must also exist
control c-jun mRNA levels, inasmuch as induction
c-jun mRNA, such as that of c-fos, occurs transiently.
for c-fos, 3' AT-rich untranslated regions of the c-j
mRNA have bee control c-jun mRNA levels, inasmuch as induction of
c-jun mRNA, such as that of c-fos, occurs transiently. As
for c-fos, 3' AT-rich untranslated regions of the c-jun
mRNA have been suggested to result in its rapid break-
d *k*-*jun* mRNA, such as that of c-*fos*, occurs transiently. A for c-*fos*, 3' AT-rich untranslated regions of the c-*ju* mRNA have been suggested to result in its rapid break down by RNAases. Transcripts encoding *fos-B*, for c-*jos*, 3 A1-rich untranslated regions of the c-*jun* type
mRNA have been suggested to result in its rapid break-
down by RNAases. Transcripts encoding *fos-B*, *jun-B*, que
krox-20, and *krox-24* are also induced mKINA have been suggested to result in its rapid break-
down by RNAases. Transcripts encoding *fos-B*, *jun-B*,
krox-20, and *krox-24* are also induced rapidly and tran-
siently in a protein-synthesis independent manner

DRAGUNOW
induction (Ryder et al., 1988; Zerial et al., 1989; Lemaire
et al., 1988; Chavrier et al., 1988). The rapid, protein DRAGUNOW
induction (Ryder et al., 1988; Zerial et al., 1989; Lemaire
et al., 1988; Chavrier et al., 1988). The rapid, protein
synthesis-independent induction of these genes in cells DRAGUNOW
induction (Ryder et al., 1988; Zerial et al., 1989; Lemaire
et al., 1988; Chavrier et al., 1988). The rapid, protein
synthesis-independent induction of these genes in cells
is characteristic of the IEGs carried by induction (Ryder et al., 1988; Zerial et al., 1989; Lemaire
et al., 1988; Chavrier et al., 1988). The rapid, protein
synthesis-independent induction of these genes in cells
is characteristic of the IEGs carried by many vir matched (Kyder et al., 1966, Zerial et al., 1969; Len
et al., 1988; Chavrier et al., 1988). The rapid, pro
synthesis-independent induction of these genes in
is characteristic of the IEGs carried by many viruses
has led to et al., 1566, Chavrier et al., 1566). The rapid, protein
synthesis-independent induction of these genes in cells
is characteristic of the IEGs carried by many viruses and
has led to the classification of this family of pro synthesis-independent madch
is characteristic of the IEGs car
has led to the classification of
genes (c-fos, c-myc, fos-B, c-ju;
and krox-24) as cellular IEGs.
After the generation of specif characteristic of the rector carried by many virtuses and
as led to the classification of this family of proto-onco-
nes (c-fos, c-myc, fos-B, c-jun, jun-B, jun-D, krox-20,
nd krox-24) as cellular IEGs.
After the generatio

*fore is a fore due to the classification of this family of proto-oncogenes (c-fos, c-myc, fos-B, c-jun, jun-B, jun-D, krox-20, and krox-24) as cellular IEGs.
After the generation of specific antibodies to the c-fos, fos-B* genes (c-fos, c-myc, fos-B, c-jun, jun-B, jun-D, krox-20,
and krox-24) as cellular IEGs.
After the generation of specific antibodies to the c-fos,
fos-B, c-jun, jun-B and jun-D gene products, (Kovary
and Bravo, 1991), stud and $krox-24$) as cellular IEGs.

After the generation of specific antibodies to the c-fos,

fos-B, c-jun, jun-B and jun-D gene products, (Kovary

and Bravo, 1991), studies at the protein level revealed

that Fos protein pr After the generation of specific antibodies to the c-fos, fos-B, c-jun, jun-B and jun-D gene products, (Kovary and Bravo, 1991), studies at the protein level revealed that Fos protein presented the most rapid and transien (bs-B, e-juh, juh-B and juh-D gene products, (Kovary and Bravo, 1991), studies at the protein level revealed that Fos protein presented the most rapid and transient increase in synthesis after stimulation of quiescent 3T3 that Fos protein presented the most rapid and transient
increase in synthesis after stimulation of quiescent 3T3
cells with serum. Fos levels were maximal at 30 min and
had decreased to low levels at 2 h . Fos-B in increase in synthesis after stimulation of quiescent 3T3
cells with serum. Fos levels were maximal at 30 min and
had decreased to low levels at 2 h. Fos-B induction was
delayed in relation to Fos being maximal at 1 h and cens with serum. Fos levels were maximal at 30 min and
had decreased to low levels at 2 h. Fos-B induction was
delayed in relation to Fos being maximal at 1 h and near
basal at 3 h. The three Jun proteins were induced rap had decreased to low levels at 2 h. Fos-B induction was
delayed in relation to Fos being maximal at 1 h and near
basal at 3 h. The three Jun proteins were induced rap-
idly (absolute level of induction was greater for Jun delayed in relation to ros being maximal at 1 h and near
basal at 3 h. The three Jun proteins were induced rap-
idly (absolute level of induction was greater for Jun-B >
c-Jun > Jun-D) and were found to have a prolonged
l idly (absolute level of induction was greater for Jun-B $>$ c-Jun $>$ Jun-D) and were found to have a prolonged life-span in relation to the two Fos proteins. Both c-Jun and Jun-B proteins remained at high levels at 8 h p s -Jun $>$ Jun-D) and were found to have a prolonged
life-span in relation to the two Fos proteins. Both c-Jun
and Jun-B proteins remained at high levels at 8 h post-
stimulation, albeit at levels much decreased from tho life-span in relation to the two Fos proteins. Both c-Jun
and Jun-B proteins remained at high levels at 8 h post-
stimulation, albeit at levels much decreased from those
seen at the time of maximal induction. Although the
 and Jun-B proteins remained at high levels at 8 h post-
stimulation, albeit at levels much decreased from those
seen at the time of maximal induction. Although the
maximal induction of Jun-D was less pronounced than
that o stimulation, albeit at levels much decreased from those
seen at the time of maximal induction. Although the
maximal induction of Jun-D was less pronounced than
that of c-Jun and Jun-B, it was the most persistent of the
Jun seen at the time of ma
maximal induction of Ju
that of c-Jun and Jun-B,
Jun proteins, with maxim
vary and Bravo, 1991).
Fra proteins, i.e., Frathat of c-Jun and Jun-B, it was the most persistent of the
Jun proteins, with maximal levels still seen at 8 h (Ko-
vary and Bravo, 1991).
Fra proteins, i.e., Fra-1, and Fra-2 also have a delayed delayed in relation to Fos being maximal at 1 h and near
basel at 3 h. The three Jum proteins were induced rap-
idly (absolute level of induction was greater for Jun-B >
c-Jun > Jun-D) and were found to have a prolonged
l

that of c-Jun and Jun-B, it was the most persistent of the
Jun proteins, with maximal levels still seen at 8 h (Ko-
vary and Bravo, 1991).
Fra proteins, i.e., Fra-1, and Fra-2 also have a delayed
and protracted induction t Jun proteins, with maximal levels still seen at 8 h (Kovary and Bravo, 1991).
Fra proteins, i.e., Fra-1, and Fra-2 also have a delayed
and protracted induction time-course, similar to that of
the Jun proteins (Kovary and B vary and Bravo, 1991).
Fra proteins, i.e., Fra-1, and Fra-2 also have a delayed
and protracted induction time-course, similar to that of
the Jun proteins (Kovary and Bravo, 1992; Cohen and
Curran, 1988; Nishina et al., 199 Fra proteins, i.e., Fra-1, and Fra-2 also have a delayed
and protracted induction time-course, similar to that of
the Jun proteins (Kovary and Bravo, 1992; Cohen and
Curran, 1988; Nishina et al., 1990; Franza et al., 1987; and protracted induction time-course, similar to that of
the Jun proteins (Kovary and Bravo, 1992; Cohen and
Curran, 1988; Nishina et al., 1990; Franza et al., 1987;
Suzuki et al., 1991). Thus, it seems that the induction the Jun proteins (Kovary and Bravo, 1992; Conen and Curran, 1988; Nishina et al., 1990; Franza et al., 1987; Suzuki et al., 1991). Thus, it seems that the induction time-courses of IEGPs are similar but not identical to so *D. Induction of IEGPs are similar but not identical to*
some species (Fra-1, Fra-2, Jun proteins), persisting
longer than others (Fos, Fos-B proteins).
D. Induction of Immediate-early Genes in PC12 Cells
The rat PC12 ph

D. Induction of Immediate-early Genes in PC12 Cells
The rat PC12 pheochromocytoma cell line has been
used to study the mechanisms of action of NGF. PC12
cells are the tumour counterparts of adrenal chromaffin
cells. When P D. Induction of Immediate-early Genes in PC12 Cells
The rat PC12 pheochromocytoma cell line has been
used to study the mechanisms of action of NGF. PC12
cells are the tumour counterparts of adrenal chromaffin
cells. When P The rat PC12 pheochromocytoma cell line has been
used to study the mechanisms of action of NGF. PC12
cells are the tumour counterparts of adrenal chromaffin
cells. When PC12 cells are treated with NGF, they ac-
quire over used to study the mechanisms of action of NGF. PC12
cells are the tumour counterparts of adrenal chromaffin
cells. When PC12 cells are treated with NGF, they ac-
quire over a period of days a sympathetic neuron-like
phenot cells. When PC12 cells are treated with NGF, they acquire over a period of days a sympathetic neuron-like phenotype characterised by the cessation of proliferation and the promotion of neurite outgrowth and electrical exci quire over a period of days a sympathetic neuron-lik
phenotype characterised by the cessation of proliferation
and the promotion of neurite outgrowth and electrice
excitability. Early reports using the PC12 cell line repor and the promotion of neurite outgrowth and electrical excitability. Early reports using the PC12 cell line reported that growth factors such as NGF and EGF induced transcription of the c-*fos* proto-oncogene (Greenberg et and the promotion of neurite outgrowth and electrical excitability. Early reports using the PC12 cell line reported that growth factors such as NGF and EGF induced transcription of the c -*fos* proto-oncogene (Greenberg excitability. Early reports using the PC12 cell line reported
that growth factors such as NGF and EGF induced tran-
scription of the c-*fos* proto-oncogene (Greenberg et al.,
1985), and peripherally active benzodiazepines that growth factoscription of the
1985), and periph
to super-induce t
Morgan, 1985).
These results ription of the c-*fos* proto-oncogene (Greenberg et al., 085), and peripherally active benzodiazepines were found super-induce the induction of c-*fos* by NGF (Curran and organ, 1985). These results were in agreement with

1985), and peripherally active benzodiazepines were found
to super-induce the induction of *c-fos* by NGF (Curran and
Morgan, 1985).
These results were in agreement with the growth fac-
tor-mediated induction of *c-fos* i These results were in agreement with the growth factor-mediated induction of *c-fos* in other cultured cell types as described above. It was suggested that *c-fos* gene expression (Greenberg et al., 1985) and, subse-Morgan, 1985).
These results were in agreement with the growth fator-mediated induction of c -*fos* in other cultured c
types as described above. It was suggested that c -*j*
gene expression (Greenberg et al., 1985) and These results were in agreement with the growth fac-
tor-mediated induction of c -fos in other cultured cell
types as described above. It was suggested that c -fos
gene expression (Greenberg et al., 1985) and, subse-
qu tor-mediated induction of c -fos in other cultured
types as described above. It was suggested that α
gene expression (Greenberg et al., 1985) and, su
quently, that of other IEGs (Milbrandt, 1987), migh
involved in pro types as described above. It was suggested that *c-fos* gene expression (Greenberg et al., 1985) and, subsequently, that of other IEGs (Milbrandt, 1987), might be involved in producing the program of rapid transcription-de gene expression (Greenberg et al., 1985) and, subsequently, that of other IEGs (Milbrandt, 1987), might be involved in producing the program of rapid transcription-dependent (Burstein and Greene, 1978) cellular changes in

PHARMACOLOGICAL REVIEW!

IMMEDIATE-EARLY GE
differentiation (Greenberg et al., 1985; Curran and Mor
gan, 1985). differentiation
gan, 1985).
Additional

IMMEDIATE-EARLY GENES Afferentiation (Greenberg et al., 1985; Curran and Mor-

Additional work in PC12 cells appeared in 1986; it

ggested that IEG induction might serve a more gendifferentiation (Greenberg et al., 1985; Curran and Morgan, 1985).
Additional work in PC12 cells appeared in 1986; it
suggested that IEG induction might serve a more gen-
eral role in the transduction of a wide variety of differentiation (Greenberg et al., 1985; Curran and Morgan, 1985).
Additional work in PC12 cells appeared in 1986; it
suggested that IEG induction might serve a more gen-
eral role in the transduction of a wide variety of gan, 1985).

Additional work in PC12 cells appeared in 1986; it

suggested that IEG induction might serve a more gen-

eral role in the transduction of a wide variety of signals

from cell-surface receptors to gene express suggested that IEG induction might serve a more general role in the transduction of a wide variety of signals platfrom cell-surface receptors to gene expression. The first frequency is that application of nicotine to nondi eral role in the transduction of a wide variety of signals
from cell-surface receptors to gene expression. The first
study reported that application of nicotine to nondivid-
ing, neuronally differentiated PC12 cells induce from cell-surface receptors to gene expression. The first from receptor activation by first-messengers (be they study reported that application of nicotine to nondivid-
neurotransmitter molecules or growth factors), to ap study reported that application of nicotine to nondividing, neuronally differentiated PC12 cells induced rapid
c-fos gene expression by activating VSCCs (Greenberg et al., 1986). The other two reports demonstrated inductio ing, neuronally differentiated PC12 cells induced r
c-*fos* gene expression by activating VSCCs (Greenbe
al., 1986). The other two reports demonstrated induc
of c-*fos* in PC12 cells after direct activation of VS
and showe c-fos gene expression by activating VSCCs (Greenberg cal., 1986). The other two reports demonstrated induction of c -fos in PC12 cells after direct activation of VSCC and showed that c -fos induction involved calmodulin al., 1986). The other two reports demonstrated induction
of c-fos in PC12 cells after direct activation of VSCCs
and showed that c-fos induction involved calmodulin-
dependent mechanisms, inasmuch as inhibitors of calmodul of c-*fos* in PC12 cells after direct activation of VSCCs
and showed that c-*fos* induction involved calmodulin-
dependent mechanisms, inasmuch as inhibitors of calm-
odulin (W7, chlorpromazine, and trifluoperazine) an-
ta and showed that c-*fos* induction is
dependent mechanisms, inasmuch and
odulin (W7, chlorpromazine, and
tagonised the induction of c-*fos* (C
1986; Morgan and Curran, 1986).
Specific patterns of proto-oncogen pendent mechanisms, inasmuch as inhibitors of calm-
ulin (W7, chlorpromazine, and trifluoperazine) an-
gonised the induction of c-*fos* (Curran and Morgan,
986; Morgan and Curran, 1986).
Specific patterns of proto-oncogene

odulin (W7, chlorpromazine, and trifluoperazine) at tagonised the induction of c-fos (Curran and Morgan 1986; Morgan and Curran, 1986).

Specific patterns of proto-oncogene expression also o curred after either growth fact tagonised the induction of c-fos (Curran and Morgan, 1986; Morgan and Curran, 1986).
Specific patterns of proto-oncogene expression also occurred after either growth factor stimulation or membrane depolarisation of PC12 c 1986; Morgan and Curran, 1986).

Specific patterns of proto-oncogene expression also oc-

curred after either growth factor stimulation or mem-

brane depolarisation of PC12 cells. For example, al-

though growth factor a Specific patterns of proto-oncogene expression also oc-
curred after either growth factor stimulation or mem-
brane depolarisation of PC12 cells. For example, al-
though growth factor application stimulated strong
inductio curred after either growth factor stimulation or membrane depolarisation of PC12 cells. For example, although growth factor application stimulated strong induction of c-fos, jun-B, c-jun and zif 268 (krox-24) genes, memb brane depolarisation of PC12 cells. For example, alto
though growth factor application stimulated strong
induction of c-*fos*, *jun*-B, c-*jun* and *zif* 268 (*krox*-24)
genes, membrane depolarisation resulted in strong i though growth factor application stimulated strong
induction of c-*fos*, *jun*-B, c-*jun* and *zif* 268 (*krox*-24)
genes, membrane depolarisation resulted in strong in-
duction of c-*fos* and *jun*-B, with a reduced indu induction of c-fos, jun-B, c-jun and zif 268 (krox-24) genes, membrane depolarisation resulted in strong induction of c-fos and jun-B, with a reduced induction of zif 268 and no induction of c-jun (Bartel et al., 1989). genes, membrane depolarisation resulted in strong in-
duction of c-fos and jun-B, with a reduced induction of
 $zif 268$ and no induction of c-jun (Bartel et al., 1989). It
also became obvious in several studies that extens duction of c-*fos* and *jun*-B, with a reduced induction zif 268 and no induction of c-*jun* (Bartel et al., 1989) also became obvious in several studies that extens post-translational modification of the Fos protein occ zif 268 and no induction of c-jun (Bartel et al., 1989). It also became obvious in several studies that extensive post-translational modification of the Fos protein can occur after induction. The extent of post-translatio also became obvious in several studies that extensive
post-translational modification of the Fos protein can
occur after induction. The extent of post-translational
modification is determined by the nature of the stimulus post-translational modification of the Fos protein can
occur after induction. The extent of post-translational
modification is determined by the nature of the stimulus
(Curran and Morgan, 1986). For example, when Fos
prote occur after induction. The extent of post-translational modification is determined by the nature of the stimulus (Curran and Morgan, 1986). For example, when Fos protein was induced by mitogens or phorbol esters (agents th modification is determined by the nature of the stimulus

(Curran and Morgan, 1986). For example, when Fos

protein was induced by mitogens or phorbol esters

(agents that activate PKC), it was extensively modified.

In c (Curran and Morgan, 1986). For example, when I
protein was induced by mitogens or phorbol est
(agents that activate PKC), it was extensively modific
In contrast, much less post-translational modification
Fos protein occurr (agents that activate PKC), it was extensively modified.
In contrast, much less post-translational modification of
Fos protein occurred when Fos was induced by depola-
rising agents or barium ions (agents that increase int cellular Ca^{2+}).
The different forms of Fos protein could be distincontrast, much less post-translational modification
os protein occurred when Fos was induced by depo
sing agents or barium ions (agents that increase inti
llular Ca^{2+}).
The different forms of Fos protein could be dist

Fos protein occurred when Fos was induced by depolarising agents or barium ions (agents that increase intra-
cellular Ca^{2+}).
The different forms of Fos protein could be distinguished on gels by their different molecula rising agents or barium ions (agents that increase intra-
cellular Ca^{2+}).
The different forms of Fos protein could be distinguished on gels by their different molecular weights
(Curran and Morgan, 1986). In addition, m The different forms of Fos protein could be distinguished on gels by their different molecular weights (Curran and Morgan, 1986). In addition, more extensive studies using 3T3 fibroblast cells demonstrated that different m guished on gels by their different molecular weights

(Curran and Morgan, 1986). In addition, more extensive

studies using 3T3 fibroblast cells demonstrated that dif-

ferent members of the IEGP family undergo different
 (Curran and Morgan, 1986). In addition, more extensive
studies using 3T3 fibroblast cells demonstrated that dif-
ferent members of the IEGP family undergo different
levels of post-translational modification when induced
by studies using 3T3 fibroblast cells demonstrated that different members of the IEGP family undergo different red
levels of post-translational modification when induced dep
by the same signal (Kovary and Bravo, 1991). After ferent members of the IEGP family undergo different
levels of post-translational modification when induced
by the same signal (Kovary and Bravo, 1991). After
stimulation with serum, Fos, Fos-B, c-Jun, Jun-B and
Jun-D prote levels of post-translational modification when induced
by the same signal (Kovary and Bravo, 1991). After
stimulation with serum, Fos, Fos-B, c-Jun, Jun-B and
Jun-D proteins are induced in 3T3 cells. Within several
hours o by the same signal (Kovary and Bravo, 1991). After 19
stimulation with serum, Fos, Fos-B, c-Jun, Jun-B and wh
Jun-D proteins are induced in 3T3 cells. Within several blows
hours of induction, Fos, Fos-B and Jun-B proteins stimulation with serum, Fos, Fos-B, c-Jun, Jun-B
Jun-D proteins are induced in 3T3 cells. Within se
hours of induction, Fos, Fos-B and Jun-B proteins
become significantly more phosphorylated than and Jun-D. In addition, po Jun-D proteins are induced in 3T3 cells. Within several blows of induction, Fos, Fos-B and Jun-B proteins have et become significantly more phosphorylated than c-Jun and Jun-D. In addition, post-translational phosphorylat nours of induction, Fos, Fos-B and Jun-B proteins have et al., 1988).

become significantly more phosphorylated than c-Jun Together, these early studies suggested that at least

and Jun-D. In addition, post-translational p and Jun-D. In addition, post-translational phosphorylation of the C-terminus of Fos has been shown to be necessary for autorepression of the c-fos promoter (Ofir et al., 1990). Because post-translational phosphorylation of IEGPs regulates both their stability—and therefore ha tion of the C-terminus of Fos has been shown to necessary for autorepression of the c-fos promoter (O) et al., 1990). Because post-translational phosphorylation of IEGPs regulates both their stability—and therefore half-li necessary for autorepression of the c-fos promoter (Ofir et al., 1990). Because post-translational phosphorylation of IEGPs regulates both their stability—and therefore half-life (Jackson et al., 1992)—and their transcript of IEGPs regulates both their stability—and therefore half-life (Jackson et al., 1992)—and their transcriptional activity (Pulverer et al., 1991; Franklin et al., 1992; Chou et al., 1992; Bannister et al., 1993), it repres of IEGPs regulates both their stability—and therefore half-life (Jackson et al., 1992)—and their transcriptional activity (Pulverer et al., 1991; Franklin et al., 1992; Chou et al., 1992; Bannister et al., 1993), it repres half-life (Jackson et
activity (Pulverer
Chou et al., 1992; l
an important cellu
trols IEG function.

The studies performed in PC12 cells were also signed.
The studies performed in PC12 cells were also signed.
Ant, because they were the first to show that IE AND GENE EXPRESSION 139
The studies performed in PC12 cells were also signif-
icant, because they were the first to show that IEGs
could be rapidly induced in nondividing cells by nonmi-AND GENE EXPRESSION
The studies performed in PC12 cells were also sign
icant, because they were the first to show that IE
could be rapidly induced in nondividing cells by non
togenic signals. They also suggested that c-fos The studies performed in PC12 cells were also significant, because they were the first to show that IEGs could be rapidly induced in nondividing cells by nonmitogenic signals. They also suggested that c-*fos* might play a could be rapidly induced in nondividing cells by nonmitogenic signals. They also suggested that c -*fos* might play a general role in the signal transduction pathway could be rapidly induced in nondividing cells by nonr togenic signals. They also suggested that c-fos mighty a general role in the signal transduction pathword from receptor activation by first-messengers (be the neurotran togenic signals. They also suggested that c-fos might
play a general role in the signal transduction pathway
from receptor activation by first-messengers (be they
neurotransmitter molecules or growth factors), to appro-
pr play a general role in the signal transduction pathway
from receptor activation by first-messengers (be they
neurotransmitter molecules or growth factors), to appro-
priate gene responses. Indeed, for neurobiologists, they from receptor activation by first-messengers (be they neurotransmitter molecules or growth factors), to appropriate gene responses. Indeed, for neurobiologists, they also raised the possibility that c -*fos* and other IE method ansimider
priate gene responds also raised the p
might be induced
function in vivo. also raised the possibility that c-fos and other IEGs
might be induced during the course of normal neuronal
function in vivo.
E. Multiple Second-Messenger Pathways Induce
Immediate-early Gene Expression by Acting on Dis

Immediate-early Gene Expression by Acting on Distinct E. Multiple Second-Messenger Pathways Induce Multiple Second-Messenger Pathways Induce
umediate-early Gene Expression by Acting on Distinct
pstream Regulatory Elements
The previous two sections have demonstrated that
G induction occurs in cultured (3T3 fibroblasts or

E. Multiple Second-Messenger Pathways Induce

Immediate-early Gene Expression by Acting on Distinct

Upstream Regulatory Elements

The previous two sections have demonstrated that

IEG induction occurs in cultured (3T3 fib Immeatate-earty Gene Expression by Acting on Distin

Upstream Regulatory Elements

The previous two sections have demonstrated the

IEG induction occurs in cultured (3T3 fibroblasts

PC12) cells in response to growth facto The previous two sections have demonstrat
TEG induction occurs in cultured (3T3 fibroblered)
PC12) cells in response to growth factors and
transmitters. The earliest example of neurotrans
mediated induction of c-fos involv The previous two sections have demonstrated that
IEG induction occurs in cultured (3T3 fibroblasts or
PC12) cells in response to growth factors and neuro-
transmitters. The earliest example of neurotransmitter-
mediated in IEG induction occurs in cultured $(3T3$ fibroblasts o PC12) cells in response to growth factors and neuro transmitters. The earliest example of neurotransmitter mediated induction of c -*fos* involved the opening o VSCCs PC12) cells in response to growth factors and neuro-
transmitters. The earliest example of neurotransmitter-
mediated induction of c-*fos* involved the opening of
VSCCs after membrane depolarisation induced by nico-
tinic mediated induction of c-fos involved the opening of VSCCs after membrane depolarisation induced by nicotinic receptor activation in PC12 cells (Greenberg et al., 1986). The resulting increase in intracellular Ca^{2+} was mediated induction of c-*fos* involved the opening of VSCCs after membrane depolarisation induced by nicotinic receptor activation in PC12 cells (Greenberg et al., 1986). The resulting increase in intracellular Ca²⁺ was VSCCs after membrane depolarisation induced by nicotinic receptor activation in PC12 cells (Greenberg et al., 1986). The resulting increase in intracellular Ca^{2+} was believed to lead to the increase in c-*fos* expressi tinic receptor activation in PC12 cells (Greenberg et al., 1986). The resulting increase in intracellular Ca^{2+} was believed to lead to the increase in c-*fos* expression. Increased intracellular Ca^{2+} produced by oth 1500). The resulting increase in intracellular Ca² was
believed to lead to the increase in c-fos expression. In-
creased intracellular Ca²⁺ produced by other methods
also resulted in c-fos expression, suggesting that also resulted in c-fos expression, suggesting that in-
creases in the concentration of intracellular Ca^{2+} leads
to the activation of cellular mechanisms that then reg-
ulate the expression of IEGs (Morgan and Curran, 1 also resulted in c-fos expression, suggesting that i
creases in the concentration of intracellular Ca^{2+} lea
to the activation of cellular mechanisms that then re
ulate the expression of IEGs (Morgan and Curran, 198
Cur creases in the concentration of intracellular Ca^{2+} leads
to the activation of cellular mechanisms that then reg-
ulate the expression of IEGs (Morgan and Curran, 1986;
Curran and Morgan, 1986). Activation of Ca^{2+} -pe to the activation of cellular mechanisms that then regulate the expression of IEGs (Morgan and Curran, 1986; Curran and Morgan, 1986). Activation of Ca^{2+} -perme-
able NMDA glutamate receptors in cultured cerebellar gran ulate the expression of Curran and Morgan, 1
able NMDA glutamate
granule cells also resul
(Szekely et al., 1987).
In contrast, growth f urran and Morgan, 1986). Activation of Ca²⁺-perme-
le NMDA glutamate receptors in cultured cerebellar
anule cells also resulted in increased c-*fos* expression
zekely et al., 1987).
In contrast, growth factor-mediated in The previous two sections have demonstrated that
IEG induction occurs in cultured (3T3 fibroblasts or
PC12) cells in response to growth factors and neuro-
transmitter-
transmitters. The earliest example of neuro-transmitt

able NMDA glutamate receptors in cultured cerebellar
granule cells also resulted in increased c-*fos* expression
(Szekely et al., 1987).
In contrast, growth factor-mediated induction of c-*fos*
gene expression in PC12 cell granule cells also resulted in increased c-fos expres

(Szekely et al., 1987).

In contrast, growth factor-mediated induction of egene expression in PC12 cells, i.e., NGF (Morgan

Curran, 1986), does not require the entry (Szekely et al., 1987).

In contrast, growth factor-mediated induction of c-

gene expression in PC12 cells, i.e., NGF (Morgan a

Curran, 1986), does not require the entry of extracel

lar Ca²⁺ ions. The pathway from gr In contrast, growth factor-mediated induction of c-fos
gene expression in PC12 cells, i.e., NGF (Morgan and
Curran, 1986), does not require the entry of extracellu-
lar Ca²⁺ ions. The pathway from growth factor activa-
 gene expression in PC12 cells, i.e., NGF (Morgan and Curran, 1986), does not require the entry of extracellular Ca^{2+} ions. The pathway from growth factor activation of its receptor to c -*fos* induction seem, in part, lar Ca^{2+} ions. The pathway from growth factor activation of its receptor to c -*fos* induction seem, in part, to involve PKC (protein kinase C) activation, inasmuch as the induction of c -*fos* in both 3T3 cells and lar Ca^{2+} ions. The pathway from growth factor activation of its receptor to c-fos induction seem, in part, to involve PKC (protein kinase C) activation, inasmuch as the induction of c-fos in both 3T3 cells and adipocyt tion of its receptor to c-fos induction seem, in part, t
involve PKC (protein kinase C) activation, inasmuch a
the induction of c-fos in both 3T3 cells and adipocytes i
reduced by phorbol-ester pretreatment of cells that c involve PKC (protein kinase C) activation, inasmuch
the induction of c-fos in both 3T3 cells and adipocytes
reduced by phorbol-ester pretreatment of cells that c
deplete cellular PKC activity (Stumpo and Blackshee
1986). T reduced by phorbol-ester pretreatment of cells that can
deplete cellular PKC activity (Stumpo and Blackshear,
1986). The protein kinase inhibitor, 2-aminopurine,
which has unknown specificity, has also been shown to
block deplete cellula
1986). The p
which has unl
block c-fos ind
et al., 1988). Together, th 86). The protein kinase inhibitor, 2-aminopurine, hich has unknown specificity, has also been shown to ock c-fos induction in 3T3 cells induced by serum (Zinn al., 1988). Together, these early studies suggested that at lea

which has unknown specificity, has also been shown to
block c-fos induction in 3T3 cells induced by serum (Zinn
et al., 1988).
Together, these early studies suggested that at least
two significantly different signalling pa block c-*fos* induction in 3T3 cells induced by serum (Zinn et al., 1988).
Together, these early studies suggested that at least two significantly different signalling pathways activate c-*fos* expression, one involving th et al., 1988). Together, these early studies suggested that at least two significantly different signalling pathways activate c -*fos* expression, one involving the activation of the inositol-phosphate-PKC pathway, the o Together, these early studies suggested that at least
two significantly different signalling pathways activate
c-fos expression, one involving the activation of the in-
ositol-phosphate-PKC pathway, the other involving an *i* o significantly different signalling pathways activate fos expression, one involving the activation of the initial-phosphate-PKC pathway, the other involving an crease in intracellular Ca²⁺ ions.
1. The serum-respon

c-jos expression, one involving the activation of the in-
ositol-phosphate-PKC pathway, the other involving an
increase in intracellular Ca^{2+} ions.
1. The serum-response element. Several regulatory re-
gions located in increase in intracellular Ca²⁺ ions.

1. The serum-response element. Several regulatory regions located in the 5' untranslated region of c-fos have

been demonstrated to play a role in controlling the in-

duction of it 1. The serum-response element. Several regulatory regions located in the 5' untranslated region of c-fos have been demonstrated to play a role in controlling the induction of its expression. Using deletion analysis of upst gions located in the 5' untranslated region of c-*fos* have
been demonstrated to play a role in controlling the in-
duction of its expression. Using deletion analysis of up-
stream regulatory regions of the c-*fos* gene, a

FREE SAND 140

rum, growth factors, and PKC-activators (phorbol 12-

myristate 13-acetate) in 3T3 cells. This "promotor" was in 140 HUGHES AND I
myristate 13-acetate) in 3T3 cells. This "promotor" was intermed the SRE (Treisman, 1985). HUGHES A

rum, growth factors, and PKC-activators (phorbol 12

myristate 13-acetate) in 3T3 cells. This "promotor" wa

termed the SRE (Treisman, 1985).

The SRE responds to both PKC-dependent and inde

pendent signals (Gil

rum, growth factors, and PKC-activators (phorbol 12-
myristate 13-acetate) in 3T3 cells. This "promotor" was
itermed the SRE (Treisman, 1985).
The SRE responds to both PKC-dependent and inde-
pendent signals (Gilman, 1988) myristate 13-acetate) in 3T3 cells. This "promotor" was
termed the SRE (Treisman, 1985).
The SRE responds to both PKC-dependent and inde-
pendent signals (Gilman, 1988). The SRE has previously
been identified as the dyad s termed the SRE (Treisman, 1985). a
The SRE responds to both PKC-dependent and inde-
pendent signals (Gilman, 1988). The SRE has previously M
been identified as the dyad symmetry element, is cen-
tered at -308, and is appr The SRE responds to both PKC-dependent and inde-
pendent signals (Gilman, 1988). The SRE has previously M
been identified as the dyad symmetry element, is cen-
tered at -308, and is approximately located between an
nucleo been identified as the dyad symmetry element, is centered at -308, and is approximately located between nucleotides -332 and -277 relative to the 5' cap site (Treisman, 1985, 1986; Sheng et al., 1988). In addition, a SRE-2 tered at -308, and is approximately located between
nucleotides -332 and -277 relative to the 5' cap site
(Treisman, 1985, 1986; Sheng et al., 1988). In addition,
a SRE-2 sequence can be found adjacent to the approx-
imat tered at -308, and is approximately located between
nucleotides -332 and -277 relative to the 5' cap site
(Treisman, 1985, 1986; Sheng et al., 1988). In addition,
a SRE-2 sequence can be found adjacent to the approx-
imate nucleotides -332 and -277 relative to the 5 cap site mes
(Treisman, 1985, 1986; Sheng et al., 1988). In addition, path
a SRE-2 sequence can be found adjacent to the approx-
imately 20 SRE base-pairs *downstream*. It resemb (Treisman, 1965, 1960, Sheng et al., 1966). In addition,
a SRE-2 sequence can be found adjacent to the approx-
imately 20 SRE base-pairs *dounstream*. It resembles
sequences seen in the metallothioneine and HSP70
genes tha nately 20 SRE base-pairs *downstream*. It resembles
quences seen in the metallothioneine and HSP70
nes that are serum-responsive and consists of several
quence repeats.
It has been shown that, rather than performing syn-
g

sequences seen in the metanothoneme and HSP70 Figenes that are serum-responsive and consists of several bisequence repeats. N
sequence repeats. N
another, and SRE-2 binds its own TFs (Visvader et al., m
1988). Less is know sequence repeats.

It has been shown that, rather than performing syn-

ergistically, the two regions act independently of one

another, and SRE-2 binds its own TFs (Visvader et al.,

1988). Less is known about the SRE-2 t ergistically, the two regions act independently of one Zifi
another, and SRE-2 binds its own TFs (Visvader et al., ma
1988). Less is known about the SRE-2 than the SRE. pho
Another binding site for a growth factor-inducib another, and SRE-2 binds its own TFs (Visvader et al., 1988). Less is known about the SRE-2 than the SRE.
Another binding site for a growth factor-inducible protein complex of unknown nature and function has also been desc 1988). Less is known about the SRE-2 than the SRE.
Another binding site for a growth factor-inducible pro-
tein complex of unknown nature and function has also
been described; it is located approximately 40 base-pairs
up Another binding site for a growth factor-induction protein complex of unknown nature and function has also the been described; it is located approximately 40 base-pairs act *upstream* of the SRE and is called the SCM (Hay been described; it is located approximately 40 base-pairs *upstream* of the SRE and is called the SCM (Hayes et al., 1987). The sequence motif $CC[AT]_6GG$, also known as a CArG box, can be found at the centre of the SRE.
Th upstream of the SRE and is called the SCM (Hayes et al., stimulation of the cell by growth factors are still not fully 1987). The sequence motif $CC[AT]_6$ GG, also known as a understood (Sassone-Corsi and Verma, 1987). For

upstream of the SRE and is called the SCM (Hayes et a
1987). The sequence motif CC/ATJ_6GG , also known as
CArG box, can be found at the centre of the SRE.
The SRE has been shown to bind a protein termed t
SRF (Treisman, 19 1967). The sequence moth CC(AT_{16} CC, also known as a under
CArG box, can be found at the centre of the SRE. ple, it
The SRE has been shown to bind a protein termed the
SRF (Treisman, 1987; Norman et al., 1988). SRE muta Ine SKE has been shown to bind a protein termed the SRF (Treisman, 1987; Norman et al., 1988). SRE mut
tions that block SRF binding, or depletion of SRF fro
cell nuclei after antibody microinjection, block the is
sponse of such that block SRF binding, or depletion of SRF from
cell nuclei after antibody microinjection, block the re-
sponse of the c-fos SRE to growth factor stimulation,
suggesting that SRF binding is important for SRE ac-
tivi cell nuclei after antibody microinjection, block the response of the c-fos SRE to growth factor stimulation, suggesting that SRF binding is important for SRE activity (Triesman, 1992). Il nuclei after antibody microinjection, block the re-
onse of the c-*fos* SRE to growth factor stimulation,
ggesting that SRF binding is important for SRE ac-
rity (Triesman, 1992).
The SRF is a 67-kD nuclear polypeptide

sponse of the c-*ros* SRE to growth factor stimulation, c-*r*
suggesting that SRF binding is important for SRE ac-
tivity (Triesman, 1992). ac
The SRF is a 67-kD nuclear polypeptide that is ex-
pressed in most cells but wh suggesting that SKF binding is important for SKE activity (Triesman, 1992).

The SRF is a 67-kD nuclear polypeptide that is ex-

pressed in most cells but whose transcription is also the

transiently increased after serum pressed in most cells but whose transcription is also
transiently increased after serum stimulation (Norman
et al., 1988). The SRF amino-terminal region contains a
conserved casein kinase II phosphorylation consensus
that pressed in most cens but whose transcription is a
transiently increased after serum stimulation (Norr
et al., 1988). The SRF amino-terminal region contain
conserved casein kinase II phosphorylation consen
that is phosphory mately increased after serum sumulation (Norman see
et al., 1988). The SRF amino-terminal region contains a
conserved casein kinase II phosphorylation consensus spot
that is phosphorylated in vivo, causing an approxi-
mate conserved casem Kinase II phosphorylation consensus
that is phosphorylated in vivo, causing an approxi-
mately three-fold increase in the DNA binding affinity of
the SRF for the SRE (Janknecht et al., 1992). The SRF
binds mately three-fold increase in the DNA binding affinity of
the SRF for the SRE (Janknecht et al., 1992). The SRF
binds to the SRE as a dimer (Norman et al., 1988),
probably in association with several other proteins, in-
cl mately three-fold increase in the DNA binding affinity of another regulatory element located at nucleotide -60 the SRF for the SRE (Janknecht et al., 1992). The SRF relative to the 5' cap site has been identified. Named t the SRF for the SRE (Janknecht et al., 1992). The SRF is binds to the SRE as a dimer (Norman et al., 1988), (probably in association with several other proteins, including a 62-kD protein p62/direct binding factor (Ryan is binds to the SRE as a dimer (Norman et al., 1988), Cal
probably in association with several other proteins, in-
cluding a 62-kD protein p62/direct binding factor (Ryan ing
et al., 1989) and p62/TCF (Shaw et al., 1989; Herr probably in association with several other proteins, in-
cluding a 62-kD protein p62/direct binding factor (Ryan
et al., 1989) and p62/TCF (Shaw et al., 1989; Herrera et cell
al., 1989). p62/TCF only binds to the SRE as pa cluding a 62-kD protein p62/direct binding factor (Ryan ing et al., 1989) and p62/TCF (Shaw et al., 1989; Herrera et cel al., 1989). p62/TCF only binds to the SRE as part of a me complex with the SRF (Shaw et al., 1989; G al., 1989). p62/TCF only binds to the SRE as part of a complex with the SRF (Shaw et al., 1989; Graham and Gilman, 1991; Treisman, 1992). The p62/TCF may be composed of one or other of the two binding proteins Elk-1 and SA all, 1989). $\frac{1}{2}$ Po $\frac{2}{1}$ Cr only binds to the SKE as part of a complex with the SRF (Shaw et al., 1989; Graham and Gilman, 1991; Treisman, 1992). The p62/TCF may be composed of one or other of the two binding pro complex with the SKF (Shaw et al., 1969; Graham and Gilman, 1991; Treisman, 1992). The p62/TCF may be composed of one or other of the two binding proteins Telk-1 and SAP-1, inasmuch as both of these proteins chave DNA bind Ginnan, 1991; Treisman, 1992). The pozition may
composed of one or other of the two binding protei
Elk-1 and SAP-1, inasmuch as both of these protei
have DNA binding properties identical to the p62/T
(Hipskind et al., 1991 composed of one of other of the two binding proteins

Elk-1 and SAP-1, inasmuch as both of these proteins ch

have DNA binding properties identical to the p62/TCF st

(Hipskind et al., 1991; Dalton and Treisman, 1992). Th

have DNA binding properties identical to the p62/TCF s

(Hipskind et al., 1991; Dalton and Treisman, 1992). T

Mutagenesis studies suggest that the p62/TCF may

have a role in serum stimulation of the c-fos SRE. In-

deed, (Hipskind et al., 1991; Dalton and Treisman, 1993
Mutagenesis studies suggest that the p62/TCF
have a role in serum stimulation of the c-fos SRI
deed, formation of the ternary complex is necessa
PKC-dependent—but not PKC-Mutagenesis studies suggest that the p62/TCF may
have a role in serum stimulation of the c-fos SRE. In-
deed, formation of the ternary complex is necessary for
PKC-dependent—but not PKC-independent—signals
acting through mave a role in serum sumulation of the c-*jos* SKE. If
deed, formation of the ternary complex is necessary for
PKC-dependent—but not PKC-independent—signa
acting through the SRE. These results suggest tha
PKC-independent s deed, formation of the ternary complex is necessary for

PKC-dependent—but not PKC-independent—signals ion

acting through the SRE. These results suggest that et

PKC-independent signals do not require p62/TCF bind-

ing t

DRAGUNOW
act alone or with accessory proteins to respond to PK
independent signals (Graham and Gilman, 1991). I DRAGUNOW
act alone or with accessory proteins to respond to PKC-
independent signals (Graham and Gilman, 1991). In
addition, the p62/TCF has been shown to be phosphor-DRAGUNOW
act alone or with accessory proteins to respond to P
independent signals (Graham and Gilman, 1991)
addition, the p62/TCF has been shown to be phosp
ylated by MAP kinase. Phosphorylation of p62/TCF act alone or with accessory proteins to respond to PKC-
independent signals (Graham and Gilman, 1991). In
addition, the p62/TCF has been shown to be phosphor-
ylated by MAP kinase. Phosphorylation of p62/TCF by
MAP kinase act alone or with accessory proteins to respond to PKC-
independent signals (Graham and Gilman, 1991). In
addition, the p62/TCF has been shown to be phosphor-
ylated by MAP kinase. Phosphorylation of p62/TCF by
MAP kinase independent signals (Graham and Gilman, 1991). In
addition, the p62/TCF has been shown to be phosphor-
ylated by MAP kinase. Phosphorylation of p62/TCF by
MAP kinase results in enhanced TCF about the SRE
(Gille et al., 199 addition, the p62/TCF has been shown to be phosph
ylated by MAP kinase. Phosphorylation of p62/TCF
MAP kinase results in enhanced TCF about the Sl
(Gille et al., 1992). Therefore p62/TCF may be viewed
an adapter that allow ylated by MAF Kinase. Friosphorylation of poz/1C.
MAP kinase results in enhanced TCF about the
(Gille et al., 1992). Therefore p62/TCF may be viewe
an adapter that allows SRF to respond to other sec
messenger pathways (PKC (Gille et al., 1992). Therefore $p62/TCF$ may be viewed as
an adapter that allows SRF to respond to other second-
messenger pathways (PKC and MAP kinase-dependent
pathways), (Graham and Gilman, 1991).

Other proteins that bind to the SRE include direct an adapter that anows SKF to respond to other second-
messenger pathways (PKC and MAP kinase-dependent
pathways), (Graham and Gilman, 1991).
Other proteins that bind to the SRE include direct
binding factor/MAPF1, SRE-ZBP, pathways), (Graham and Gilman, 1991).

Other proteins that bind to the SRE include direct

binding factor/MAPF1, SRE-ZBP, NF-IL-6, E12 and

Phoxl. At this stage however, the significance of their

binding is unknown, altho Other proteins that bind to the SRE include direct
binding factor/MAPF1, SRE-ZBP, NF-IL-6, E12 and
Phoxl. At this stage however, the significance of their
binding is unknown, although one of these proteins,
NF-IL-6, may a Phoxl. At this stage however, the significance of the binding is unknown, although one of these prote NF-IL-6, may allow regulation of the SRE by cAMP at thus be an adapter in the mold of p62/TCF (Metz a Ziff, 1991), where binding is unknown, although one of these proteins,
NF-IL-6, may allow regulation of the SRE by cAMP and
thus be an adapter in the mold of p62/TCF (Metz and
Ziff, 1991), whereas the presence of the Phoxl homeodo-
main prot phosphorylation by casein kinase II.

Although the an adapter in the mold of p62/TCF (Metz an

Ziff, 1991), whereas the presence of the Phoxl homeodo

main protein has similar effects on SRF DNA binding a

phosphorylation

Phoxl. At this stage however, the significance of their
binding is unknown, although one of these proteins,
 $\text{NIF}\cdot \text{II}\cdot \mathbf{6}$, may allow regulation of the SRE by cAMP and
thus be an adapter in the mold of p62/TCF (Met Ziff, 1991), whereas the presence of the Phoxl homeodomain protein has similar effects on SRF DNA binding as phosphorylation by casein kinase II.
Although the c -*fos* SRE has received much attention, the series of bioch main protein has similar effects on SRF DNA binding as
phosphorylation by casein kinase II.
Although the c-fos SRE has received much attention,
the series of biochemical events that are responsible for
activation of c-fos phosphorylation by casem Kinase 11.
Although the c-fos SRE has received much attention,
the series of biochemical events that are responsible for
activation of c-fos transcription through the SRE after
stimulation of the c Atthough the c- $76s$ SRE has received much attention,
the series of biochemical events that are responsible for
activation of c- f os transcription through the SRE after
stimulation of the cell by growth factors are still activation of c-*fos* transcription through the SRE after
stimulation of the cell by growth factors are still not fully
understood (Sassone-Corsi and Verma, 1987). For exam-
ple, it has been shown that the SRF is bound to sumulation of the cell by growth factors are still not fully
understood (Sassone-Corsi and Verma, 1987). For exam-
ple, it has been shown that the SRF is bound to the SRE
before, during, and after growth factor stimulation understood (Sassone-Corsi and Verma, 1987). For example, it has been shown that the SRF is bound to the SRE
before, during, and after growth factor stimulation of
cells (Herrera et al., 1989). Therefore it is not known
wh ple, it has been shown that the SRF is bound to the SRE
before, during, and after growth factor stimulation of
cells (Herrera et al., 1989). Therefore it is not known
whether in the simplest case DNA binding of the SRF to
 cells (Herrera et al., 1989). Therefore it is not known
whether in the simplest case DNA binding of the SRF to
the SRE in conjunction with other proteins activates
c-fos transcription or whether post-translational modifi-
 cells (Herrera et al., 1989). Therefore it is not know
whether in the simplest case DNA binding of the SRF
the SRE in conjunction with other proteins activat
c-fos transcription or whether post-translational modi
cation of whether in the simplest case DNA binding of the SRF to
the SRE in conjunction with other proteins activates
c-fos transcription or whether post-translational modifi-
cation of the SRF and binding of other growth factor-
ac the SKE in conjunction with other proteins activates
c-fos transcription or whether post-translational modifi-
cation of the SRF and binding of other growth factor-
activated proteins, such as p62/TCF, Phoxl or NF-IL-6,
t cation of the SKF and binding of other
activated proteins, such as $p62/TCF$, Ph
to the complex is required to increase
the c-fos gene. Within the next few years,
see these mechanisms further elucidate
2. The calcium/cyclic *2. The calcium Icyclic-adenosine monophosphate*
 2. The calcium/cyclic-adenosine monophosphate

the c-*fos* gene. Within the hext lew years, we are interpreted see these mechanisms further elucidated.

2. The calcium/cyclic-adenosine monophosphate response element. Although several second-messenger signals seem to a 2. The calcium/cyclic-adenosine monophosphate response element. Although several second-messenger signals seem to activate c-fos transcription via the SRE, another regulatory element located at nucleotide -60 relative to sponse element. Although several second-messenger signals seem to activate c -*fos* transcription via the SRE, another regulatory element located at nucleotide -60 relative to the 5' cap site has been identified. Named t nals seem to activate c-fos transcription via the SI
another regulatory element located at nucleotide
relative to the 5' cap site has been identified. Named
CaRE/CRE, this regulatory DNA region functions
both a calcium- an indular regulatory element located at nucleotide -
relative to the 5' cap site has been identified. Named to
CaRE/CRE, this regulatory DNA region functions
both a calcium- and cAMP-responsive element, increase
ing transcri CARE/CRE, this regulatory DNA region functions as
both a calcium- and cAMP-responsive element, increas-
ing transcription of the c-*fos* gene in response to intra-
cellular increases in the levels of either of these second 1988). g transcription of the c-*fos* gene in response to intra-
llular increases in the levels of either of these second-
essenger molecules (Fisch et al., 1987; Sheng et al.,
988).
The CaRE/CRE contains the consensus sequence
G

cellular increases in the levels of either of these second-
messenger molecules (Fisch et al., 1987; Sheng et al.,
1988).
The CaRE/CRE contains the consensus sequence
 $TGACGTTT$, which is very similar to the previously
charact messenger molecules (Fisch et al., 1987; Sheng et al., 1988).
The CaRE/CRE contains the consensus sequence $TGACGTTT$, which is very similar to the previously characterised CRE promotor sequence found in the up-
stream regions The CaRE/CRE contains the consensus sequence *TGACGTTT*, which is very similar to the previously characterised CRE promotor sequence found in the upstream regions of cAMP-inducible genes (*TGACGTCA*). The CaRE/CRE does not FOACOTTT, which is very similar to the previously
characterised CRE promotor sequence found in the up-
stream regions of cAMP-inducible genes (*TGACGTCA*).
The CaRE/CRE does not confer inducibility of the c-fos
gene to gr characterised CRE promotor sequence found in the up-
stream regions of cAMP-inducible genes (*TGACGTCA*).
The CaRE/CRE does not confer inducibility of the c-fos
gene to growth factors or phorbol esters that activate
PKC-d stream regions of cAMP-inducible genes (*TGACGTCA*).
The CaRE/CRE does not confer inducibility of the c-fos
gene to growth factors or phorbol esters that activate
PKC-dependent signalling pathways (Sheng et al.,
1990). Ce gene to growth factors or phorbol esters that activate PKC-dependent signalling pathways (Sheng et al., 1990). Central to activation of the CaRE/CRE by Ca^{2+} ions or cAMP is the DNA binding TF CREB (Montminy et al., 199 pressed, post-translationally activated TF was first PRC-aependent signaling pathways (Sheng et al., 1990). Central to activation of the CaRE/CRE by Ca^{2+} ions or cAMP is the DNA binding TF CREB (Montminy et al., 1990; Sheng et al., 1991). This constitutively expressed, p 1990). Central to activation of the Carte/Crie by Cations or cAMP is the DNA binding TF CREB (Montminy et al., 1990; Sheng et al., 1991). This constitutively expressed, post-translationally activated TF was first identifie

PHARMACOLOGICAL REVIEW

IMMEDIATE-EARLY GENES
tempted to characterise the DNA binding factors that
interacted with the CRE of cAMP-inducible genes IMMEDIATE-EARLY GENES A
tempted to characterise the DNA binding factors that
interacted with the CRE of cAMP-inducible genes
(Montminy and Bilezikjiun, 1987). Treatment of cells IMMEDIATE-EARLY GENES A

interacted with the CRE of cAMP-inducible genes

(Montminy and Bilezikjiun, 1987). Treatment of cells

with the drug forskolin, which increases intracellular

Ievels of cAMP, increased the transcri lempted to characterise the DNA binding factors that
interacted with the CRE of cAMP-inducible genes
(Montminy and Bilezikjiun, 1987). Treatment of cells
with the drug forskolin, which increases intracellular
revels of cAM interacted with the CRE of cAMP-inducible genes susce
(Montminy and Bilezikjiun, 1987). Treatment of cells toma
with the drug forskolin, which increases intracellular regul
levels of cAMP, increased the transcriptional eff with the drug faith with the drug faith levels of cAMP, if
the CREB proteins and affected.
CREB is a 43th the drug forskolin, which increases intracellular
vels of cAMP, increased the transcriptional efficacy of
e CREB protein, although the DNA binding of CREB
as not affected.
CREB is a 43-kD protein, 341 amino acids in len

levels of cAMP, increased the transcriptional efficacy of 1
the CREB protein, although the DNA binding of CREB 1
was not affected.
CREB is a 43-kD protein, 341 amino acids in length.
CREB has been purified using cyanogen the CREB protein, although the DNA binding of CREB locations and affected. The constant of the CREB is a 43-kD protein, 341 amino acids in length. Kb CREB has been purified using cyanogen bromide $\left[\ldots$ TGACGTCA... $\right]$ was not affected. get CREB is a 43-kD protein, 341 amino acids in length. know CREB has been purified using cyanogen bromide [.. TGACGTCA..]_n-activated silica beads (Montminy and Bilezikjiun, 1987; Yamamoto et al., 1988 CREB is a 43-kD protein, 341 amino acids in lengt
CREB has been purified using cyanogen bromic
[.. TGACGTCA..]_n-activated silica beads (Montminy ar
Bilezikjiun, 1987; Yamamoto et al., 1988). Cloning
CREB suggests that m CREB has been purified using cyanogen bromide
[.. TGACGTCA..]_n-activated silica beads (Montminy and F. Reg.
Bilezikjiun, 1987; Yamamoto et al., 1988). Cloning of Gene F
CREB suggests that multiple CREB cDNAs exist (Hoef [.. TGACGTCA..]_n-activated silica beads (Montminy and Bilezikjiun, 1987; Yamamoto et al., 1988). Cloning of CREB suggests that multiple CREB cDNAs exist (Hoeffer et al., 1988; Gonzalez and Montminy, 1989). From *astruct* Bilezikjiun, 1987; Yamamoto et al., 1988). Cloning of CREB suggests that multiple CREB cDNAs exist (Hoef-
fler et al., 1988; Gonzalez and Montminy, 1989). From actructural analysis of the amino-acid sequence, it was bo
de CREB suggests that multiple CREB cDNAs exist (Hoef-
fler et al., 1988; Gonzalez and Montminy, 1989). From
structural analysis of the amino-acid sequence, it was
determined that three functional domains exist within
CREB. fler et al., 1988; Gonzalez and Montminy, 1989). From *act* structural analysis of the amino-acid sequence, it was *boi* determined that three functional domains exist within at CREB. The three domains are (a) the transstructural analysis of the amino-acid sequence, it was bedetermined that three functional domains exist within at CREB. The three domains are (a) the trans-activation the region, which contains sites for phosphorylation, determined that three functional domains exist within CREB. The three domains are (a) the trans-activation region, which contains sites for phosphorylation, (b) the DNA binding domain, which consists primarily of basic a CREB. The three domains are (a) the trans-activation the region, which contains sites for phosphorylation, (b) the IDNA binding domain, which consists primarily of basic samino acids, and (c) the leucine-zipper dimeris DNA binding domain, which consists primarily of basic amino acids, and (c) the leucine-zipper dimerisation domain (Montminy et al., 1990). The CREB protein binds to the CaRE/CRE either as a monomer or as a homo-dimer, ho DNA binding domain, which consists primarily of basic
amino acids, and (c) the leucine-zipper dimerisation do-
main (Montminy et al., 1990). The CREB protein binds
to the CaRE/CRE either as a monomer or as a homo-
dimer, amino acids, and (c) the leucine-zipper dimerisation do-
main (Montminy et al., 1990). The CREB protein binds
to the CaRE/CRE either as a monomer or as a homo-
exa
dimer, however the affinity for DNA is significantly remain (Montminy et al., 1990)
to the CaRE/CRE either as a
dimer, however the affinity fa
duced in the monomer form. I
of its leucine-zipper domain.
The transcriptional ability the CaRE/CRE either as a monomer or as a homo-examer, however the affinity for DNA is significantly rescription
ced in the monomer form. Dimerisation occurs by way ing
its leucine-zipper domain.
The transcriptional ability

most all the monomer form. Dimerisation occurs by way ing the duced in the monomer form. Dimerisation occurs by way ing the of its leucine-zipper domain. The transcriptional ability of CREB is activated by prom phosphoryla The transcriptional ability of CREB is activated by
phosphorylation. Both PKA, which is activated by cAMP
binding (Gonzalez and Montminy, 1989), and CaM ki-
nases I and II (Sheng et al., 1991), which are activated
by Ca^{2 Ine transcriptional ability of CREB is activated by
phosphorylation. Both PKA, which is activated by cAMP
binding (Gonzalez and Montminy, 1989), and CaM ki-
nases I and II (Sheng et al., 1991), which are activated
by Ca²⁺ binding (Gonzalez and Montminy, 1989), and CaM kiprometers I and II (Sheng et al., 1991), which are activated the et by Ca^{2+} , phosphorylate CREB on the same Serine-133 gene residue that is located within the transactiv has also find in (sheng et al., 1991), which are activated the by Ca^{2+} , phosphorylate CREB on the same Serine-133 ger residue that is located within the transactivation do-
main. Potential phosphorylation sites on CREB by Ca²⁺, phosphorylate CREB on the same Serine-133
residue that is located within the transactivation do-
main. Potential phosphorylation sites on CREB for PKC
also exist within this domain. Phosphorylation results in
ac residue that is located within the transactivation do-
main. Potential phosphorylation sites on CREB for PKC
also exist within this domain. Phosphorylation results in DN
activation of CREB, which then leads to increased c main. Potential phosphorylation sites on CREB for PKC
also exist within this domain. Phosphorylation results in
activation of CREB, which then leads to increased c-*fos*
cexpression (Sheng et al., 1990). In this manner, b activation of CREB, which then leads to increased c -*fos* or
expression (Sheng et al., 1990). In this manner, both h
cAMP and Ca^{2+} second-messenger pathways converge a
synergistically within the cell to induce the ex expression (Sheng et al., 1990). In this manner, both cAMP and Ca^{2+} second-messenger pathways converge synergistically within the cell to induce the expression of c-fos (Sheng and Greenberg, 1990). In addition to the Ca pression (Sheng et al., 1990). In this manner, both had MP and Ca^{2+} second-messenger pathways converge allotlenergistically within the cell to induce the expression of 1987 os (Sheng and Greenberg, 1990). generation to

cAMP and Ca²⁺ second-messenger pathways converg
synergistically within the cell to induce the expression of
c-*fos* (Sheng and Greenberg, 1990).
In addition to the CaRE/CRE site with which CRE:
interacts, at least one o synergistically within the cell to induce the expression of c-*fos* (Sheng and Greenberg, 1990).
In addition to the CaRE/CRE site with which CREB interacts, at least one other Ca²⁺/cAMP-responsive element exists within t c-fos (Sheng and Greenberg, 1990).

In addition to the CaRE/CRE site with which CREB

interacts, at least one other $Ca^{2+}/cAMP$ -responsive ele-

ment exists within the *c*-fos promotor, because internal

mutations of the Ca In addition to the CaRE/CRE site with which CREB
interacts, at least one other $Ca^{2+}/cAMP$ -responsive ele-
ment exists within the c -*fos* promotor, because internal
mutations of the CaRE/CRE do not abolish calcium in-
duc ment exists within the c -*fos* promotor, because internal mutations of the CaRE/CRE do not abolish calcium inducibility of an otherwise intact c -*fos* gene (Sheng et al., 1990). Furthermore, it has been shown that a C ment exists within the c -*fos* promotor, because internal sumutations of the CaRE/CRE do not abolish calcium in-
ducibility of an otherwise intact c -*fos* gene (Sheng et al., co
1990). Furthermore, it has been shown t mutations of the Carte/Cree do not abous in carcium in-
ducibility of an otherwise intact c-fos gene (Sheng et al., c
1990). Furthermore, it has been shown that a CaRE/
CRE-like region exists upstream of the SRE. Located
a CRE-like region exists upstream of the SRE. Located I
approximately at nucleotide -350, the function of this c-for
region remains unknown (Sassone-Corsi et al., 1988b). the
Other gene regions that may be involved in certa

approximately at nucleotide -350, the function of this
region remains unknown (Sassone-Corsi et al., 1988b).
Other gene regions that may be involved in certain
aspects of the control of c-*fos* induction have also been
ide region remains unknown (Sassone-Corsi et al., 15660).
Other gene regions that may be involved in certain
aspects of the control of c-fos induction have also been
identified. One of these identified elements is the AP-1/
TR Other gene regions that may be involved in certain paspects of the control of c-fos induction have also been tidentified. One of these identified elements is the AP-1/ c TRE-like site that lies adjacent to the 3' side of aspects of the control of c -*fos* induction have also been the identified. One of these identified elements is the AP-1/ \overline{C} TRE-like site that lies adjacent to the 3' side of the SRE. are The fact that the presenc sometimed. One of these identified elements is the Ar-1 complete that the presence of this element is conserved identify many SREs in other genes suggests that it will have tional some functional role to play. Indeed, this The fact that the presence of this element is conserved id
by many SREs in other genes suggests that it will have ti
some functional role to play. Indeed, this site does seem site
to bind members of the AP-1 (Fos/Jun), CR by many SREs in other genes suggests that it will have some functional role to play. Indeed, this site does seen
to bind members of the AP-1 (Fos/Jun), CREB/ATF pro
tein family of TFs (Triesman, 1992). In addition to this
 some functional role to play. Indeed, this site does seem sites (Rauscher et al., 1988). The stable Fos and c-Jun
to bind members of the AP-1 (Fos/Jun), CREB/ATF procomplex can be reproduced in vitro (Sassone-Corsi et al.,

AND GENE EXPRESSION
shown to bind the protein-product of the retinoblastoma
susceptibility gene (RB-1). By binding to the retinoblas SAND GENE EXPRESSION
shown to bind the protein-product of the retinoblast
susceptibility gene (RB-1). By binding to the retino
toma-control element, this protein-product negat 141
shown to bind the protein-product of the retinoblastoma
susceptibility gene (RB-1). By binding to the retinoblas-
toma control element, this protein-product negatively
regulates the induction of c-*fos* by serum (Robbi shown to bind the protein-product of the retinoblastoma
susceptibility gene (RB-1). By binding to the retinoblas-
toma control element, this protein-product negatively
regulates the induction of c-*fos* by serum (Robbins e susceptibility gene (RB-1). By binding to the retinoblastoma control element, this protein-product negatively regulates the induction of c-*fos* by serum (Robbins et al., 1990). An estrogen-responsive element has also been toma control element, this protein-product negatively
regulates the induction of c-*fos* by serum (Robbins et al.,
1990). An estrogen-responsive element has also been
located to the untranslated 3'-flanking region of the c regulates the induction of c-*fos* by seru
1990). An estrogen-responsive eleme
located to the untranslated 3'-flanking
gene, 5 kb downstream from the c-*fos*
kb downstream of the poly(A) signal. *F. Regulation of Gene Expression by Immediate-early* Gene, 5 kb downstream from the c-fos promoter and 1 kb downstream of the poly(A) signal.
F. Regulation of Gene Expression by Immediate-early Gene Proteins *Gene, 5 kb down*
Kb downstream
F. Regulation of
Gene Proteins
1. Fos and c-

kb downstream of the poly(A) signal.
 F. Regulation of Gene Expression by Immediate-early
 Gene Proteins
 1. Fos and c-Jun and related proteins bind to the

activatorprotein-1 /TPA response element site in deoxyrib. Regulation of Gene Expression by Immediate-early
 bonucleic acid. C-Jun and related proteins bind to the
 activator protein-1/TPA response element site in deoxyri-
 bonucleic acid. Cellular proto-oncogenes encod Gene Proteins
1. Fos and c-Jun and related proteins bind to the
activator protein-1/TPA response element site in deoxyri-
bonucleic acid. Cellular proto-oncogenes encode proteins
at three major sites: the cell membrane, th 1. Fos and c-Jun and related proteins bind to the activator protein- $1/TPA$ response element site in deoxyribonucleic acid. Cellular proto-oncogenes encode proteins at three major sites: the cell membrane, the cytosol, and activator protein-1/TPA response element site in deoxyribonucleic acid. Cellular proto-oncogenes encode proteins
at three major sites: the cell membrane, the cytosol, and
the nucleus. Because of the nuclear localisation an bonactet acta. Centuar prow-oncogenes encode proteins
at three major sites: the cell membrane, the cytosol, and
the nucleus. Because of the nuclear localisation and
DNA binding ability of some proto-oncogenes, it was
sugge at three major sites. the cent membrane, the cytosol, and
the nucleus. Because of the nuclear localisation and
DNA binding ability of some proto-oncogenes, it was
suggested that they might act as DNA binding TFs to
directl suggested that they might act as DNA binding TFs to directly control gene expression. Early work that had been published indirectly supported this suggestion. For example, the possibility that Fos protein affected tran-sc directly control gene expression. Early work that had directly control gene expression. Early work that
been published indirectly supported this suggestion.
example, the possibility that Fos protein affected transcription was initially suggested by experiments rep
ing that a been published indirectly supported this suggestion. For
example, the possibility that Fos protein affected tran-
scription was initially suggested by experiments report-
ing that a v -fos expression vector stimulated tr example, the possibility that Fos protein affected transcription was initially suggested by experiments reporting that a *v*-*fos* expression vector stimulated transcription from a cotransfected mouse α_1 (III) collage scription was initially suggested by experiments reporting that a *v*-*fos* expression vector stimulated transcription from a cotransfected mouse α_1 (III) collagen gene promoter (Setoyama et al., 1986) and that the Fo ing that a *v*-*fos* expression vector stimulated transcription from a cotransfected mouse α_1 (III) collagen gene promoter (Setoyama et al., 1986) and that the Fos protein or a Fos-related antigen formed a complex wit tion from a cotransfected mouse α_1 (III) collagen gene
promoter (Setoyama et al., 1986) and that the Fos pro-
tein or a Fos-related antigen formed a complex with the
promoter region of the adipocyte-specific aP2 gene promoter (setoyama et al., 1560) and that the Fos pro-
tein or a Fos-related antigen formed a complex with the
promoter region of the adipocyte-specific aP2 gene (Dis
tel et al., 1987). Continued work with adipocyte aP2
ge bein or a ros-related antigen formed a complex with the
promoter region of the adipocyte-specific aP2 gene (Dis-
tel et al., 1987). Continued work with adipocyte aP2
gene promotor regions demonstrated that Fos-associated
p gene promotor regions demonstrated that Fos and Fos-associated proteins (the most abundant Fos-associated protein having a molecular weight of 39 kD) bound to a DNA-specific sequence that was identical to the previgene promotor regions demonstrated that ros and ros-
associated proteins (the most abundant Fos-associated
protein having a molecular weight of 39 kD) bound to a
DNA-specific sequence that was identical to the previ-
ously protein having a molecular weight of 39 kD) bound to a
DNA-specific sequence that was identical to the previ-
ously identified AP-1 site. The AP-1 site (or TRE site)
had been identified in the promoters of the human met-
a DINA-specific sequence that was identical to the previously identified AP-1 site. The AP-1 site (or TRE site) had been identified in the promoters of the human metallothioneine gene and simian virus 40 (Lee et al., 1987 busity identified AI-1 site. The AI-1 site (of Title site)
had been identified in the promoters of the human met-
allothioneine gene and simian virus 40 (Lee et al.,
1987a) and was involved in the activation of cellular
ge anotifionelle gene and similar virus 40 (Lee et al., 1987a) and was involved in the activation of cellular genes by the tumour promotor substance 2-tetrade-
canoyl-phorbol-13-acetate (Lee et al., 1987b; Angel et al., 1987) genes by the tumour promotor substance 2-tetrade-
canoyl-phorbol-13-acetate (Lee et al., 1987b; Angel et al.,
1987). The AP-1/TRE site contained the octomer consen-
sus sequence ATGACTCA and bound a DNA binding
factor desi canoyl-phorbol-13-acetate (Lee et al., 1987b; Angel et al., 1987). The AP-1/TRE site contained the octomer consensus sequence $ATGACTCA$ and bound a DNA binding factor designated AP-1. AP-1 was subsequently found to contain t 1987). The AF-DTRE site contained the ocsus sequence ATGACTCA and bound a factor designated AP-1. AP-1 was subsequentain the proto-oncogene homolog of the virus gene v-jun (Bohmann et al., 1987). It therefore seemed that t at three major sites: the cell membrane, the cytosol, and
the nucleus. Because of the nuclear localisation and
DNA binding ability of some proto-oncogenes, it was
suggested that they might act as DNA binding TFs to
direct

1990). Furthermore, it has been shown that a CaRE/ virus gene v-jun (Bohmann et al., 1987).
CRE-like region exists upstream of the SRE. Located It therefore seemed that the protein products of both
approximately at nucleo factor designated AP-1. AP-1 was subsequently found to
contain the proto-oncogene homolog of the avian tumour
virus gene v-jun (Bohmann et al., 1987).
It therefore seemed that the protein products of both
c-*fos* and c-jun contain the proto-oncogene homolog of the avian tumour
virus gene v-jun (Bohmann et al., 1987).
It therefore seemed that the protein products of both
c-fos and c-jun bound to the same DNA sequence. When
the 39-kD Fos-asso virus gene v-*jun* (Bohmann et al., 1987).
It therefore seemed that the protein products of both
c-*fos* and c-*jun* bound to the same DNA sequence. When
the 39-kD Fos-associated protein was identified as the
product of th It therefore seemed that the protein products of both
c-fos and c-jun bound to the same DNA sequence. When
the 39-kD Fos-associated protein was identified as the
product of the c-jun proto-oncogene, it became obvious
that the 39-kD Fos-associated protein was identified as the product of the c-*jun* proto-oncogene, it became obvious that the products of the two proto-oncogenes were *major* components of AP-1. Thus, it was postulated that Fos product of the $c-jun$ proto-oncogene, it became obvious
that the products of the two proto-oncogenes were *major*
components of AP-1. Thus, it was postulated that Fos
and c -Jun bound together forming a complex, previousl product of the c-jun proto-oncogene, it became obv
that the products of the two proto-oncogenes were m
components of AP-1. Thus, it was postulated that
and c-Jun bound together forming a complex, previo
identified as AP-1 that the products of the two proto-oncogenes were *major*
components of AP-1. Thus, it was postulated that Fos
and c-Jun bound together forming a complex, previously
identified as AP-1, which then associated with transcrip simplements of AF-1. Thus, it was posturated that Fos and c-Jun bound together forming a complex, previously identified as AP-1, which then associated with transcriptional control elements containing AP-1/TRE binding sites i988a). mai control elements containing AF-11 KE binding
les (Rauscher et al., 1988). The stable Fos and c-Jun
mplex can be reproduced in vitro (Sassone-Corsi et al.,
88a).
By binding to c-Jun, Fos directly modulates c-Jun
anscrip sites (Rauscher et al., 1988). The stable Fos and c-Jun
complex can be reproduced in vitro (Sassone-Corsi et al.,
1988a).
By binding to c-Jun, Fos directly modulates c-Jun
transcriptional ability by forming a heterodimer o

and c-Jun proteins (Kouzarides and Ziff, 1988). Although c-Jun proteins (Kouzarides and Ziff, 1988).

though c-Jun proteins can form homodimers (c-Jun

Jun) that bind to, and weakly transactivate, gene HUGHES ANI

and c-Jun proteins (Kouzarides and Ziff, 1988). Al-

though c-Jun proteins can form homodimers (c-Jun/c-

Jun) that bind to, and weakly transactivate, gene ex-

pression from AP-1/TRE sites, Fos proteins do not and c-Jun proteins (Kouzarides and Ziff, 1988). Al-
though c-Jun proteins can form homodimers (c-Jun/c-
Jun) that bind to, and weakly transactivate, gene ex-
pression from AP-1/TRE sites, Fos proteins do not form initiati
 and c-Jun proteins (Kouzarides and Ziff, 1988). Al-
though c-Jun proteins can form homodimers (c-Jun/c-
Jun) that bind to, and weakly transactivate, gene ex-
lat
pression from AP-1/TRE sites, Fos proteins do not form ini
h ship is the transactivate, gene expression from AP-1/TRE sites, Fos proteins do not form initial pression from AP-1/TRE sites, Fos proteins do not form initial homodimers and hence can not bind to the AP-1/TRE Altes to tra pression from AP-1/TRE sites, Fos proteins do not form
homodimers and hence can not bind to the AP-1/TRE
sites to transactivate gene expression. However, in a
Fos/c-Jun heterodimer, not only is the Fos protein able
to regu homodimers and hence can not bind to the sites to transactivate gene expression. However, hot only is the Fost to regulate gene transcription, but the transpotential of c-Jun is significantly increased.
2. The leucine zipp Fos/c-Jun heterodimer, not only is the Fos protein able
to regulate gene transcription, but the transactivating
potential of c-Jun is significantly increased.
2. The leucine zipper. Formation of the dimer is pos-
sible bec

conserved structural motif, or binding region, called the *2. The leucine zipper*. Formation of the dimer is possible because both Fos and c-Jun proteins contain a the conserved structural motif, or binding region, called 2. The leucine zipper. Formation of the dimer is possible because both Fos and c-Jun proteins contain a conserved structural motif, or binding region, called the "leucine zipper", which allows strong protein-protein intera sible because both Fos and c-Jun proteins contain a th
conserved structural motif, or binding region, called the
"leucine zipper", which allows strong protein-protein in-
teractions to occur (Kouzarides and Ziff, 1988, 198 conserved structural motif, or binding region, called the "leucine zipper", which allows strong protein-protein in-
teractions to occur (Kouzarides and Ziff, 1988, 1989). tei
The leucine-zipper structure is found within pr "leucine zipper", which allows strong protein-protein in-
teractions to occur (Kouzarides and Ziff, 1988, 1989). te
The leucine-zipper structure is found within proteins of
the b-zip family. TFs in this family include Myc teractions to occur (Kouzarides and Ziff, 1988, 1989).
The leucine-zipper structure is found within proteins of
the b-zip family. TFs in this family include Myc, the
yeast TFs GCN4, and yAP-1, CCAAT-enhancer binding
prote The leucine-zipper structure is found within proteins of
the b-zip family. TFs in this family include Myc, the
yeast TFs GCN4, and yAP-1, CCAAT-enhancer binding
protein, and CREB. The leucine zipper is an α -helical
dom the b-zip family. TFs in this family include Myc, the yeast TFs GCN4, and yAP-1, CCAAT-enhancer binding protein, and CREB. The leucine zipper is an α -helical domain in which four or five leucine residues occur at regul yeast TFs GCN4, and yAP-1, CCAAT-enhancer binding site and therefore represents a potential anti-oncogene
protein, and CREB. The leucine zipper is an α -helical (Auwerx and Sassone-Corsi, 1991; Auwerx and Sassone-
domai protein, and CREB. The leucine zipper is an α -helical domain in which four or five leucine residues occur at regular seven-residue intervals. These leucine residues locate on the same rotational position of the α -he domain in which four or five leucine residues occur at C
regular seven-residue intervals. These leucine residues is
locate on the same rotational position of the α -helix ce
because of this regular spacing and thus form regular seven-residue intervals. These leucine residues
locate on the same rotational position of the α -helix
because of this regular spacing and thus form a linear
crest of leucine residues that protrudes from the sid locate on the same rotational position of the α -helbecause of this regular spacing and thus form a line
crest of leucine residues that protrudes from the side
the protein helix. Proteins that have a leucine-zippe
domai because of this regular spacing and thus form a linear a b crest of leucine residues that protrudes from the side of site the protein helix. Proteins that have a leucine-zipper tion domain bind to each other because of hyd crest of leucine residues that protrudes from the side of sthe protein helix. Proteins that have a leucine-zipper domain bind to each other because of hydrophobic inter-
actions between the linear leucine crests of the two the protein helix. Proteins that have a leucine-zipper tion
domain bind to each other because of hydrophobic inter-
actions between the linear leucine crests of the two
molecules. Although substitution of one leucine resid domain bind to each other because of hydrophobic inter-
actions between the linear leucine crests of the two
molecules. Although substitution of one leucine residue
does not alter dimer formation, substitution of two
leuci actions between the linear leucine crests of the two numolecules. Although substitution of one leucine residue to
does not alter dimer formation, substitution of two tra
leucine residues will greatly reduce or entirely eli does not alter dimer formation, substitution of two trans-activation by Jun proteins (Masquilier and Sas-
leucine residues will greatly reduce or entirely eliminate sone-Corsi, 1992). Both CREB and CREM recognise both
form does not alter dimer formation, substitution of two
leucine residues will greatly reduce or entirely eliminate
formation of the Fos/c-Jun dimer. Although it has been
demonstrated that Fos and c-Jun interact through the
leu leucine residues will greatly reduce or entirely eliminate
formation of the Fos/c-Jun dimer. Although it has been
demonstrated that Fos and c-Jun interact through the
leucine zipper, the mere presence of a leucine zipper
(formation of the Fos/c-Jun dimer. Although it has been
demonstrated that Fos and c-Jun interact through the
leucine zipper, the mere presence of a leucine zipper
(i.e., among b-zip proteins) is not sufficient for dimer
for demonstrated that Fos and c-Jun interact through the Teucine zipper, the mere presence of a leucine zipper si
(i.e., among b-zip proteins) is not sufficient for dimer the
formation. Because the positions of the leucines in leucine zipper, the mere presence of a leucine zipper
(i.e., among b-zip proteins) is not sufficient for dimer
formation. Because the positions of the leucines in all
zippers are invariant, the amino-acid residues between
 nonpermissable protein-protein interactions. ppers are invariant, the amino-acid residues between
 i e leucines, which differ significantly between different
 zip family members, may determine permissable and
 *n*permissable protein-protein interactions.
 3. Int the leucines, which differ significantly between different rep
b-zip family members, may determine permissable and Fos
nonpermissable protein-protein interactions. site
3. Interactions with deoxyribonucleic acid. Currently

b-zip family members, may determine permissable and Fractions and nonpermissable protein-protein interactions.
3. Interactions with deoxyribonucleic acid. Currently, we five Fos (c-Fos, Fos-B(L), FosB(S), Fra-1, Fra-2) and nonpermissable protein-protein interactions.

3. Interactions with deoxyribonucleic acid. Currently,

five Fos (c-Fos, Fos-B(L), FosB(S), Fra-1, Fra-2) and

three Jun (c-Jun, Jun-B, Jun-D) family members have

been identif 3. Interactions with deoxyribonucleic acid. Currentl
five Fos (c-Fos, Fos-B(L), FosB(S), Fra-1, Fra-2) ar
three Jun (c-Jun, Jun-B, Jun-D) family members hav
been identified. They all contain leucine-zipper domain
and can a five Fos (c-Fos, Fos-B(L), FosB(S), Fra-1, Fra-2) and
three Jun (c-Jun, Jun-B, Jun-D) family members have
been identified. They all contain leucine-zipper domains
and can associate together to form various heterodimers.
Ju three Jun (c-Jun, Jun-B, Jun-D) family members have
been identified. They all contain leucine-zipper domains
and can associate together to form various heterodimers.
Jun, but not Fos, proteins also form homodimers (Vogt
an been identified. They all contain leucine-zipper domains to and can associate together to form various heterodimers. Folder, but not Fos, proteins also form homodimers (Vogt Crand Bos, 1990). These different homodimers and and can associate together to form various neteroalmers. For
Jun, but not Fos, proteins also form homodimers (Vogt Cre
and Bos, 1990). These different homodimers and het-
crodimers have unique transactivating abilities at Jun, but not Fos, proteins also form homodimers (Vogt C
and Bos, 1990). These different homodimers and het-C
erodimers have unique transactivating abilities at the
AP-1/TRE site and therefore have differing effects on
gene and Bos, 1990). These different homodimers and het-
erodimers have unique transactivating abilities at the
 $AP-1/TRE$ site and therefore have differing effects on
gene expression (see next section). The DNA binding inh
regio erodimers have unique transactivating abilities at the ra
AP-1/TRE site and therefore have differing effects on
gene expression (see next section). The DNA binding in
regions of Fos and Jun proteins interact with the dyad AP-1/TRE site and therefore have differing effects on It gene expression (see next section). The DNA binding inhivelepsions of Fos and Jun proteins interact with the dyad ATI symmetry DNA consensus sequence $ATGACTCA$. In th gene expression (see next section). The DNA binding in
regions of Fos and Jun proteins interact with the dyad AT
symmetry DNA consensus sequence $ATGACTCA$. In the in
AP-1 complex, both Fos and Jun proteins directly bind to CI regions of Fos and Jun proteins interact with the dyad A'l
symmetry DNA consensus sequence ATGACTCA. In the
AP-1 complex, both Fos and Jun proteins directly bind to
CI
DNA. These DNA binding regions lie adjacent to the
leu symmetry DNA consensus sequence $ATGACTCA$. In the
AP-1 complex, both Fos and Jun proteins directly bind to
DNA. These DNA binding regions lie adjacent to the
leucine zipper and contain a high density of basic amino
acids (Ab AP-1 complex, both Fos and Jun proteins directly bind to C.
DNA. These DNA binding regions lie adjacent to the releucine zipper and contain a high density of basic amino fo
acids (Abate et al., 1990). In addition to enabli DNA. These DNA binding regions lie adjacent to the
leucine zipper and contain a high density of basic amin
acids (Abate et al., 1990). In addition to enabling dimen
sation, the leucine zipper is believed to hold the bas
am deucine zipper and contain a high density of basic amin
acids (Abate et al., 1990). In addition to enabling dimeri
sation, the leucine zipper is believed to hold the basi
amino-acid DNA contact surface in the correct three

to regulate gene transcription, but the transactivating of DNA bending during the binding phase (Kerppola and potential of c-Jun is significantly increased.
2. The leucine zipper. Formation of the dimer is pos-
ies that a DRAGUNOW
When the dimer binds to DNA, it causes DNA bending.
Protein-induced DNA bending participates in the regu-DRAGUNOW
When the dimer binds to DNA, it causes DNA bending
Protein-induced DNA bending participates in the regu
lation of transcription by facilitating the assembly o DRAGUNOW
When the dimer binds to DNA, it causes DNA bending.
Protein-induced DNA bending participates in the regulation of transcription by facilitating the assembly of
initiation complexes (Kerppola and Curran, 1991a, b). When the dimer binds to DNA, it causes DNA bending.
Protein-induced DNA bending participates in the regulation of transcription by facilitating the assembly of
initiation complexes (Kerppola and Curran, 1991a, b).
Although When the dimer binds to DNA, it causes DNA bending.
Protein-induced DNA bending participates in the regulation of transcription by facilitating the assembly of initiation complexes (Kerppola and Curran, 1991a, b).
Although Protein-induced DNA bending participates in the regulation of transcription by facilitating the assembly of initiation complexes (Kerppola and Curran, 1991a, b).
Although the AP-1/TRE site is palindromic, it seems that Fos station of transcription by facintating the assembly of
initiation complexes (Kerppola and Curran, 1991a, b).
Although the AP-1/TRE site is palindromic, it seems
that Fos/Jun binding does not recognise the AP-1/TRE
site in initiation complexes (Kerppola and Curran, 1991a, b).
Although the AP-1/TRE site is palindromic, it seems
that Fos/Jun binding does not recognise the AP-1/TRE
site in a symmetrical way. This probably occurs because
of DNA Although the AP-1/TRE site is palindromic, it seem
that Fos/Jun binding does not recognise the AP-1/TRI
site in a symmetrical way. This probably occurs becaus
of DNA bending during the binding phase (Kerppola an
Curran, 19 site in a symmetrical way. This probably occurs because the $AP-1/TRE$ site (Risse et al., 1989). DNA bending during the binding phase (Kerppola and
urran, 1991a, b) and is consistent with mutation stud-
is that also suggest asymmetric binding of Fos/Jun to
e AP-1/TRE site (Risse et al., 1989).
Recently, a cellular pro

formation. Because the positions of the leucines in all only differ by one nucleotide: an additional guanidine

zippers are invariant, the amino-acid residues between uncleotide is found in the CRE (i.e., $TCACgTCA$). This
 Curran, 1991a, b) and is consistent with mutation studies that also suggest asymmetric binding of Fos/Jun to the AP-1/TRE site (Risse et al., 1989). Recently, a cellular protein termed IP-1 has been identified. IP-1 is a c ies that also suggest asymmetric binding of Fos/Jun to
the AP-1/TRE site (Risse et al., 1989).
Recently, a cellular protein termed IP-1 has been
identified. IP-1 is a constitutively expressed, labile pro-
tein of 30 to 40 the AP-1/TRE site (Risse et al., 1989).
Recently, a cellular protein termed IP-1 has been
identified. IP-1 is a constitutively expressed, labile pro-
tein of 30 to 40 kD that is found in both the cytoplasm
and nucleus of Recently, a cellular protein termed IP-1 has been
identified. IP-1 is a constitutively expressed, labile pro-
tein of 30 to 40 kD that is found in both the cytoplasm
and nucleus of cells. IP-1 can specifically block the DN netter and therefore represents a potential anti-oncogene
and nucleus of cells. IP-1 can specifically block the DNA
binding of AP-1 (i.e., Fos/Jun complex) to the AP-1/TRE
site and therefore represents a potential anti-onc and nucleus of cells. IP-1 can specifically block the DNA
binding of AP-1 (i.e., Fos/Jun complex) to the AP-1/TRE
site and therefore represents a potential anti-oncogene
(Auwerx and Sassone-Corsi, 1991; Auwerx and Sassonebinding of Ar-1 (i.e., Fosour complex) to the Ar-1/The
site and therefore represents a potential anti-oncogene
(Auwerx and Sassone-Corsi, 1991; Auwerx and Sassone-
Corsi, 1992). The ability of IP-1 to block Fos/Jun binding (Auwerx and Sassone-Corsi, 1991; Auwerx and Sassone-Corsi, 1992). The ability of IP-1 to block Fos/Jun binding
is modulated by phosphorylation. In the nonstimulated
cell, IP-1 exists in a nonphosphorylated form and acts as Corsi, 1992). The ability of IP-1 to block Fos/Jun bind
is modulated by phosphorylation. In the nonstimulatell, IP-1 exists in a nonphosphorylated form and act
a basal repressor of transcription from the AP-1/J
site. Upon a basal repressor of transcription from the AP-1/TRE
site. Upon stimulation of PKA or PKC signal transduc-
tion pathways, IP-1 becomes phosphorylated and there-
fore inactivated. In addition, a report has shown that
nuclea fore inactivated. In addition, a report has shown that a basal repressor of transcription from the AP-1/TRE
site. Upon stimulation of PKA or PKC signal transduc-
tion pathways, IP-1 becomes phosphorylated and there-
fore inactivated. In addition, a report has shown that
nuclea site. Upon stimulation of PKA or PKC signal transduction pathways, IP-1 becomes phosphorylated and there-
fore inactivated. In addition, a report has shown that
nuclear TF CREB and the associated DNA binding fac-
tor CREM tion pathways, IP-1 becomes phosphorylated and there-
fore inactivated. In addition, a report has shown that
nuclear TF CREB and the associated DNA binding fac-
tor CREM also bind to the AP-1/TRE site and inhibit
trans-act fore-mactivated. In addition, a report has shown that
nuclear TF CREB and the associated DNA binding fac-
tor CREM also bind to the AP-1/TRE site and inhibit
trans-activation by Jun proteins (Masquilier and Sas-
sone-Corsi tor CREM also bind to the AP-1/TRE site and inhibit
trans-activation by Jun proteins (Masquilier and Sas-
sone-Corsi, 1992). Both CREB and CREM recognise both
the CRE site and the CaRE/CRE site of the c-*fos* gene.
These p sone-Corsi, 1992). Both CREB and CREM recognise both sone-Corsi, 1992). Both CREB and CREM recognise both
the CRE site and the CaRE/CRE site of the c-fos gene.
These proteins also seem able to bind to the AP-1/TRE
site because of the sequence homology between it and
the CRE. the CRE site and the CaRE/CRE site of the c-fos gene.
These proteins also seem able to bind to the AP-1/TRE
site because of the sequence homology between it and
the CRE. Indeed, the CRE and the AP-1/TRE sequences
only diff These proteins also seem able to bind to the AP-1/TRE
site because of the sequence homology between it and
the CRE. Indeed, the CRE and the AP-1/TRE sequences
only differ by one nucleotide: an additional guanidine
nucleoti site because of the sequence homology between it and
the CRE. Indeed, the CRE and the AP-1/TRE sequences
only differ by one nucleotide: an additional guanidine
nucleotide is found in the CRE (i.e., *TCACgTCA*). This
report the CRE. Indeed, the CRE and the AP-1/TRE sequences
only differ by one nucleotide: an additional guanidine
nucleotide is found in the CRE (i.e., $TCACgTCA$). This
report demonstrates that CREB/CREM proteins disrupt
Fos/Jun st omy unter by one nucleotide: an additional guantume
nucleotide is found in the CRE (i.e., *TCACgTCA*). This
report demonstrates that CREB/CREM proteins disrupt
Fos/Jun stimulated *trans*-activation from the AP-1/TRE
site (report demonstrates that CREB/CREM proteins disrupt
Fos/Jun stimulated *trans*-activation from the AP-1/TRE
site (ATGACTCA). Neither protein seems to dimerise
with Fos or Jun proteins (Lamph et al., 1990; Masquilier
and Sa rosoun sumulated *trans*-activation from the AP-1/1 RE
site (ATGACTCA). Neither protein seems to dimerise
with Fos or Jun proteins (Lamph et al., 1990; Masquilier
and Sassone-Corsi, 1992), suggesting that inhibition oc-
cu and nucleus of cells. IP-1 can specifically block the DNA binding of AP-1 (i.e., Pos¹Jum complex) to the AP-1/TRE site and therefore represents a potential anti-oncogene (Auwerx and Sassone-Corsi, 1991; Auwerx and Sasso with Fos or Jun proteins (Lamph et al., 1990; Masquilier
and Sassone-Corsi, 1992), suggesting that inhibition oc-
curs by competitive binding of CREB and CREM dimers
to the AP-1/TRE site: this results in displacement of th and Sassone-Corsi, 1992), suggesting that inhibition occurs by competitive binding of CREB and CREM dimers
to the AP-1/TRE site: this results in displacement of the
Fos/Jun dimer (Masquilier and Sassone-Corsi, 1992).
Cross curs by competitive binding of CREB and CREM dimers
to the AP-1/TRE site: this results in displacement of the
Fos/Jun-dimer (Masquilier and Sassone-Corsi, 1992)
Cross-family dimerisation of Fos and Jun-with ATFs
CREB also to the AP-1/1
Fos/Jun dim
Cross-family
CREB also a
ran, 1991).
It has rec It has recently dimerisation of Fos and Jun with ATFs.

It has recently dimerisation of Fos and Jun with ATFs.

It has recently been demonstrated that CREB will

hibit the transcriptional ability of certain ATFs (i.e.,

Cross-family dimerisation of Fos and Jun with ATFs/
CREB also alters DNA binding specificity (Hai and Curran, 1991).
It has recently been demonstrated that CREB will
inhibit the transcriptional ability of certain ATFs (i.e CREB also alters DNA binding specificity (Hai and Curran, 1991).
It has recently been demonstrated that CREB will
inhibit the transcriptional ability of certain ATFs (i.e.,
ATF-4) at a given promoter by mechanisms that do ran, 1991).
It has recently been demonstrated that CREB will
inhibit the transcriptional ability of certain ATFs (i.e.,
ATF-4) at a given promoter by mechanisms that do not
involve heterodimerisation with the ATF or bindin It has recently been demonstrated that CREB w
inhibit the transcriptional ability of certain ATFs (i.
ATF-4) at a given promoter by mechanisms that do n
involve heterodimerisation with the ATF or binding to
CRE within the inhibit the transcriptional ability of certain ATFs (i.e.,
ATF-4) at a given promoter by mechanisms that do not
involve heterodimerisation with the ATF or binding to a
CRE within the promoter. Rather, CREB may down-
regula ATF-4) at a given promoter by mechanisms that do not
involve heterodimerisation with the ATF or binding to a
CRE within the promoter. Rather, CREB may down-
regulate the expression of another TF that is necessary
for the t involve heterodimerisation with the ATF or binding to a

CRE within the promoter. Rather, CREB may down-

regulate the expression of another TF that is necessary

for the transcriptional ability of the ATF (Lemaigre et

al CRE within the promoter. Rather, CREB may down-
regulate the expression of another TF that is necessary
for the transcriptional ability of the ATF (Lemaigre et
al., 1993). It will be interesting to see whether CREB
and ATF regulate the expression of another TF that is necessary
for the transcriptional ability of the ATF (Lemaigre et
al., 1993). It will be interesting to see whether CREB
and ATFs interact with IEGP TFs in a similar manner.
Li for the transcriptional ability of the ATF (Lemaigre et al., 1993). It will be interesting to see whether CREB and ATFs interact with IEGP TFs in a similar manner. Ligand-activated TFs, i.e., the glucocorticoid and thyroid

PHARMACOLOGICAL REVIEWS

IMMEDIATE-EARLY GENES AND GENE EXPRESSION
plexes to modulate their transactivational ability (Luci- in the Jun-B homodi
bello et al., 1990; Lopez et al., 1993; Schmidt et al., transactivational abil IMMEDIATE-EARLY GENES
plexes to modulate their transactivational ability (Luci-
bello et al., 1990; Lopez et al., 1993; Schmidt et al.,
1993). Inasmuch as Fos and Jun proteins can also bind IMMEDIATE-EARLY GENES AN

plexes to modulate their transactivational ability (Luci-

bello et al., 1990; Lopez et al., 1993; Schmidt et al., tra

1993). Inasmuch as Fos and Jun proteins can also bind (Fr

to the CRE site (plexes to modulate their transactivational ability (Lucibility of the CRE site (Hoeffler et al., 1989; Sassone-Corsi et al., 1990), it is clear that cell stimulation will result in plexes to modulate their transactivational ability (Luci- in the bello et al., 1990; Lopez et al., 1993; Schmidt et al., tran 1993). Inasmuch as Fos and Jun proteins can also bind (Fra to the CRE site (Hoeffler et al., 198 bello et al., 1990; Lopez et al., 1993; Schmidt et al., 1993). Inasmuch as Fos and Jun proteins can also bind to the CRE site (Hoeffler et al., 1989; Sassone-Corsi et al., 1990), it is clear that cell stimulation will resu 1993). Inasmuch as Fos an
to the CRE site (Hoeffler e
al., 1990), it is clear that c
multiple interactions betwe
of cellular TFs and DNA.
4. Specificity of response the CKE site (Hoeffier et al., 1969, Sassone-Corsi et al., 1990), it is clear that cell stimulation will result in ultiple interactions between the three major varieties cellular TFs and DNA.
4. Specificity of response. Wh

the interactions between the three major varieties
of cellular TFs and DNA.

4. Specificity of response. Whereas Fos and Jun pro-

teins have near identical DNA binding activities within

their families because of conserva of cellular TFs and DNA.
4. Specificity of response. Whereas Fos and Jun p
teins have near identical DNA binding activities with
their families because of conservation of basic amin
acid sequences that confer DNA binding a teins have near identical DNA binding activities within
their families because of conservation of basic amino-
acid sequences that confer DNA binding ability (Naka-
beppu et al., 1988) outside of the DNA binding domains,
t teins have near identical DNA binding activities within tive their families because of conservation of basic amino-
acid sequences that confer DNA binding ability (Naka-
beppu et al., 1988) outside of the DNA binding domai beppu et al., 1988) outside of the DNA binding domains, there is more limited sequence identity between family members (Nakabeppu and Nathans, 1991). Therefore, the transactivational ability of the various dimers that acid sequences that confer DNA binding ability (Nakabeppu et al., 1988) outside of the DNA binding domains, there is more limited sequence identity between family members (Nakabeppu and Nathans, 1991). Therefore, the trans beppu et al., 1988) outside of the DNA binding domains,
there is more limited sequence identity between family
members (Nakabeppu and Nathans, 1991). Therefore,
the transactivational ability of the various dimers that
form there is more limited sequence identity between family find members (Nakabeppu and Nathans, 1991). Therefore, bit the transactivational ability of the various dimers that III form at the AP-1/TRE site differs markedly, dep members (Nakabeppu and Nathans, 1991). Therefore, bin
the transactivational ability of the various dimers that III
form at the AP-1/TRE site differs markedly, depending 28
upon their composition. A number of reports have s the transactivational ability of the various dimers that III
form at the AP-1/TRE site differs markedly, depending 28
upon their composition. A number of reports have shown an
that Fos family members do not form homodimers form at the AP-1/TRE site differs markedly, depending 28
upon their composition. A number of reports have shown and
that Fos family members do not form homodimers and uni
therefore cannot bind to or effect transcription f upon their composition. A number of reports have shown
that Fos family members do not form homodimers and
therefore cannot bind to or effect transcription from the
coor
AP-1/TRE site. However, Jun homodimers do form, and
s that Fos family members do not form homodimers and
therefore cannot bind to or effect transcription from the
AP-1/TRE site. However, Jun homodimers do form, and
some dimers (c-Jun/c-Jun, Jun-D/Jun-D) are able to bind
to AP therefore cannot bind to or effect transcription from the coorse AP-1/TRE site. However, Jun homodimers do form, and two some dimers (c-Jun/c-Jun, Jun-D/Jun-D) are able to bind able to AP-1/TRE sites and weakly stimulate t AP-1/TRE site. Home dimers (c-Ju
to AP-1/TRE site
(Suzuki et al., 1991).
Nathans, 1991).
In contrast, Jur me dimers (c-Jun/c-Jun, Jun-D/Jun-D) are able to bind
AP-1/TRE sites and weakly stimulate transcription
uzuki et al., 1991; Chiu et al., 1989; Nakabeppu and
athans, 1991).
In contrast, Jun-B homodimers (Jun-B/Jun-B) are al

to AP-1/TRE sites and weakly stimulate transcription
(Suzuki et al., 1991; Chiu et al., 1989; Nakabeppu and
Nathans, 1991).
In contrast, Jun-B homodimers (Jun-B/Jun-B) are al-
most inactive and only activate transcription (Suzuki et al., 1991; Chiu et al., 1989; Nakabeppu and
Nathans, 1991).
In contrast, Jun-B homodimers (Jun-B/Jun-B) are al-
most inactive and only activate transcription from pro-
moters containing multiple AP-1/TRE sites (let

1991). let

1989; In contrast, Jun-B homodimers (Jun-B/Jun-B) are al-

1989; Nakabeppu and Nathans, 1991). Therefore, the

1989; Nakabeppu and Nathans, 1991). Therefore, the

1989; Nakabeppu and Nathans, 1991). Theref In contrast, Jun-B homodimers (Jun-B/Jun-B) are al-
most inactive and only activate transcription from pro-
moters containing multiple AP-1/TRE sites (Chiu et al., bindi
1989; Nakabeppu and Nathans, 1991). Therefore, the most mactive and only activate transcription from pro-
moters containing multiple AP-1/TRE sites (Chiu et al.
1989; Nakabeppu and Nathans, 1991). Therefore, the
binding of (the inactive) Jun-B protein to c-Jun or Jun-
resu 1989; Nakabeppu and Nathans, 1991). Inerefore, the Both
binding of (the inactive) Jun-B protein to c-Jun or Jun-D GCG
results in the formation of Jun heterodimers (Jun-B/c-
Jun and Jun-B/Jun-D) with lower transactivation results in the formation of Jun heterodimers (Jun-B/c-Jun and Jun-D/Jun-D) with lower transactivational ability than c-Jun/c-Jun and Jun-D/Jun-D homodimers (Chiu et al., 1989; Schutte et al., 1989). Thus, Jun-B inhibits th Jun and Jun-B/Jun-D) with lower transactivational ability than c-Jun/c-Jun and Jun-D/Jun-D homodimers
(Chiu et al., 1989; Schutte et al., 1989). Thus, Jun-B
inhibits the transactivational ability of c-Jun and Jun-D.
We ass ity than c-Jun/c-Jun and Jun-D/Jun-D homodin
(Chiu et al., 1989; Schutte et al., 1989). Thus, Juinhibits the transactivational ability of c-Jun and Jun
We assume that the Jun heterodimer formed betw
c-Jun and Jun-D (c-Jun inhibits the transactivational ability of c-Jun and Jun-D.
We assume that the Jun heterodimer formed between
c-Jun and Jun-D (c-Jun/Jun-D) would have transcrip-
tional activity comparable to the c-Jun and Jun-D homodimers.

In comparison, the binding of Fos and Fos-B(L) proe-Jun and Jun-D (e-JunJun-D) would have transcrip-
tional activity comparable to the c-Jun and Jun-D ho-
modimers.
In comparison, the binding of Fos and Fos-B(L) pro-
teins with Jun family members to form Fos/Jun het-
erod modimers.

In comparison, the binding of Fos and Fos-B(L) proteins with Jun family members to form Fos/Jun het-

erodimers (i.e., Fos/c-Jun, Fos/Jun-B, Fos/Jun-D, Fos-

B(L)/c-Jun, Fos-B(L)/Jun-B, Fos-B(L)/Jun-D) results i In comparison, the binding of Fos and Fos-B(L) proteins with Jun family members to form Fos/Jun heterodimers (i.e., Fos/c-Jun, Fos/Jun-B, Fos/Jun-D, Fos-B(L)/c-Jun, Fos-B(L)/Jun-B, Fos-B(L)/Jun-D) results in a dramatic inc teins with Jun family members to form Fos/Jun het-
erodimers (i.e., Fos/c-Jun, Fos/Jun-B, Fos/Jun-D, Fos-
B(L)/c-Jun, Fos-B(L)/Jun-B, Fos-B(L)/Jun-D) results in
a dramatic increase in the transcriptional ability of the
Jun erodimers (i.e., Fos/c-Jun, Fos/Jun-B, Fos/Jun-D, Fos-
B(L)/c-Jun, Fos-B(L)/Jun-B, Fos-B(L)/Jun-D) results in
a dramatic increase in the transcriptional ability of the
Jun proteins (Nakabeppu and Nathans, 1991; Suzuki et
a B(L)/c-Jun, Fos-B(L)/Jun-B, Fos-B(L)/Jun-D) result a dramatic increase in the transcriptional ability c
Jun proteins (Nakabeppu and Nathans, 1991; Suzu
al., 1991). The other members of the Fos family
Fos/Jun heterodimers w a dramatic increase in the transcriptional ability of the
Jun proteins (Nakabeppu and Nathans, 1991; Suzuki et
al., 1991). The other members of the Fos family form
Fos/Jun heterodimers with widely differing transactiva-
ti Jun proteins (Nakabeppu and Nathans, 1991; Suzuki et al., 1991). The other members of the Fos family form Fos/Jun heterodimers with widely differing transactivational abilities, depending on their composition. For example, al., 1991). The other members of the Fos family form
Fos/Jun heterodimers with widely differing transactiva-
tional abilities, depending on their composition. For ex-
ample, Fos/Jun heterodimers containing the Fos-B(S)
pro Fos/Jun heterodimers with widely differing transactivational abilities, depending on their composition. For example, Fos/Jun heterodimers containing the Fos-B(S) protein (Fos-B(S)/c-Jun, Fos-B(S)/Jun-B, Fos-B(S)/Jun-D) ha tional abilities, depending on their composition. For example, Fos/Jun heterodimers containing the Fos-B(S) $\frac{1}{10}$
protein (Fos-B(S)/c-Jun, Fos-B(S)/Jun-B, Fos-B(S)/Jun-D) have little or no transcriptional ability (Na ample, Fos/Jun heterodimers containing the Fos-B(S)
protein (Fos-B(S)/c-Jun, Fos-B(S)/Jun-B, Fos-B(S)/Jun-D) have little or no transcriptional ability (Nakabeppu et
al., 1991). Fos/Jun heterodimers containing Fra-1 and
Fra protein (Fos-B(S)/c-Jun, Fos-B(S)/Jun-B, Fos-B(S)/Jun-D) have little or no transcriptional ability (Nakabeppu et al., 1991). Fos/Jun heterodimers containing Fra-1 and Fra-2 proteins show differing transcriptional ability, D) have little or no transcriptional ability (Nakabeppu et al., 1991). Fos/Jun heterodimers containing Fra-1 and Fra-2 proteins show differing transcriptional ability, depending on the Jun protein they contain. For example al., 1991). Fos/Jun heterodimers containing Fra-1 and
Fra-2 proteins show differing transcriptional ability, de-
pending on the Jun protein they contain. For example,
although the transcriptional ability of Jun-D is in-
c Fra-2 proteins show differing transcriptional ability, de-
pending on the Jun protein they contain. For example, plasm
although the transcriptional ability of Jun-D is in-
creased in the Fra/Jun-D heterodimers (Fra-1/Junpending on the Jun protein they contain. For example, planet
although the transcriptional ability of Jun-D is in-
creased in the Fra/Jun-D heterodimers (Fra-1/Jun-D, Est
Fra-2/Jun-D), the transactivational ability of Jun-

AND GENE EXPRESSION 143
in the Jun-B homodimer (Jun-B/Jun-B), whereas the
transactivational ability of c-jun in the heterodimers AND GENE EXPRESSION 143
in the Jun-B homodimer (Jun-B/Jun-B), whereas the
transactivational ability of c-jun in the heterodimers
(Fra-1/c-Jun, Fra-2/c-Jun) decreases below that found in AND GENE EXPRESSION 143

in the Jun-B homodimer (Jun-B/Jun-B), whereas the

transactivational ability of c-jun in the heterodimers

(Fra-1/c-Jun, Fra-2/c-Jun) decreases below that found in

the c-Jun homodimer (c-Jun/c-Jun 1991). (Fra-1/c-Jun, Fra-2/c-Jun) decreases below that found in the c-Jun homodimer (c-Jun/c-Jun), (Suzuki et al., 1991).
We have used these results to construct summary table 1, which shows the relative transactivational abil-

(Fra-1/c-Jun, Fra-2/c-Jun) decreases below that found in the c-Jun homodimer (c-Jun/c-Jun), (Suzuki et al. 1991).
We have used these results to construct summary table 1, which shows the relative transactivational ability ity of various Jun/Jun and Fos/Jun heterodimers to ac-
tivate 1, which shows the relative transactivational abil-
ity of various Jun/Jun and Fos/Jun heterodimers to ac-
tivate reporter genes from an AP-1/TRE-containing pro We have use
table 1, which slity of various Ju
tivate reporter g
moter in vitro.
The Krox-20 (ble 1, which shows the relative transactivational abil-

7 of various Jun/Jun and Fos/Jun heterodimers to ac-

7 of various Jun/Jun and Fos/Jun heterodimers to ac-

7 oter in vitro.

The Krox-20 (Chavrier et al., 1988) and

tivate reporter genes from an AP-1/TRE-containing pro-
moter in vitro.
The Krox-20 (Chavrier et al., 1988) and Krox-24 (Le-
maire et al., 1988) TFs are characterised by their *"zinc-*
finger" DNA binding domains. Zinc-fi tivate reporter genes from an AP-1/TRE-containing pro-
moter in vitro.
The Krox-20 (Chavrier et al., 1988) and Krox-24 (Le-
maire et al., 1988) TFs are characterised by their "zinc-
finger" DNA binding domains. Zinc-finger moter in vitro.

The Krox-20 (Chavrier et al., 1988) and Krox-24 (Le-

maire et al., 1988) TFs are characterised by their "zinc-

finger" DNA binding domains. Zinc-fingers are DNA

binding domains that were first identifie The Krox-20 (Chavrier et al., 1988) and Krox-24 (Lemaire et al., 1988) TFs are characterised by their "*zinc-finger*" DNA binding domains. Zinc-fingers are DNA binding domains that were first identified in TF, TF IIIA. Zin mare et al., 1966) IFS are characterised by their *zinc-finger*" DNA binding domains. Zinc-fingers are DNA binding domains that were first identified in TF, TF IIIA. Zinc fingers consist of tandemly repeated units of 28 to IIIA. Zinc fingers consist of tandemly repeated units of 28 to 30 amino-acid residues, containing two cysteine and two histidine residues at invariant positions. This unit of amino-acid residues centres around a Zn^{2+} binding domains that were first identified in TF, TF IIIA. Zinc fingers consist of tandemly repeated units of 28 to 30 amino-acid residues, containing two cysteine and two histidine residues at invariant positions. This u IIIA. Zinc fingers consist of tandemly repeated units of 28 to 30 amino-acid residues, containing two cysteine and two histidine residues at invariant positions. This unit of amino-acid residues centres around a Zn^{2+} 28 to 30 amino-acid residues, containing two cysteine
and two histidine residues at invariant positions. This
unit of amino-acid residues centres around a Zn^{2+} ion
coordinated by the four invariant residues (two cyste and two histidine residues at invariant positions. The unit of amino-acid residues centres around a Zn^{2+} is coordinated by the four invariant residues (two cystein two histidine). This complex is called a zinc-finger unit of amino-acid residues centres around a Zn^{2+} ior coordinated by the four invariant residues (two cysteine two histidine). This complex is called a zinc-finger and is able to bind DNA in a sequence-specific ma coordinated by the four invariant residues (two cysteine two histidine). This complex is called a zinc-finger and i
able to bind DNA in a sequence-specific manner deper
dent upon the sequence of three base-pair variant am
 two histidine). This complex is called a zinc-finger and is
able to bind DNA in a sequence-specific manner depen-
dent upon the sequence of three base-pair variant ami-
no-acid residues that come to lie next to the DNA (Pa able to bind DNA in a sequence-specific manner dependent upon the sequence of three base-pair variant am no-acid residues that come to lie next to the DNA (Paveletich and Pabo, 1991) and exist between the invarian "zinc-fi dent upon the sequence of three base-pair variant ami-
no-acid residues that come to lie next to the DNA (Pav-
letich and Pabo, 1991) and exist between the invariant
"zinc-finger structural" residues. Several TFs, in addi no-acid residues that come to lie next to the DNA (Pav-
letich and Pabo, 1991) and exist between the invariant
"zinc-finger structural" residues. Several TFs, in addi-
tion to Krox-20 and Krox-24, use zinc-fingers as DNA
b letich and Pabo, 1991) and exist between the invariant
"zinc-finger structural" residues. Several TFs, in addi-
tion to Krox-20 and Krox-24, use zinc-fingers as DNA
binding domains, for example, Spl, SW15, and TF IIIA.
Bot "zinc-finger structural" residues. Several TFs, in addition to Krox-20 and Krox-24, use zinc-fingers as DNA binding domains, for example, Spl, SW15, and TF IIIA. Both Krox-20 and Krox-24 recognise the same sequence *GCGTGG* tion to Krox-20 and Krox-24, use zinc-finger
binding domains, for example, Spl, SW15, an
Both Krox-20 and Krox-24 recognise the same
GCGTGGGGCG in DNA (Christy and Nath
Charvier et al., 1990; Lemaire et al., 1988).

TABLE 1 *Descending order of transactivational ability of various Fos IJun* TABLE 1
hetero- and Jun/Jun homo-dimers from an AP-1 containing
*hetero- and Jun/Jun homo-dimers from an AP-1 containing
promoter.CAT fusion gene* **PRICE 1**
 promoter. CAT fusion generally of vector- and Jun / Jun homo-dimers from an AH
 promoter. CAT fusion gene
 Pransactivational
 ability
 promoter. CAT fusion generally below the property of the property o

Transactivational ability	Dimer
High	Fos/c-Jun, ^{1,2} Fos/Jun-D. ^{1,2}
	FosB(L)/c-Jun, ² FosB(L)/Jun-D ²
Medium	Fos/Jun-B, ^{1,2} FosB(L)/Jun-B ²
	Fra-1/Jun-D.1 Fra-2/Jun-D ¹
Medium-Low	c-Jun/c-Jun, 1,2,3,4 Jun-D/Jun-D ^{1,2}
	c-Jun/Jun-Dt
Low-Not detectible	$F \text{os} B(S)/\text{Jun-B.}^2$ $F \text{os} B(S)/c$ -Jun ²
	F osB(S)/Jun-D. ² Fra-1/Jun-B ¹
	$Fra-1/c$ -Jun. ¹ Fra-2/Jun-B ¹
	Fra-2/c-Jun, ¹ Jun-B/Jun-B ^{1,2,3}
	c-Jun/Jun-B ^{3,4}

tured F9 teratocarcinoma cells. Cells were transfected with an AP-i containing promoter linked to a chloramphenicol acetyltransferase Transcriptional activation experiments were performed in cultured F9 teratocarcinoma cells. Cells were transfected with an AP-1 containing promoter linked to a chloramphenicol acetyltransferase marker gene (AP-1.CAT fusion various dimers at the AP-incontrol of PS teratocarcinoma cells. Cells were transfected with an AP-1 containing promoter linked to a chloramphenicol acetyltransferase marker gene (AP-1.CAT fusion plasmid). Transactivational containing promoter linked to a chloramphenicol acetyltransferase
marker gene (AP-1.CAT fusion plasmid). Transactivational ability of
various dimers at the AP-1 site was measured by assaying CAT
enzyme activity induced by marker gene (AP-1.CAT fusion plasmid). Transactivational ability
various dimers at the AP-1 site was measured by assaying C.
enzyme activity induced by cotransfection of Fos and Jun expressi
plasmids with the AP-1 containi Frous dimers at the AP-1 site was measured by assaying CA
gyme activity induced by cotransfection of Fos and Jun expression
smids with the AP-1 containing promoter.CAT fusion plasmid.
References: ¹ Suzuki et al., (1991);

enzyme activity induced by cotransfection of Fos and Jun expression
plasmids with the AP-1 containing promoter.CAT fusion plasmid.
References: ¹ Suzuki et al., (1991); ² Nakabeppu and Nathans,
(1991); ³ Chiu et al., members, Fos family members, Fostmann, Form homo-
(1991); ³ Chiu et al., (1999); ⁴ Deng and Karin, (1993); † No ref.
Estimated transactivational ability. Note that unlike Jun family
members, Fos family members (Fos, Fo

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In view of what is currently understood, it is easy to (Me
In view of what is currently understood, it is easy to (Me
e how a small number of immediate-early gene pro-HUGHES AN
In view of what is currently understood, it is easy to
see how a small number of immediate-early gene pro-
teins can, by combinatorial control, lead to the formation HUGHES AND D
In view of what is currently understood, it is easy to
see how a small number of immediate-early gene pro-
teins can, *by combinatorial control*, lead to the formation
of a large number of AP-1 TF complexes wi In view of what is currently understood, it is easy to (l'
see how a small number of immediate-early gene pro-
teins can, by combinatorial control, lead to the formation bi
of a large number of AP-1 TF complexes with diffe In view of what is currently understood, it is easy to
see how a small number of immediate-early gene pro-
teins can, by combinatorial control, lead to the formation
of a large number of $AP-1$ TF complexes with differing
 see how a small number of immediate-early gene proteins can, by combinatorial control, lead to the formation bof a large number of AP-1 TF complexes with differing st transcriptional abilities. Full characterisation of tw teins can, by combinatorial control, lead to the formation of a large number of AP-1 TF complexes with differing transcriptional abilities. Full characterisation of two parameters is required to understand the role that th of a large number of A
transcriptional abilities
rameters is required to
proteins play within th
rotransmitter binding.
The first parameter anscriptional abilities. Full characterisation of two pa-
meters is required to understand the role that these
oteins play within the cell after growth factor or neu-
transmitter binding.
The first parameter to be determi

rameters is required to understand the role that these
proteins play within the cell after growth factor or neu-
rotransmitter binding.
The first parameter to be determined is the specific
IEG proteins that are formed afte proteins play within the cell after growth factor or neu-

rotransmitter binding.

The first parameter to be determined is the specific ion

IEG proteins that are formed after stimulation of the cell

crowth factor or neur rotransmitter binding.
The first parameter to be determined is the specific if IEG proteins that are formed after stimulation of the cell
by *that* growth factor or neurotransmitter. The second relative parameter to be de The first parameter to be determined is the specific id IEG proteins that are formed after stimulation of the cell
by *that* growth factor or neurotransmitter. The second nearameter to be determined is this: how the relati IEG proteins that are formed after stimulation of the cell
by *that* growth factor or neurotransmitter. The second
parameter to be determined is this: how the relative
expression of proteins induced by *that* growth factor by *indi* growth lactor or heurotransmitter. The second in
parameter to be determined is this: how the relative accepts
expression of proteins induced by *that* growth factor or
neurotransmitter changes over time. These pa neurotransmitter changes over time. These parameters
must be characterised, because the composition of the
AP-1 TF complex is dynamic, and its composition will
determine the genetic response of the cell. II. The characterised, because the composition of
1 TF complex is dynamic, and its composition vermine the genetic response of the cell.
II. Immediate-early Genes and the Central
Nervous System

etic response of the cell.
 Example 3-carly Genes and the Nervous System
 P within the Central Ner **A. I. Immediate-early Genes and the Central Nervous**
A. Basal Expression within the Central Nervous
System

System

Nervous System

Basal Expression within the Central Nervous

stem

IEG TFs show constitutive expression within the ind

NS. For certain members of the IEGs, constitutive zo A. Basal Expression within the Central Nervous
System
IEG TFs show constitutive expression within the
CNS. For certain members of the IEGs, constitutive
expression is low. For example, low but noticeable Fos-A. Basal Expression within the Central Nerools
System
IEG TFs show constitutive expression within the
CNS. For certain members of the IEGs, constitutive
expression is low. For example, low but noticeable Fos-
like immunost the interest of the IEGs, constitutive expression within the interests. For certain members of the IEGs, constitutive zero expression is low. For example, low but noticeable Fositive interesting is apparent within the nucl IEG TFs show constitutive expression within the
CNS. For certain members of the IEGs, constitutive
expression is low. For example, low but noticeable Fos-
like immunostaining is apparent within the nuclei of
adult nerve ce CNS. For certain members of the IEGs, constitutivexpression is low. For example, low but noticeable Fosike immunostaining is apparent within the nuclei could nerve cells scattered throughout the amygdals striatum and pirif expression is low. For example, low but noticeable Fos-
like immunostaining is apparent within the nuclei of
cinadult nerve cells scattered throughout the amygdala,
striatum and piriform cortex, and hippocampus (Dra-
1987) adult nerve cells scattered throughout the amygdala, striatum and piriform cortex, and hippocampus (Dragunow et al., 1987; Morgan et al., 1987; Dragunow and Robertson, 1988a), although hippocampal Fos-like im-
munoreactivi striatum and piriform cortex, and hippocampus (Dragunow et al., 1987; Morgan et al., 1987; Dragunow and Robertson, 1988a), although hippocampal Fos-like im-
munoreactivity may be caused by constitutive expres-
sion of Fras striatum and piritorm cortex, and mppocampus (Dra-
gunow et al., 1987; Morgan et al., 1987; Dragunow and cou
Robertson, 1988a), although hippocampal Fos-like im-
munoreactivity may be caused by constitutive expres-
in of F Robertson, 1988a), although hippocampal Fos-like im-
munoreactivity may be caused by constitutive expression of Fras in dentate gyrus (Hughes et al., 1992). In mRi
addition, Fos-B protein is also expressed constitutively i munoreactivity may be caused by constitutive expres-
sion of Fras in dentate gyrus (Hughes et al., 1992). In
addition, Fos-B protein is also expressed constitutively ind
in rat brain, and low levels of expression can be fo sion of Fras in dentate gyrus (Hu_i
addition, Fos-B protein is also exp
in rat brain, and low levels of expre
cerebral cortex, striatum, amygdal
dentate gyrus (Dragunow, 1990).
In contrast, the expression of Kr dition, Fos-B protein is also expressed constitutively in rat brain, and low levels of expression can be found in reebral cortex, striatum, amygdala, hippocampus, and no notate gyrus (Dragunow, 1990). In contrast, the exp

in rat brain, and low levels of expression can be found in rem
cerebral cortex, striatum, amygdala, hippocampus, and nor
dentate gyrus (Dragunow, 1990). and
In contrast, the expression of Krox family members is mid
high wi dentate gyrus (Dragunow, 1990). and the dentate gyrus (Dragunow, 1990).

In contrast, the expression of Krox family members is more high within the CNS. Both *krox-24* mRNA (*zif* 268 wmRNA; Schlingensiepen et al., 1991) a In contrast, the expression of Krox family members is midgh within the CNS. Both $krox-24$ mRNA ($zif 268$ ver mRNA; Schlingensiepen et al., 1991) and protein (Mack Fore tal., 1990) are expressed at high levels within forebr mRNA; Schlingensiepen et al., 1991) and protein (Mack
et al., 1990) are expressed at high levels within forebrain
neurons. Highest levels of expression can be seen in deep
layers of the neocortex (layers IV and VI) and hip mRNA; Schlingensiepen et al., 1991) and protein (Mack
et al., 1990) are expressed at high levels within forebrain
neurons. Highest levels of expression can be seen in deep
layers of the neocortex (layers IV and VI) and hip et al., 1990) are expressed at high levels within forebrain
neurons. Highest levels of expression can be seen in deep
layers of the neocortex (layers IV and VI) and hippocam-
pus (CA1) (Schlingensiepen et al., 1991; Hughes heurons. Highest levels of expression can be seen in deep
layers of the neocortex (layers IV and VI) and hippocam-
pus (CA1) (Schlingensiepen et al., 1991; Hughes et al.,
1992). Krox-20 protein is also expressed at high le hayers of the heocortex (layers IV and VI) and implocant-
pus (CA1) (Schlingensiepen et al., 1991; Hughes et al.,
1992). Krox-20 protein is also expressed at high levels
basally within the superficial layers of the neocort basally within the superficial layers of the neocortex (layers II and III), caudate-putamen, globus pallidus and nucleus accumbens, but not hippocampus (Herd-egen et al., 1993a). Currently, reports regarding basal 1992). Krox-20 protein is also expressed at high levels basally within the superficial layers of the neocortex (layers II and III), caudate-putamen, globus pallidus and nucleus accumbens, but not hippocampus (Herdegen et basally within the superficial layers of the neocortex *j* (layers II and III), caudate-putamen, globus pallidus hand nucleus accumbens, but not hippocampus (Herdegen et al., 1993a). Currently, reports regarding basal (ex (layers II and III), caudate-putamen, globus pallidus
and nucleus accumbens, but not hippocampus (Herd-
egen et al., 1993a). Currently, reports regarding basal
expression of $krox-20$ mRNA are contradictory (Mack et
al., 19 and nucleus accumbens, but not hippocampus (Herdegen et al., 1993a). Currently, reports regarding basal (expression of $k \tau \alpha x$ -20 mRNA are contradictory (Mack et pal., 1992; Bhat et al., 1992b). The c-Jun protein is expr egen et al., 1993a). Currently, reports regarding basal (Sa
expression of *krox*-20 mRNA are contradictory (Mack et pro
al., 1992; Bhat et al., 1992b). The c-Jun protein is ex-
pressed at high levels within neurons of the expression of *krox*-20 mRNA are contradictory (Mack
al., 1992; Bhat et al., 1992b). The c-Jun protein is
pressed at high levels within neurons of the dent
gyrus of the hippocampus (Hughes et al., 1992) a
piriform cortex al., 1992; Bhat et al., 1992b). The c-Jun protein is ex-
pressed at high levels within neurons of the dentate
gyrus of the hippocampus (Hughes et al., 1992) and
piriform cortex (Hughes et al., unpublished observa-
tions); pressed at high levels within neurons of the dentate
gyrus of the hippocampus (Hughes et al., 1992) and
piriform cortex (Hughes et al., unpublished observa-
tions); c-jun mRNA is expressed weakly in cerebral cor-
tex, with gyrus of the hippocampus (Hughes et al., 1992) and
piriform cortex (Hughes et al., unpublished observa-
tions); c-jun mRNA is expressed weakly in cerebral cor-
tex, with strongest expression in piriform cortex, den-
tate g

DRAGUNOW
(Mellstrom et al., 1991). The mRNAs coding for *jun*-B
and *jun*-D are expressed at high levels throughout the DRAGUNOW
(Mellstrom et al., 1991). The mRNAs coding for *jun*-B
and *jun*-D are expressed at high levels throughout the
brain in hippocampus (dentate gyrus and CA1/CA3), DRAGUNOW
(Mellstrom et al., 1991). The mRNAs coding for *jun*-B
and *jun*-D are expressed at high levels throughout the
brain in hippocampus (dentate gyrus and CA1/CA3),
striatum, thalamus, cortex, amygdala, and cerebellum (Mellstrom et al., 1991). The mRNAs coding for jun -B and jun -D are expressed at high levels throughout the brain in hippocampus (dentate gyrus and CA1/CA3), striatum, thalamus, cortex, amygdala, and cerebellum (Mellstrom (Mellstrom et al., 1991).

and *jun*-D are expressed

brain in hippocampus (d

striatum, thalamus, corte

(Mellstrom et al., 1991).

P. Industion within the C brain in hippocampus (dentate gyrus and CA1/CA3), striatum, thalamus, cortex, amygdala, and cerebellum (Mellstrom et al., 1991).
B. Induction within the Central Nervous System

Numerous recent studies have demonstrated that var-
Numerous recent studies have demonstrated that var-
Numerous recent studies have demonstrated that var-
us treatments to the nervous system result in in-Induction within the Central Nervous System

Numerous recent studies have demonstrated that var-

ious treatments to the nervous system result in in-

creased expression of IEG mRNA and protein in both

neurons and non-neu B. Induction within the Central Nervous System
Numerous recent studies have demonstrated that var-
ious treatments to the nervous system result in in-
creased expression of IEG mRNA and protein in both
neurons and non-neur Numerous recent studies have demonstrated that various treatments to the nervous system result in increased expression of IEG mRNA and protein in both neurons and non-neuronal cells. For example, seizure activity (chemical ious treatments to the nervous system result
creased expression of IEG mRNA and protein i
neurons and non-neuronal cells. For example, a
activity (chemically and electrically induced), ki
brain-injury (i.e., mechanical, HI creased expression of EG IIRRNA and protein in both
neurons and non-neuronal cells. For example, seizure
activity (chemically and electrically induced), kindling,
brain-injury (i.e., mechanical, HI, spreading-depres-
sion) meurons and non-neuronal cens. For example, seizure
activity (chemically and electrically induced), kindling,
brain-injury (i.e., mechanical, HI, spreading-depres-
sion), sensory stimulation (noxious, visual, olfactory, so brain-injury (i.e., mechanical, HI, spreading-depression), sensory stimulation (noxious, visual, olfactory, so-
matosensory), stress, learning, and the induction of LTP
result in increased expression of IEGs within the ner brain-injury (i.e., mechanical, ril, spreading-depres-
sion), sensory stimulation (noxious, visual, olfactory, so-
matosensory), stress, learning, and the induction of LTP
result in increased expression of IEGs within the exist. *1. Electrically and drug-induced seizure activity.*
 1. Electrically and drug-induced seizure activity.

Chemically and electrically induced seizures rapidly in-

crease the expression of IEGs in mouse and rat brain. In

and refers the reader to appropriate reviews where they
exist.

1. Electrically and drug-induced seizure activity.

Chemically and electrically induced seizures rapidly in-

crease the expression of IEGs in mouse and rat exist.

1. Electrically and drug-induced seizure activity.

Chemically and electrically induced seizures rapidly increase the expression of IEGs in mouse and rat brain. In

the first two studies demonstrating seizure-media 1. Electrically and drug-induced seizure acchemically and electrically induced seizures rapident crease the expression of IEGs in mouse and rat brather first two studies demonstrating seizure-me induction of c-*fos*, the c Chemically and electrically induced seizures rapidly increase the expression of IEGs in mouse and rat brain. In the first two studies demonstrating seizure-mediated induction of c-fos, the convulsant drug pentylenetetrazol matosensory), stress, learning, and the induction of LTP
result in increased expression of IEGs within the ner-
vous system. This section briefly discusses these topics
and refers the reader to appropriate reviews where t induction of c-*fos*, the convulsant drug pentylenetetra-
zole was found to induce c-*fos* mRNA and protein firstly
in nuclei of neurons of the dentate gyrus, pyriform and
cingulate cortices, and, subsequently, throughout induction of c-fos, the convulsant drug pentylenetetra-
zole was found to induce c-fos mRNA and protein firstly
in nuclei of neurons of the dentate gyrus, pyriform and
cingulate cortices, and, subsequently, throughout corzole was found to mattee c-*fos* mRNA and protein firstly
in nuclei of neurons of the dentate gyrus, pyriform and
cingulate cortices, and, subsequently, throughout cor-
tex, hippocampus, and limbic system (Morgan et al.,
1 tex, hippocampus, and limbic system (Morgan et al., 1987; Dragunow and Robertson, 1987a). The time-
course of c-*fos* mRNA induction in vivo was protracted
compared with that in serum-stimulated fibroblasts and
in PC12 ce tex, hippocampus, and limbic system (Morgan et al., 1987; Dragunow and Robertson, 1987a). The time-
course of c-*fos* mRNA induction in vivo was protracted
compared with that in serum-stimulated fibroblasts and
in PC12 cel 1987; Dragunow and Robertson, 1987a). The time-
course of c-*fos* mRNA induction in vivo was protracted
compared with that in serum-stimulated fibroblasts and
in PC12 cells treated with NGF. Induction of c-*fos*
mRNA was course of c-*fos* mRNA induction in vivo was protracted compared with that in serum-stimulated fibroblasts and in PC12 cells treated with NGF. Induction of c-*fos* mRNA was refractory to additional seizure-mediated inducti compared with that in serum-stimulated fibroblasts a
in PC12 cells treated with NGF. Induction of c-
mRNA was refractory to additional seizure-mediat
induction, whereas Fos protein-like immunoreactiv
remained induced throu m FC12 cens treated with NGF. Induction of c -*jos* mRNA was refractory to additional seizure-mediated induction, whereas Fos protein-like immunoreactivity remained induced throughout the brain. Fos-like immunoreactivity induction, whereas Fos protein-like immunoreactivity
remained induced throughout the brain. Fos-like immu-
noreactivity was only found to be increased in neurons
and not glia (Morgan et al., 1987). The benzodiazepine
midaz remained induced throughout the brain. Fos-like immuremained induced throughout the brain. Fos-like immu-
noreactivity was only found to be increased in neurons
and not glia (Morgan et al., 1987). The benzodiazepine
midazolam that prevented seizure activity also pre-
vented noreactivity was only found to be increased in neurons
and not glia (Morgan et al., 1987). The benzodiazepine
midazolam that prevented seizure activity also pre-
vented Fos induction (Dragunow and Robertson, 1987a).
Fos in and not glia (Morgan et al., 1987). The benzodiazepine
midazolam that prevented seizure activity also pre-
vented Fos induction (Dragunow and Robertson, 1987a).
Fos induction generally only occurred in those areas that
exp 1990). Fos induction generally only occurred in those areas that
experienced seizures (Le Gal La Salle and Naquet,
1990).
Additional studies have shown that a coordinated in-
duction of IEGs occurs in the brain after seizure acti

duction of lEGs occurs in the brain after seizure activity experienced seizures (Le Gal La Salle and Naquet, 1990).

Additional studies have shown that a coordinated in-

duction of IEGs occurs in the brain after seizure activity

(Saffen et al., 1988; Sonnenberg et al., 1989a). c 1990).
Additional studies have shown that a coordinated in-
duction of IEGs occurs in the brain after seizure activity
(Saffen et al., 1988; Sonnenberg et al., 1989a). c-jun,
jun-B, zif 268, and jun-D mRNAs are also induce Additional studies have shown that a coordinated iduction of IEGs occurs in the brain after seizure activ (Saffen et al., 1988; Sonnenberg et al., 1989a). c -*ju* in -B, z *if* 268, and *jun*-D mRNAs are also induced in duction of EGs occurs in the brain after seizure activity
(Saffen et al., 1988; Sonnenberg et al., 1989a). c-jun,
jun-B, zif 268, and jun-D mRNAs are also induced in rat
brain neurons when animals are administered convul-
 jun-B, $zif268$, and jun-D mRNAs are also induced in rat
brain neurons when animals are administered convul-
sant drugs or given electroshock-induced seizures
(Saffen et al., 1988; Cole et al., 1990a). The increase in
prot brain neurons when animals are administered convulsant drugs or given electroshock-induced seizures
(Saffen et al., 1988; Cole et al., 1990a). The increase in
proto-oncogene mRNA is paralleled by an increase in
AP-1-like D sant arugs or given electrosnock-induced seizures.
(Saffen et al., 1988; Cole et al., 1990a). The increase
proto-oncogene mRNA is paralleled by an increase
AP-1-like DNA binding activity that persists on aver
for at least (Saffen et al., 1988; Cole et al., 1990a). The increase in proto-oncogene mRNA is paralleled by an increase in AP-1-like DNA binding activity that persists on average for at least 6 to 8 h after initiation of seizures (So proto-oncogene mRNA is paralleled by an increase in
AP-1-like DNA binding activity that persists on average
for at least 6 to 8 h after initiation of seizures (Sonnen-
berg et al., 1989a, b). Fos protein induction occurs b AP-1-like DNA binding activity that persists on average for at least 6 to 8 h after initiation of seizures (Sonner berg et al., 1989a, b). Fos protein induction occurs briefl within the first few hours and is not present for at least 6 to 8 h after initiation of seizures (Sonnen-
berg et al., 1989a, b). Fos protein induction occurs briefly
within the first few hours and is not present 6 to 8 h
after seizure-initiation, although AP-1-like within the first few hours and is not present 6 to 8 h after seizure-initiation, although AP-1-like DNA binding persists at these timepoints. This suggests that two Fos-related species of molecular weight 35 (possibly

IMMEDIATE-EARLY GENES A
Fra-1; Cohen and Curran, 1988) and 46 kD (possibly
Fra-2; Nishina et al., 1990), which show delayed induc-IMMEDIATE-EARLY GI
Fra-1; Cohen and Curran, 1988) and 46 kD (possit
Fra-2; Nishina et al., 1990), which show delayed inducion with respect to Fos, might participate with lat IMMEDIATE-EARLY GEN
Fra-1; Cohen and Curran, 1988) and 46 kD (possibly
Fra-2; Nishina et al., 1990), which show delayed induc
tion with respect to Fos, might participate with late
expressed Jun proteins to form Fra/Jun dim Fra-1; Cohen and Curran, 1988) and 46 kD (p
Fra-2; Nishina et al., 1990), which show delayed
tion with respect to Fos, might participate wit
expressed Jun proteins to form Fra/Jun dimers.
These results and those of others ra-1; Cohen and Curran, 1988) and 46 kD (possibly ra-2; Nishina et al., 1990), which show delayed induc-
on with respect to Fos, might participate with late-
pressed Jun proteins to form Fra/Jun dimers. These results and

tion with respect to Fos, might participate with late-
expressed Jun proteins to form Fra/Jun dimers.
These results and those of others suggest that seizure
activity results in the formation of a dynamic AP-1 com-
plex who tion with respect to Fos, might participate with late-
expressed Jun proteins to form Fra/Jun dimers. These results and those of others suggest that seizure clastivity results in the formation of a dynamic AP-1 com-
plex w expressed Jun proteins to form Fra/Jun dimers.

These results and those of others suggest that seizure

activity results in the formation of a dynamic AP-1 com-

plex whose composition changes with time, Fos/Jun

dimers in These results and those of others suggest that seizure
activity results in the formation of a dynamic AP-1 com-
plex whose composition changes with time, Fos/Jun
dimers initially, whereas Fos-B/Jun or Fra/Jun dimers
predom activity results in the formation of a dynamic AP-1 com-
plex whose composition changes with time, Fos/Jun at
dimers initially, whereas Fos-B/Jun or Fra/Jun dimers ca
predominate at later time points (Sonnenberg et al., nu plex whose composition changes with time, rossom
dimers initially, whereas Fos-B/Jun or Fra/Jun dimers
predominate at later time points (Sonnenberg et al., 1
1989a; Gass et al., 1992a). Krox-20 protein, such as
Krox-24 (zi dimers initially, whereas Fos-B/Jun or Fra/Jun dimers corredominate at later time points (Sonnenberg et al., nost 1989a; Gass et al., 1992a). Krox-20 protein, such as conversed to the Krox-24 (zif268), is also induced by s predominate at later time points (Sonnenberg et al., 1989a; Gass et al., 1992a). Krox-20 protein, such as (Krox-24 (zif268), is also induced by seizure activity (Bhat et al., 1992b; Hughes et al., 1994). Other forms of sei 1989a; Gass et al., 1992a). Krox-20 protein, such as ces of the ipsilateral hemisphere (Hughes et al., 1994).

Krox-24 (zif268), is also induced by seizure activity 3. Focal brain-injury and spreading depression.

(Bhat e (Bhat et al., 1992b; Hughes et al., 1994). Other forms of
seizures have also been shown to induce IEG expression in
within the nervous system. Kainic-acid (Popovici et al., a)
1988), bicuculline (Gass et al., 1992a), pilo seizures have also been shown to induce IEG expression
within the nervous system. Kainic-acid (Popovici et al.,
1988), bicuculline (Gass et al., 1992a), pilocarpine or
lithium and pilocarpine (Barone et al., 1993), MK801
a within the nervous system. Kainic-acid (Popovici et al., a
1988), bicuculline (Gass et al., 1992a), pilocarpine or
lithium and pilocarpine (Barone et al., 1993), MK801
and pilocarpine (Hughes et al., 1993c; Hughes et al., 1988), bicuculline (Gass et al., 1992a), pilocarpine or

lithium and pilocarpine (Barone et al., 1993), MK801

and pilocarpine (Hughes et al., 1993c; Hughes et al., $\frac{10}{1994}$), and audiogenic-induced seizures (Le Gal lithium and pilocarpine (Barone et al., 1993), MK&
and pilocarpine (Hughes et al., 1993c; Hughes et a
1994), and audiogenic-induced seizures (Le Gal La Sa
and Naquet, 1990) result in increased expression
IEGs. It has recen and pilocarpine (Hughes et al., 1993c; Hughes et al., 1994), and audiogenic-induced seizures (Le Gal La Salle and Naquet, 1990) result in increased expression of IEGs. It has recently been suggested that, like 2-deoxy-gluc 1994), and audiogenic-induced seizures (Le Gal La Salle and Naquet, 1990) result in increased expression of IEGs. It has recently been suggested that, like 2-deoxy-glucose use, Fos induction could be used as a general mark and Naquet, 1990) result in increased expression of IEGs. It has recently been suggested that, like 2-deoxy-
glucose use, Fos induction could be used as a general
marker of neuronal activity (Dragunow and Faull,
1989a; Sag IEGs. It has recently been suggested that, like 2-deoxy-
glucose use, Fos induction could be used as a general
marker of neuronal activity (Dragunow and Faull, neuronal
1989a; Sagar et al., 1988). Inasmuch as seizure-induc glacose use, Fos mudchon could be used as a general marker of neuronal activity (Dragunow and Faull, 1989a; Sagar et al., 1988). Inasmuch as seizure-induced c-fos induction does not occur in newborn rats given a convulsant 1989a; Sagar et al., 1988). Inasmuch as seizure-induc
c-*fos* induction does not occur in newborn rats giver
convulsant dose of kainic-acid before postnatal day P
this suggests that mechanisms responsible for seizure
media c-fos induction does not occur in newborn rats given a

convulsant dose of kainic-acid before postnatal day P13, and F

this suggests that mechanisms responsible for seizure-

mediated c-fos induction are not present at b convulsant dose of kainic-acid before postna
this suggests that mechanisms responsible
mediated c-fos induction are not present at h
iber et al., 1992b), (For a review of seizure-m
induction see Morgan and Curran, 1991a).
 is suggests that mechanisms responsible for seizure-
ediated c-*fos* induction are not present at birth (Schre-
er et al., 1992b), (For a review of seizure-mediated IEG
duction see Morgan and Curran, 1991a).
2. *Kindling*.

mediated c-fos induction are not present at birth (Schreiber et al., 1992b), (For a review of seizure-mediated IEG induction see Morgan and Curran, 1991a).
2. *Kindling*. Kindling is an animal model of seizure development iber et al., 1992b), (For a review of seizure-mediated II
induction see Morgan and Curran, 1991a).
2. *Kindling*. Kindling is an animal model of seizu
development or epileptogenesis, whereby periodic (i
daily or twice dail 2. *Kindling*. Kindling is an animal model of seizu
development or epileptogenesis, whereby periodic (i.
daily or twice daily) applications of an initially subco
vulsive focal electrical stimulation eventually lead (ov
a p development or epileptogenesis, whereby periodic (i.e., $\frac{1}{12}$ and dily or twice daily) applications of an initially subconvulsive focal electrical stimulation eventually lead (over induced a period of days or weeks) daily or twice daily) applications of an initially subconvulsive focal electrical stimulation eventually lead (over a period of days or weeks) to the formation of a generalised seizure. Focal electrical stimulation (usuall vulsive focal electrical stimulation eventually lead (over

a period of days or weeks) to the formation of a gener-

alised seizure. Focal electrical stimulation (usually to

the amygdala or hippocampus, two brain areas t a period of days or weeks) to the formation of a gener-

alised seizure. Focal electrical stimulation (usually to

the amygdala or hippocampus, two brain areas that

show kindling) results in a brief focal seizure or AD. T aised seizure. Focal electrical sumulation (usually to glial-like cells around the wound margin (but not distal
the amygdala or hippocampus, two brain areas that
show kindling) results in a brief focal seizure or AD. The
A show khidning) results in a brief local seizure of AD. The
AD is an absolute prerequisite for kindling to occur. ADs
in both the hippocampus and amygdala result in the
induction of IEGs. Within the hippocampus, a single
ki in both the hippocampus and amygdala result in the induction of IEGs. Within the hippocampus, a single $\frac{1}{72}$ kindling AD results in the strong induction of Fos, $\frac{1}{72}$ Fos-B, Fras, c-Jun, Jun-B, Jun-D, and Krox-2 induction of IEGs. Within the hippocampus, a single
kindling AD results in the strong induction of Fos
Fos-B, Fras, c-Jun, Jun-B, Jun-D, and Krox-24 proteins
in dentate granule cells and Fos, Jun-D, and Krox-24
proteins in kindling AD results in the strong induction of Fos,
Fos-B, Fras, c-Jun, Jun-B, Jun-D, and Krox-24 proteins in
in dentate granule cells and Fos, Jun-D, and Krox-24
proteins in somatostatin-containing neurons of the den-
ta Fos-B, Fras, c-Jun, Jun-B, Jun-D, and Krox-24 proteins $\frac{1}{10}$ in dentate granule cells and Fos, Jun-D, and Krox-24 Investigation is transient, with basal levels $\frac{1}{100}$ reached for all IEGs investigated by 48 h (D in dentate granule cells and Fos, Jun-D, and Krox-24
proteins in somatostatin-containing neurons of the den-
tate hilus. Induction is transient, with basal levels
reached for all IEGs investigated by 48 h (Dragunow and
Rob proteins in somatostatin-containing neurons of the dentate hilus. Induction is transient, with basal levels reached for all IEGs investigated by 48 h (Dragunow and Robertson, 1987b; Dragunow et al., 1992; Hughes et al., su tate hilus. Induction is transient, with basal levels
reached for all IEGs investigated by 48 h (Dragunow and
Robertson, 1987b; Dragunow et al., 1992; Hughes et al.,
submitted). In addition, mRNAs coding for c-fos, c-jun,
 reached for all IEGs investigated by 48 h (Dragunow and Robertson, 1987b; Dragunow et al., 1992; Hughes et al., submitted). In addition, mRNAs coding for c-fos, c-jun, and *NGFI-A* (*zif* 268/*krox-24*) are also induced by submitted). In addition, mRNAs coding for c-fos, c-jun, and NGFI-A ($zif 268/krox-24$) are also induced by kindling ADs within the hippocampus (Shin et al., 1990; Simonato et al., 1991; Hughes et al., submitted; Drasubmitted). In addition, mRNAs coding for c-fos, c-jun,
and *NGFI-A* (*zif* 268/*krox-24*) are also induced by kin-
dling ADs within the hippocampus (Shin et al., 1990;
Simonato et al., 1991; Hughes et al., submitted; Draand *NGFI-A* (*zif* 268/*krox-24*) are also induced by kindling ADs within the hippocampus (Shin et al., 1990; m
Simonato et al., 1991; Hughes et al., submitted; Dra-19
gunow et al., 1989b). Amygdala kindling also induces dling ADs within the hippocampus (Shin et al., 1990;
Simonato et al., 1991; Hughes et al., submitted; Dra-
gunow et al., 1989b). Amygdala kindling also induces
increased expression of c-*fos* mRNA and Fos protein
(Dragunow Simonato et al., 1991; Hughes et al., submitted; Dra-
gunow et al., 1989b). Amygdala kindling also induces cell
increased expression of c-fos mRNA and Fos protein inji
(Dragunow et al., 1988; Clark et al., 1991a; Teskey et increased expression of c-fos mRNA and Fos protein (Dragunow et al., 1988; Clark et al., 1991a; Teskey et al., 1991) c-jun, jun-B, krox-24 mRNA and protein, and Krox-20 protein in rat brain (Hughes et al., 1994).

IMMEDIATE-EARLY GENES AND GENE EXPRESSION 145
and 46 kD (possibly The distribution of IEG expression depends upon the
h show delayed induc-stage of kindling and the length of the AD (Clark et al., and GENE EXPRESSION 145
The distribution of IEG expression depends upon the
stage of kindling and the length of the AD (Clark et al.,
1991a; Tesky et al., 1991). We have found that in naive
rats (except for a single test s The distribution of IEG expression depends upon the stage of kindling and the length of the AD (Clark et al., 1991a; Tesky et al., 1991). We have found that in naive rats (except for a single test stimulation that was used stage of Kindling and the length of the AD (Clark et 1991a; Tesky et al., 1991). We have found that in na rats (except for a single test stimulation that was used check electrode placement), a single amygdala AD sults in u rats (except for a single test stimulation that was used to check electrode placement), a single amygdala AD results in unilateral increases in IEG expression, moderately within amygdala (basolateral/lateral/medial/corti-c rats (except for a single test stimulation that was used to check electrode placement), a single amygdala AD results in unilateral increases in IEG expression, moderately within amygdala (basolateral/lateral/medial/cortica check electrode placement), a single amygdala AD results in unilateral increases in IEG expression, mode
ately within amygdala (basolateral/lateral/medial/cort
cal and basomedial nuclei) and claustrum/endopiriform
nucleus suits in unitateral increases in LEG expression, moderately within amygdala (basolateral/lateral/medial/cortical and basomedial nuclei) and claustrum/endopiriform nucleus and maximally in piriform and perirhinal cortices o cal and basomedial nuclei) and claustrum/endopirifunucleus and maximally in piriform and perirhinal coses of the ipsilateral hemisphere (Hughes et al., 199
3. Focal brain-injury and spreading depressi
Wounding of a fibrobl

(Bhat et al., 1992b; Hughes et al., 1994). Other forms of Wounding of a fibroblast monolayer in vitro by scratch-
seizures have also been shown to induce IEG expression ing a line into a confluent layer of NIH 3T3 cells l nucleus and maximally in piriform and perirhinal cortices of the ipsilateral hemisphere (Hughes et al., 1994).
3. Focal brain-injury and spreading depression.
Wounding of a fibroblast monolayer in vitro by scratching a lin ces of the ipsilateral hemisphere (Hughes et al., 1994).

3. Focal brain-injury and spreading depression.

Wounding of a fibroblast monolayer in vitro by scratch-

ing a line into a confluent layer of NIH 3T3 cells leads t 3. Focal brain-injury and spreading depression.
Wounding of a fibroblast monolayer in vitro by scratching a line into a confluent layer of NIH 3T3 cells leads to
a rapid induction of Fos-like immunoreactivity in cells
lin Wounding of a fibroblast monolayer in vitro by scratching a line into a confluent layer of NIH 3T3 cells leads to a rapid induction of Fos-like immunoreactivity in cells lining the wound (Verrier et al., 1986). In rodents a rapid induction of Fos-like immunoreactivity in cells
lining the wound (Verrier et al., 1986). In rodents, injury
to the cortex produced by insertion of a drill bit 2 mm
into underlying cortex (Dragunow and Robertson,
19 a rapid mudch of Fos-like immunoreactivity in cens
lining the wound (Verrier et al., 1986). In rodents, injury
to the cortex produced by insertion of a drill bit 2 mm
into underlying cortex (Dragunow and Robertson,
1988b; to the cortex produced by insertion of a drill bit 2 mm
into underlying cortex (Dragunow and Robertson,
1988b; Dragunow et al., 1990c), suction removal of cor-
tex (Sharp et al., 1990), or disruption of pia-arachnoid
(Herr into underlying cortex (Dragunow and Robertson, 1988b; Dragunow et al., 1990c), suction removal of cortex (Sharp et al., 1990), or disruption of pia-arachnoid (Herrera and Robertson, 1990a) leads to unilateral induction of 1988b; Dragunow et al., 1990c), suction removal of cortex (Sharp et al., 1990), or disruption of pia-arachnoid (Herrera and Robertson, 1990a) leads to unilateral induction of c -*fos* mRNA and Fos and Fra proteins in neu (Herrera and Robertson, 1990a) leads to unilateral induction of c -*fos* mRNA and Fos and Fra proteins in neurons of the injured cortex but not of the undamaged hippocampus. After injury ipsilateral cingulate, piriform a (Herrera and Robertson, 1990a) leads to unilateral induction of c-*fos* mRNA and Fos and Fra proteins in neurons of the injured cortex but not of the undamaged hippocampus. After injury ipsilateral cingulate, piriform and duction of c-fos mRNA and Fos and Fra proteins in
neurons of the injured cortex but not of the undamaged
hippocampus. After injury ipsilateral cingulate, piriform
and neocortex show increased levels of both c-fos mRNA
and neurons of the injured cortex but not of the undamaged
hippocampus. After injury ipsilateral cingulate, piriform
and neocortex show increased levels of both c-fos mRNA
and Fos protein. Within the neocortex the induction of mppocampus. Arter mjury ipsilateral cingulate, piritorm
and neocortex show increased levels of both c-fos mRNA
and Fos protein. Within the neocortex the induction of
Fos-like immunoreactivity (antibody detects Fos and
Fras and Fos protein. Within the neocortex the indu
Fos-like immunoreactivity (antibody detects F
Fras) is laminar, with highest induction seen in
2,3,5, and 6 (Dragunow and Faull, 1990; Dragun
Robertson, 1988b; Dragunow et al. Fos-like immunoreactivity (antibody detects Fos and Fras) is laminar, with highest induction seen in layers 2,3,5, and 6 (Dragunow and Faull, 1990; Dragunow and Robertson, 1988b; Dragunow et al., 1990b, c).
Induction of c-

Robertson, 1988b; Dragunow et al., 1990b, c).

induction see Morgan and Curran, 1991a).

2. Kindling. Kindling is an animal model of seizure

development or epileptogenesis, whereby periodic (i.e.,

daily or twice daily) Fras) is iaminar, with mighest madciton seen in layers
2,3,5, and 6 (Dragunow and Faull, 1990; Dragunow and
Robertson, 1988b; Dragunow et al., 1990b, c).
Induction of c-fos (30 min) and Fos (1 h) occurs rapidly
in cortex. modertson, 19660, Dragunow et al., 19900, C.

Induction of c-fos (30 min) and Fos (1 h) occurs rapidly

in cortex. Fos is essentially absent at 4 h. Induction of

Fra is persistent remaining for at least 24 and possibly

7 Fra is persistent remaining for at least 24 and possibly Fra is persistent remaining for at least 24 and possibly 72 h (Sharp et al., 1990). In addition, injury leads to induction of Fos-like immunoreactivity in ependyma lining the lateral and occasionally the third ventricle, i 72 h (Sharp et al., 1990). In addition, injury leads to induction of Fos-like immunoreactivity in ependyma lining the lateral and occasionally the third ventricle, in glial-like cells around the wound margin (but not dista ing the lateral and occasionally the third ventricle, in to the wound), and in cells of the pia (Dragunow and gnai-nke cells around the wound margin (but not distal
to the wound), and in cells of the pia (Dragunow and
Robertson, 1988b; Dragunow et al., 1990c; Sharp et al.,
1990). Fos-like immunoreactivity was expressed maxi-
mally to the wound), and in cells of the pla (Dragunow and Robertson, 1988b; Dragunow et al., 1990c; Sharp et al., 1990). Fos-like immunoreactivity was expressed maximally in glial cells between 12 to 24 h, but was gone by 72 h 1990). Fos-like immunoreactivity was expressed mailly in glial cells between 12 to 24 h, but was gone 72 h after injury, suggesting that injury-mediated pression of Fos-like immunoreactivity is more persist in nerve versus ally in glial cells between 12 to 24 h, but was gone by
 ℓ h after injury, suggesting that injury-mediated ex-

ession of Fos-like immunoreactivity is more persistent

nerve versus glial cells (Dragunow et al., 1990a).

The injury, suggesting that injury-inethated expression of Fos-like immunoreactivity is more persistent
in nerve versus glial cells (Dragunow et al., 1990a).
Unilateral induction of Fos proteins in nerve cells
throughout t pression of ros-ike immunoreactivity is more persistent
in nerve versus glial cells (Dragunow et al., 1990a).
Unilateral induction of Fos proteins in nerve cells
throughout the injured hemisphere may result from in-
jury-i Unilateral induction of Fos proteins in nerve cells
throughout the injured hemisphere may result from in-
jury-induced cortical spreading depression. Literature
supporting this idea demonstrates that direct applica-
tion o throughout the injured hemisphere may result from in-
jury-induced cortical spreading depression. Literature
supporting this idea demonstrates that direct applica-
tion of KCl (potassium chloride) to neocortex, which
induc jury-induced cortical spreading depression. Literature
supporting this idea demonstrates that direct applica-
tion of KCl (potassium chloride) to neocortex, which
induces spreading depression, results in Fos protein in-
du supporting this idea demonstrates that direct application of KCl (potassium chloride) to neocortex, which induces spreading depression, results in Fos protein in duction in a pattern very similar to that seen after mechani tion of KCl (potassium chloride) to neocortex, which
induces spreading depression, results in Fos protein in-
duction in a pattern very similar to that seen after
mechanical cortical injury (Herrera and Robertson,
1990b; H mauces spreading depression, results in ros protein in-
duction in a pattern very similar to that seen after
mechanical cortical injury (Herrera and Robertson,
1990b; Herrera, et al., 1993). Induction in non-nerve
cells ma mechanical cortical injury (Herrera and Kobertson
1990b; Herrera, et al., 1993). Induction in non-nerve
cells may be induced by injury-released factors at the
injury site (Dragunow and Robertson, 1988b; Dragunov
et al., 19 1990b; Herrera, et al., 1993). Induction in non-nerve cells may be induced by injury-released factors at the injury site (Dragunow and Robertson, 1988b; Dragunow et al., 1990c). Focal brain injury to the hippocampus produ cells may be induced by injury-released factors at the injury site (Dragunow and Robertson, 1988b; Dragunow et al., 1990c). Focal brain injury to the hippocampus produced by needle insertion and saline injection results in

REVI

PHARMACOLOGICAL

¹
HUGHES AND DRAGUNOW
mRNA, and protein (Hughes et al., 1993a) and Krox-20, (For review see l
Fos-B, and Jun-D protein in nerve cells of the dentate 1992). In awake HUGHES AND I
Fos-B, and protein (Hughes et al., 1993a) and Krox-20,
Fos-B, and Jun-D protein in nerve cells of the dentate
gyrus (Dragunow and Hughes, 1993). In contrast, in HUGHES AND DRA
mRNA, and protein (Hughes et al., 1993a) and Krox-20, (Fo
Fos-B, and Jun-D protein in nerve cells of the dentate 199
gyrus (Dragunow and Hughes, 1993). In contrast, in res
non-nerve cells, Fos, Krox-24, c-Ju Fos-B, and Jun-D protein in nerve cells of the dentate 19
gyrus (Dragunow and Hughes, 1993). In contrast, in res
non-nerve cells, Fos, Krox-24, c-Jun, Jun-B and Jun-D, pr
but not Krox-20 or Fos-B proteins, are induced in c gyrus (Dragunow and Hughes, 1993). In contrast, in
non-nerve cells, Fos, Krox-24, c-Jun, Jun-B and Jun-D,
but not Krox-20 or Fos-B proteins, are induced in cells
around the wound margin, lining the ventricles or in the
pia m-nerve cells, Fos, Krox-24, c-Jun, Jun-B and Jun-D, present to Krox-20 or Fos-B proteins, are induced in cells (L
found the wound margin, lining the ventricles or in the all
found the wound margin, lining the ventricles o

but not Krox-20 or Fos-B proteins, are induced in cells
around the wound margin, lining the ventricles or in the
pial surfaces of the brain (Dragunow and Hughes, 1993).
4. Hypoxic-ischemic stroke. A number of studies have
 pial surfaces of the brain (Dragunow and Hughes, 1993). and $zif 268$ mRNA and Krox-20 and Krox-24 proteins in
4. Hypoxic-ischemic stroke. A number of studies have dentate gyrus neurons (Richardson et al., 1992;
investigat 4. Hypoxic-ischemic stroke. A number of studies have 4. Hypoxic-ischemic stroke. A number of studies have dinvestigated the expression of IEGs in HI brain injury, Walthough the results have been contradictory. HI in the infant rat brain was associated with induction of Fos i investigated the expression of IEGs in HI brain injury, V
although the results have been contradictory. HI in the
infant rat brain was associated with induction of Fos in
neurons only in the neocortex on the nonligated si although the results have been contradictory. HI in the
infant rat brain was associated with induction of Fos in
neurons only in the neocortex on the nonligated side of
the brain (because of seizures). Induction of Fos-lik miant rat brain was associated with induction of Fos in
neurons only in the neocortex on the nonligated side of
the brain (because of seizures). Induction of Fos-lik
immunoreactivity was, however, induced in glial-lik
cell ieurons omy in the heocortex on the homigated side of
the brain (because of seizures). Induction of Fos-like
immunoreactivity was, however, induced in glial-like
cells on the ligated side (Gunn et al., 1990). Other stud-
i the brain (because of seizures). Induction of Fos-like
immunoreactivity was, however, induced in glial-like
cells on the ligated side (Gunn et al., 1990). Other stud-
ies have found both strong and weak induction of other
 immunoreactivity was, however, induced in glial-like (cells on the ligated side (Gunn et al., 1990). Other studies have found both strong and weak induction of other I
IEGs and IEGPs in the injured brain after HI (Abe et a cells on the ligated side (Gunn et al., 1990). Other studies have found both strong and weak induction of other lifeds and IEGPs in the injured brain after HI (Abe et al., 1991b; An et al., 1992; Onodera et al., 1989; Wess ies have found both strong and weak induction of other IEC
IEGs and IEGPs in the injured brain after HI (Abe et al., of 1
1991b; An et al., 1992; Onodera et al., 1989; Wessel et per
al., 1991; Ikeda et al., 1990; Popvici e IEGs and IEGPs in the injured brain after HI (Abe et al., 1991); An et al., 1992; Onodera et al., 1989; Wessel et al., 1991; Ikeda et al., 1990; Popvici et al., 1990; Gubits et al., 1993; Gass et al., 1992b); induction occ 1991b; An et al., 1992; Onodera et al., 1989; Wessel et al., 1991; Ikeda et al., 1990; Popvici et al., 1990; Gubits et al., 1993; Gass et al., 1992b); induction occurred only in areas surrounding the ischaemic core (Uemura al., 1991; Ikeda et al., 1990; Popvici et al., 1990; Gubits slet al., 1993; Gass et al., 1992b); induction occurred only (time areas surrounding the ischaemic core (Uemura et al., st 1991b) or in neurons resistant to injur et al., 1993; Gass et al., 1992b); induction occurred only
in areas surrounding the ischaemic core (Uemura et al.,
1991b) or in neurons resistant to injury (Uemura et al.,
1991a). The reasons for these differences are prob in areas surrounding the ischaemic core (Uemura et al., s
1991b) or in neurons resistant to injury (Uemura et al.,
1991a). The reasons for these differences are probably to
associated with differences in the animal models 1991b) or in neurons resistant to injury (Uemura et al., 1991a). The reasons for these differences are probably associated with differences in the animal models used, the severity of the strokes, and the possibility of sei associated with differences in the animal models used, the severity of the strokes, and the possibility of seizure activity or spreading depression, all of which could conassociated with differences in the animal models used, hip
the severity of the strokes, and the possibility of seizure thr
activity or spreading depression, all of which could con-
found the results (Gunn et al., 1990; Gas the severity of
activity or spr
found the rest
Additional wo
clear picture.
5. Nerve tro Evity of spreading depression, an of which codid con-

ind the results (Gunn et al., 1990; Gass et al., 1992b). The

ditional work in this area is required to present any

levar picture.

5. Nerve transection. Transection

Additional work in this area is required to present a clear picture.

5. Nerve transection. Transection of nerve fibres c

induce complex changes in the axotomised neuronal c

body, including increased expression of growth clear picture.
5. Nerve transection. Transection of nerve fibres cinduce complex changes in the axotomised neuronal cody, including increased expression of growth associated proteins, cytoskeleton proteins, and neuropeptid 5. Nerve transection. Transection of nerve fibres can induce complex changes in the axotomised neuronal celled
body, including increased expression of growth associated proteins, cytoskeleton proteins, and neuropeptides
Mo induce complex changes in the axotomised neuronal cell
body, including increased expression of growth associ-
ated proteins, cytoskeleton proteins, and neuropeptides.
More recently, it has been identified that rapid but lo body, including increased expression of growth asset at proteins, cytoskeleton proteins, and neuropeptic More recently, it has been identified that rapid but lo lasting increases in specific IEGs and IEGPs also occ
in the ated proteins, cytoskeleton proteins, and neuropeptides. c-J
More recently, it has been identified that rapid but long-
lasting increases in specific IEGs and IEGPs also occurs sil
in the axotomised neuron cell body after More recently, it has been identified that rapid but lon
lasting increases in specific IEGs and IEGPs also occu
in the axotomised neuron cell body after nerve transe
tion. In most studies, Jun mRNA and proteins (c-Ju
and J lasting increases in specific IEGs and IEGPs also occurs sible in the axotomised neuron cell body after nerve transec-
tion. In most studies, Jun mRNA and proteins (c-Jun Cal
and Jun-B and Jun-D) are strongly induced in ax in the axotomised neuron cell body after nerve transec-
tion. In most studies, Jun mRNA and proteins (c-Jun Ca
and Jun-B and Jun-D) are strongly induced in axoto-
mised neurons, whereas the induction of other IEGs only one tion. In most studies, Jun mRNA and proteins (c-Ju and Jun-B and Jun-D) are strongly induced in axot mised neurons, whereas the induction of other IEGs on occurs in rare cases, and always in combination wit Jun-family memb and Jun-B and Jun-D) are strongly induced in axoto-
mised neurons, whereas the induction of other IEGs only
occurs in rare cases, and always in combination with
Jun-family members (Jenkins and Hunt, 1991; Herd-
egen et al. mised neurons, whereas the induction of other IEGs only
occurs in rare cases, and always in combination with
Jun-family members (Jenkins and Hunt, 1991; Herd-
egen et al., 1992; Leah et al., 1991, 1993; Jenkins et al.,
199 Jun-family members (Jenkins and Hunt, 1991; Herd-
egen et al., 1992; Leah et al., 1991, 1993; Jenkins et al.,
1993; Haas et al., 1993; Dragunow, 1992; Rutherford et
al., 1993).
6. Long-term potentiation and memory formatio **6.** *Long-term potentiation and memory formation.*

Brief episodes of tetanic activation and memory formation. The performance of the performation of the perforant path input to the dentate gyrus result in a persistent in

1993; Haas et al., 1993; Dragunow, 1992; Rutherford et al., 1993).

6. Long-term potentiation and memory formation.

Brief episodes of tetanic activation of the perforant path

input to the dentate gyrus result in a persi ach, 1993).

6. Long-term potentiation and memory formation. expressively be extended to the dentate gyrus result in a persistent in-

ing crease, or long-term potentiation, in the synaptic effi-

cacy of this monosynaptic Brief episodes of tetanic activation of the perforant p
input to the dentate gyrus result in a persistent
crease, or long-term potentiation, in the synaptic ϵ
cacy of this monosynaptic excitatory pathway (Bliss a
Lomo, input to the dentate gyrus result in a persistent i
crease, or long-term potentiation, in the synaptic ef
cacy of this monosynaptic excitatory pathway (Bliss an
Lomo, 1973). LTP is a persistent activity-depende
form of syn crease, or long-term potentiation, in the synaptic efficacy of this monosynaptic excitatory pathway (Bliss and Lomo, 1973). LTP is a persistent activity-dependent form of synaptic plasticity that stands as a good candidate cacy of this monosynaptic excitatory pathway (Bliss and PH
Lomo, 1973). LTP is a persistent activity-dependent lave
form of synaptic plasticity that stands as a good candi-
indate for the mechanism involved in associative Lomo, 1973). LTP is a persistent activity-dependent lavanarr et al., 1993). Songbirds hear the songs of other
form of synaptic plasticity that stands as a good candi-
individuals of their species and respond by modifying
d form of synaptic plasticity that stands as a good candidate for the mechanism involved in associative memory. The mechanisms underlying the persistence of LTP are the believed to rely on de-novo protein synthesis (Otani et al., 1989; Fazeli et al., 1993). puttodies performed t

Fos-B, and Jun-D protein in nerve cells of the dentate 1992). In awake animals, various stimulus paradigms gyrus (Dragunow and Hughes, 1993). In contrast, in resulting in LTP reliably increase the expression of Fra non-ne DRAGUNOW
(For review see Dragunow et al., 1989b; Abraham et al.,
1992). In awake animals, various stimulus paradigms DRAGUNOW
(For review see Dragunow et al., 1989b; Abraham et al.,
1992). In awake animals, various stimulus paradigms
resulting in LTP reliably increase the expression of Fra DRAGUNOW
(For review see Dragunow et al., 1989b; Abraham et al.,
1992). In awake animals, various stimulus paradigms
resulting in LTP reliably increase the expression of Fra
proteins but not c-fos mRNA, Fos or Fos-B protei (For review see Dragunow et al., 1989b; Abraham et al., 1992). In awake animals, various stimulus paradigms resulting in LTP reliably increase the expression of Fra proteins but not c-*fos* mRNA, Fos or Fos-B proteins (Dra (For review see Dragunow et al., 1989b; Abraham et al., 1992). In awake animals, various stimulus paradigms resulting in LTP reliably increase the expression of Fra proteins but not c -*fos* mRNA, Fos or Fos-B proteins (1992). In awake animals, various stimulus paradigms
resulting in LTP reliably increase the expression of Fra
proteins but not c-fos mRNA, Fos or Fos-B proteins
(Dragunow et al., 1989a; Demmer et al., 1993; Jeffery et
al., resulting in LTP reliably increase the expression of Fra
proteins but not c-fos mRNA, Fos or Fos-B proteins
(Dragunow et al., 1989a; Demmer et al., 1993; Jeffery et
al., 1990), c-jun, jun-B and jun-D mRNA and proteins
and procession for c-*jos* finality, Fos or Fos-B processes
(Dragunow et al., 1989a; Demmer et al., 1993; Jeffery et
al., 1990), c-*jun, jun*-B and *jun*-D mRNA and proteins
and *zif* 268 mRNA and Krox-20 and Krox-24 proteins (Dragunow et al., 1993)
al., 1990), c-jun, jun-B
and $zif 268$ mRNA and
dentate gyrus neuro:
Williams et al., 1995).
In the dentate gyrus ., 1990), c-jun, jun-B and jun-D mRNA and proteins
id $zif 268$ mRNA and Krox-20 and Krox-24 proteins in
ntate gyrus neurons (Richardson et al., 1992;
illiams et al., 1995).
In the dentate gyrus of anaesthetised rats, indu

and $zif 268$ mRNA and Krox-20 and Krox-24 proteins in
dentate gyrus neurons (Richardson et al., 1992;
Williams et al., 1995).
In the dentate gyrus of anaesthetised rats, induction
of LTP reliably results in increased expr mentate gyrus neurons (Kicharuson et al., 1992,
Williams et al., 1995).
In the dentate gyrus of anaesthetised rats, induction
of LTP reliably results in increased expression of *zif* 268
mRNA, less reliable induction of *j* In the dentate gyrus of anaesthetised rats, induction
of LTP reliably results in increased expression of zif 268
mRNA, less reliable induction of jun -B and c - jun mRNA,
and little or no induction of c - fos mRNA or Fos of LTP renably results in increased expression of zij 206 mRNA, less reliable induction of jun -B and $c-jun$ mRNA, and little or no induction of c -fos mRNA or Fos protein (Douglas et al., 1988; Schreiber et al., 1991a; and little or no induction of c-*fos* mRNA or Fos protein (Douglas et al., 1988; Schreiber et al., 1991a; Cole et al., 1989, 1990b; Wisden et al., 1990). The lesser induction of IEGs in anaesthetised animals is thought to (Douglas et al., 1966, Schleiber et al., 1991a, Cole et al., 1989, 1990b; Wisden et al., 1990). The lesser induction of IEGs in anaesthetised animals is thought to be because of the effects of anaesthesia, which also reduc 1969, 1990b, Wisten et al., 1990). The lesser induction of
IEGs in anaesthetised animals is thought to be because
of the effects of anaesthesia, which also reduces LTP
persistence (Jeffery et al., 1990). Correlational stud IEGS In anaesthetised animals is thought to be because
of the effects of anaesthesia, which also reduces LTP
persistence (Jeffery et al., 1990). Correlational studies
show that Krox-24 (Abraham et al., 1993) and Krox-20
(W persistence (Jeffery et al., 1990). Correlational studies
show that Krox-24 (Abraham et al., 1993) and Krox-20
(Williams et al., 1995) are most likely to be involved in
stabilising LTP.

Additional work in this area is required to present any levels after 2 h (Tischmeyer et al., 1990). The levels of clear picture.
both c-fos and c-jun mRNA are also seen to rise in the 5. Nerve transection. Transection of Learning-related phenomenon also induce lEG formashow that Krox-24 (Abraham et al., 1993) and Krox-20 (Williams et al., 1995) are most likely to be involved in stabilising LTP.
Learning-related phenomenon also induce IEG formation in the brain (Kaczmarek, 1993a, b). For (williams et al., 1995) are most likely to be involved in
stabilising LTP.
Learning-related phenomenon also induce IEG forma-
tion in the brain (Kaczmarek, 1993a, b). For example,
hippocampal c-fos mRNA levels in rats are tion in the brain (Kaczmarek, 1993a, b). For example, hippocampal c-fos mRNA levels in rats are increased three-fold immediately after training to attain foot-shock-motivated brightness discrimination in a Y-maze. Learning-related phenomenon also induce IEG formation in the brain (Kaczmarek, 1993a, b). For example, hippocampal c-fos mRNA levels in rats are increased three-fold immediately after training to attain footshock-motivated tion in the brain (Kaczmarek, 1993a, b). For example,
hippocampal c-fos mRNA levels in rats are increased
three-fold immediately after training to attain foot-
shock-motivated brightness discrimination in a Y-maze.
The ele mppocampar c-jos mKNA levels in rats are increased
three-fold immediately after training to attain foot-
shock-motivated brightness discrimination in a Y-maze.
The elevated levels of c-fos mRNA had returned to basal
levels three-told immediately after training to attain foot-
shock-motivated brightness discrimination in a Y-maze.
The elevated levels of c-*fos* mRNA had returned to basal
levels after 2 h (Tischmeyer et al., 1990). The levels shock-motivated brightness discrimination in a 1-maz-
The elevated levels of c-*fos* mRNA had returned to bass
levels after 2 h (Tischmeyer et al., 1990). The levels of
both c-*fos* and c-*jun* mRNA are also seen to rise i 1989, 1990b; Wisden et al., 1990). The lesser induction of 5 Ses, in anases
the the effects of anases having is is thought to be because of the effects of anases
having his is hought to be because α of the effects of c-jun mRNA, suggesting that the learning of the dis*c-jun* mRNA, suggesting that the learning of chicks that have previously learnt the behaviour and are just repeating it show lower expression of c-*fos* and c-*jun* mRNA, suggesting that the learning of the dis-
criminati of the side for enhanced expression of *c-fos* and *c-jun* mRNA, suggesting that the learning of the discrimination task itself, and not the behaviour, is responsible for enhanced expression of *c-fos* and *c-jun* mRNA (An c-jun mRNA, suggesting that the learning of the commination task itself, and not the behaviour, is resp sible for enhanced expression of c-fos and c-jun mR (Anokhin and Rose, 1990). In addition, imprinting (I Cabe et al., crimination task itself, and not the behaviour, is respon-
sible for enhanced expression of c-*fos* and c-*jun* mRNA
(Anokhin and Rose, 1990). In addition, imprinting (Mc-
Cabe et al., 1993), exposure of chicks to a rich e sible for enhanced expression of c-*fos* and c-*jun* mRNA
(Anokhin and Rose, 1990). In addition, imprinting (Mc-
Cabe et al., 1993), exposure of chicks to a rich environ-
ment (Anokhin et al., 1991) or training of chicks i (Anokhin and Rose, 1990). In addition, imprinting (Mc-

Cabe et al., 1993), exposure of chicks to a rich environ-

ment (Anokhin et al., 1991) or training of chicks in a

one-trial passive avoidance task (Rose, 1991; Anok Cabe et al., 1993), exposure of chicks to a rich environment (Anokhin et al., 1991) or training of chicks in a one-trial passive avoidance task (Rose, 1991; Anokhin et al., 1991), leads to increased expression of c-*fos* m ment (Anokhin et al., 1991) or training of chicks in
one-trial passive avoidance task (Rose, 1991; Anokhin
al., 1991), leads to increased expression of c-fos mRN
and Fos-like immunoreactivity within a specific regi
of the one-trial passive avoidance task (Rose, 1991; Anokhin et al., 1991), leads to increased expression of c-fos mRNA and Fos-like immunoreactivity within a specific region of the chick forebrain, the intermediate medial hypers ., 1991), leads to increased expression of c-fos mRNA
in Fos-like immunoreactivity within a specific region
the chick forebrain, the intermediate medial hyper-
riatum ventrale.
The majority of neurons (96.5%) that express

and Fos-like immunoreactivity within a specific region
of the chick forebrain, the intermediate medial hyper-
striatum ventrale.
The majority of neurons (96.5%) that express Fos also
express the gamma protein kinase C iso of the cinck forebrain, the intermediate medial hyper-
striatum ventrale.
The majority of neurons (96.5%) that express Fos also
express the gamma protein kinase C isoenzyme (PKC γ),
suggesting that a connection may exis The majority of neurons $(96.5%)$ that express Fos also
express the gamma protein kinase C isoenzyme $(PKC\gamma)$,
suggesting that a connection may exist between learn-
ing, the intermediate medial hyperstriatum ventrale,
and F express the gamma protein kinase C isoenzyme (PKC
suggesting that a connection may exist between lead
ing, the intermediate medial hyperstriatum ventra
and Fos expression. That is, learning could active
PKC, which would th suggesting that a connection may exist between learning, the intermediate medial hyperstriatum ventrale, and Fos expression. That is, learning could activate PKC, which would then lead to Fos production (Ambalayanarr et al ing, the intermediate medial hyperstriatum ventrale,
and Fos expression. That is, learning could activate
PKC, which would then lead to Fos production (Amba-
lavanarr et al., 1993). Songbirds hear the songs of other
indivi PKC, which would then lead to Fos production (Amba-
lavanarr et al., 1993). Songbirds hear the songs of other
individuals of their species and respond by modifying
their own vocal and social behaviour. Young birds learn
th lavanarr et al., 1993). Songbirds hear the songs of other individuals of their species and respond by modifying their own vocal and social behaviour. Young birds learn their songs by imitating models that they hear (Mello individuals of their species and respond by modifying
their own vocal and social behaviour. Young birds learn
their songs by imitating models that they hear (Mello et
al., 1992). It is significant then that species-specifi their own vocal and social behaviour. Young birds learn
their songs by imitating models that they hear (Mello et
al., 1992). It is significant then that species-specific song
presentation to songbirds has also been seen to their songs by imitating models that they hear (wield et al., 1992). It is significant then that species-specific song presentation to songbirds has also been seen to causes large increases in the expression of $ZENK$ mRNA

REVIEW

PHARMACOLOGICAL

IMMEDIATE-EARLY GENES AND GENE EXPRESSION
identified in chick learning processes. In the songbird manipulation) causes the expression of c-Fos protein-
these areas include the hyperstriatum ventrale and cau- like immunorea IMMEDIATE-EARLY GEN
identified in chick learning processes. In the songbird
these areas include the hyperstriatum ventrale and cau-
dal neostriatum. Presentation of other auditory stimu-IMMEDIATE-EARLY G.

identified in chick learning processes. In the songbi

these areas include the hyperstriatum ventrale and ca

dal neostriatum. Presentation of other auditory stimulation was less effective or ineffectiv identified in chick learning processes. In the songbird
these areas include the hyperstriatum ventrale and cau-
dal neostriatum. Presentation of other auditory stimu-
lation was less effective or ineffective in increasing
 identified in chick learning processes. In the songbised these areas include the hyperstriatum ventrale and cadal neostriatum. Presentation of other auditory stime lation was less effective or ineffective in increasin *ZEN* these areas include the hyperstriatum ventrale and caudal neostriatum. Presentation of other auditory stimulation was less effective or ineffective in increasing $ZENK$ expression. (Mello et al., 1992). Furthermore, behavio dal neostriatum. Presentation of other auditory stimulation was less effective or ineffective in increasing ZENK expression. (Mello et al., 1992). Furthermore, behavioural training of a two-way passive avoidance response i lation was less effective or ineffective in increasing $ZENK$ expression. (Mello et al., 1992). Furthermore, is behavioural training of a two-way passive avoidance sesponse induces c -*fos* and $zif 268$ mRNA in rat hippoc ZENK expression. (Mello et al., 1992). Furthermore, ical behavioural training of a two-way passive avoidance suppressions induces c-fos and $zif268$ mRNA in rat hipmocampus and visual cortex during training (Nikolaev et na behavioural training of a two-way passive avoidance s
response induces c-fos and $zif 268$ mRNA in rat hip-
pocampus and visual cortex during training (Nikolaev et n
al., 1992a, b): this seems to be related to learning and response induces c-fos and a
pocampus and visual cortex d
al., 1992a, b): this seems to l
not to motor activity or reacti
(Nikolaev et al., 1992a, b).
Others reports have show: campus and visual cortex during training (Nikolaev et n. 1992a, b): this seems to be related to learning and T
t to motor activity or reaction to pain during training the
ikolaev et al., 1992a, b). The contract contract c

al., 1992a, b): this seems to be related to learning and Theories to motor activity or reaction to pain during training the (Nikolaev et al., 1992a, b).

Chers reports have shown a delayed expression of TV or *fos* in rat not to motor activity or reaction to pain during training the (Nikolaev et al., 1992a, b).

Chers reports have shown a delayed expression of Γ c-fos in rat sensory cortex after sexual learning in male trats (Bialy et al (Nikolaev et al., 1992a, b).

Others reports have shown a delayed expression c -*fos* in rat sensory cortex after sexual learning in mal

rats (Bialy et al., 1992), increased expression of c -F c

and Krox-24, but not Others reports have shown a delayed expression of IV t c-fos in rat sensory cortex after sexual learning in male tras rats (Bialy et al., 1992), increased expression of c-Fos hain and Krox-24, but not c-Jun, protein in ac c-fos in rat sensory cortex after sexual learning in male
rats (Bialy et al., 1992), increased expression of c-Fos
hand Krox-24, but not c-Jun, protein in accessory olfac-
tory bulb during the formation of an olfactory mem rats (Bialy et al., 1992), increased expression of c-
and Krox-24, but not c-Jun, protein in accessory of
tory bulb during the formation of an olfactory memor
mice (Brennan et al., 1992), and increased expressio
c-*fos* an and Krox-24, but not c-Jun, protein in accessory olfatory bulb during the formation of an olfactory memory i
mice (Brennan et al., 1992), and increased expression of the original c-fos and c-jun mRNAs specifically within t tory bulb during the formation of an olfactory memory in
mice (Brennan et al., 1992), and increased expression of
c-fos and c-jun mRNAs specifically within the hippocam-
pus of mice during learning of a bar-pressing task (mice (Brennan et al., 1992), and increased expression of c-*fos* and c-*jun* mRNAs specifically within the hippocampus of mice during learning of a bar-pressing task (Heurteaux et al., 1993). Apamin, a bee venom neurotoxin c-fos and c-jun mRNAs specifically within the hippocam-
pus of mice during learning of a bar-pressing task (Heu-
rteaux et al., 1993). Apamin, a bee venom neurotoxin
induced increase in lEG expression
within the hippocamp rteaux et al., 1993). Apamin, a bee venom neurotoxin
that can improve learning and memory retention, en-
hanced the learning-induced increase in IEG expression
within the hippocampus (Heurteaux et al., 1993). In-
creased e rteaux et al., 1993). Apamin, a bee venom neurotoxin info
that can improve learning and memory retention, en-
hanced the learning-induced increase in IEG expression of f
within the hippocampus (Heurteaux et al., 1993). Inthat can improve learning and memory retention, en-
hanced the learning-induced increase in IEG expression of i
within the hippocampus (Heurteaux et al., 1993). In-
creased expression of Fos-like immunoreactivity in I
brai hanced the learning-induced increase in IEG expression
within the hippocampus (Heurteaux et al., 1993). In-
creased expression of Fos-like immunoreactivity in
brain nuclei is also associated with conditioning and
pseudo-co within the hippocampus (Heurteaux et al., 1993). In-
creased expression of Fos-like immunoreactivity in D
brain nuclei is also associated with conditioning and occu
pseudo-conditioning of the rabbit nictitating membrane st creased expression of Fos-like immunoreactivity in
brain nuclei is also associated with conditioning and
pseudo-conditioning of the rabbit nictitating membrane
reflex (Irwin et al., 1992). In addition, performance in an
From Finder is also associated with conditioning and obseudo-conditioning of the rabbit nictitating membrane spectral reflex (Irwin et al., 1992). In addition, performance in an Λ escape task induces c-Fos in the motor

reflex (Irwin et al., 1992). In addition, performance in an escape task induces c-Fos in the motor cortex of rats (Castro-Alamancos et al., 1992).

7. Stress. Various forms of stress lead to increased expression of IEGs wi escape task induces c-Fos in the motor cortex of rats

(Castro-Alamancos et al., 1992).

7. Stress. Various forms of stress lead to increased

expression of IEGs within the brain (Ceccatelli et al.,

1989). For example, im The Stress response after capsaich administration stressed
expression of IEGs within the brain (Ceccatelli et al., we
1989). For example, immobilisation stress or the general ho
stress response after capsaicin administrati expression of IEGs within the brain (Ceccatelli et al., 1989). For example, immobilisation stress or the general hat
ress response after capsaicin administration strongly vincreases expression of IEGs in two brain regions 1989). For example, immobilisation stress or the general hor
stress response after capsaicin administration strongly var
increases expression of IEGs in two brain regions: the pay
central amygdaloid nucleus and PVN. Stress stress response after capsaicin administration strongly
increases expression of IEGs in two brain regions: the
central amygdaloid nucleus and PVN. Stress associated
with capsaicin administration induces c -*fos*, c -*ju* increases expression of IEGs in two brain regions: the paws (Naranjo et al., 1991).

central amygdaloid nucleus and PVN. Stress associated c-Jun protein can be induced in layers I and II of

with capsaicin administration $jun-B$ in both central amygdaloid nucleus and PVN, with capsaicin administration induces c-fos, c-jun, and die jun-B in both central amygdaloid nucleus and PVN, powhereas jun-D expression is selectively increased in the (HPVN (Honkaniemi et al. 1992). Immobilisation stres jun-B in both central amygdaloid nucleus and PVN,
whereas jun -D expression is selectively increased in the
PVN (Honkaniemi et al. 1992). Immobilisation stress
will also induce Fos-like immunoreactivity in both of
these re nereas jun-D expression is selectively increased in the (H_ON (Honkaniemi et al. 1992). Immobilisation stress in 11 also induce Fos-like immunoreactivity in both of Injese regions (Covenas et al., 1993; Honkaniemi, 1992).

PVN (Honkaniemi et al. 1992). Immobilisation strewill also induce Fos-like immunoreactivity in both these regions (Covenas et al., 1993; Honkaniemi, 199
The stress associated with earclipping has also be shown to increase will also induce Fos-like immunoreactivity in both of Ir
these regions (Covenas et al., 1993; Honkaniemi, 1992). 23
The stress associated with earclipping has also been in
shown to increase c -*fos* mRNA in mouse brain (these regions (Covenas et al., 1993; Honkaniemi, 1992). 2
The stress associated with earclipping has also been is
shown to increase c-fos mRNA in mouse brain (Naka-
jima et al., 1989a). Handling and a single injection of r The stress associated with earclipping has also been in shown to increase c-*fos* mRNA in mouse brain (Naka-
jima et al., 1989a). Handling and a single injection of nisotonic saline has been reported to result in increased shown to increase c-*fos* mRNA in mouse brain (Naka-spima et al., 1989a). Handling and a single injection of noisotonic saline has been reported to result in increased 19 and neocortex (Sharp cheap PVN, amygdala, hippocamp jima et al., 1989a). Handling and a single injection of isotonic saline has been reported to result in increased c-*fos* mRNA levels in various brain regions, including the PVN, amygdala, hippocampus, and neocortex (Sharp *c-fos* mRNA levels in various brain regions, including the PVN, amygdala, hippocampus, and neocortex (Sharp et al., 1991b). Other IEG mRNAs (i.e., *fos-B*, *jun-B*, *c-jun, zif* 268 and *fra-*1), as detected by Northern b the PVN, amygdala, hippocampus, and neocortex (Sharp cessing of odours have been shown to influence IEG et al., 1991b). Other IEG mRNAs (i.e., *fos-B*, *jun-B*, expression. For example, Fos-like immunoreactivity inc-*jun* the PVN, amygdala, hippocampus, and neocortex
et al., 1991b). Other IEG mRNAs (i.e., *fos-B*,
c-*jun, zif* 268 and *fra*-1), as detected by Norther
ting, may also be increased in brain by injection s
h after injection of s *8. Sensory stimulation (noxious, non-noxious, dfactory*
 8. Sensory stimulation (noxious, non-noxious, olfactory
 and visual) and circadian rhythms. Both noxious
 (Fitzgerald, 1990) and non-noxious (sensory) peripher

ting, may also be increased in brain by injection stress 1
h after injection of saline (Perisco et al., 1993).
8. Sensory stimulation (noxious, non-noxious, olfactory
and visual) and circadian rhythms. Both noxious
(Fitzge and visual) and circadian rhythms. Both noxious tufted cells of the main olfactory bulb in response to brief (Fitzgerald, 1990) and non-noxious (sensory) peripheral exposure of male rats to peppermint or isoamyl acetate st 8. Sensory stimulation (noxious, non-noxious, olfactory
and visual) and circadian rhythms. Both noxious
(Fitzgerald, 1990) and non-noxious (sensory) peripheral
stimuli induce c-fos expression in spinal dorsal horn
neurons. and *usual)* and circuidan rightness. Both hoxious
(Fitzgerald, 1990) and non-noxious (sensory) peripheral
stimuli induce c-fos expression in spinal dorsal horn
neurons. For example, physiological stimulation of rat
primar

AND GENE EXPRESSION
manipulation) causes the expression of c-Fos prote
like immunoreactivity in nuclei of postsynaptic neuro AND GENE EXPRESSION 147

manipulation) causes the expression of c-Fos protein-

like immunoreactivity in nuclei of postsynaptic neurons

of the dorsal horn (Hunt et al., 1987). Activation of small AND GENE EXPRESSION 147

manipulation) causes the expression of c-Fos protein-

like immunoreactivity in nuclei of postsynaptic neurons

of the dorsal horn (Hunt et al., 1987). Activation of small

diameter cutaneous senso manipulation) causes the expression of c-Fos protein like immunoreactivity in nuclei of postsynaptic neuros of the dorsal horn (Hunt et al., 1987). Activation of smaliameter cutaneous sensory afferents by noxious chemical manipulation) causes the expression of c-Fos protein-
like immunoreactivity in nuclei of postsynaptic neurons
of the dorsal horn (Hunt et al., 1987). Activation of small
diameter cutaneous sensory afferents by noxious chem of the dorsal horn (Hunt et al., 1987). Activation of small diameter cutaneous sensory afferents by noxious chemical or heat stimulation strongly induces Fos, mainly in superficial layers I and II of the dorsal horn where ical or heat stimulation strongly induces Fos, mainly in This effect is reasonably general being independent of rear or heat stimulation strongly induces ros, mainly in
superficial layers I and II of the dorsal horn where the
majority of unmyelinated nociceptive afferents termi-
nate, although lower induction occurs in layers III to majority of uninyemiated nociceptive afferents terminate, although lower induction occurs in layers III to V.
This effect is reasonably general being independent of
the noxious agent applied, although some stimuli in-
crea This effect is reasonably general being independent of
the noxious agent applied, although some stimuli in-
crease Fos-like immunoreactivity more in layers III and
IV than do others (Strassman and Vos, 1993). In con-
trast the noxious agent applied, although some stimuli in-
crease Fos-like immunoreactivity more in layers III and
IV than do others (Strassman and Vos, 1993). In con-
trast, activation of low-threshold cutaneous afferents by
ha crease Fos-like immunoreactivity more in layers III and
IV than do others (Strassman and Vos, 1993). In con-
trast, activation of low-threshold cutaneous afferents by
hair-brushing and gentle joint manipulation induced
wea IV than do others (Strassman and Vos, 1993). In contrast, activation of low-threshold cutaneous afferents by hair-brushing and gentle joint manipulation induced weaker Fos expression in layers II to IV (and rarely in layer trast, activation of low-threshold cutaneous afferents by
hair-brushing and gentle joint manipulation induced
weaker Fos expression in layers II to IV (and rarely in
layer I), a finding consistent with termination zones fo Hair-brushing and gentie joint mampulation induced
weaker Fos expression in layers II to IV (and rarely in
layer I), a finding consistent with termination zones for
Aδ and C primary afferent fibres (Hunt et al., 1987).
No layer I), a finding consistent with termination zones $A\delta$ and C primary afferent fibres (Hunt et al., 198
Noxious peripheral stimulation also results in Fos
duction in thalamic areas known to process nocicept
informatio Ao and C primary anerent incres (riunt et al., 1967).
Noxious peripheral stimulation also results in Fos in-
duction in thalamic areas known to process nociceptive
information (Bullitt, 1989, 1990). In addition, non-nox-
i duction in thalamic areas known to process nociceptive
information (Bullitt, 1989, 1990). In addition, non-nox-
ious sensory stimulation produced by tactile stimulation
of face whiskers induces Fos in somatosensory cortex
 information (Bullitt, 1989, 1990). In addition, non-noxformation (Bullitt, 1989, 1990). In addition, non-nox-
us sensory stimulation produced by tactile stimulation
face whiskers induces Fos in somatosensory cortex
lack and Mack, 1992).
Differential induction of IEGs has been

ious sensory stimulation produced by tactile stimulation
of face whiskers induces Fos in somatosensory cortex
(Mack and Mack, 1992).
Differential induction of IEGs has been reported to
occur in dorsal horn neurons after no of face whiskers induces Fos in somatosensory cortex
(Mack and Mack, 1992).
Differential induction of IEGs has been reported to
occur in dorsal horn neurons after noxious (hot water)
stimulation of the hind paw. Specifical (Mack and Mack, 1992).

Differential induction of IEGs has been reported to

occur in dorsal horn neurons after noxious (hot water)

stimulation of the hind paw. Specifically, c-fos, c-jun and
 NGFI-A (*zif* 268/*krox*-2 Differential induction of TEGs has been reported to
occur in dorsal horn neurons after noxious (hot water)
stimulation of the hind paw. Specifically, c-fos, c-jun and
NGFI-A (zif 268/krox-24), but not jun-B or jun-D mRNA,
 occur in dorsal horn neurons after noxious (hot water)
stimulation of the hind paw. Specifically, c-fos, c-jun and
NGFI-A (zif 268/krox-24), but not jun-B or jun-D mRNA,
is induced in neurons located mainly in laminae I a stimulation of the hind paw. Specifically, c-fos, c-jun and NGFI-A (zif 268/krox-24), but not jun-B or jun-D mRNA, is induced in neurons located mainly in laminae I and II, but also in V and X (Wisden et al., 1990). In ano *NGFI-A (zif 268/krox-24)*, but not *jun-B* or *jun-D* mRNA, is induced in neurons located mainly in laminae I and II, but also in V and X (Wisden et al., 1990). In another study, c-fos and *jun-B*, but not c-*jun* or *ju* is induced in neurons located mainly in laminae I and I
but also in V and X (Wisden et al., 1990). In anothe
study, c-fos and jun-B, but not c-jun or jun-D, mRNA
were induced mainly in superficial layers of the dorse
horn but also in V and X (Wisden et al., 1990). In anothe
study, c-fos and jun-B, but not c-jun or jun-D, mRNA
were induced mainly in superficial layers of the dorsa
horn after either peripheral injection of Freund's adju
vant study, c-fos and jun-B, but n
were induced mainly in supe
horn after either peripheral i
vant (inflammation model) or
paws (Naranjo et al., 1991).
c-Jun protein can be indu ere induced mainly in superficial layers of the dorsal
rn after either peripheral injection of Freund's adju-
nt (inflammation model) or heat stimulation of hind-
ws (Naranjo et al., 1991).
c-Jun protein can be induced in

horn after either peripheral injection of Freund's adjuvant (inflammation model) or heat stimulation of hind-
paws (Naranjo et al., 1991).
c-Jun protein can be induced in layers I and II of
dorsal horn (with slight inducti vant (inflammation model) or heat stimulation of hind-
paws (Naranjo et al., 1991).
c-Jun protein can be induced in layers I and II of
dorsal horn (with slight induction in layer III) by re-
peated squeezing of the plantar paws (Naranjo et al., 1991).

c-Jun protein can be induced in layers I and II of

dorsal horn (with slight induction in layer III) by re-

peated squeezing of the plantar surface of rat hind-paw

(Herdegen et al., 1991). O c-Jun protein can be induced in layers I and II dorsal horn (with slight induction in layer III) by repeated squeezing of the plantar surface of rat hind-par
(Herdegen et al., 1991). Opiates modify induction of c-fc
in th dorsal horn (with slight induction in layer III) by repeated squeezing of the plantar surface of rat hind-paw (Herdegen et al., 1991). Opiates modify induction of c-fos in the spinal cord of the rat after noxious stimulat peated squeezing of the plantar surface of rat hind-paw
(Herdegen et al., 1991). Opiates modify induction of c-*fos*
in the spinal cord of the rat after noxious stimulation.
Injection of morphine (10 mg/kg i.v.) reduced t (Herdegen et al., 1991). Opiates modify induction of c-fos
in the spinal cord of the rat after noxious stimulation.
Injection of morphine (10 mg/kg i.v.) reduced to 14% and
23% of control the number of Fos-positive neuron in the spinal cord of the rat after noxious stimulation.
Injection of morphine $(10 \text{ mg/kg} \text{ i.v.})$ reduced to 14% and
 23% of control the number of Fos-positive neurons seen
in deep (III-VI and X) and superficial (I a Injection of morphine (10 mg/kg i.v.) reduced to 14% and 23% of control the number of Fos-positive neurons seen in deep (III-VI and X) and superficial (I and II) layers of spinal dorsal horn, respectively, after hot water 1990). deep (III-VI and X) and superficial (I and II) layers of
inal dorsal horn, respectively, after hot water (52°C)
xious stimulation of rat right hind paw (Tolle et al.,
90).
In addition, olfactory information and sensory pro

spinal dorsal norn, respectively, after not water (32 C)
noxious stimulation of rat right hind paw (Tolle et al.,
1990).
In addition, olfactory information and sensory pro-
cessing of odours have been shown to influence IE 1990).
In addition, olfactory information and sensory processing of odours have been shown to influence IEG
expression. For example, Fos-like immunoreactivity in-
creases in accessory olfactory structures of female rats
ex exposed to male odours (Dudley et al., 1992), whereas cessing of odours have been shown to influence IEG
expression. For example, Fos-like immunoreactivity in-
creases in accessory olfactory structures of female rats
exposed to male odours (Dudley et al., 1992), whereas
c-*fo* expression. For example, Fos-like immunoreactivity increases in accessory olfactory structures of female rats
exposed to male odours (Dudley et al., 1992), whereas
e-fos mRNA increases dramatically in cells of the glo-
mer creases in accessory olfactory structures of female rats
exposed to male odours (Dudley et al., 1992), whereas
c-fos mRNA increases dramatically in cells of the glo-
merular layer and underlying granule, mitral, and
tufted exposed to male odours (Dudley et al., 1992), whereas c-fos mRNA increases dramatically in cells of the glomerular layer and underlying granule, mitral, and tufted cells of the main olfactory bulb in response to brief expo c-jos mixixa increases dramat
merular layer and underlyin
tufted cells of the main olfactor
exposure of male rats to peppo
odours (Guthrie et al., 1993).
Visual input also controls II mertuar layer and underlying grantie, mitral, and
tufted cells of the main olfactory bulb in response to brief
exposure of male rats to peppermint or isoamyl acetate
odours (Guthrie et al., 1993).
Visual input also control

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and protein in visual cortex depends on ongoing visual
input. Blockade of afferent visual activity with intraoc-HUGHES AND I

and protein in visual cortex depends on ongoing visual

input. Blockade of afferent visual activity with intraoc-

ular injections of tetrodotoxin results in rapid, dramatic

reductions of $krox-24$ mRNA and pr and protein in visual cortex depends on ongoing visual winput. Blockade of afferent visual activity with intraoc-
ular injections of tetrodotoxin results in rapid, dramatic L
reductions of $krox-24$ mRNA and protein in this input. Blockade of afferent visual activity with intraccular injections of tetrodotoxin results in rapid, dramatic reductions of $krox-24$ mRNA and protein in this area (Worley et al., 1991). Indeed, mono-ocular visual depr ular injections of tetrodotoxin results in rapid, dramatic LC
reductions of $krox-24$ mRNA and protein in this area roi
(Worley et al., 1991). Indeed, mono-ocular visual depri-
duration and Krox-24 immunohistochemistry revea reductions of $krox-24$ mRNA and protein in this area
(Worley et al., 1991). Indeed, mono-ocular visual depri-
vation and Krox-24 immunohistochemistry reveals ocu-
lar dominance columns in monkey visual cortex
(Chaudhuri an worley et al., 1991). Indeed, mono-octuar visual depi-
vation and Krox-24 immunohistochemistry reveals ocu-
lar dominance columns in monkey visual cortex te
(Chaudhuri and Cynader, 1993). Brief visual experience al
induces valuon and Krox-24 minimum isochemistry reveals ocular
lar dominance columns in monkey visual cortex
(Chaudhuri and Cynader, 1993). Brief visual experience
induces c-fos, jun-B and $krox-24$ (egr-1) but not c-jun
mRNAs in c induces c-fos, $jun-B$ and $krox-24$ ($egr-1$) but not c- jun mRNAs in cat visual cortex (Beaver et al., 1993, Rosen et al., 1992b), whereas light also induces a Fos-like nuclear antigen in retinal neurons (Sagar and Sharp, 1990) (Chaudhuri and Cynader, 1993). Brief visual experience al.

induces c-fos, jun-B and $krox-24$ (egr-1) but not c-jun

mRNAs in cat visual cortex (Beaver et al., 1993, Rosen et *in*

al., 1992b), whereas light also induces a induces c-fos, jun-B and $krox-24$ (egr-1) but not c-jun
mRNAs in cat visual cortex (Beaver et al., 1993, Rosen et in
al., 1992b), whereas light also induces a Fos-like nuclear contigen in retinal neurons (Sagar and Sharp, mkivks in cat visual cortex (beaver et al., 1990, losending and al., 1992b), whereas light also induces a Fos-like nuclearitigen in retinal neurons (Sagar and Sharp, 1990). Induced IEGs might be involved in the process whe tigen in retinal neurons (Sagar and Sharp, 1990). The
duced IEGs might be involved in the process whereby
sually elicited activity controls visual cortical develop-
ent (i.e., visual system plasticity).
Light pulses that a

induced IEGs might be involved in the process whereby depres
visually elicited activity controls visual cortical develop-
tial bl
ment (i.e., visual system plasticity). al., 19
Light pulses that alter the phasing of the i visually elicited activity controls visual cortical develoption is
ment (i.e., visual system plasticity). The haster the phasing of the internal ture
increadian clock result in IEG induction within the SCN cle
of the hypot Eight pulses that alter the phasing of the internal tus circadian clock result in IEG induction within the SCN cleum of the hypothalamus (Rea, 1989; Rusak et al., 1990). The child SCN seems to contain a light-entrainable c circadian clock result in IEG induction within the SCN
of the hypothalamus (Rea, 1989; Rusak et al., 1990). The
SCN seems to contain a light-entrainable circadian
pacemaker that is responsible for the generation of a
wide SCIN seems to contain a ngin-entrainable circulant
pacemaker that is responsible for the generation of a
wide range of circadian physiological and behavioural
rhythms in mammals. Bilateral destruction of the SCN
abolishes, pacemaker that is responsible for the generation of a

wide range of circadian physiological and behavioural

rhythms in mammals. Bilateral destruction of the SCN

Du

abolishes, whereas transplantation of fetal SCN re-

l rhythms in mammais. Bliateral destruction of the SCN
abolishes, whereas transplantation of fetal SCN re-
stores, circadian rhythmicity in rodents (Rusak and
Zucker, 1979; Rea, 1989). It seems that gene expression
is import abolishes, whereas transplantation of feta
stores, circadian rhythmicity in rodents (
Zucker, 1979; Rea, 1989). It seems that gene
is important for both the generation and co
cadian rhythms (Kornhauser et al., 1992).
Photi pres, circadian rhythmicity in rodents (Rusak and
cker, 1979; Rea, 1989). It seems that gene expression
important for both the generation and control of cir-
dian rhythms (Kornhauser et al., 1992).
Photic induction of IEGs

Zucker, 1979; Rea, 1989). It seems that gene expression sio
is important for both the generation and control of cir-
cadian rhythms (Kornhauser et al., 1992). 199
Photic induction of IEGs occurs in subjective night but
and is important for both the generation and control of circle cadian rhythms (Kornhauser et al., 1992).
Photic induction of IEGs occurs in subjective night bu
not subjective day. This finding links IEG induction wit
phase ent cadian rhythms (Kornhauser et al., 1992). 19

Photic induction of IEGs occurs in subjective night but

not subjective day. This finding links IEG induction with

phase entrainment, inasmuch as the phase of the circa-

vali not subjective day. This finding links IEG induction with
phase entrainment, inasmuch as the phase of the circa-
dian clock is only sensitive to photic entrainment during
subjective night. The induction of IEGs is predomin not subjective day. This finding links IEG induction with
phase entrainment, inasmuch as the phase of the circa-
dian clock is only sensitive to photic entrainment during
subjective night. The induction of IEGs is predomin phase entrainment, inasmuch as the phase of the circadian clock is only sensitive to photic entrainment during
subjective night. The induction of IEGs is predominantly
located within the ventrolateral subdivision of the SC dian clock is only sensitive to photic entrainment during 1
subjective night. The induction of IEGs is predominantly
located within the ventrolateral subdivision of the SCN,
although weaker induction occurs in rostral SCN subjective night. The induction of IEGs is predominantly located within the ventrolateral subdivision of the SCN, although weaker induction occurs in rostral SCN dorsal and lateral borders (Rea, 1989; Rusak et al., 1990; A located within the ventrolateral subdivision of the SCN,
although weaker induction occurs in rostral SCN dorsal
and lateral borders (Rea, 1989; Rusak et al., 1990; Abe et
al., 1992). Photic exposure of rodents during subje although weaker induction occurs in rostral SCN dorsal
and lateral borders (Rea, 1989; Rusak et al., 1990; Abe et
al., 1992). Photic exposure of rodents during subjective
night can induce Fos-like immunoreactivity (Rea, 19 and *iateral borders* (*i.ea, 1969*; *i.usak et al., 1990*; *i.be et al., 1992*). Photic exposure of rodents during subjective night can induce Fos-like immunoreactivity (Rea, 1989; Rusak et al., 1990; Earnest et al., 1990 might can induce Fos-like immunoreactivity (Rea, 1989;
Rusak et al., 1990; Earnest et al., 1990; Abe et al., 1991a,
1992), c-*fos* mRNA and *NGFI*-A (*zif* 268) mRNA (Rusak
et al., 1990, 1992), and *jun*-B, *jun*-D and c-Rusak et al., 1990; Earnest et al., 1990; Abe et al., 1991a, 1992), c-fos mRNA and *NGFI*-A (zif 268) mRNA (Rusak et al., 1990, 1992), and *jun*-B, *jun*-D and *c-jun* mRNAs (Rusak et al., 1992). The increase in *c-jun* 1992), c-fos mRNA and *NGFI*-A (*zif* 268) mRNA (Rusak et al., 1990, 1992), and *jun*-B, *jun*-D and c-*jun* mRNAs (Rusak et al., 1992). The increase in c-*jun* mRNA is small, however (Kornhauser et al., 1992), and prelim et al., 1990, 1992), and *jun*-B, *jun*-D and c-*jun* mRNAs (Rusak et al., 1992). The increase in c-*jun* mRNA is small, however (Kornhauser et al., 1992), and preliminary results suggest that c-Jun protein may not be indu usak et al., 1992). The increase in c -*jun* mRNA is
nall, however (Kornhauser et al., 1992), and prelimi-
rry results suggest that c -Jun protein may not be in-
ced in SCN by photic stimulation (Rusak et al., 1992).
Re

sman, nowever (Kornmauser et al., 1992), and premin-
harry results suggest that c-Jun protein may not be in-
duced in SCN by photic stimulation (Rusak et al., 1992).
Recently, it has also been demonstrated that the con-
st duced in SCN by photic stimulation (Rusak et al., 1992)
Recently, it has also been demonstrated that the constitutively expressed TF CREB becomes phosphorylate
on Serine-133 (and therefore transcriptionally activated) in S Recently, it has also been demonstrated that the constitutively expressed TF CREB becomes phosphorylated
on Serine-133 (and therefore transcriptionally activated) in SCN in response to photic stimulation. Inas-
much as IEG Sulturively expressed IF CREB becomes phosphorylated the condensity on Serine-133 (and therefore transcriptionally acti-
Vated) in SCN in response to photic stimulation. Inas-
much as IEG promoters contain CREB binding sit vated) in SCN in response to photic stimulation. Inasmuch as IEG promoters contain CREB binding sites, it
is possible that CREB-P controls IEG expression in SCN
in response to photic stimulation. Photic stimulation-
induce much as IEG promoters contain CREB binding sites, it
is possible that CREB-P controls IEG expression in SCN
in response to photic stimulation. Photic stimulation-
induced CREB phosphorylation only occurs during sub-
jectiv 1993). in response to photic stimulation. Photic stimulation-
induced CREB phosphorylation only occurs during sub-
jective night, supporting this possibility (Ginty et al.,
1993).
9. Sleep/sleep deprivation. Cholinergically-induc

rapid exercise phosphoryiation only occurs during sub-
jective night, supporting this possibility (Ginty et al., S
1993).
9. Sleep / sleep deprivation. Cholinergically-induced
rapid eye movement sleep can induce Fos-like

input. Blockade of afferent visual activity with intraoc-
sal tegmental and pedunculopontine tegmental nuclei,
ular injections of tetrodotoxin results in rapid, dramatic
LC, dorsal raphe, and pontine reticular formation (HUGHES AND DRAGUNOW
1990 oing visual with rapid eye movement sleep, such as the lateral dor-DRAGUNOW
with rapid eye movement sleep, such as the lateral dor-
sal tegmental and pedunculopontine tegmental nuclei,
LC, dorsal raphe, and pontine reticular formation (Shi-
romani et al., 1992). In addition, sleep depriva with rapid eye movement sleep, such as the lateral dor-
sal tegmental and pedunculopontine tegmental nuclei,
LC, dorsal raphe, and pontine reticular formation (Shi-
romani et al., 1992). In addition, sleep deprivation in-
 with rapid eye movement sleep, such as the lateral dor-
sal tegmental and pedunculopontine tegmental nuclei,
LC, dorsal raphe, and pontine reticular formation (Shi-
romani et al., 1992). In addition, sleep deprivation in-
 Example in a manuformation per text and perfect that the LC, dorsal raphe, and pontine reticular formation (S
romani et al., 1992). In addition, sleep deprivation
duces Fos-like immunoreactivity (Pompeiano et
1992) and c-LC, uorsal raphe, and pontine reticular formation (Shi-
romani et al., 1992). In addition, sleep deprivation in-
duces Fos-like immunoreactivity (Pompeiano et al.,
1992) and c-*fos* and *NGFI*-A mRNAs and, less consis-
ten duces Fos-like immunoreactivity (Pompeiano et al., 1992) and c-fos and *NGFI*-A mRNAs and, less consistently, *jun*-B but not c-*jun* mRNA in rat brain (O'Hara et al., 1993).
10. Cardiovascular control and immediate-early 1992) and c-fos and *NGFI*-A mRNAs and, less consistently, *jun*-B but not c-*jun* mRNA in rat brain (O'Hara et al., 1993).
 10. Cardiovascular control and immediate-early gene
 induction. In studies attempting to iden

of the hypothalamus (Rea, 1989; Rusak et al., 1990). The chial nucleus, LC, supraoptic nucleus, inferior olive,
SCN seems to contain a light-entrainable circadian subfornical organ, organ vasculosum, hypothalamus,
pacemake cuits, *Jah-B* but not c-*Jah* influed in rat brain (O Hara
al., 1993).
10. Cardiovascular control and immediate-early geinduction. In studies attempting to identify central c
cuits involved in cardiovascular control in all, 1995).

10. Cardiovascular control and immediate-early gene

induction. In studies attempting to identify central cir-

cuits involved in cardiovascular control in rats, a lower-

ing of blood pressure either by stimu 10. Caraloouscular control and immediate-early ginduction. In studies attempting to identify central cuits involved in cardiovascular control in rats, a low ing of blood pressure either by stimulation of the adepressor ner maaction. In studies attempting to identify central circuits involved in cardiovascular control in rats, a lower-
ing of blood pressure either by stimulation of the aortic
depressor nerve (McKitrick et al., 1992) or by sub cuits involved in cardiovascular control in rats, a lower
ing of blood pressure either by stimulation of the aortic
depressor nerve (McKitrick et al., 1992) or by substan
tial blood-volume removal (Dun et al., 1993; Badoer tus solitarius, area postrema, ventrolateral medulla, nu-
tial, 1992) causes Fos protein induction in nucleus trac-
tus solitarius, area postrema, ventrolateral medulla, nu-
cleus ambiguus, medullary reticular formation, p depressor nerve (MCKLLICK et al., 1992) of by substial blood-volume removal (Dun et al., 1993; Badoe
al., 1992) causes Fos protein induction in nucleus t
tus solitarius, area postrema, ventrolateral medulla,
cleus ambiguus tial blood-volume removal (Dun et al., 1993; Badoer et al., 1992) causes Fos protein induction in nucleus tractus solitarius, area postrema, ventrolateral medulla, nucleus ambiguus, medullary reticular formation, parabrach al., 1992) causes Fos protein induction in nucleus tratus solitarius, area postrema, ventrolateral medulla, n
cleus ambiguus, medullary reticular formation, parabrehial nucleus, LC, supraoptic nucleus, inferior oliv
subfor tus solitarius, area postrema, ventrolateral medulla, nucleus ambiguus, medullary reticular formation, parabra-
chial nucleus, LC, supraoptic nucleus, inferior olive,
subformical organ, organ vasculosum, hypothalamus,
cent cleus ambiguus, medullary reticular formation, parabrachial nucleus, LC, supraoptic nucleus, inferior olive, subfornical organ, organ vasculosum, hypothalamus, central nucleus of the amygdala, bed nucleus of the stria term chial nucleus, LC, supraoptic nucleus, inferior oliversubfornical organ, organ vasculosum, hypothalamu
central nucleus of the amygdala, bed nucleus of the stiterminalis, and islands of Calleja (McKitrick et al., 1992).
Dun subfornical organ, organ vasculosum, hypothalamus,
central nucleus of the amygdala, bed nucleus of the stria
terminalis, and islands of Calleja (McKitrick et al., 1992;
Dun et al., 1993; Badoer et al., 1992). Electrical st central nucleus of the amygdala, bed nucleus of the st
terminalis, and islands of Calleja (McKitrick et al., 19!
Dun et al., 1993; Badoer et al., 1992). Electrical stin
lation of the vagus nerve or mechanical stimulation
t terminalis, and islands of Calleja (McKitrick et al., 1992;
Dun et al., 1993; Badoer et al., 1992). Electrical stimu-
lation of the vagus nerve or mechanical stimulation of
the carotid sinus (stretching) leads to increased Dun et al., 1993; Badoer et al., 1992). Electrical stimulation of the vagus nerve or mechanical stimulation of the carotid sinus (stretching) leads to increased expression of c-fos and NGFI-A mRNA in nucleus tractus solita lation of the vagus nerve or mechanical stimulation of
the carotid sinus (stretching) leads to increased expres-
sion of c-*fos* and *NGFI*-A mRNA in nucleus tractus soli-
tarius and paratrigeminal nucleus (Rutherford et a the carotid sinus (stretching) leads to increased expression of c-fos and NGFI-A mRNA in nucleus tractus solitarius and paratrigeminal nucleus (Rutherford et al., 1992b). In addition, it has been shown that circulating ang sion of c-fos and NGFI-A mRNA in nucleus tractus soli-
tarius and paratrigeminal nucleus (Rutherford et al.,
1992b). In addition, it has been shown that circulating
angiotensin II (iv infusion of 30 to 55 pmol/kg/min over tarius and paratrigeminal nucleus (Rutherford et al., 1992b). In addition, it has been shown that circulating angiotensin II (iv infusion of 30 to 55 pmol/kg/min over 2 h) induces Fos in the subformical organ and organum v 1992). 2 h) induces Fos in the subfornical organ and organum
vasculosum of the lamina terminalis (McKinley et al.,
1992).
III. Activation of Specific Neurotransmitter
Receptors Results in Increased Immediate-early
Gene Expre

Franchise Contribution of the lamina terminalis (McKinley et al.

1992).
 **Receptors Results in Increased Immediate-early

Gene Expression within the Central Nervous** ^{92).}
 III. Activation of Specific Neurotransmitter
 eceptors Results in Increased Immediate-early
 Gene Expression within the Central Nervous

System **System Receptors Results in Increased Immediate-
Gene Expression within the Central Nerv
System
A. Glutamate Receptors: N-methyl-D-aspartate / non-non-N-D-aspartate
methyl-D-aspartate**

methyl-D-aspartate

System

System

Glutamate Receptors: N-methyl-D-aspartate / non-N-

ethyl-D-aspartate

Activation of both NMDA and non-NMDA receptors

sults in increased expression of IEGs within the ner-A. Glutamate Receptors: N-methyl-D-aspartate/non-N-
methyl-D-aspartate
Activation of both NMDA and non-NMDA receptors
results in increased expression of IEGs within the ner-
vous system. MK801 is a noncompetitive antagonis Activation of both NMDA and non-NMDA receptors
results in increased expression of IEGs within the ner-
vous system. MK801 is a noncompetitive antagonist of
the NMDA receptor. The distribution of MK801 binding methyl-D-aspartate

Activation of both NMDA and non-NMDA receptors

results in increased expression of IEGs within the ner-

vous system. MK801 is a noncompetitive antagonist of

the NMDA receptor. The distribution of MK80 Activation of both NMDA and non-NMDA receptors
results in increased expression of IEGs within the ner-
vous system. MK801 is a noncompetitive antagonist of
the NMDA receptor. The distribution of MK801 binding
sites closely results in increased expression of IEGs within the ner-
vous system. MK801 is a noncompetitive antagonist of
the NMDA receptor. The distribution of MK801 binding
sites closely parallels the distribution of Fos-positive
cel vous system. MK801 is a noncompetitive antagonist of
the NMDA receptor. The distribution of MK801 binding
sites closely parallels the distribution of Fos-positive
cells found within the rat brain after administration of
th the NMDA receptor. The distribution of MK801 binding
sites closely parallels the distribution of Fos-positive
cells found within the rat brain after administration of
the convulsant metrazole, suggesting that activation of sites closely parallels the distribution of Fos-positive
cells found within the rat brain after administration of
the convulsant metrazole, suggesting that activation of
NMDA receptors by seizure activity may lead to Fos
p cells found within the rat brain after administration of
the convulsant metrazole, suggesting that activation of
NMDA receptors by seizure activity may lead to Fos
production within these neurons (Morgan et al., 1987).
Glu the convulsant metrazole, suggesting that activation of NMDA receptors by seizure activity may lead to Fos production within these neurons (Morgan et al., 1987).
Glutamate receptor agonists (acting on both NMDA and non-NMD NMDA receptors by seizure activity may lead to Fos
production within these neurons (Morgan et al., 1987).
Glutamate receptor agonists (acting on both NMDA and
non-NMDA receptors) also increase the expression of
Fos in brai production within these neurons (Morgan et al., 1987).
Glutamate receptor agonists (acting on both NMDA and
non-NMDA receptors) also increase the expression of
Fos in brain (Sonnenberg et al., 1989b; Abbud et al.,
1992; Pa Glutamate receptor a
non-NMDA receptors
Fos in brain (Sonner
1992; Page and Ever
Saitoh et al., 1991).
Although antagonis non-NMDA receptors) also increase the expression of
Fos in brain (Sonnenberg et al., 1989b; Abbud et al., 1992; Page and Everitt, 1993; Sugimoto et al., 1993;
Saitoh et al., 1991).
Although antagonists of the NMDA receptor Fos in brain (Sonnenberg et al., 1989b; Abbud et al., 1992; Page and Everitt, 1993; Sugimoto et al., 1993; Saitoh et al., 1991).

Although antagonists of the NMDA receptor, such as MK801, have been reported to have little

1992; Page and Everitt, 1993; Sugimoto et al., 1993;
Saitoh et al., 1991).
Although antagonists of the NMDA receptor, such as
MK801, have been reported to have little effect on IEG
induction produced by electroshock (Cole Saitoh et al., 1991).
Although antagonists of the NMDA receptor, such as
MK801, have been reported to have little effect on IEG
induction produced by electroshock (Cole et al., 1990a)
or lindane-induced seizures (Vendrell

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administration of MK801 (1 to 1.5 mg/kg) will attenuate
(by 50%) the increase in expression of c-fos mRNA in IMMEDIATE-EARLY GENES AND

administration of MK801 (1 to 1.5 mg/kg) will attenuate abol

(by 50%) the increase in expression of c-*fos* mRNA in tive

hippocampal dentate gyrus neurons produced by a sin-199 IMMEDIATE-EARLY GENI
administration of MK801 (1 to 1.5 mg/kg) will attenuate
(by 50%) the increase in expression of c-fos mRNA in
hippocampal dentate gyrus neurons produced by a sin-
gle hippocampal kindling AD (Labiner et administration of MK801 (1 to 1.5 mg/kg) will attenuate
(by 50%) the increase in expression of c-fos mRNA in
hippocampal dentate gyrus neurons produced by a sin-
gle hippocampal kindling AD (Labiner et al., 1989; La-
biner administration of MK801 (1 to 1.5 mg/kg) will attenuate abelief (by 50%) the increase in expression of c-fos mRNA in tiverpocampal dentate gyrus neurons produced by a sin-
gle hippocampal kindling AD (Labiner et al., 1989 (by 50%) the increase in expression of c-fos mRNA is hippocampal dentate gyrus neurons produced by a sigle hippocampal kindling AD (Labiner et al., 1989; Libiner et al., 1993). In accordance with these results, whave foun hippocampal dentate gyrus neurons produced by a single hippocampal kindling AD (Labiner et al., 1989; Labiner et al., 1993). In accordance with these results, we have found that MK801 significantly, but differentially, att gle hippocampal kindling AD (Labiner et al., 1989; La-
biner et al., 1993). In accordance with these results, we do
have found that MK801 significantly, but differentially, re-
attenuates the rise in IEG mRNA and protein i biner et al., 1993). In accordance with these results, we do
have found that MK801 significantly, but differentially, re
attenuates the rise in *IEG* mRNA and protein in rat L
dentate gyrus neurons produced by a single AD have found that MK801 significantly, but differentially, reattenuates the rise in IEG mRNA and protein in rat L dentate gyrus neurons produced by a single AD. MK801 p strongly attenuates the rise in c-*fos* mRNA and prote attenuates the rise in IEG mRNA and protein in rat Lac
dentate gyrus neurons produced by a single AD. MK801 pal
strongly attenuates the rise in c-fos mRNA and protein (by 1
 $(25 \pm 5\%, 38 \pm 4\%)$ and *krox*-20 protein (30 strongly attenuates the rise in c-fos mRNA and protein $(25 \pm 5\%)$, as a lesser effect on jun-B mRNA and protein $(66 \pm 4\%)$, has a lesser effect on jun-B mRNA and protein $(66 \pm 4\%)$, $59 \pm 3\%)$ and c-jun mRNA and protei (25 \pm 5%, 38 \pm 4%) and *krox*-20 protein (30 \pm 5%), has
a lesser effect on *jun*-B mRNA and protein (66 \pm 4%, 59
 \pm 3%) and c-*jun* mRNA and protein (60 \pm 15%, 67 \pm 7%)
but does not markedly attenuate a lesser effect on *jun*-B mRNA and protein $(66 \pm 4\%, 59 \pm 3\%)$ and c-*jun* mRNA and protein $(60 \pm 15\%, 67 \pm 7\%)$
but does not markedly attenuate *krox*-24 mRNA or protein $(85 \pm 2, 92 \pm 6\%)$. These results suggest th \pm 3%) and c-jun mRNA and protein (60 \pm 15%, 67 \pm
but does not markedly attenuate krox-24 mRNA or j
tein (85 \pm 2, 92 \pm 6%). These results suggest t
seizure-mediated induction of IEGs in neurons occ
through b but does not markedly attenuate $krox-24$ mRNA or protein $(85 \pm 2, 92 \pm 6\%)$. These results suggest that seizure-mediated induction of IEGs in neurons occurs through both NMDA receptor-dependent and -independent mechanisms seizure-mediated induction of IEGs in neurons occurs been shown to result in increased expression of c-fos through both NMDA receptor-dependent and -indepen-
dent mechanisms. In addition, these results suggest that tivity seizure-mediated induction of IEGs in neurons occurs
through both NMDA receptor-dependent and -indepen-
dent mechanisms. In addition, these results suggest that
different members of the IEG family (i.e., the *krox-*24
gene through both NMDA receptor-dependent and -inc
dent mechanisms. In addition, these results sugges
different members of the IEG family (i.e., the ki
gene and the c-fos and $krox-20$ genes) differ in
responsiveness to inducti dent mechanisms. In addition, these results suggest that
different members of the IEG family (i.e., the $kroz-24$
gene and the c-fos and $krox-20$ genes) differ in their
responsiveness to induction by NMDA receptor-depen-
den gene and the c -*fos* and $krox-20$ genes) differ in their responsiveness to induction by NMDA receptor-dependent and independent signalling pathways (Hughes et al., submitted). It is likely that NMDA receptor-independent responsiveness to induction by NMDA receptor-depenresponsiveness to induction by NMDA receptor-dependent and independent signalling pathways (Hughes et al., submitted). It is likely that NMDA receptor-independent signalling pathways may involve activation of non-NMDA glut dent and independent signalling pathways (Hughes et mual., submitted). It is likely that NMDA receptor-independent signalling pathways may involve activation of non-prot NMDA glutamate receptors, L-type VSCCs (Murphy et tu al., submitted). It is likely that NMDA receptor-independent signalling pathways may involve activation of non-
NMDA glutamate receptors, L-type VSCCs (Murphy et al., 1991; Lerea et al., 1992), or receptors sensitive to
pl dent signalling pathways may involve activation of non-
NMDA glutamate receptors, L-type VSCCs (Murphy et
al., 1991; Lerea et al., 1992), or receptors sensitive to
nicelet-activating factor (Marcheselli et al., 1990).
Bloc NMDA glutamate receptors, L-type VSCCs (Murphy et al., 1991; Lerea et al., 1992), or receptors sensitive to platelet-activating factor (Marcheselli et al., 1990). Blockade of the NMDA receptor with MK801 before induction o al., 1991; Lerea et al., 1992), or receptors sensitive to net platelet-activating factor (Marcheselli et al., 1990). a Blockade of the NMDA receptor with MK801 before dinduction of LTP in the hippocampus (Cole et al., 1989 platelet-activating factor (Marcheselli et al., 1990).
Blockade of the NMDA receptor with MK801 before
induction of LTP in the hippocampus (Cole et al., 1989;
Dragunow et al., 1989a; Cole et al., 1990b) or before Blockade of the NMDA receptor with MK801 before
induction of LTP in the hippocampus (Cole et al., 1989;
Dragunow et al., 1989a; Cole et al., 1990b) or before
traumatic mechanical brain injury to the cortex or hip-
pocampus induction of LTP in the hippocampus (Cole et al., 1989;
Dragunow et al., 1989a; Cole et al., 1990b) or before
traumatic mechanical brain injury to the cortex or hip-
pocampus (Dragunow et al., 1990b; Dragunow et al.,
1990c Dragunow et al., 1989a; Cole et al., 1990b) or before r
traumatic mechanical brain injury to the cortex or hip-
pocampus (Dragunow et al., 1990b; Dragunow et al., i
1990c; Herrera and Robertson, 1990a; Sharp et al., 1990; traumatic mechanical brain injury to the cortex or hip-
potention being highest in layers 4 and 6 with lower in-
pocampus (Dragunow et al., 1990b; Dragunow et al., duction seen in layers 2 and 5 (Hughes and Dragunow,
1990c pocampus (Dragunow et al., 1990b; Dragunow et al
1990c; Herrera and Robertson, 1990a; Sharp et al., 1990
Hughes et al., 1993a) totally prevents the increase
expression of IEGs in neurons. However the increase
expression of 1990c; Herrera and Robertson, 1990a; Sharp et al., 1990;
Hughes et al., 1993a) totally prevents the increased
expression of IEGs in neurons. However the increased
expression of IEGs seen in glia after brain injury (Dra-
gu Hughes et al., 1993a) totally prevents the increa
expression of IEGs in neurons. However the increa
expression of IEGs seen in glia after brain injury (I
gunow et al., 1990a; Dragunow and Hughes, 1993) is
significantly aff expression of IEGs in neurons. However the increased Arexpression of IEGs seen in glia after brain injury (Dragunow et al., 1990a; Dragunow and Hughes, 1993) is not an significantly affected, suggesting that NMDA receptorexpression of IEGs seen in glia after brain injury (Dragunow et al., 1990a; Dragunow and Hughes, 1993) is not significantly affected, suggesting that NMDA receptor-independent signalling pathways induce IEGs in glia after gunow et al., 1990a; Dragunow a
significantly affected, suggesting
independent signalling pathway
after mechanical brain injury (1989b; Dragunow et al., 1990a).
NMDA receptor blockade has a significantly affected, suggesting that NMDA receptor-
independent signalling pathways induce IEGs in glia
after mechanical brain injury (Dragunow and Faull,
1989b; Dragunow et al., 1990a).
NMDA receptor blockade has also

independent signalling pathways induce IEGs in glia
after mechanical brain injury (Dragunow and Faull,
1989b; Dragunow et al., 1990a).
NMDA receptor blockade has also been shown to abol-
ish induction of Fos produced by co after mechanical brain injury (Dragunow and Faull, tra
1989b; Dragunow et al., 1990a). pos
NMDA receptor blockade has also been shown to abol-
1989; Herrera and Robertson, 1989; Herrera and see
Robertson, 1990b), induction 1989b; Dragunow et al., 1990a).
NMDA receptor blockade has also been shown to abo
ish induction of Fos produced by cortical spreading de
pression (Herrera and Robertson, 1989; Herrera an
Robertson, 1990b), induction of Fos NMDA receptor blockade has also been shown to abol-
ish induction of Fos produced by cortical spreading de-
pression (Herrera and Robertson, 1989; Herrera and se
Robertson, 1990b), induction of Fos in cells of the arcu-
at ish induction of Fos produced by cortical spreading de-
pression (Herrera and Robertson, 1989; Herrera and
Robertson, 1990b), induction of *Fos* in cells of the arcu-
ate nucleus-median eminence after systemic injection of pression (Herrera and Robertson, 1989; Herrera and Robertson, 1990b), induction of Fos in cells of the arcuate nucleus-median eminence after systemic injection of NMDA (MacDonald et al., 1990), and induction of c-fos mRNA Robertson, 1990b), induction of Fos in cells of the arcu-
ate nucleus-median eminence after systemic injection of
NMDA (MacDonald et al., 1990), and induction of c-fos
mRNA in cortex after excitotoxin stimulation of cortic ate nucleus-median eminence after systemic injection of NMDA (MacDonald et al., 1990), and induction of c-fos mRNA in cortex after excitotoxin stimulation of cortical inputs (Wood and de Belleroche, 1991). In addition, NMD NMDA (MacDonald et al., 1990), and induction of c-fos seems that Fos induction occurs predominantly in neumRNA in cortex after excitotoxin stimulation of cortical rons of the striosomal compartment (Hughes and Drainputs (mRNA in cortex after excitotoxin stimulation of cortical
inputs (Wood and de Belleroche, 1991). In addition,
NMDA receptors are involved in regulating central ex-
pression of IEGs at a more physiological level. NMDA
recept inputs (Wood and de Belleroche, 1991). In addition,
NMDA receptors are involved in regulating central ex-
pression of IEGs at a more physiological level. NMDA
receptor blockade partially prevents light-induced c-fos
and *N* NMDA receptors are involved in regulating central expression of IEGs at a more physiological level. NMDA norea
receptor blockade partially prevents light-induced c-fos atum
and NGFI-A mRNA expression in rat retina (Gudehit pression of IEGs at a more physiological level. NMDA
receptor blockade partially prevents light-induced c-fos
and NGFI-A mRNA expression in rat retina (Gudehithlu
et al., 1993) and, in addition, blockade of both NMDA
and n receptor blockade partially prevents light-induced c-f and NGFI-A mRNA expression in rat retina (Gudehith et al., 1993) and, in addition, blockade of both NMI and non-NMDA receptors inhibits the photic-mediat induction of and *NGFI*-A mRNA expression in rat retina (Gudehithlu et al., 1993) and, in addition, blockade of both NMDA and non-NMDA receptors inhibits the photic-mediated induction of Fos protein in ventrolateral, but not dorsolate et al., 1993) and, in addition, blockade of both NMDA
and non-NMDA receptors inhibits the photic-mediated
induction of Fos protein in ventrolateral, but not dorso-
lateral or dorsomedial, suprachiasmatic nucleus (Abe et
al

AND GENE EXPRESSION
abolishes the synaptic activity-dependent high const
tive-expression of *zif* 268 in rat cortex (Worley et AND GENE EXPRESSION 149
abolishes the synaptic activity-dependent high constitu-
tive expression of *zif* 268 in rat cortex (Worley et al.,
1991). In contrast, the constitutive expression of AND GENE EXPRESSION 149
abolishes the synaptic activity-dependent high constitu-
tive expression of $zif 268$ in rat cortex (Worley et al.,
1991). In contrast, the constitutive expression of
Krox-20 protein in superficial abolishes the synaptic activity-dependent high constitu-
tive expression of $zif 268$ in rat cortex (Worley et al.,
1991). In contrast, the constitutive expression of
Krox-20 protein in superficial layers of the neocortex
 abolishes the synaptic activity-dependent high constitu-
tive expression of $zif 268$ in rat cortex (Worley et al.,
1991). In contrast, the constitutive expression of
Krox-20 protein in superficial layers of the neocortex
 tive expression of *zif* 268 in rat cortex (Worley et a 1991). In contrast, the constitutive expression Krox-20 protein in superficial layers of the neocortdoes not seem to be dependent upon activation of NMD receptors (Dr 1991). In contrast, the constitutive expression
Krox-20 protein in superficial layers of the neoco
does not seem to be dependent upon activation of NM
receptors (Dragunow et al., unpublished observatio
Lactation has recent Krox-20 protein in superficial layers of the neccortex
does not seem to be dependent upon activation of NMDA
receptors (Dragunow et al., unpublished observations).
Lactation has recently been shown to inhibit hippocam-
pa does not seem to be dependent upon activation of NMDA
receptors (Dragunow et al., unpublished observations).
Lactation has recently been shown to inhibit hippocam-
pal and cortical activation of Fos-like immunoreactivity
b receptors (Dragunow et al., unpo
Lactation has recently been show
pal and cortical activation of Fos
by NMDA (40 mg/kg i.v.) but r
mg/kg i.v.) (Abbud et al., 1992). pal and cortical activation
by NMDA (40 mg/kg i.v.)
mg/kg i.v.) (Abbud et al., 1
B. Cholinergic Receptors
1. *Muscarinic*. Adminis

1. MMDA (40 mg/kg i.v.) but not kainate (1.5 to 2.5 mg/kg i.v.) (Abbud et al., 1992).
 1. Muscarinic. Administration of the nonselective uscarinic agonist pilocarpine (1 to 100 mg/kg i.p.) has mg/kg i.v.) (Abbud et al., 1992).

B. Cholinergic Receptors

1. Muscarinic. Administration of the nonselective

muscarinic agonist pilocarpine (1 to 100 mg/kg i.p.) has

been shown to result in increased expression of c-fo B. Cholinergic Receptors
1. Muscarinic. Administration of the nonselective
muscarinic agonist pilocarpine (1 to 100 mg/kg i.p.) has
been shown to result in increased expression of c-fos
mRNA (Weiner et al., 1991) and Fos-l B. Cholinergic Receptors
1. Muscarinic. Administration of the nonsele
muscarinic agonist pilocarpine (1 to 100 mg/kg i.p.
been shown to result in increased expression of
mRNA (Weiner et al., 1991) and Fos-like immuno
tivit 1. Muscarinic. Administration of the nonselective muscarinic agonist pilocarpine (1 to 100 mg/kg i.p.) has been shown to result in increased expression of c-fos mRNA (Weiner et al., 1991) and Fos-like immunoreactivity i muscarinic agonist pilocarpine (1 to 100 mg/kg i.p.) has
been shown to result in increased expression of c-fos
mRNA (Weiner et al., 1991) and Fos-like immunoreac-
tivity in rat brain (Hughes and Dragunow, 1994). In ad-
dit been shown to result in increased expression of c-fos mRNA (Weiner et al., 1991) and Fos-like immunoreactivity in rat brain (Hughes and Dragunow, 1993; Bernard et al., 1993; Hughes and Dragunow, 1994). In addition, another mRNA (Weiner et al., 1991) and Fos-like immunoreactivity in rat brain (Hughes and Dragunow, 1993; Bernard et al., 1993; Hughes and Dragunow, 1994). In addition, another nonselective muscarinic agonist oxotremorine (0.5 mg/ tivity in rat brain (Hughes and Dragunow, 1993; Bernard et al., 1993; Hughes and Dragunow, 1994). In addition, another nonselective muscarinic agonist oxotremorine (0.5 mg/kg i.p.) also increases Fos-like immunoreactivity nard et al., 1993; Hughes and Dragunow, 1994). In addition, another nonselective muscarinic agonist oxotremorine (0.5 mg/kg i.p.) also increases Fos-like im-
munoreactivity in rat brain (Bernard et al., 1993). Upon adminis dition, another nonselective muscarinic agoni
oxotremorine (0.5 mg/kg i.p.) also increases Fos-like in
munoreactivity in rat brain (Bernard et al., 1993). Upo
administration of pilocarpine, particularly intense F
protein i oxotremorine (0.5 mg/kg i.p.) also increases Fos-like im-
munoreactivity in rat brain (Bernard et al., 1993). Upon
administration of pilocarpine, particularly intense Fos
protein induction occurs in many rat forebrain stru munoreactivity in rat brain (Bernard et al., 1993). Upon
administration of pilocarpine, particularly intense Fos
protein induction occurs in many rat forebrain struc-
tures, including the primary olfactory (piriform) corte administration of pilocarpine, particularly intense Fos
protein induction occurs in many rat forebrain struc-
tures, including the primary olfactory (piriform) cortex,
nucleus accumbens, amygdala, hippocampus, neocortex,
a protein induction occurs in many rat forebrain structures, including the primary olfactory (piriform) cortanucleus accumbens, amygdala, hippocampus, neocortand supraoptic nucleus of the hypothalamus. Lesser iduction is see tures, including the primary olfactory (piriform) cortex,
nucleus accumbens, amygdala, hippocampus, neocortex,
and supraoptic nucleus of the hypothalamus. Lesser in-
duction is seen in the striatum, septum, inferior colli nucleus accumbens, amygdala, hippocampus, neocortex, and supraoptic nucleus of the hypothalamus. Lesser induction is seen in the striatum, septum, inferior colliculus, thalamus, hypothalamus, and in several brainstem nucle and supraoptic nucleus of the hypothalamus. Lesser induction is seen in the striatum, septum, inferior colliculus, thalamus, hypothalamus, and in several brainstem nuclei. Within the neocortex, induction follows a laminar duction is seen in the striatum, septum, inferior collicu
lus, thalamus, hypothalamus, and in several brainsten
nuclei. Within the neocortex, induction follows a laminar
pattern being highest in layers 4 and 6 with lower i lus, thalamus, hypothalamus, and in several brainstem
nuclei. Within the neocortex, induction follows a laminar
pattern being highest in layers 4 and 6 with lower in-
duction seen in layers 2 and 5 (Hughes and Dragunow,
19 nuclei. Within the neocortex, induction follows a laminar
pattern being highest in layers 4 and 6 with lower in-
duction seen in layers 2 and 5 (Hughes and Dragunow,
1993; Bernard et al., 1993; Hughes and Dragunow, 1994).
 pattern being highest in layers 4 and 6 with lower in-
duction seen in layers 2 and 5 (Hughes and Dragunow,
1993; Bernard et al., 1993; Hughes and Dragunow, 1994).
Induction of Fos within the hippocampus is localised to
Am duction seen in layers 2 and 5 (Hughes and Dragunow, 1993; Bernard et al., 1993; Hughes and Dragunow, 1994).
Induction of Fos within the hippocampus is localised to Ammon's horn (CA1 and CA2) with only faint staining seen 1993; Bernard et al., 1993; Hughes and Dragunow, 1994
Induction of Fos within the hippocampus is localised t
Ammon's horn (CA1 and CA2) with only faint stainin
seen in the upper blade of the dentate gyrus (Hughe
and Dragun duction of Fos within the hippocampus is localised to
mmon's horn (CA1 and CA2) with only faint staining
en in the upper blade of the dentate gyrus (Hughes
ind Dragunow, 1993; Hughes and Dragunow, 1994).
The distribution o

Ammon's horn (CA1 and CA2) with only faint staining
seen in the upper blade of the dentate gyrus (Hughes
and Dragunow, 1993; Hughes and Dragunow, 1994).
The distribution of Fos protein induced by pilocarpine
in the striatu seen in the upper blade of the dentate gyrus (Hughes
and Dragunow, 1993; Hughes and Dragunow, 1994).
The distribution of Fos protein induced by pilocarpine
in the striatum is predominantly medio-ventral in ros-
tral and me and Dragunow, 1993; Hughes and Dragunow, 1994).
The distribution of Fos protein induced by pilocarpine
in the striatum is predominantly medio-ventral in ros-
tral and medio-dorsal in caudal striatum. Very few Fos-
positive The distribution of Fos protein induced by pilocarpine
in the striatum is predominantly medio-ventral in ros-
tral and medio-dorsal in caudal striatum. Very few Fos-
positive cells are seen in lateral striatum (Hughes and
 in the striatum is predominantly medio-ventral in ros-

tral and medio-dorsal in caudal striatum. Very few Fos-

positive cells are seen in lateral striatum (Hughes and

Dragunow, 1993; Bernard et al., 1993). The distribu positive cells are seen in lateral striatum (Hughes and Dragunow, 1993; Bernard et al., 1993). The distribution of medio-dorsal located Fos-positive cells in the striatum seems patchy, possibly suggesting matrix/striosomal positive cells are seen in lateral striatum (Hughes and
Dragunow, 1993; Bernard et al., 1993). The distribution
of medio-dorsal located Fos-positive cells in the striatum
seems patchy, possibly suggesting matrix/striosoma
 Dragunow, 1993; Bernard et al., 1993). The distribution
of medio-dorsal located Fos-positive cells in the striatum
seems patchy, possibly suggesting matrix/striosomal
compartmentalisation. Inasmuch as few neurons dou-
bleof medio-dorsal located Fos-positive cells in the striatum
seems patchy, possibly suggesting matrix/striosoma
compartmentalisation. Inasmuch as few neurons dou
ble-label for Fos and calbindin, a matrix protein, if
seems th seems patchy, possibly suggesting matrix/striosoma
compartmentalisation. Inasmuch as few neurons dou
ble-label for Fos and calbindin, a matrix protein, i
seems that Fos induction occurs predominantly in neu
rons of the str compartmentalisation. Inasmuch as few neurons double-label for Fos and calbindin, a matrix protein, it seems that Fos induction occurs predominantly in neurons of the striosomal compartment (Hughes and Dragunow, 1993). How ble-label for Fos and calbindin, a matrix protein, seems that Fos induction occurs predominantly in ne rons of the striosomal compartment (Hughes and Digunow, 1993). However, whereas both oxotremorine a pilocarpine seem to seems that Fos induction occurs predominantly in neu-
rons of the striosomal compartment (Hughes and Dra-
gunow, 1993). However, whereas both oxotremorine and
pilocarpine seem to preferentially induce Fos-like immu-
noreac rons of the striosomal compartment (Hughes and Dragunow, 1993). However, whereas both oxotremorine and pilocarpine seem to preferentially induce Fos-like immunoreactivity in the striosomal compartment of the striatum, less gunow, 1993). However, whereas both oxotremorine and
pilocarpine seem to preferentially induce Fos-like immu-
noreactivity in the striosomal compartment of the stri-
atum, lesser induction also occurs within the matrix
com pilocarpine seem to preferentially induce Fos-like immu-
noreactivity in the striosomal compartment of the stri-
atum, lesser induction also occurs within the matrix
compartment (Bernard et al., 1993). Within olfactory
and noreactivity in the striosomal compartment of the stri-
atum, lesser induction also occurs within the matrix
compartment (Bernard et al., 1993). Within olfactory
and amygdaloid areas the highest levels of Fos induction
are atum, lesser induction also occurs within the matricompartment (Bernard et al., 1993). Within olfactor and amygdaloid areas the highest levels of Fos inductio are seen in piriform cortex, bed nucleus of the accessor olfact compartment (Bernard et al., 1993). Within olfactor and amygdaloid areas the highest levels of Fos induction are seen in piriform cortex, bed nucleus of the accessor olfactory tract, endopiriform nucleus, taenia tecta, ant and amygdaloid areas the highest levels of Fos induction
are seen in piriform cortex, bed nucleus of the accessory
olfactory tract, endopiriform nucleus, taenia tecta, ante-
rior cortical, medial, posteriomedial cortical,

150
also seen in the cortex-amygdala transition zone and the ag
amygdala-hippocampal area (Hughes and Dragunow, an HUGHES AN HUGHES AN HUGHES A
also seen in the cortex-amygdala transition zone and the
amygdala-hippocampal area (Hughes and Dragunow,
1993). 1993). So seen in the cortex-amygdala transition zone and the hygdala-hippocampal area (Hughes and Dragunow 193).
Coadministration of atropine (10 mg/kg) to pilo-
rpine-treated rats effectively reduces Fos protein in-

amygdala-hippocampal area (Hughes and Dragunow, 1993).
Coadministration of atropine (10 mg/kg) to pilo-
carpine-treated rats effectively reduces Fos protein in-
duction in hippocampus and neocortex to vehicle-in-
jected co amygdala-hippocampal area (Hughes and Dragur
1993).
Coadministration of atropine (10 mg/kg) to p
carpine-treated rats effectively reduces Fos protein
duction in hippocampus and neocortex to vehicle
jected control levels, s 1993). ju
Coadministration of atropine (10 mg/kg) to pilo-
carpine-treated rats effectively reduces Fos protein in-
duction in hippocampus and neocortex to vehicle-in-
jected control levels, suggesting that induction of Coadministration of atropine (10 mg/kg) to pilo-
carpine-treated rats effectively reduces Fos protein in-
duction in hippocampus and neocortex to vehicle-in-
jected control levels, suggesting that induction of Fos
protei carpine-treated rats effectively reduces Fos protein in-
duction in hippocampus and neocortex to vehicle-in-
jected control levels, suggesting that induction of Fos
crea
protein is mediated by muscarinic cholinergic recept duction in hippocampus and neocortex to vehicle-in-
jected control levels, suggesting that induction of Fos
protein is mediated by muscarinic cholinergic receptors
(Hughes and Dragunow, 1993). Atropine (5 and 40
mg/kg i.p. jected control levels, suggesting that induction of protein is mediated by muscarinic cholinergic reces
(Hughes and Dragunow, 1993). Atropine (5 an mg/kg i.p.) also abolishes Fos labeling induced by otremorine (Bernard et protein is mediated by muscarinic cholinergic receptors ture
(Hughes and Dragunow, 1993). Atropine (5 and 40 how
mg/kg i.p.) also abolishes Fos labeling induced by ox-
otremorine (Bernard et al., 1993). Systemic administra (Hughes and Dragunow, 1993). Atropine (5 a mg/kg i.p.) also abolishes Fos labeling induced otremorine (Bernard et al., 1993). Systemic admition of pirenzepine is less effective than atrop reducing pilocarpine-induced Fos-l mg/kg i.p.) also abolishes Fos labeling induced by ox-
otremorine (Bernard et al., 1993). Systemic administra-
tion of pirenzepine is less effective than atropine in
interation of penetration of the blood (W
brain barrier otremorine (Bernard et al., 1993). Systemic administra-
tion of pirenzepine is less effective than atropine in
reducing pilocarpine-induced Fos-like immunoreactiv-
ity, possibly because of its poor penetration of the bloo tion of pirenzepine is less effective than atropine in reducing pilocarpine-induced Fos-like immunoreactivity, possibly because of its poor penetration of the blood brain barrier (Hughes and Dragunow, 1993), however when reducing pilocarpine-induced Fos-like immunoreactiv
ity, possibly because of its poor penetration of the blood
brain barrier (Hughes and Dragunow, 1993), however
when injected centrally $(200 \mu g \text{ i.c.v.})$ pirenzepine to
ta 1994). ain barrier (Hughes and Dragunow, 1993), howe
hen injected centrally $(200 \mu g \text{ i.c.v.})$ pirenzepine
lly abolishes Fos induction (Hughes and Draguno
94).
It has also been shown that the muscarinic anta
sts atropine and scop

when injected centrally $(200 \mu g \text{ i.c.}v.)$ pirenzepine
tally abolishes Fos induction (Hughes and Dragund
1994).
It has also been shown that the muscarinic antag
nists atropine and scopolamine induce Fos-like imm
noreactiv tally abolishes Fos induction (Hughes and Dragunow, 2004).

1994).

It has also been shown that the muscarinic antagonists atropine and scopolamine induce Fos-like immu-

noreactivity in rat brain. Atropine (2.5 to 40 mg/ 1994).

It has also been shown that the muscarinic antago-

mists atropine and scopolamine induce Fos-like immu-

noreactivity in rat brain. Atropine (2.5 to 40 mg/kg i.p.)

induce Fos-like (immunoreactivity in striatum, It has also been shown that the muscarinic antagonists atropine and scopolamine induce Fos-like immunoreactivity in rat brain. Atropine $(2.5 \text{ to } 40 \text{ mg/kg i.p.})$ and scopolamine $(0.2 \text{ to } 50 \text{ mg/kg i.p.})$ induce Fos-like immun nists atropine and scopolamine induce Fos-like immu-
noreactivity in rat brain. Atropine (2.5 to 40 mg/kg i.p.) indu
and scopolamine (0.2 to 50 mg/kg i.p.) induce Fos-like (for
immunoreactivity in striatum, nucleus accumbe nore
activity in rat brain. Atropine $(2.5 \text{ to } 40 \text{ mg/kg i.p.})$ in and scopolamine $(0.2 \text{ to } 50 \text{ mg/kg i.p.})$ induce Fos-like (for immunore
activity in striatum, nucleus accumbens, cincles activity in striatum, nucleus accumben and scopolamine (0.2 to 50 mg/kg i.p.) induce Fos-like (for immunoreactivity in striatum, nucleus accumbens, cingulate cortex, septum and olfactory tubercle, but not in neocortex, substantia nigra, or pallidum. Within the immunore
activity in striatum, nucleus accumbens, cin-
gulate cortex, septum and olfactory tubercle, but not in
neocortex, substantia nigra, or pallidum. Within the wh
striatum, most Fos-immunore
active nuclei are located gulate cortex, septum and olfactory tubercle, but not in neocortex, substantia nigra, or pallidum. Within the within striatum, most Fos-immunoreactive nuclei are located su in neurons of the dorsal and medial striatum and neocortex, substantia nigra, or pallidum. Within
striatum, most Fos-immunoreactive nuclei are loc:
in neurons of the dorsal and medial striatum and
preferentially located within the matrix, although s
are also seen in stri In addition, inost Fos-Inimumoreactive interef are focal neurons of the dorsal and medial striatum and eferentially located within the matrix, although se also seen in striosomes (Bernard et al., 1993). In addition, it has

in neurons of the dorsal and medial striatum and are preferentially located within the matrix, although some P are also seen in striosomes (Bernard et al., 1993). Compared to all adminis- P tration of pilocarpine produces preferentially located within the matrix, although some Pare also seen in striosomes (Bernard et al., 1993).

In addition, it has recently been shown that adminis-
 c-fos, jun-B, and *krox-24* (*zif* 268) mRNA and prote are also seen in striosomes (Bernard et al., 1995).

In addition, it has recently been shown that adminis-

ration of pilocarpine produces increased expression of

c-fos, jun-B, and krox-24 (zif 268) mRNA and protein

cand tration of pilocarpine produces increased expression of crease c-fos expression in this cell line, inasmuch as c-fos, jun-B, and krox-24 (zif 268) mRNA and protein carbachol retained the ability to stimulate c-fos express and Krox-20 protein in neurons of the hippocampus and
notein in PKC-deficient cells (Blackshear et al., 1987).
neocortex (Hughes and Dragunow, 1994). Induction oc-
neterstingly, if cytosolic Ca^{2+} levels are buffered in and Krox-20 protein in neurons of the hippocampus and
neocortex (Hughes and Dragunow, 1994). Induction oc-
curs in a similar spatial pattern to Fos protein induction
after pilocarpine. Induction of c-*fos*, *jun*-B, *krox* neocortex (Hughes and Dragunow, 1994). Induction curs in a similar spatial pattern to Fos protein induction after pilocarpine. Induction of c-fos, $jun-B$, $krox-20$, a $krox-24$ gene expression occurs rapidly (30 min to 1 after curs in a similar spatial pattern to Fos protein induction 13
after pilocarpine. Induction of c-fos, jun-B, krox-20, and
krox-24 gene expression occurs rapidly $(30 \text{ min to } 1 \text{ h})$ sid
after administration of pilocarpine wi after pilocarpine. Induction of c -*fos*, *ju*
*krox-24 gene expression occurs rapid
after administration of pilocarpine w
tion preceding induction in hippocar
expression of IEGPs is near baseline.
Systemic administratio* ox-24 gene expression occurs rapidly $(30 \text{ min to } 1 \text{ h})$
ter administration of pilocarpine with cortical induc-
on preceding induction in hippocampus. By 8 h the
pression of IEGPs is near baseline.
Systemic administration

tion preceding induction in hippocampus. By 8 h the expression of IEGPs is near baseline.
Systemic administration of either atropine (10 mg/kg) or scopolamine (5 mg/kg) reduces induction of all IEGs to levels seen in vehi expression of IEGPs is near baseline.
Systemic administration of either atropine (10 mg/kg
or scopolamine (5 mg/kg) reduces induction of all IEGs t
levels seen in vehicle-injected rats. In addition, centra
unilateral inje Systemic administration of either atropine (10 mg/kg)
or scopolamine (5 mg/kg) reduces induction of all IEGs to
levels seen in vehicle-injected rats. In addition, central
unilateral injection of pirenzepine (200 μ g i.c or scopolamine (5 mg/kg) reduces induction of all IEGs to
levels seen in vehicle-injected rats. In addition, central
unilateral injection of pirenzepine (200 μ g i.c.v.) abol-
ishes IEG induction in hippocampus and cort levels seen in vehicle-injected rats. In addition, central (Tre unilateral injection of pirenzepine (200 μ g i.c.v.) abol-
ishes IEG induction in hippocampus and cortex, sug-
in presting that activation of central musca unilateral injection of pirenzepine $(200 \mu g \text{ i.c.v.})$ a
ishes IEG induction in hippocampus and cortex, s
gesting that activation of central muscarinic (M1 but
M2) receptors results in increased expression of IEG
rat brain ishes IEG induction in hippocampus and cortex, sug-
gesting that activation of central muscarinic (M1 but not
M2) receptors results in increased expression of IEGs in
hat brain neurons. Furthermore, pilocarpine adminis-
t gesting that activation of central muscarinic (M1 but not
M2) receptors results in increased expression of IEGs in
rat brain neurons. Furthermore, pilocarpine adminis-
tration does not detectibly induce the expression of M2) receptors results in increased expression of IEGs in h
rat brain neurons. Furthermore, pilocarpine adminis-
tration does not detectibly induce the expression of c -*jun* an
mRNA or protein or jun-D protein in neurons rat brain neurons. Furthermore, pilocarpine administration does not detectibly induce the expression of c-jun mRNA or protein or jun-D protein in neurons of the neocortex or hippocampus, suggesting that activation of centr tration does not detectibly induce the expression of α mRNA or protein or jun-D protein in neurons of neocortex or hippocampus, suggesting that activation central pirenzepine-sensitive muscarinic receptors sults in the mRNA or protein or jun-D protein in neurons of the
neocortex or hippocampus, suggesting that activation o
central pirenzepine-sensitive muscarinic receptors re
sults in the induction of a specific pattern of immediate
earl neocortex or hip
central pirenze
sults in the indu
early gene exp
gunow, 1994).
These results ntral pirenzepine-sensitive muscarinic receptors re-
lits in the induction of a specific pattern of immediate-
rly gene expression in neurons (Hughes and Dra-
mow, 1994).
These results are in contrast to in vitro studies t sults in the induction of a specific pattern of immediate-
early gene expression in neurons (Hughes and Dragunow, 1994).
These results are in contrast to in vitro studies that
have shown that carbachol, a nonselective musc

DRAGUNOW
agonist, increases c-*jun* mRNA (Trejo and Brown, 1991)
and c-Jun protein in addition to c-*fos*, possibly *fos*-B, and pragunow
agonist, increases c-*jun* mRNA (Trejo and Brown, 1991)
and c-Jun protein in addition to c-*fos*, possibly *fos*-B, and
jun-B mRNA in human 1321N1 astrocytoma cells. The provide the mass of the mRNA (Trejo and Brown, 1991)
and c-Jun protein in addition to c-fos, possibly fos-B, and
jun-B mRNA in human 1321N1 astrocytoma cells. The
expression of jun-D, fra-1, and fra-2 mRNAs seemed agonist, increases c-jun mRNA (Trejo and Brown, 1991)
and c-Jun protein in addition to c-fos, possibly fos-B, and
jun-B mRNA in human 1321N1 astrocytoma cells. The
expression of jun-D, fra-1, and fra-2 mRNAs seemed
unalter agonist, increases c-jun mRNA (Trejo and Brown, 1991)
and c-Jun protein in addition to c-fos, possibly fos-B, and
jun-B mRNA in human 1321N1 astrocytoma cells. The
expression of jun-D, fra-1, and fra-2 mRNAs seemed
unalte and c-Jun protein in addition to c-*fos*, possibly *fos*-B, and *jun*-B mRNA in human 1321N1 astrocytoma cells. The expression of *jun*-D, *fra*-1, and *fra*-2 mRNAs seemed unaltered (Trejo et al., 1992). In addition, in expression of jun-D, fra-1, and fra-2 mRNAs seemed
unaltered (Trejo et al., 1992). In addition, in cultured
cerebellar granule cells, carbachol seemed unable to in-
crease c-fos mRNA levels (Szekely et al., 1989). In culcerebellar granule cells, carbachol seemed unable to increase *c-fos* mRNA levels (Szekely et al., 1989). In cultured Neuroblastoma × Glioma Hybrid NG108-15 cells, however, carbachol does seem to increase *zif* 268 mRNA ex crease c-fos mRNA levels (Szekely et al., 1989). In cul-

Within rat cortex, Northern blots show that a single tured Neuroblastoma × Glioma Hybrid NG108-15 cells,
however, carbachol does seem to increase $zif 268$ mRNA
expression (Katayama et al., 1993).
Within rat cortex, Northern blots show that a single
intraperitoneal injection however, carbachol does seem to increase *zif* 268 mRNA expression (Katayama et al., 1993).
Within rat cortex, Northern blots show that a single intraperitoneal injection of lithium chloride significantly augments pilocarp intraperitoneal injection of lithium chloride significantly
augments pilocarpine-induced c-fos mRNA expression
(Weiner et al., 1991). This effect has also been demon-
strated in PC12 cells (Kalasapudi et al., 1990; Divish Within rat cortex, Northern blots show that a single
intraperitoneal injection of lithium chloride significantly
augments pilocarpine-induced c-fos mRNA expression
(Weiner et al., 1991). This effect has also been demon-
st intraperitoneal injection of lithium chloride significantly
augments pilocarpine-induced c-fos mRNA expression
(Weiner et al., 1991). This effect has also been demon-
strated in PC12 cells (Kalasapudi et al., 1990; Divish augments pilocarpine-induced c-fos mRNA expressio
(Weiner et al., 1991). This effect has also been demointant strated in PC12 cells (Kalasapudi et al., 1990; Divish al., 1991), where it can be shown that, although lithium (Weiner et al., 1991). This effect has also been dem
strated in PC12 cells (Kalasapudi et al., 1990; Divish
al., 1991), where it can be shown that, although lithis
augments phosphatidyl inositol biphosphate₂-media
c-*fos* strated in PC12 cells (Kalasapudi et al., 1990; Divish et al., 1991), where it can be shown that, although lithium augments phosphatidyl inositol biphosphate₂-mediated c-fos expression induced by activation of either mu al., 1991), where it can be shown that, although lithium
augments phosphatidyl inositol biphosphate₂-mediated
c-*fos* expression induced by activation of either musca-
rinic cholinergic receptors or phorbol esters that augments phosphatidyl inositol biphosphate₂-mediated
c-fos expression induced by activation of either musca-
rinic cholinergic receptors or phorbol esters that directly
activate PKC, lithium does not augment c-fos expre c-fos expression induced by activation of either musca-
rinic cholinergic receptors or phorbol esters that directly
activate PKC, lithium does not augment c-fos expression
induced by receptor (prostaglandin E_1) or post rinic cholinergic receptors or
activate PKC, lithium does no
induced by receptor (prostag
(forskolin, 3-isobutyl-1-meth
cAMP (Divish et al., 1991).
In addition, in human 13 tivate PKC, lithium does not augment c-fos expression
duced by receptor (prostaglandin E_1) or post-receptor
prskolin, 3-isobutyl-1-methyl xanthine) activators of
MP (Divish et al., 1991).
In addition, in human 1321N1 a

tion preceding induction in hippocampus. By 8 h the ionophore ionomycin while c-jun expression is repressed,
expression of IEGPs is near baseline.
Systemic administration of either atropine (10 mg/kg) will potentiate the induced by receptor (prostaglandin E_1) or post-recepto (forskolin, 3-isobutyl-1-methyl xanthine) activators (cAMP (Divish et al., 1991).
In addition, in human 1321N1 astrocytoma cells is which PKC has been down-regulat (forskolin, 3-isobutyl-1-methyl xanthine) activators of cAMP (Divish et al., 1991).
In addition, in human 1321N1 astrocytoma cells in which PKC has been down-regulated by prolonged exposure to phorbol esters, carbachol no *cAMP* (Divish et al., 1991).

In addition, in human 1321N1 astrocytoma cells in

which PKC has been down-regulated by prolonged expo-

sure to phorbol esters, carbachol no longer stimulates

c-*fos* or c-*jun* expression, In addition, in human 1321N1 astrocytoma cells in
which PKC has been down-regulated by prolonged expo-
sure to phorbol esters, carbachol no longer stimulates
 c -*fos* or c -*jun* expression, suggesting a critical role f which PKC has been down-regulated by prolonged exposure to phorbol esters, carbachol no longer stimulates c-fos or c-jun expression, suggesting a critical role for PKC in these responses (Trejo and Brown, 1991). In contras sure to phorbol esters, carbachol no longer stimulates c-fos or c-jun expression, suggesting a critical role for PKC in these responses (Trejo and Brown, 1991). In contrast, an earlier paper suggested that activation of PK PKC in these responses (Trejo and Brown, 1991).
contrast, an earlier paper suggested that activation
PKC-independent pathways by carbachol could also
crease c-fos expression in this cell line, inasmuch
carbachol retained t PKC-independent pathways by carbachol could also in-
crease c-fos expression in this cell line, inasmuch as
carbachol retained the ability to stimulate c-fos expres-
sion in PKC-deficient cells (Blackshear et al., 1987).
 PKC-independent pathways by carbachol could also in-
crease c-*fos* expression in this cell line, inasmuch as
carbachol retained the ability to stimulate c-*fos* expres-
sion in PKC-deficient cells (Blackshear et al., 198 crease c-*fos* expression in this cell line, inasmuch as carbachol retained the ability to stimulate c-*fos* expression in PKC-deficient cells (Blackshear et al., 1987). Interestingly, if cytosolic Ca^{2+} levels are buff carbachol retained the ability to stimulate c -*fos* expr
sion in PKC-deficient cells (Blackshear et al., 198
Interestingly, if cytosolic Ca^{2+} levels are buffered
1321N1 cells, c -*fos* expression induced by muscari
 sion in PKC-deficient cells (Blackshear et al., 1987).
Interestingly, if cytosolic Ca^{2+} levels are buffered in
1321N1 cells, c-*fos* expression induced by muscarinic
receptor activation is augmented, whereas c-*jun* ex is a repression induced by muscaring
receptor activation is augmented, whereas c-jun expression is attenuated. Furthermore, activation of c-fos ex-
pression by phorbol esters is potentiated by the Ca²⁺
ionophore ionomyc sion is attenuated. Furthermore, activation of c-*fos* ex-
pression by phorbol esters is potentiated by the Ca²⁺
ionophore ionomycin while c-*jun* expression is repressed,
suggesting that concomitant rises in intracellul pression by phorbol esters is potentiated by the Ca^{2+}
ionophore ionomycin while c-*jun* expression is repressed,
suggesting that concomitant rises in intracellular Ca^{2+}
will potentiate the induction of c-*fos*, but ionophore ionomycin while c-*jun* expression is repressed,
suggesting that concomitant rises in intracellular Ca^{2+}
will potentiate the induction of c-*fos*, but repress the
induction of c-*jun* after muscarinic recepto suggesting that concomitant rises in intracellular Ca^{2+} will potentiate the induction of c -*jun* after muscarinic receptor activation (Trejo and Brown, 1991). It has also recently been shown that lithium alone increa will potentiate the induction of c-*fos*, but repress the induction of c-*jun* after muscarinic receptor activation (Trejo and Brown, 1991). It has also recently been shown that lithium alone increases Fos-like immunoreac induction of c-jun after muscarinic receptor activation (Trejo and Brown, 1991). It has also recently been shown
that lithium alone increases Fos-like immunoreactivity
in parabrachial nucleus, area postrema, and nucleus o (Trejo and Brown, 1991). It has also recently been shown
that lithium alone increases Fos-like immunoreactivity
in parabrachial nucleus, area postrema, and nucleus of
the tractus solitarius (Yamamoto et al., 1992), and we
 that lithium alone increases Fos-like immunorea
in parabrachial nucleus, area postrema, and nuc
the tractus solitarius (Yamamoto et al., 1992), ε
have observed that i.c.v. injection of polymyxin B
a selective inhibito in parabrachial nucleus, area postrema, and nucleus of
the tractus solitarius (Yamamoto et al., 1992), and we
have observed that i.c.v. injection of polymyxin B (PMB,
a selective inhibitor of PKC) abolishes pilocarpine-med the tractus solitarius (Yankave observed that i.c.v. is a selective inhibitor of PK
ated induction of IEGs in
unpublished observations
Taken together, these These observed that i.c.v. injection of polymyxin B (PMB)
a selective inhibitor of PKC) abolishes pilocarpine-mediated induction of IEGs in hippocampus (Dragonow et al.
unpublished observations).
Taken together, these obse

ated induction of IEGs in hippocampus (Dragonow et a
unpublished observations).
Taken together, these observations suggest that ac
vation of central pirenzepine-sensitive muscarinic rece
tors linked to phosphatidyl inosit unpublished observations).

Taken together, these observations suggest that activation of central pirenzepine-sensitive muscarinic receptors linked to phosphatidyl inositol biphosphate₂ hydrolysis and PKC activation res Taken together, these observations suggest that activation of central pirenzepine-sensitive muscarinic receptors linked to phosphatidyl inositol biphosphate₂ hydrolysis and PKC activation results in a transient temporal vation of central pirenzepine-sensitive muscarinic receptors linked to phosphatidyl inositol biphosphate₂ hydrolysis and PKC activation results in a transient temporal, spatially distinct, combination specific, pattern o tors linked to phosphatidyl inositol biphosphate₂ hydrolysis and PKC activation results in a transient temporal, spatially distinct, combination specific, pattern of IEG expression in rat brain. Within the rat retina bl

IMMEDIATE-EARLY GENES A
strated to partially reduce light-induced expression of ce
both c-fos and NGFI-A mRNA (Gudehithlu et al., 1993). **IMMEDIATE-EARLY GENES**
strated to partially reduce light-induced expression of
both c-fos and *NGFI-A* mRNA (Gudehithlu et al., 1993).
2. *Nicotinic*. Nicotine has previously been shown to

2. IMMEDIATE-EARLY GENES AND
 2. Nicotinic. Nicotine has previously been shown to antique c-fos in differentiated PC12 cells (Greenberg et light) induced to partially reduce light-induced expression of
both c-fos and *NGFI-A* mRNA (Gudehithlu et al., 1993).
2. *Nicotinic*. Nicotine has previously been shown to
induce c-fos in differentiated PC12 cells (Greenberg et strated to partially reduce light-induced expression of co
both c-fos and *NGFI-A* mRNA (Gudehithlu et al., 1993).
2. *Nicotinic*. Nicotine has previously been shown to
induce c-fos in differentiated PC12 cells (Greenberg both c-fos and NGFI-A mRNA (Gudehithlu et al., 1993). exp
2. Nicotinic. Nicotine has previously been shown to ant
induce c-fos in differentiated PC12 cells (Greenberg et ligh
al., 1986). Induction by nicotine relies upon 2. *Nicotinic*. Nicotine has previously been shown to induce c-fos in differentiated PC12 cells (Greenberg et lal., 1986). Induction by nicotine relies upon a flux of Ca^{2+} ions into the cell through VSCCs. Nicotine at induce c-fos in differentiated PC12 cells (Greenberg et lig

al., 1986). Induction by nicotine relies upon a flux of in

Ca²⁺ ions into the cell through VSCCs. Nicotine at a

dose of 2 mg/kg i.v. (1 h cannula infusion i Ca^{2+} ions into the cell through VSCCs. Nicotine at a dose of 2 mg/kg i.v. (1 h cannula infusion in free-moving rats) induces Fos immunoreactivity in specific rat brain regions that include primary visual structures, in dose of 2 mg/kg i.v. (1 h cannula infusion in free-moving C. Adrenergic Receptors
rats) induces Fos immunoreactivity in specific rat brain Treatments that cause brain NE release can be shown
regions that include primary rats) induces Fos immunoreactivity in specific rat brain regions that include primary visual structures, including the superficial grey layer of the superior colliculus and medial terminal nucleus of the accessory optic tr regions that include primary visual structures, including the superficial grey layer of the superior colliculus and medial terminal nucleus of the accessory optic tract and in the rostral subnucleus of the interpeduncular regions that include primary visual structures, including the superficial grey layer of the superior colliculus and medial terminal nucleus of the accessory optic tract sand in the rostral subnucleus of the interpeduncula ing the superficial grey layer of the superior colliculus and medial terminal nucleus of the accessory optic tract and in the rostral subnucleus of the interpeduncular pucleus (Ren and Sagar, 1992). Induction occurred wit and medial terminal nucleus of the accessory optic tract
and in the rostral subnucleus of the interpeduncular
nucleus (Ren and Sagar, 1992). Induction occurred
within 60 min of infusion initiation and was reduced at
180 an and in the rostral subnucleus of the interpeduncular genucleus (Ren and Sagar, 1992). Induction occurred crucis within 60 min of infusion initiation and was reduced at β -180 and 240 min. The nicotinic receptor antagoni nucleus (Ren and Sagar, 1992). Induction occurred
within 60 min of infusion initiation and was reduced at
180 and 240 min. The nicotinic receptor antagonist
mecamylamine (5 mg/kg i.p.) significantly reduced Fos
expression within 60 min of infusion initiation and was reduced at β -ad 180 and 240 min. The nicotinic receptor antagonist et a mecamylamine (5 mg/kg i.p.) significantly reduced Fos aptiex pression in these areas. Subcutaneous in 180 and 240 min. The nicotinic receptor antagonis mecamylamine (5 mg/kg i.p.) significantly reduced Fo expression in these areas. Subcutaneous injection of nicotine at the same dose has been shown to result in induction of mecamylamine (5 mg/kg i.p.) significantly reduced expression in these areas. Subcutaneous injection of otine at the same dose has been shown to result induction of Fos in these structures as well as in modellular neurons o expression in these areas. Subcutaneous injection of ni
otine at the same dose has been shown to result i
induction of Fos in these structures as well as in may
nocellular neurons of the paraventricular and supraor
tic nuc induction of Fos in these structures as well as in magnocellular neurons of the paraventricular and supraoptic nuclei of the hypothalamus and in the medial habenula (Sagar et al., 1990).
It is likely that nicotine acts pre

tic nuclei of the hypothalamus and in the medial habe-
nula (Sagar et al., 1990).
It is likely that nicotine acts presynaptically, possibly
in the retina, to stimulate the release of an unidentified
neurotransmitter that t tic nuclei of the hypothalamus and in the medial habe-
nula (Sagar et al., 1990). (α_1)
It is likely that nicotine acts presynaptically, possibly (Bir
in the retina, to stimulate the release of an unidentified Y
neurotr nula (Sagar et al., 1990). (a
It is likely that nicotine acts presynaptically, possibly (E
in the retina, to stimulate the release of an unidentified
neurotransmitter that then increases Fos expression in ea
the superior c It is likely that nicotine acts presynaptically, possil
in the retina, to stimulate the release of an unidentifi
neurotransmitter that then increases Fos expression
the superior colliculus and medial terminal nucleus
the o in the retina, to stimulate the release of an unidentified
neurotransmitter that then increases Fos expression in
the superior colliculus and medial terminal nucleus of
the optic tract; blockade of retinal activity with in neurotransmitter that then increases Fos expression in each
the superior colliculus and medial terminal nucleus of bii
the optic tract; blockade of retinal activity with intrav-
itreal injections of tetrodotoxin blocks nic the superior colliculus and medial terminal nucleus of
the optic tract; blockade of retinal activity with intrav-
itreal injections of tetrodotoxin blocks nicotine-induced
Fos immunostaining in these regions. The site at w the optic tract; blockade of retinal activity with intrav-
itreal injections of tetrodotoxin blocks nicotine-induced
Fos immunostaining in these regions. The site at which
nicotine acts to increase Fos in the interpeduncul itreal injections of tetrodotoxin blocks nicotine-induced I
Fos immunostaining in these regions. The site at which
nicotine acts to increase Fos in the interpeduncular nu-
cleus is unknown at present, but this nucleus cont Fos immunostaining in these regions. The site at which
nicotine acts to increase Fos in the interpeduncular nu-
cleus is unknown at present, but this nucleus contains
both pre- and post-synaptic nicotinic receptors. Becaus micotine acts to increase Fos in the interpeduncular nucleus is unknown at present, but this nucleus contains poth pre- and post-synaptic nicotinic receptors. Because c.
i.v. nicotine-fails to induce-Fos expression in sev cleus is unknown at present, but this nucleus contains
both pre- and post-synaptic nicotinic receptors. Because
i.v. nicotine fails to induce Fos expression in severa
areas that have high densities of nicotine-binding site both pre- and post-synaptic nicotinic receptors. Becausiv. nicotine fails to induce Fos expression in severareas that have high densities of nicotine-binding siticle, substantia nigra, ventral tegmental area, and the amus) i.v. nicotine fails to induce Fos expression in several
areas that have high densities of nicotine-binding sites
(i.e., substantia nigra, ventral tegmental area, and thal-
amus), it has been suggested that in these areas (i.e., substantia nigra, ventral tegmental area, and thal-
are β -adrenoceptors, inasmuch as propranolol is more effec-
amus), it has been suggested that in these areas activa-
tion of presynaptic nicotine receptors cau (i.e., substantia nigra, ventral tegmental area, and thal-
amus), it has been suggested that in these areas activa-
tion of presynaptic nicotine receptors causes the release exp
of neurotransmitters that are unable to ind amus), it has been suggested that in these areas a
tion of presynaptic nicotine receptors causes the re
of neurotransmitters that are unable to induce F
the post-synaptic cell (i.e., release of γ -aminobutyri
in the tha tion of presynaptic nicotine receptors causes the release
of neurotransmitters that are unable to induce Fos in
the post-synaptic cell (i.e., release of γ -aminobutyric acid
in the thalamus is unlikely to induce Fos imm of neurotransmitters that are unable to induce Fos in
the post-synaptic cell (i.e., release of γ -aminobutyric acid
in the thalamus is unlikely to induce Fos immunostain-
ing) (Ren and Sagar, 1992). However, in another the post-synaptic cell (i.e., release of γ -aminobutyric acid
in the thalamus is unlikely to induce Fos immunostain-
ing) (Ren and Sagar, 1992). However, in another study
nicotine (0.4 to 1.4 mg/kg sc) was shown to indu in the thalamus is unlikely to induce Fos immunostain-
ing) (Ren and Sagar, 1992). However, in another study,
nicotine (0.4 to 1.4 mg/kg sc) was shown to induce Fos-
like immunoreactivity, mostly in nondopaminergic neu-
ro g) (Ren and Sagar, 1992). However, in another study, cotine (0.4 to 1.4 mg/kg sc) was shown to induce Foster immunoreactivity, mostly in nondopaminergic neums of the ventral tegmental area (Pang et al. 1993). Fos induction

nicotine (0.4 to 1.4 mg/kg sc) was shown to induce Fos-
like immunoreactivity, mostly in nondopaminergic neu-
rons of the ventral tegmental area (Pang et al. 1993).
Fos induction has also been demonstrated in PVN,
nucleus like immunoreactivity, mostly in nondopaminergic neu-
rons of the ventral tegmental area (Pang et al. 1993). For
Fos induction has also been demonstrated in PVN, pre
nucleus tractus solitarius, LC, supraoptic nucleus, cenrons of the ventral tegmental area (Pang et al. 1993). Fos-like
Fos induction has also been demonstrated in PVN, produce
nucleus tractus solitarius, LC, supraoptic nucleus, cenced cells
tral nucleus of the amygdala, cingul Fos induction has also been demonstrated in PVN, pucleus tractus solitarius, LC, supraoptic nucleus, central nucleus of the amygdala, cingulate gyrus of the ocortex and dentate gyrus of the hippocampus 60 min a after a si nucleus tractus solitarius, LC, supraoptic nucleus, central nucleus of the amygdala, cingulate gyrus of the of cortex and dentate gyrus of the hippocampus 60 min al. after a single i.v. injection of 0.1 mg/kg nicotine (Ma tral nucleus of the amygdala, cingulate gyrus of the of Fos in neccortex produced by restraint stress (Bing et cortex and dentate gyrus of the hippocampus 60 min al., 1992b). The majority of noradrenergic fibres that after cortex and dentate gyrus of the hippocampus 60 mi
after a single i.v. injection of 0.1 mg/kg nicotine (Matt
et al., 1993). Nicotine at 2 mg/kg i.p. also induces rapi
expression of c-*fos*, *jun*-B, and *NGFI*-A mRNA and
sl after a single i.v. injection of 0.1 mg/kg nicotine (Matta i et al., 1993). Nicotine at 2 mg/kg i.p. also induces rapid texpression of c-fos, jun-B, and NGFI-A mRNA and a uslower increase of c-jun and jun-D mRNAs in rat su et al., 1993). Nicotine at 2 mg/kg i.p. also induces rapid
expression of c-fos, jun-B, and NGFI-A mRNA and a
slower increase of c-jun and jun-D mRNAs in rat supe-
rior cervical ganglion (Koistinaho et al., 1993). c-fos
mRN expression of c-*fos*, *jun*-B, and *NGFI*-A mRNA and a us
slower increase of c-*jun* and *jun*-D mRNAs in rat supe-
rior cervical ganglion (Koistinaho et al., 1993). c-*fos* the
mRNA also was induced in rat brain after n slower increase of c-jun and jun-D mRNAs in rat super
rior cervical ganglion (Koistinaho et al., 1993). c-fos
mRNA also was induced in rat brain after nicotine ad-
ininistration, suggesting that increased transcription of
 rior cervical ganglion (Koistinaho et al., 1993). c-fos mRNA also was induced in rat brain after nicotine administration, suggesting that increased transcription of the c-fos gene is responsible for increased levels of Fos

IMMEDIATE-EARLY GENES AND GENE EXPRESSION 151 IMMEDIATE-EARLY GENES AND GENE EXPRESSION 151
induced expression of ceptors also seems to be required for light-induced IEG
indehithlu et al., 1993). expression in hamster SCN, with the nicotinic receptor AND GENE EXPRESSION 151

ceptors also seems to be required for light-induced IEG

expression in hamster SCN, with the nicotinic receptor

antagonist drug mecamylamine significantly reducing AND GENE EXPRESSION

ceptors also seems to be required for light-induced IEG

expression in hamster SCN, with the nicotinic receptor

antagonist drug mecamylamine significantly reducing

light-induced Fos-like immunoreacti reversion in hamster SCN, with the nicotinic receptor
expression in hamster SCN, with the nicotinic receptor
antagonist drug mecamylamine significantly reducing
light-induced Fos-like immunoreactivity, predominantly
in dor ceptors also seems to be required for light-
expression in hamster SCN, with the nicot
antagonist drug mecamylamine significan
light-induced Fos-like immunoreactivity, pr
in dorsomedial SCN (Zhang et al., 1993). **Example 12 Adventured Eventure 2016**
 C. Adrenergic Receptors
 C. Adrenergic Receptors
 C. Adrenergic Receptors
 Treatments that cause b

nocellular neurons of the paraventricular and supraop-
ic nuclei of the hypothalamus and in the medial habe-
nula (Sagar et al., 1990).
 $(\alpha_1 \text{ receptor} \text{antagonist}, 5 \text{ mg/kg} \text{ i.p.})$ in combination
It is likely that nicotine acts pres tht-induced Fos-like immunoreactivity, predominantly
dorsomedial SCN (Zhang et al., 1993).
Adrenergic Receptors
Treatments that cause brain NE release can be shown
increase the expression of c-fos in rat brain. For exin dorsomedial SCN (Zhang et al., 1993).

C. Adrenergic Receptors

Treatments that cause brain NE release can be shown

to increase the expression of c-fos in rat brain. For ex-

ample, stress associated with restraint han C. Adrenergic Receptors
Treatments that cause brain NE release can be shown
to increase the expression of c-fos in rat brain. For ex-
ample, stress associated with restraint handling and
saline injection increases expressi C. *Aarenergic Receptors*
Treatments that cause brain NE release can be shown
to increase the expression of *c-fos* in rat brain. For ex-
ample, stress associated with restraint handling and
saline injection increases expr Treatments that cause brain NE release can be shown
to increase the expression of c-*fos* in rat brain. For ex-
ample, stress associated with restraint handling and
saline injection increases expression of c-*fos* and *zi* to increase the expression of c-*fos* in rat brain. For example, stress associated with restraint handling and saline injection increases expression of c-*fos* and *zif* 268 genes (Gubits et al., 1989; Bing et al., 1991). ample, stress associated with restraint handling and saline injection increases expression of c-fos and $zif 268$ genes (Gubits et al., 1989; Bing et al., 1991). This increase can be abolished by pharmacological blockade o saline injection increases expression of c-fos and zif 2 genes (Gubits et al., 1989; Bing et al., 1991). This crease can be abolished by pharmacological blockade β -adrenoceptors with propranolol (10 mg/kg i.p.), (Biet genes (Gubits et al., 1989; Bing et al., 1991). This in-
crease can be abolished by pharmacological blockade of
 β -adrenoceptors with propranolol (10 mg/kg i.p.), (Bing
et al., 1991). Agents that release NE by blocking crease can be abolished by pharmacological blockade of β -adrenoceptors with propranolol (10 mg/kg i.p.), (Bing et al., 1991). Agents that release NE by blocking presynaptic autoinhibitory α_2 receptors (i.e., yohimb β -adrenoceptors with propranolol (10 mg/kg i.p.), (Bing
et al., 1991). Agents that release NE by blocking presyn-
aptic autoinhibitory α_2 receptors (i.e., yohimbine, 5
mg/kg i.p.) also strongly induces c-fos mRNA (et al., 1991). Agents that release NE by blocking presynaptic autoinhibitory α_2 receptors (i.e., yohimbine, 5 mg/kg i.p.) also strongly induces c-fos mRNA (Gubits et al., 1989) and *zif* 268 mRNA in rat brain (Bing et aptic autoinhibitory α_2 receptors (i.e., yohimbine, 5 mg/kg i.p.) also strongly induces c-fos mRNA (Gubits et al., 1989) and $zif268$ mRNA in rat brain (Bing et al., 1991). Induction of c-fos and $zif268$ mRNA after NE mg/kg i.p.) also strongly induces c-fos mRNA (Gubits et al., 1989) and $zif268$ mRNA in rat brain (Bing et al., 1991). Induction of c-fos and $zif268$ mRNA after NE release produced by yohimbine can be partially prevented b al., 1989) and *zif* 268 mRNA in rat brain (Bing et al., 1991). Induction of c-*fos* and *zif* 268 mRNA after NE release produced by yohimbine can be partially prevented by administration of propranolol and prazosin $(\alpha_1$ release produced by yohimbine can be partially prevented by administration of propranolol and prazosin vented by administration of propranolol and prazosin $(\alpha_1$ receptor antagonist, 5 mg/kg i.p.) in combination (Bing et al., 1991).

Yohimbine induces Fos-like immunoreactivity in areas of rat brain that contain a high den

(α_1 receptor antagonist, 5 mg/kg i.p.) in combinati(Bing et al., 1991).

Yohimbine induces Fos-like immunoreactivity in a

eas of rat brain that contain a high density of α_2 -recept

binding sites such as the LC, b (Bing et al., 1991).

Yohimbine induces Fos-like immunoreactivity in areas of rat brain that contain a high density of α_2 -receptor

binding sites such as the LC, bed nucleus of stria termi-

nalis, the central nucleus Yohimbine induces Fos-like immunoreactivity in a
eas of rat brain that contain a high density of α_2 -recepto
binding sites such as the LC, bed nucleus of stria term
nalis, the central nucleus of the amygdaloid complex, binding sites such as the LC, bed nucleus of stria terminalis, the central nucleus of the amygdaloid complex, the PVN, the nucleus tractus solitarius, and ventrolateral medulla oblongata (Tsujino et al., 1992). Yohimbine a nalis, the central nucleus of the amygdaloid complex, the PVN, the nucleus tractus solitarius, and ventrolateral
medulla oblongata (Tsujino et al., 1992). Yohimbine also
increases Fos-like immunoreactivity in neocortex and PVN, the nucleus tractus
medulla oblongata (Tsujinc
increases Fos-like immun
piriform cortex, Islands of
cleus (Bing et al., 1992b).
Within the neocortex in edulla oblongata (Tsujino et al., 1992). Yohimbine also
creases Fos-like immunoreactivity in neocortex and
riform cortex, Islands of Calleja, and supraoptic nu-
us (Bing et al., 1992b).
Within the neocortex induction seems

et al., 1991). Agents that release NE by blocking presyntaria aptic autoinhibitory α_2 receptors (i.e., yohimbine, 5 mg/kg i.p.) lake strongly induces c -fos mRNA (Gubits et al., 1989) and $zif 268$ mRNA in rat brain (increases Fos-like immunoreactivity in neocortex and
piriform cortex, Islands of Calleja, and supraoptic nu-
cleus (Bing et al., 1992b).
Within the neocortex induction seems laminar (Bing
et al., 1992b). Induction is pred piriform cortex, Islands of Calleja, and supraoptic nucleus (Bing et al., 1992b).
Within the neocortex induction seems laminar (Bingter al., 1992b). Induction is predominantly mediated b
 β -adrenoceptors, inasmuch as pr cleus (Bing et al., 1992b).
Within the neocortex induction seems laminar (Bing et al., 1992b). Induction is predominantly mediated by β -adrenoceptors, inasmuch as propranolol is more effective than prazosin in reducing Within the neocortex induction seems laminar (Bing
et al., 1992b). Induction is predominantly mediated by
 β -adrenoceptors, inasmuch as propranolol is more effec-
tive than prazosin in reducing the increased cortical
ex et al., 1992b). Induction is predominantly mediated by β -adrenoceptors, inasmuch as propranolol is more effective than prazosin in reducing the increased cortical expression of Fos-like immunoreactivity produced by yo- β -adrenoceptors, inasmuch as propranolol is more effective than prazosin in reducing the increased cortical expression of Fos-like immunoreactivity produced by yo-
himbine (Bing et al., 1992b). Although the majority of tive than prazosin in reducing the increased cortical
expression of Fos-like immunoreactivity produced by yo-
himbine (Bing et al., 1992b). Although the majority of
neocortical β-adrenoceptors exist on astrocytes (Stone et expression of Fos-like immunoreactivity produced by
himbine (Bing et al., 1992b). Although the majorit
neocortical β -adrenoceptors exist on astrocytes (Stor
al., 1990), Fos-like immunoreactivity seems to be loc
almost mbine (Bing et al., 1992b). Although the majority of occortical β -adrenoceptors exist on astrocytes (Stone et , 1990), Fos-like immunoreactivity seems to be located most exclusively in neurons (Bing et al., 1992a). The

neocortical β -adrenoceptors exist on astrocytes (Stone et al., 1990), Fos-like immunoreactivity seems to be located almost exclusively in neurons (Bing et al., 1992a). The effect of stress associated with saline inject al., 1990), Fos-like immunoreactivity seems to be located
almost exclusively in neurons (Bing et al., 1992a).
The effect of stress associated with saline injection
alone had little effect on the number of cells that showed almost exclusively in neurons (Bing et al., 1992a).
The effect of stress associated with saline inject
alone had little effect on the number of cells that show
Fos-like immunoreactivity, however restraint str
produced stro The effect of stress associated with saline injection
alone had little effect on the number of cells that showed
Fos-like immunoreactivity, however restraint stress
produced strong Fos-like immunoreactivity in neocorti-
ca alone had little effect on the number of cells that showed
Fos-like immunoreactivity, however restraint stress
produced strong Fos-like immunoreactivity in neocorti-
cal cells. Propranolol significantly reduced the inducti Fos-like immunoreactivity, however restraint stress
produced strong Fos-like immunoreactivity in neocorti-
cal cells. Propranolol significantly reduced the induction
of Fos in neocortex produced by restraint stress (Bing e produced strong Fos-like immunoreactivity in neocortical cells. Propranolol significantly reduced the induction
of Fos in neocortex produced by restraint stress (Bing et
al., 1992b). The majority of noradrenergic fibres th cal cells. Propranolol significantly reduced the induction
of Fos in neocortex produced by restraint stress (Bing et
al., 1992b). The majority of noradrenergic fibres that
innervate the neocortex originate from the LC, whe of Fos in neocortex produced by restraint stress (Bing et al., 1992b). The majority of noradrenergic fibres that innervate the neocortex originate from the LC, where their neuronal cell bodies reside. Lesioning of the LC u al., 1992b). The majority of noradrenergic fibres that
innervate the neocortex originate from the LC, where
their neuronal cell bodies reside. Lesioning of the LC
using the neurotoxin 6-OHDA effectively abolishes no-
radre their neuronal cell bodies reside. Lesioning of the LC
using the neurotoxin 6-OHDA effectively abolishes no-
radrenergic innervation of the neocortex. Lesioning of
the LC also markedly attenuates the induction of Fos-
like their neuronal cell bodies reside. Lesioning of the LC
using the neurotoxin 6-OHDA effectively abolishes no-
radrenergic innervation of the neocortex. Lesioning of
the LC also markedly attenuates the induction of Fos-
lik using the neurotoxin 6-OHDA effectively abolishes no-
radrenergic innervation of the neocortex. Lesioning of
the LC also markedly attenuates the induction of Fos-
like immunoreactivity in rat neocortex produced by ei-
the radrenergic innervation of the neocortex. Lesioning of
the LC also markedly attenuates the induction of Fos-
like immunoreactivity in rat neocortex produced by ei-
ther restraint stress or the α_2 -adrenoceptor antagoni the LC also markedly attenuates the induction of Fos-
like immunoreactivity in rat neocortex produced by ei-
ther restraint stress or the α_2 -adrenoceptor antagonist
yohimbine, suggesting that it is a release of NE aft

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sults in increased Fos production in neocortical neurons HUGHES

sults in increased Fos production in neocortical neuro

(Stone et al., 1993). Lesioning of the LC with the neuro

toxin N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine h sults in increased Fos production in neocortical neuro
(Stone et al., 1993). Lesioning of the LC with the neur
toxin N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine h
also been shown to markedly suppress the high cons
tutive sults in increased Fos production in neocortical neurons
(Stone et al., 1993). Lesioning of the LC with the neuro-
toxin N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine has
also been shown to markedly suppress the high const (Stone et al., 1993). Lesioning of the LC with the neuro-
toxin N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine has
also been shown to markedly suppress the high consti-
tutive expression of $zif 268$ mRNA that is found in ra also been shown to markedly suppress the high constitutive expression of $zif 268$ mRNA that is found in rat neocortex. Basal expression of $zif 268$ in hippocampus (CA1) was not altered by LC lesion.
These results show tha so been shown to markedly suppress the high constitive expression of $zif 268$ mRNA that is found in rat and cocortex. Basal expression of $zif 268$ in hippocampus de (A1) was not altered by LC lesion. $g!$
These results sh

tutive expression of $zif 268$ mRNA that is found in rat neocortex. Basal expression of $zif 268$ in hippocampus (CA1) was not altered by LC lesion.
These results show that constitutive expression of $zif 268$ in neocortex, zif 268 in neocortex, but not hippocampus, is dependent upon tonic activity of the forebrain noradrenergic neu-
rotransmitter system (Bhat and Baraban, 1992). Furthermore, within the rat pineal gland, both c-fos and These results show that constitutive expression of *zif* 268 in neocortex, but not hippocampus, is dependent inc
upon tonic activity of the forebrain noradrenergic neu-
informal pinear (Bhat and Baraban, 1992). Fur-8-C
the *zif* 268 in neocortex, but not hippocampus, is depend upon tonic activity of the forebrain noradrenergic rotransmitter system (Bhat and Baraban, 1992). I thermore, within the rat pineal gland, both c-fos *jun*-B mRNA can upon tonic activity of the forebrain noradrenergic ne
rotransmitter system (Bhat and Baraban, 1992). Fu
thermore, within the rat pineal gland, both c-fos a
 $jun-$ B mRNA can be regulated by activation of noradre
ergic recept rotransmitter system (Bhat and Baraban, 1992). Fur-
thermore, within the rat pineal gland, both c-fos and 5
jun-B mRNA can be regulated by activation of noradren-
ergic receptors. Although both phenylephrine (α_1 -ago-
 thermore, within the rat pineal gland, both c-fos and 5 jun-B mRNA can be regulated by activation of noradren-
ergic receptors. Although both phenylephrine (α_1 -ago-
inist) and isoproterenol (β -agonist) induce simil jun-B mRNA can be regulated by activation of noradren-
ergic receptors. Although both phenylephrine $(\alpha_1$ -ago-
inist) and isoproterenol (β -agonist) induce similar levels
of expression of jun-B mRNA in pineal neurons (ergic receptors. Although both phenylephrine $(\alpha_1$ -ago-
mist) and isoproterenol (β -agonist) induce similar levels the
of expression of *jun*-B mRNA in pineal neurons (al-
though isoproterenol was somewhat more effecti mist) and isoproterenol (β -agonist) induce similar levels the of expression of jun -B mRNA in pineal neurons (al-
though isoproterenol was somewhat more effective), the con
expression of c-fos mRNA is differentially reg of expression of *jun*-B mRNA in pineal neurons (altertional though isoproterenol was somewhat more effective), the expression of c-*fos* mRNA is differentially regulated by these two drugs. The α -agonist phenylephrine expression of c-*fos* mRNA is differentially regulated
these two drugs. The α -agonist phenylephrine cause
far more significant increase in pineal c-*fos* mRNA lev
than does isoproterenol (Carter, 1993). Activation of
a these two drugs. The α -agonist phenylephrine causes a tive
far more significant increase in pineal c-fos mRNA levels atte
than does isoproterenol (Carter, 1993). Activation of α_2 - mRl
adrenoceptors by the highly se midine has also been shown to suppress the increase in
c-Fos, Fos-B, c-Jun, Jun-B, and Krox-24 proteins seen in E . Dopamine Receptors
the dorsal horn of the spinal cord after peripheral nox-Recent studies have adrenoceptors by the highly selective α_2 -agonist medeto-
midine has also been shown to suppress the increase in
c-Fos, Fos-B, c-Jun, Jun-B, and Krox-24 proteins seen in
the dorsal horn of the spinal cord after periphe adrenoceptors by the highly selective α_2 -agonist medeto-
midine has also been shown to suppress the increase in
c-Fos, Fos-B, c-Jun, Jun-B, and Krox-24 proteins seen in
the dorsal horn of the spinal cord after periphe midine has also been shown to suppress the increase in c-Fos, Fos-B, c-Jun, Jun-B, and Krox-24 proteins seen in the dorsal horn of the spinal cord after peripheral noxious stimulation. Suppression was stronger in the deep c-Fos, Fos-B, c-Jun, Jun-B, and Krox-24 pro
the dorsal horn of the spinal cord after perious stimulation. Supression was stronger
(III to VI) rather than superficial (I and I
the dorsal horn (Pertovaara et al., 1993). *D. Supres*
D. Serotonin Receptors
D. Serotonin Receptors
P. Serotonin Receptors
Fenfluramine is an ind

I to VI) rather than superficial (I and II) laminae of
e dorsal horn (Pertovaara et al., 1993).
Serotonin Receptors
Fenfluramine is an indirect 5-HT agonist. It increases
HT availability at nerve terminals by enhancing 5-H the dorsal horn (Pertovaara et al., 1993). Sione sione is an indirect at al., 1993.

D. Serotonin Receptors at al. Fenfluramine is an indirect 5-HT agonist. It increases later

5-HT availability at nerve terminals by enhan D. Serotonin Receptors
Fenfluramine is an indirect 5-HT agonist. It incre
5-HT availability at nerve terminals by enhancing {
release but blocking 5-HT uptake. Systemic admini
tion of fenfluramine (25 mkg/kg i.p.) results Let be a seroton therefore a seroton of Fenfluramine is an indirect 5-HT agonist. It increases late 5-HT availability at nerve terminals by enhancing 5-HT release but blocking 5-HT uptake. Systemic administration of fenflu Fenfluramine is an indirect 5-HT agonist. It increases
5-HT availability at nerve terminals by enhancing 5-HT
release but blocking 5-HT uptake. Systemic administra-
tion of fenfluramine (25 mkg/kg i.p.) results in marked
i 5-HT availability at nerve terminals by enhancing 5-HT redease but blocking 5-HT uptake. Systemic administra-
redion of fenfluramine (25 mkg/kg i.p.) results in marked c-H
increases in Fos-like immunoreactivity in striatum release but blocking 5-HT uptake. Systemic administra-
tion of fenfluramine (25 mkg/kg i.p.) results in marked
increases in Fos-like immunoreactivity in striatum (but
not nucleus accumbens), parvocellular division of the
h tion of fenfluramine (25 mkg/kg i.p.) results in marked c-Fo
increases in Fos-like immunoreactivity in striatum (but cont
not nucleus accumbens), parvocellular division of the dal i
hypothalamic PVN, and in the central amy increases in Fos-like immunoreactivity in striatum (but contract nucleus accumbens), parvocellular division of the dippothalamic PVN, and in the central amygdaloid nucleus (Richard et al., 1992). In addition, it also seems not nucleus accumbens), parvocellular division of the
hypothalamic PVN, and in the central amygdaloid nu-
cleus (Richard et al., 1992). In addition, it also seems to
induce Fos-like immunoreactivity in the bed nucleus of
t hypothalamic PVN, and in the central amygdaloid nucleus (Richard et al., 1992). In addition, it also seems to producleus of the stria terminalis, midline thalamic nuclei, habenular no nuclei, lateral parabrachial nucleus, cleus (Richard et al., 1992). In addition,
induce Fos-like immunoreactivity in the
the stria terminalis, midline thalamic n
nuclei, lateral parabrachial nucleus, an
solitary tract (Li and Rowland, 1993).
At parenteral dose duce Fos-like immunoreactivity in the bed nucleus of
e stria terminalis, midline thalamic nuclei, habenular
iclei, lateral parabrachial nucleus, and nucleus of the
litary tract (Li and Rowland, 1993).
At parenteral doses o

the stria terminalis, midline thalamic nuclei, habenu
nuclei, lateral parabrachial nucleus, and nucleus of t
solitary tract (Li and Rowland, 1993).
At parenteral doses of 2 or 8 mg/kg, the $5-HT_2$
receptor agonist DOI cau nuclei, lateral parabrachial nucleus, and nucleus of the recepsolitary tract (Li and Rowland, 1993). deplement the piritor of Fosis in frontal, parietal, cingulate, and piriform select cortex as well as in claustrum, mami solitary tract (Li and Rowland, 1993).

At parenteral doses of 2 or 8 mg/kg, the 5-HT_{2/1C}

receptor agonist DOI causes a highly localised expres-

sion of Fos in frontal, parietal, cingulate, and piriform

cortex as we At parenteral doses of 2 or 8 mg/kg, the 5-HT_!
receptor agonist DOI causes a highly localised explained and pirific
sion of Fos in frontal, parietal, cingulate, and pirific
cortex as well as in claustrum, mamillary bodie receptor agonist DOI causes a highly localised expression of Fos in frontal, parietal, cingulate, and piriform cortex as well as in claustrum, mamillary bodies, globus pallidus, amygdala, nucleus accumbens, and dorsomedial sion of Fos in frontal, parietal, cingulate, and piriform sele
cortex as well as in claustrum, mamillary bodies, globus c-fos
pallidus, amygdala, nucleus accumbens, and dorsome-eral
dial striatum. Within the primary somato cortex as well as in claustrum, mamillary bodies, globus
pallidus, amygdala, nucleus accumbens, and dorsome-
dial striatum. Within the primary somatosensory cortex,
induction occurs within layer Va, which is reported to
re pallidus, amygdala, nucleus accumbens, and dorsomedial striatum. Within the primary somatosensory cortex, induction occurs within layer Va, which is reported to receive innervation from the dorsal raphe nucleus.
Chronic li dial striatum. Within the primary somatosensory cortex, tinduction occurs within layer Va, which is reported to receive innervation from the dorsal raphe nucleus. Notice through the method of Fos by DOI (Leslie et al., 19 induction occurs within layer Va, which is reported to receive innervation from the dorsal raphe nucleus.
Chronic lithium treatment of rats enhances cortical induction of Fos by DOI (Leslie et al., 1993b). No induction of receive innervation from the dorsal raphe nucleus.
Chronic lithium treatment of rats enhances cortical induction of Fos by DOI (Leslie et al., 1993b). No induction of Fos was found in hippocampus, although $5-\text{HT}_{2/1C}$ r pronic lithium treatment of rats enhances cortical in-
totion of Fos by DOI (Leslie et al., 1993b). No induction
Fos was found in hippocampus, although 5-HT_{2/1C}
ceptors can be found here.
The 5-HT_{2/1C} antagonist, rita duction of Fos by DOI (Leslie et al., 1993b). No induction
of Fos was found in hippocampus, although $5\text{-}HT_{2/1C}$
receptors can be found here.
The $5\text{-}HT_{2/1C}$ antagonist, ritanserin (0.4 mg/kg),
markedly attenuated t

% of Fos was found in hippocampus, although $5\text{-}HT_{2/1C}$
receptors can be found here.
The $5\text{-}HT_{2/1C}$ antagonist, ritanserin (0.4 mg/kg),
markedly attenuated the increased Fos expression pro-
duced by DOI. Induction

toxin N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine has levels by 24 h. Induction occurred only in neurons, bebragunow
became evident after 30 min, reached a maximum level
at 3 h, and declined to background or near background DRAGUNOW
became evident after 30 min, reached a maximum level
at 3 h, and declined to background or near background
levels by 24 h. Induction occurred only in neurons, be-DRAGUNOW
became evident after 30 min, reached a maximum level
at 3 h, and declined to background or near background
levels by 24 h. Induction occurred only in neurons, be-
cause, although many neurons double-labeled for Fo became evident after 30 min, reached a maximum level
at 3 h, and declined to background or near background
levels by 24 h. Induction occurred only in neurons, be-
cause, although many neurons double-labeled for Fos
and neu at 3 h, and declined to background or near background
levels by 24 h. Induction occurred only in neurons, be-
cause, although many neurons double-labeled for Fos
and neuron-specific enolase, no neurons could be seen to
dou cause, although many neurons double-labeled for Fos use, although many neurons double-labeled for Fos
d neuron-specific enolase, no neurons could be seen to
uble-label for Fos and glial fibrillary acidic protein (a
ial-specific marker) (Leslie et al., 1993a).
The 5-HT_{1A} r

expression of c-*fos* mRNA is differentially regulated by the induction of IEGs in striatum by cocaine, with selectiese two drugs. The α-agonist phenylephrine causes a tive denervation of 5-HT projections to the striatum glial-specific marker) (Leslie et al., 1993a).
The 5-HT_{1A} receptor agonist 8-OH-DPAT also slightly
increases Fos protein levels in cortex. Chronic lithium and neuron-specific enolase, no neurons could be seen to
double-label for Fos and glial fibrillary acidic protein (a
glial-specific marker) (Leslie et al., 1993a).
The 5-HT_{1A} receptor agonist 8-OH-DPAT also slightly
inc did not seem to enhance Fos expression induced by 8-OH-DPAT. This lack of effect may occur because glial-specific marker) (Leslie et al., 1993a).
The 5-HT_{1A} receptor agonist 8-OH-DPAT also slightly
increases Fos protein levels in cortex. Chronic lithium
did not seem to enhance Fos expression induced by
8-OH-DPAT. Thi The 5-HT_{1A} receptor agonist 8-OH-DPAT also slightly
increases Fos protein levels in cortex. Chronic lithium
did not seem to enhance Fos expression induced by
8-OH-DPAT. This lack of effect may occur because
5-HT_{1A} and increases Fos protein levels in cortex. Chronic lithium
did not seem to enhance Fos expression induced by
8-OH-DPAT. This lack of effect may occur because
5-HT_{1A} and 5-HT_{2A} receptors are linked to different
second-mes did not seem to enhance Fos expression induced by 8-OH-DPAT. This lack of effect may occur because 5-HT_{1A} and 5-HT_{2A} receptors are linked to different second-messenger systems. The 5-HT_{2A} receptor is linked to the h 8-OH-DPAT. This lack of effect may occur because 5-HT_{1A} and 5-HT_{2A} receptors are linked to different second-messenger systems. The 5-HT_{2A} receptor is linked to the hydrolysis of phosphoinositides, whereas the 5-HT₁ linked to the hydrolysis of phosphoinositides, whereas the 5- HT_{1A} receptor activates adenylate cyclase (Leslie et al., 1993b). Serotonin systems also seem necessary (in conjunction with dopamine systems, see next section) for conjunction with dopamine systems, see next section) for
the induction of IEGs in striatum by cocaine, with selec-
tive denervation of 5-HT projections to the striatum
attenuating the increased expression of c-fos and zif the induction of IEGs in striative denervation of 5-HT p
attenuating the increased ex
mRNA produced in striatum
(Bhat and Baraban, 1993). attenuating the increased expression of c-fos and *zif* 268

second-messenger systems. The 5-HT_{2A} receptor is
three 5-HT_{1A} receptor attivates adenyhiosticles, whereas
the 5-HT_{1A} receptor activates adenyhiosticles, whereas
et al., 1993b). Serotonin systems also seem necessary Recent studies have shown a link between dopamin-
ergic neurotransmission and the IEGP Fos/Fras in rat (Bhat and Baraban, 1993).

E. Dopamine Receptors

Recent studies have shown a link between dopamin-

ergic neurotransmission and the IEGP Fos/Fras in rat

basal ganglia neurons. For example, in 6-OHDA-le-E. Dopamine Receptors
Recent studies have shown a link between dopar
ergic neurotransmission and the IEGP Fos/Fras in
basal ganglia neurons. For example, in 6-OHD/
sioned rats, administration of the dopamine precur E. Dopamine Receptors
Recent studies have shown a link between dopamin-
ergic neurotransmission and the IEGP Fos/Fras in rat
basal ganglia neurons. For example, in 6-OHDA-le-
sioned rats, administration of the dopamine pre Recent studies have shown a link between dopamin-
ergic neurotransmission and the IEGP Fos/Fras in rat
basal ganglia neurons. For example, in 6-OHDA-le-
sioned rats, administration of the dopamine precursor,
levodopa, prod ergic neurotransmission and the IEGP Fos/Fras in rat
basal ganglia neurons. For example, in 6-OHDA-le-
sioned rats, administration of the dopamine precursor,
levodopa, produced a large induction of Fos/Fras in stri-
atal basal ganglia neurons. For example, in 6-OHDA-le-
sioned rats, administration of the dopamine precursor,
levodopa, produced a large induction of Fos/Fras in stri-
atal neurons (Robertson et al., 1989a). This effect was
la sioned rats, administration of the dopamine precursor,
levodopa, produced a large induction of Fos/Fras in stri-
atal neurons (Robertson et al., 1989a). This effect was
later found to be caused by D_1 , but not D_2 , do levodopa, produced a large induction of Fos/Fras in stri-
atal neurons (Robertson et al., 1989a). This effect was
later found to be caused by D_1 , but not D_2 , dopamine
receptor agonism (Robertson et al., 1989b), alth atal neurons (Robertson et al., 1989a). This effect was

later found to be caused by D_1 , but not D_2 , dopamine

receptor agonism (Robertson et al., 1989b), although D_2

receptors do seem to play a small part in th later found to be caused by D_1 , but not D_2 , dopamin
receptor agonism (Robertson et al., 1989b), although D
receptors do seem to play a small part in the induction c -Fos after levodopa injection (Morelli et al., 19 receptor agonism (Robertson et al., 1989b), although D_2
receptors do seem to play a small part in the induction of
c-Fos after levodopa injection (Morelli et al., 1993a). In
contrast, D_2 receptor agonists induce Fos ceptors do seem to play a small part in the induction \mathbf{r} ⁵os after levodopa injection (Morelli et al., 1993a). I
ntrast, \mathbf{D}_2 receptor agonists induce Fos/Fras in pall
l neurons after dopamine-depletion (Paul

c-Fos after levodopa injection (Morelli et al., 1993a). In contrast, D_2 receptor agonists induce Fos/Fras in palli-
dal neurons after dopamine-depletion (Paul et al., 1992).
 D_1 -agonists induce Fos specifically in st contrast, D_2 receptor agonists induce Fos/Fras in palli-
dal neurons after dopamine-depletion (Paul et al., 1992).
 D_1 -agonists induce Fos specifically in striato-nigral
projection neurons (Robertson et al., 1990, 19 dal neurons after dopamine-depletion (Paul et al., 1992).
 D_1 -agonists induce Fos specifically in striato-nigral

projection neurons (Robertson et al., 1990, 1992; Cenci

et al., 1992) that contain dynorphin and substa D₁-agonists induce Fos specifically in striato-ni
projection neurons (Robertson et al., 1990, 1992; C
et al., 1992) that contain dynorphin and substance P,
not enkephalin (Zhang et al., 1992). Activation of
receptors is projection neurons (Robertson et al., 1990, 1992; Cenci
et al., 1992) that contain dynorphin and substance P, but
not enkephalin (Zhang et al., 1992). Activation of D₁-
receptors is involved in c-*fos* induction in dopa et al., 1992) that contain dynorphin and substance P, but
not enkephalin (Zhang et al., 1992). Activation of D_1 -
receptors is involved in c-*fos* induction in dopamine-
depleted striatum (Simson et al., 1992; Johnson e not enkephalin (Zhang et al., 1992). Activation of D_1 -
receptors is involved in c-*fos* induction in dopamine-
depleted striatum (Simson et al., 1992; Johnson et al.,
1992). More recently, it has been shown that combin receptors is involved in c-fos induction in dopamine-
depleted striatum (Simson et al., 1992; Johnson et al.,
1992). More recently, it has been shown that combined
treatment of dopamine-depleted rats with D_1 - and D_2 depleted striatum (Simson et al., 1992; Johnson et al., 1992). More recently, it has been shown that combined treatment of dopamine-depleted rats with D_1 - and D_2 -selective agonists produces a synergistic induction o 1992). More recently, it has been shown that combin
treatment of dopamine-depleted rats with D_1 - and I
selective agonists produces a synergistic induction
c-*fos* in the striosomal compartment and in the dorsola
eral c treatment of dopamine-depleted rats with D_1 - and D_2 -
selective agonists produces a synergistic induction of
c-*fos* in the striosomal compartment and in the dorsolat-
eral caudoputamen (Paul et al., 1992). This c-*f* selective agonists produces a synergistic induction of c-fos in the striosomal compartment and in the dorsolateral caudoputamen (Paul et al., 1992). This c-fos induction (and turning behaviour) is blocked by D_1 or D_2 c-*fos* in the striosomal compartment and in the dorsol
eral caudoputamen (Paul et al., 1992). This c-*fos* ind
tion (and turning behaviour) is blocked by D_1 or
antagonists and also by the NMDA receptor antagor
MK801 (eral caudoputamen (Paul et al., 1992). This c-fos induction (and turning behaviour) is blocked by D_1 or D_2 antagonists and also by the NMDA receptor antagonist MK801 (Paul et al., 1992). In contrast, MK801 potentiat tion (and turning behaviour) is blocked by D_1 or D_2
antagonists and also by the NMDA receptor antagonist
MK801 (Paul et al., 1992). In contrast, MK801 potenti-
ates induction of Fos by the D_1 agonist SKF 38393 in antagonists and also by the NMDA receptor antagonist MK801 (Paul et al., 1992). In contrast, MK801 potentiates induction of Fos by the D_1 agonist SKF 38393 in the dorsolateral aspect of the depleted striatum (Morelli e MK801 (Paul et al., 1992). In contrast, MK801 potentiates induction of Fos by the D_1 agonist SKF 38393 in the dorsolateral aspect of the depleted striatum (Morelli et al., 1992). The reason for these different results ates induction of Fos by the D_1 agonist SKF 38393 in the dorsolateral aspect of the depleted striatum (Morelli et al., 1992). The reason for these different results is unclear, however, recently it has been demonstrate dorsolateral aspect of the depleted striatum (Morelli
al., 1992). The reason for these different results is i
clear, however, recently it has been demonstrated th
transection of glutaminergic cortico-fugal fibres reduced
a al., 1992). The reason for these different results is unclear, however, recently it has been demonstrated that transection of glutaminergic cortico-fugal fibres reduces amphetamine- and apomorphine-induced Fos expression (

PHARMACOLOGICAL REVIEW

been demonstrated that muscarinic antagonists potentially of the demonstrated that muscarinic antagonists potentials D_1 **-receptor (but not** D_2 **-receptor)-mediated turnic** IMMEDIATE-EARLY GENES A
results (Paul et al., 1992). In addition it has recently the
been demonstrated that muscarinic antagonists poten-
tiate D₁-receptor (but not D₂-receptor)-mediated turning 1
and Fos expression in results (Paul et al., 1992). In addition it has recent
been demonstrated that muscarinic antagonists pot
tiate D_1 -receptor (but not D_2 -receptor)-mediated turn
and Fos expression in lesioned striatal neurons, sugge
i results (Paul et al., 1992). In addition it has recently the
been demonstrated that muscarinic antagonists poten-
tiate D_1 -receptor (but not D_2 -receptor)-mediated turning 19
and Fos expression in lesioned striatal n been demonstrated that muscarinic antagonists poten-
tiate D_1 -receptor (but not D_2 -receptor)-mediated turning 19
and Fos expression in lesioned striatal neurons, suggest-
ing that both glutamate and acetylcholine sy tiate D_1 -receptor (but not D_2 -rece
and Fos expression in lesioned str
ing that both glutamate and ace
involved in the D_1 -mediated indu
striatum (Morelli et al., 1993b).
Although D_1 -agonists induce d Fos expression in lesioned striatal neurons, sugge that both glutamate and acetylcholine systems volved in the D_1 -mediated induction of Fos/Fras in riatum (Morelli et al., 1993b).
Although D_1 -agonists induce Fos i

ing that both glutamate and acetylcholine systems are
involved in the D_1 -mediated induction of Fos/Fras in the
striatum (Morelli et al., 1993b).
Although D_1 -agonists induce Fos in the dopamine-
depleted striatum, th involved in the D_1 -mediated induction of Fos/Fras in the striatum (Morelli et al., 1993b).
Although D_1 -agonists induce Fos in the dopamine-
depleted striatum, they do not induce it on the intact
side (Robertson et a striatum (Morelli et al., 1993b).

Although D_1 -agonists induce Fos in the dopamine-

depleted striatum, they do not induce it on the intact

side (Robertson et al., 1989a, b; also see Dilts et al.,

1993, who found tha depleted striatum, they do not induce it on the intact side (Robertson et al., 1989a, b; also see Dilts et al., 1993, who found that a high dose of apomorphine induced Fos and Fras). It seems that direct-acting dopa-
mine depleted striatum, they do not induce it on the intact side (Robertson et al., 1989a, b; also see Dilts et al., 1993, who found that a high dose of apomorphine induced Fos and Fras). It seems that direct-acting dopamine r side (Robertson et al., 1989a, b; also see Dilts et al., c-ju
1993, who found that a high dose of apomorphine in-
duced Fos and Fras). It seems that direct-acting dopa-
mine receptor agonists induce Fos through D_1 rece 1993, who found that a high dose of apomorphine in-
duced Fos and Fras). It seems that direct-acting dopa-
mine receptor agonists induce Fos through D_1 receptors
made supersensitive by dopamine-depletion with
6-OHDA or duced Fos and Fras). It seems that direct-acting dopa-
mine receptor agonists induce Fos through D_1 receptors
made supersensitive by dopamine-depletion with
6-OHDA or reserpine (Cole et al., 1992; Robertson et al.,
198 mine receptor agonists induce Fos through D_1 receptor and supersensitive by dopamine-depletion 6-OHDA or reserpine (Cole et al., 1992; Robertson e 1989a). The reason for this selectivity for supersens D_1 -receptors i made supersensitive by dopamine-depletion with 6-OHDA or reserpine (Cole et al., 1992; Robertson et al., 1989a). The reason for this selectivity for supersensitive D_1 -receptors is unclear, but it may be subtle neuroche 6-OHDA or reserpine (Cole et al., 1992; Robertson et al., 1989a). The reason for this selectivity for supersensitive D_1 -receptors is unclear, but it may be subtle neurochemical alterations occurring after dopamine-depl 1989a). The reason for this selectivity for supersensitive D_1 -receptors is unclear, but it may be subtle neurochemical alterations occurring after dopamine-depletion caused this selectivity (Thomas et al., 1992). Howev D_1 -receptors is unclear, but it may be subtle neurochemical alterations occurring after dopamine-depletion caused this selectivity (Thomas et al., 1992). However, c-Fos induction seems to provide a biochemical marker o ical alterations occus
caused this selectivity
c-Fos induction seems
of D₁-receptor sensitiv
Lahoste et al., 1993).
In contrast, dopamin used this selectivity (Thomas et al., 1992). Howeve
Fos induction seems to provide a biochemical marke
 D_1 -receptor sensitivity (Asin and Wirtshafter, 1993)
hoste et al., 1993).
In contrast, dopamine-releasing drugs (in

c-Fos induction seems to provide a biochemical marker in t
of D_1 -receptor sensitivity (Asin and Wirtshafter, 1993; ing
Lahoste et al., 1993). When In contrast, dopamine-releasing drugs (indirect dopa-bio
mine agonists) of D₁-receptor sensitivity (Asin and Wirtshafter, 1993; in
Lahoste et al., 1993).
In contrast, dopamine-releasing drugs (indirect dopa-
mine agonists), such as cocaine, amphetamine, and
MDMA, induce Fos in intact striat Lahoste et al., 1993).

In contrast, dopamine-releasing drugs (indirect dopamine agonists), such as cocaine, amphetamine, and

MDMA, induce Fos in intact striatal neurons via D_1 -

receptor activation (Dragunow et al., In contrast, dopamine-releasing drugs (indirect dopa-bioc mine agonists), such as cocaine, amphetamine, and In MDMA, induce Fos in intact striatal neurons via D_1 - mine receptor activation (Dragunow et al., 1991b; Grayb mine agonists), such as cocaine, amphetamine, and Ir MDMA, induce Fos in intact striatal neurons via D_1 - min
receptor activation (Dragunow et al., 1991b; Graybiel et cau
al., 1990; Snyder-Keller, 1991; Young et al., 19 MDMA, induce Fos in intact striatal neurons
receptor activation (Dragunow et al., 1991b; Gra
al., 1990; Snyder-Keller, 1991; Young et al., 1991
striato-nigral projection neurons (Cenci et al., 1
fact, dopamine depletion ab receptor activation (Dragunow et al., 1991b; Graybiel et causal., 1990; Snyder-Keller, 1991; Young et al., 1991) and in gun striato-nigral projection neurons (Cenci et al., 1992). In inerfact, dopamine depletion abolishes al., 1990; Snyder-Keller, 1991; Young et al., 1991) and
striato-nigral projection neurons (Cenci et al., 1992)
fact, dopamine depletion abolishes amphetamine-m
ated induction of Fos, indicating that it is caused
dopamine r striato-nigral projection neurons (Cenci et al., 1992). In in
fact, dopamine depletion abolishes amphetamine-medi-
ated induction of Fos, indicating that it is caused by rc
dopamine release (Robertson et al., 1989b). Inter fact, dopamine depletion abolishes amphetamine-medi-
ated induction of Fos, indicating that it is caused by
dopamine release (Robertson et al., 1989b). Interest-
imply, MDMA- and amphetamine-induced expression of may
Fos i ated induction of Fos, indicating that it is caused by
dopamine release (Robertson et al., 1989b). Interest-
ingly, MDMA- and amphetamine-induced expression of
Fos in caudo-putamen is inhibited by MK801 (Dragunow
et al., 1 dopamine release (Robertson et al., 1989b). Interest-
ingly, MDMA- and amphetamine-induced expression of m
Fos in caudo-putamen is inhibited by MK801 (Dragunow on
et al., 1991b; Snyder-Keller, 1991) and induction by am-
ph ingly, MDMA- and amphetamine-induced expression of m
Fos in caudo-putamen is inhibited by MK801 (Dragunow or
et al., 1991b; Snyder-Keller, 1991) and induction by am-
phetamine is also slightly inhibited by morphine (Fuxe T Fos in caudo-putamen is inhibited by MK801 (Dragund et al., 1991b; Snyder-Keller, 1991) and induction by an phetamine is also slightly inhibited by morphine (Fu et al., 1991), which, along with caffeine, also induces F exp phetamine is also slightly inhibited by morphine (Fuxe
et al., 1991), which, along with caffeine, also induces Fos
expression in the striatum (Chang et al., 1988; Naka-
jima et al., 1989b; Johansson et al., 1992). A detail et al., 1991), which, along with caffeine, also induces Foscurression in the striatum (Chang et al., 1988; Naka-
jima et al., 1989b; Johansson et al., 1992). A detailed s
study of the types of striatal neurons expressing F expression in the striatum (Chang et al., 1988; Naka-
jima et al., 1989b; Johansson et al., 1992). A detailed
study of the types of striatal neurons expressing Fos
after amphetamine and cocaine reveals that induction
occur ilma et al., 1989b; Johansson et al., 1992). A detailed strial study of the types of striatal neurons expressing Fos al., after amphetamine and cocaine reveals that induction It occurs in DARPP-22-positive neurons but not study of the types of striatal neurons expressing Fos
after amphetamine and cocaine reveals that induction
occurs in DARPP-22-positive neurons but not in en-
kephalin-positive cells. Fos induction was not seen in
neurons after amphetamine and cocaine reveals that induction
occurs in DARPP-22-positive neurons but not in en-
kephalin-positive cells. Fos induction was not seen in
neurons that co-expressed enkephalin and DARPP-22. It
was ther occurs in DARPP-22-positive neurons but not in
kephalin-positive cells. Fos induction was not see
neurons that co-expressed enkephalin and DARPP-2
was therefore suggested that D_1 -receptor agonists n
induce Fos via DARP phalin-positive cells. Fos induction was not seen
urons that co-expressed enkephalin and DARPP-22
as therefore suggested that D_1 -receptor agonists mig
duce Fos via DARPP-22 (Berretta et al., 1992).
In addition to induci meurons that co-expressed enkephalin and DARPP-22. It
was therefore suggested that D_1 -receptor agonists might
induce Fos via DARPP-22 (Berretta et al., 1992).
In addition to inducing c-fos gene expression, dopam-
ine-r

was therefore suggested that D_1 -receptor agonists might
induce Fos via DARPP-22 (Berretta et al., 1992).
In addition to inducing c-fos gene expression, dopam-
ine-releasing drugs, such as amphetamine and cocaine,
also induce Fos via DARPP-22 (Berretta et al., 1992).
In addition to inducing c-*fos* gene expression, dopam
ine-releasing drugs, such as amphetamine and cocaine
also lead to the expression of *jun*-B (Cole et al., 1992;
Morata In addition to inducing c-fos gene expression, dopamine-releasing drugs, such as amphetamine and cocaine, also lead to the expression of *jun*-B (Cole et al., 1992; Moratalla et al., 1992), but not c-*jun* (Moratalla et al ine-releasing drugs, such as amphetamine and cocaine, also lead to the expression of jun -B (Cole et al., 1992; Moratalla et al., 1992), but not $c-jun$ (Moratalla et al., 1993; but see Hope et al., 1992). These results sugg also lead to the expression of *jun*-B (Cole et al., 1992; sion
Moratalla et al., 1993), $zif 268$ (Cole et al., 1992; Mor-
atalla et al., 1992), but not c -*jun* (Moratalla et al., 1993; cor
but see Hope et al., 1992). T Moratalla et al., 1993), $zif268$ (Cole et al., 1992; Mor-1992). Furthermore, cortical stimulation that activates atalla et al., 1992), but not c-jun (Moratalla et al., 1993; cortico-striatal glutaminergic pathways induces atalla et al., 1992), but not c -*jun* (Moratalla et al., 1993; but see Hope et al., 1992). These results suggest that dopamine-releasing drugs induce mainly Fos/Jun-B dimers as well as $zif 268$. $zif 268$ is also express but see Hope et al., 1992). These results suggest that st dopamine-releasing drugs induce mainly Fos/Jun-B w dimers as well as $zif 268$. $zif 268$ is also expressed at high hevels basally in the striatum (and other brain r dopamine-releasing drugs induce mainly Fos/Jun-B whe
dimers as well as $zif 268$. $zif 268$ is also expressed at high hald
levels basally in the striatum (and other brain regions), very
and this basal expression can be redu dimers as well as *zif* 268. *zif* 268 is also expressed at high levels basally in the striatum (and other brain regions), and this basal expression can be reduced by blocking D_1 -dopamine receptors (Mailleux et al., 19

IMMEDIATE-EARLY GENES AND GENE EXPRESSION
results (Paul et al., 1992). In addition it has recently though the 5-HT system does not contribute to basal
been demonstrated that muscarinic antagonists poten-expression of *zif* AND GENE EXPRESSION 153
though the 5-HT system does not contribute to basal
expression of *zif* 268 in the striatum (Bhat and Baraban, AND GENE EXPRESSION 153
though the 5-HT system does not contribute to basal
expression of *zif* 268 in the striatum (Bhat and Baraban,
1992), it seems that the induction of IEGs, including 153

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1592), it seems that the induction of IEGs, including

1992), it seems that the induction of IEGs, including

1992), it seems that the induction of IEGs, including

197268, by dopamine-releasing drugs such as coc **zifabrical drugs such as a contribute to basal expression of zif 268 in the striatum (Bhat and Baraban, 1992), it seems that the induction of IEGs, including zif 268, by dopamine-releasing drugs such as cocaine is partly** though the 5-HT system does not contribute to basal expression of $zif 268$ in the striatum (Bhat and Baraban, 1992), it seems that the induction of IEGs, including $zif 268$, by dopamine-releasing drugs such as cocaine is expression of *zif* 2
1992), it seems the *zif* 268, by dopaming partly caused by a Baraban, 1993).
In contrast to the z if 268, by dopamine-releasing drugs such as cocaine is partly caused by activation of 5-HT receptors (Bhat and Baraban, 1993).
In contrast to the effects of acute drug administration, chronic administered cocaine leads

 z if 268, by dopamine-releasing drugs such as cocaine is
partly caused by activation of 5-HT receptors (Bhat and
Baraban, 1993).
In contrast to the effects of acute drug administration,
chronic administered cocaine leads partly caused by activation of 5-HT receptors (Bhat and Baraban, 1993).
In contrast to the effects of acute drug administration, chronic administered cocaine leads to a suppression of basal $zif 268$ expression (Bhat et al Baraban, 1993).

In contrast to the effects of acute drug administration,

chronic administered cocaine leads to a suppression of

basal *zif* 268 expression (Bhat et al., 1992a), and of c-fos,

c-jun, fos-B, jun-B, and *z* In contrast to the effects of acute drug administration,
chronic administered cocaine leads to a suppression of
basal *zif* 268 expression (Bhat et al., 1992a), and of c-fos,
c-jun, fos-B, jun-B, and *zif* 268 expression, chronic administered cocaine leads to a suppression of basal *zif* 268 expression (Bhat et al., 1992a), and of c-fos, c-jun, fos-B, jun-B, and *zif* 268 expression, although AP-1 binding activity remained elevated (Hope e basal *zif* 268 expression (Bhat et al., 1992a), and of c-fos, c-jun, fos-B, jun-B, and *zif* 268 expression, although AP-1 binding activity remained elevated (Hope et al., 1992). Also, repeated treatment of rats with the c-jun, fos-B, jun-B, and zif 268 expression, although
AP-1 binding activity remained elevated (Hope et al.,
1992). Also, repeated treatment of rats with the D₁-
agonist A-77636 fails to induce either turning or striatal AP-1 binding activity remained elevated (Hope et al., 1992). Also, repeated treatment of rats with the D_1 -agonist A-77636 fails to induce either turning or striatal Fos expression in dopamine-depleted rats (Asin and Wi 1992). Also, repeated treatment of rats with the D_1 -
agonist A-77636 fails to induce either turning or striatal
Fos expression in dopamine-depleted rats (Asin and
Wirtshafter, 1993). In contrast, 2.5 mg/kg amphetamine
 agonist A-77636 fails to induce either turning or striatal
Fos expression in dopamine-depleted rats (Asin and
Wirtshafter, 1993). In contrast, 2.5 mg/kg amphetamine
induces a greater expression of Fos in the striatum of
ra Fos expression in dopamine-depleted rats (Asin and
Wirtshafter, 1993). In contrast, 2.5 mg/kg amphetamine
induces a greater expression of Fos in the striatum of
rats treated 3 days earlier with amphetamine compared
with ra Wirtshafter, 1993). In contrast, 2.5 mg/kg amphetamine
induces a greater expression of Fos in the striatum of
rats treated 3 days earlier with amphetamine compared
with rats treated 3 days earlier with saline (Norman et
al induces a greater expression of Fos in the striatum of
rats treated 3 days earlier with amphetamine compared
with rats treated 3 days earlier with saline (Norman et
al., 1993). The reason for these different results may li rats treated 3 days earlier with amphetamine compared
with rats treated 3 days earlier with saline (Norman et
al., 1993). The reason for these different results may lie
in the different dosing regimes, with short-interval with rats treated 3 days earlier with saline (Norman et al., 1993). The reason for these different results may lie in the different dosing regimes, with short-interval dosing suppressing Fos and causing behavioural toleran al., 1993). The reason for these different results m
in the different dosing regimes, with short-interval
ing suppressing Fos and causing behavioural tole
whereas the 3-day interval leads to behavioura
biochemical sensiti the different dosing regimes, with short-interval dot g suppressing Fos and causing behavioural tolerance nereas the 3-day interval leads to behavioural an ochemical sensitisation (Norman et al., 1993). In addition to dop ing suppressing Fos and causing behavioural tolerance,
whereas the 3-day interval leads to behavioural and
biochemical sensitisation (Norman et al., 1993).
In addition to dopamine agonists, D_2 but not D_1 dopa-
mine

et al., 1991b; Snyder-Keller, 1991) and induction by am-
phetamine is also slightly inhibited by morphine (Fuxe These results suggest that dopamine, acting on D_2 re-
et al., 1991), which, along with caffeine, also indu whereas the 3-day interval leads to behavioural and biochemical sensitisation (Norman et al., 1993).
In addition to dopamine agonists, D_2 but not D_1 dopamine receptor antagonists induce Fos and Fras in racaudate put biochemical sensitisation (Norman et al., 1993).
In addition to dopamine agonists, D_2 but not D_1 dop
mine receptor antagonists induce Fos and Fras in r
caudate putamen and nucleus accumbens neurons (D
gunow et al., In addition to dopamine agonists, D_2 but not D_1 dopamine receptor antagonists induce Fos and Fras in rat caudate putamen and nucleus accumbens neurons (Dragunow et al., 1990d; Miller, 1990). Furthermore, dopaminergi mine receptor antagonists induce Fos and Fras in rat
caudate putamen and nucleus accumbens neurons (Dra-
gunow et al., 1990d; Miller, 1990). Furthermore, dopam-
inergic denervation with 6-OHDA leads to a long-term
increase caudate putamen and nucleus accumbens neurons (Dragunow et al., 1990d; Miller, 1990). Furthermore, dopam-
inergic denervation with 6-OHDA leads to a long-term
increase in Fra, but not Fos, expression in striatal neu-
rons gunow et al., 1990d; Miller, 1990). Furthermore, dopaminergic denervation with 6-OHDA leads to a long-term
increase in Fra, but not Fos, expression in striatal neurons projecting to the globus pallidus (Dragunow et al.,
19 inergic denervation with 6-OHDA leads to a long-term
increase in Fra, but not Fos, expression in striatal neu-
rons projecting to the globus pallidus (Dragunow et al.,
1991a; Jian et al., 1993). This increased Fra expressi increase in Fra, but not Fos, expression in striatal neurons projecting to the globus pallidus (Dragunow et al., 1991a; Jian et al., 1993). This increased Fra expression may account for the inhibitory effect of 6-OHDA lesi rons projecting to the globus pallidus (Dragunow et a 1991a; Jian et al., 1993). This increased Fra expressionary account for the inhibitory effect of 6-OHDA lesion haloperidol induction of Fos (Robertson and Fibige 1992), 1991a; Jian et al., 1993). This increased Fra expression
may account for the inhibitory effect of 6-OHDA lesions
on haloperidol induction of Fos (Robertson and Fibiger,
1992), inasmuch as Fras may inhibit c-fos transcript may account for the inhibitory effect of 6-OHDA lesions
on haloperidol induction of Fos (Robertson and Fibiger
1992), inasmuch as Fras may inhibit c-fos transcription
These results suggest that dopamine, acting on D_2 r on haloperidol induction of Fos (Robertson and Fibiger,
1992), inasmuch as Fras may inhibit c-fos transcription.
These results suggest that dopamine, acting on D_2 re-
ceptors, tonically inhibits Fos and Fras in striata 1992), inasmuch as Fras may inhibit c-fos transcription.
These results suggest that dopamine, acting on D_2 receptors, tonically inhibits Fos and Fras in striatal neurons. Induction of Fos by D_2 antagonists occurs in These resul
ceptors, ton
rons. Induc
striato-palli
al., 1992).
It has bec ptors, tonically inhibits Fos and Fras in striatal neu-

ns. Induction of Fos by D₂ antagonists occurs in

riato-pallidal enkephalinergic neurons (Robertson et

1992).

It has been suggested that the induction of Fos by rons. Induction of Fos by D_2 antagonists occurs
striato-pallidal enkephalinergic neurons (Robertson
al., 1992).
It has been suggested that the induction of Fos by
antagonists may be because of blockade of dopam
mediate

striato-pallidal enkephalinergic neurons (Robertson et al., 1992).
It has been suggested that the induction of Fos by D_2 antagonists may be because of blockade of dopamine-
mediated inhibition of glutamate release onto al., 1992).
It has been suggested that the induction of Fos by D_2
antagonists may be because of blockade of dopamine-
mediated inhibition of glutamate release onto striatal
neurons (Dragunow et al., 1990d). This belief It has been suggested that the induction of Fos by D
antagonists may be because of blockade of dopamine
mediated inhibition of glutamate release onto striata
neurons (Dragunow et al., 1990d). This belief is sup
ported by antagonists may be because of blockade of dopamine-
mediated inhibition of glutamate release onto striatal
neurons (Dragunow et al., 1990d). This belief is sup-
ported by observations that the D_2 receptor antagonist,
h mediated inhibition of glutamate release onto striatal
neurons (Dragunow et al., 1990d). This belief is sup-
ported by observations that the D_2 receptor antagonist,
haloperidol, increases the release of glutamate into neurons (Dragunow et al., 1990d). This belief is sup-
ported by observations that the D_2 receptor antagonist,
haloperidol, increases the release of glutamate into stri-
atum, whereas intra-striatal injection of quinoli ported by observations that the D_2 receptor antagonist, haloperidol, increases the release of glutamate into striatum, whereas intra-striatal injection of quinolinic acid, an NMDA receptor agonist, results in increased expression of Fos and Fras (Aronin et al., 1991; Berretta e atum, whereas intra-striatal injection of quinolinic acid,
an NMDA receptor agonist, results in increased expres-
sion of Fos and Fras (Aronin et al., 1991; Berretta et al.,
1992). Furthermore, cortical stimulation that ac an NMDA receptor agonist, results in increased expression of Fos and Fras (Aronin et al., 1991; Berretta et al., 1992). Furthermore, cortical stimulation that activates cortico-striatal glutaminergic pathways induces Fos i sion of Fos and Fras (Aronin et al., 1991; Berretta et al., 1992). Furthermore, cortical stimulation that activates cortico-striatal glutaminergic pathways induces Fos in striatal neurons (Fu and Beckstead, 1992). However, 1992). Furthermore, cortical stimulation that activates cortico-striatal glutaminergic pathways induces Fos in striatal neurons (Fu and Beckstead, 1992). However, whereas block of NMDA receptors with MK801 inhibits haloper cortico-striatal glutaminergic pathways induces Fos
striatal neurons (Fu and Beckstead, 1992). Howev
whereas block of NMDA receptors with MK801 inhibi
haloperidol-mediated induction of Fos in rat striatu
very high doses of striatal neurons (Fu and Beckstead, 1992). However,
whereas block of NMDA receptors with MK801 inhibits
haloperidol-mediated induction of Fos in rat striatum,
very high doses of antagonist are required, and induc-
tion is whereas block of NMDA receptors with MK801 inhibits
haloperidol-mediated induction of Fos in rat striatum,
very high doses of antagonist are required, and induc-
tion is never completely abolished (Dragunow et al.,
1990d). tion is never completely abolished (Dragunow et al., 1990d). In mouse striatum, MK801 seems more effective (Ziolkowska and Hollt, 1993).

PHARMACOLOGICAL REVIEW

154 HUGHES AN HUGHES AN More recently, the muscarinic antagonist scopolamine
has also been shown to attenuate haloperidol-induced
Fos expression in the striatum, suggesting that D_2 and FOST HUGHES ANT HUGHES ANT More recently, the muscarinic antagonist scopolamine
has also been shown to attenuate haloperidol-induced
Fos expression in the striatum, suggesting that D_2 an-
tagonist-mediated induction of More recently, the muscarinic antagonist scopolamine 198
has also been shown to attenuate haloperidol-induced 80%
Fos expression in the striatum, suggesting that D_2 an-
tagonist-mediated induction of Fos in striatum ma More recently, the muscarinic antagonist scopolamine 194
has also been shown to attenuate haloperidol-induced 80⁶
Fos expression in the striatum, suggesting that D_2 an-
tagonist-mediated induction of Fos in striatum has also been shown to attenuate haloperidol-induced Fos expression in the striatum, suggesting that D_2 antagonist-mediated induction of Fos in striatum may also be partially mediated by cholinergic mechanisms (Guote a Fos expression in the striatum, suggesting that D_2 antagonist-mediated induction of Fos in striatum may also lattice partially mediated by cholinergic mechanisms (Guo et al., 1992). Furthermore, the muscarinic agonist, tagonist-mediated induction of Fos in striatum may also lat
be partially mediated by cholinergic mechanisms (Guo
et al., 1992). Furthermore, the muscarinic agonist, pilo-
carpine, induces Fos in striatal neurons (Hughes a be partially mediated by cholinergic mechanisms (Guo
et al., 1992). Furthermore, the muscarinic agonist, pilo-
carpine, induces Fos in striatal neurons (Hughes and
Dragunow, 1993). Others reports, however, have found
that et al., 1992). Furthermore, the muscarinic agonist, pilocarpine, induces Fos in striatal neurons (Hughes and Dragunow, 1993). Others reports, however, have found en that another muscarinic antagonist, atropine, does not du carpine, induces Fos in striatal neurons (Hughes and Dragunow, 1993). Others reports, however, have found that another muscarinic antagonist, atropine, does not block haloperidol-induced c -*fos* mRNA expression in the c Dragunow, 1993). Others reports, however, have found that another muscarinic antagonist, atropine, does not oblock haloperidol-induced c-fos mRNA expression in the caudate (Merchant and Dorsa, 1993). Although pilocarpine i that another muscarinic antagonist, atropine, does not duo
block haloperidol-induced c-fos mRNA expression in the vul
caudate (Merchant and Dorsa, 1993). Although pilo-
the carpine induces Fos strongly in the striatum, thi block haloperidol-induced c-fos mRNA expression in the caudate (Merchant and Dorsa, 1993). Although pilo-
carpine induces Fos strongly in the striatum, this occurs t
most prominently in the posterior caudate (Hughes and C
 caudate (Merchant and Dorsa, 1993). Although pilo-
carpine induces Fos strongly in the striatum, this occurs
most prominently in the posterior caudate (Hughes and
Dragunow, 1993), whereas haloperidol induction occurs
most carpine induces Fos strongly in the striatum, this occurs tory t
most prominently in the posterior caudate (Hughes and ceptor
Dragunow, 1993), whereas haloperidol induction occurs C-fos
most strongly in anterior caudate (D most prominent
Dragunow, 1993
most strongly
1990d), suggest
is not involved.
The transcrip ragunow, 1993), whereas haloperidol induction occurs
ost strongly in anterior caudate (Dragunow et al.,
90d), suggesting perhaps that the muscarinic system
not involved.
The transcriptional program switched on in striatal

most strongly in anterior caudate (Dragunow et al., 1990d), suggesting perhaps that the muscarinic system
is not involved.
The transcriptional program switched on in striatal
neurons by D_2 antagonists such as haloperid 1990d), suggesting perhaps that the muscarinic system
is not involved.
The transcriptional program switched on in striatal
neurons by D_2 antagonists such as haloperidol has re-
cently been characterised in detail (Rogu is not involved. The transcriptional program switched on in striatal sulful neurons by D_2 antagonists such as haloperidol has recently been characterised in detail (Rogue and Vincedon, motion 1992; MacGibbon et al., 19 The transcriptional program switched on in striatal
neurons by D_2 antagonists such as haloperidol has re-
cently been characterised in detail (Rogue and Vincedon,
1992; MacGibbon et al., 1994; Nguyen et al., 1992). In neurons by D_2 antagonists such as haloperidol has recently been characterised in detail (Rogue and Vincedon, 1992; MacGibbon et al., 1994; Nguyen et al., 1992). In a comprehensive study measuring both mRNA and protein cently been characterised in detail (Rogue and Vincedon, 1992; MacGibbon et al., 1994; Nguyen et al., 1992). In a comprehensive study measuring both mRNA and protein levels, it has been shown that haloperidol induces c-Fos 1992; MacGibbon et al., 1994; Nguyen et al., 1992). In a wootcomprehensive study measuring both mRNA and pro-
tein levels, it has been shown that haloperidol induces
c-Fos, Fras, Fos-B, Jun-B, Jun-D and Krox-24, but not comprehensive study measuring both mRNA and p
tein levels, it has been shown that haloperidol indu
c-Fos, Fras, Fos-B, Jun-B, Jun-D and Krox-24, but i
c-Jun, in striatal neurons (although see Rogue a
Vincedon, 1992, who su tein levels, it has been shown that haloperidol induces c-Fos, Fras, Fos-B, Jun-B, Jun-D and Krox-24, but not c-Jun, in striatal neurons (although see Rogue and Vincedon, 1992, who suggest that c -*jun* mRNA expression i c-Fos, Fras, Fos-B, Jun-B, Jun-D and Krox-24, but not
c-Jun, in striatal neurons (although see Rogue and
Vincedon, 1992, who suggest that c -*jun* mRNA expression is increased). Therefore, it seems that a complex
transcr c-Jun, in striatal neurons (although see Rogue and Vincedon, 1992, who suggest that $c-jun$ mRNA expression is increased). Therefore, it seems that a complex extranscriptional gene program is activated by haloperidol est in Vincedon, 1992, who suggest that $c-jun$ mRNA expression is increased). Therefore, it seems that a complex transcriptional gene program is activated by haloperidol in striatal neurons, and it has been suggested that these c sion is increased). Therefore, it seems that a complex transcriptional gene program is activated by haloperidol in striatal neurons, and it has been suggested that these thanges in gene expression may be involved in the ex transcriptional gene program is activated by ha
in striatal neurons, and it has been suggested the
changes in gene expression may be involved in
trapyramidal side effects of typical neurolept
such as haloperidol (MacGibbon changes in gene expression may be involved in the ex-
trapyramidal side effects of typical neuroleptic drugs
such as haloperidol (MacGibbon et al., 1994).
In contrast to the effects of haloperidol, clozapine,

changes in gene expression may be involved in the ex-
trapyramidal side effects of typical neuroleptic drugs
such as haloperidol (MacGibbon et al., 1994).
In contrast to the effects of haloperidol, clozapine,
which is an a trapyramidal side effects of typical neuroleptic drugs due
such as haloperidol (MacGibbon et al., 1994). bra
In contrast to the effects of haloperidol, clozapine, Ma
which is an atypical neuroleptic that lacks appreciable such as haloperidol (MacGibbon et al., 1994).
In contrast to the effects of haloperidol, clozapine,
which is an atypical neuroleptic that lacks appreciable
extra-pyramidal side-effects, induced Fras, Jun-B, and
Krox-24, bu In contrast to the effects of haloperidol, clozapine,
which is an atypical neuroleptic that lacks appreciable
extra-pyramidal side-effects, induced Fras, Jun-B, and
Krox-24, but not c-Fos or Jun-D (MacGibbon et al.,
1994). extra-pyramidal side-effects, induced Fras, Jun-B, and
Krox-24, but not c-Fos or Jun-D (MacGibbon et al.,
1994). The inability of clozapine to alter the expression extra-pyramidal side-effects, induced Fras, Jun-B, and
Krox-24, but not c-Fos or Jun-D (MacGibbon et al.,
1994). The inability of clozapine to alter the expression
of c-Fos has also been demonstrated by others (Robert-
son Krox-24, but not c-Fos or Jun-D (MacGibbon et al., 1994). The inability of clozapine to alter the expression of c-Fos has also been demonstrated by others (Robert-son and Fibiger, 1992; Nguyen et al., 1992; Deutch et al., 1994). The inability of clozapine to alter the expression
of c-Fos has also been demonstrated by others (Robert-
son and Fibiger, 1992; Nguyen et al., 1992; Deutch et al.,
1992). Furthermore, clozapine, but not haloperidol son and Fibiger, 1992; Nguyen et al., 1992; Deutch et al., mg i.v. = 4 units) to hypophysectomised rats results in 1992). Furthermore, clozapine, but not haloperidol, pro-c-fos expression in specific brain regions. Induct 1992). Furthermore, clozapine, but not haloperidol, protherapeutic effects of clozapine on negative symptoms of also occurs within the periventricular nucleus of the schizophrenia (MacGibbon et al., 1994). by pothalamus. Induction in both areas was transient, duces a strong induction of Fras in the isla
It is possible that the changes in Fra gene
this area of the brain may be involved in
therapeutic effects of clozapine on negativ
schizophrenia (MacGibbon et al., 1994).
F. Opin *F. Opiate area* of the brain
therapeutic effects of schizophrenia (MacGi
 $F.$ Opiate Receptors
Activation of centra erapeutic effects of clozapine on negative symptoms of all
hizophrenia (MacGibbon et al., 1994).
be
 $\begin{array}{c} \text{b} \\ \text{b} \end{array}$
Activation of central opiate receptors by an acute dose 19
morphine (10 mg/kg s.c.) results in

schizophrenia (MacGibbon et al., 1994).

F. Opiate Receptors

Activation of central opiate receptors by an acute dose

of morphine (10 mg/kg s.c.) results in an increase in c-fos

mRNA and Fos-like immunoreactivity in rat *F. Opiate Receptors*
Activation of central opiate receptors by an acute dof morphine (10 mg/kg s.c.) results in an increase in c
mRNA and Fos-like immunoreactivity in rat cauda
putamen. c-fos mRNA was significantly increa putation of central opiate receptors by an acute dose 199
of morphine (10 mg/kg s.c.) results in an increase in c-fos P
mRNA and Fos-like immunoreactivity in rat caudate-
putamen. c-fos mRNA was significantly increased at Activation of central opiate receptors by an acute dof morphine (10 mg/kg s.c.) results in an increase in c-mRNA and Fos-like immunoreactivity in rat cauda putamen. c-fos mRNA was significantly increased at min, but not at of morphine (10 mg/kg s.c.) results in an increase in c-fos mRNA and Fos-like immunoreactivity in rat caudate-
putamen. c-fos mRNA was significantly increased at 45 min, but not at 90 min, after morphine administration.
Fo mRNA and Fos-like immunoreactivity in rat caudate-
putamen. c-fos mRNA was significantly increased at 45 min, but not at 90 min, after morphine administration. h
Fos protein was also increased 3 h after morphine administr putamen. c-fos mRNA was significantly increased at 45 min, but not at 90 min, after morphine administration. h
Fos protein was also increased 3 h after morphine administration in caudate-putamen but not in olfactory D
tub min, but not at 90 min, after morphine administration
Fos protein was also increased 3 h after morphine ad
ministration in caudate-putamen but not in olfactory
tubercle, which does not express the μ -type of opiat
recep Fos protein was also increased 3 h after morphine administration in caudate-putamen but not in olfactory tubercle, which does not express the μ -type of opiate receptor. Coadministration of naloxone blocked the morphine

HUGHES AND DRAGUNOW
More recently, the muscarinic antagonist scopolamine 1988). Morphine has also been shown to reduce, by up to
has also been shown to attenuate haloperidol-induced 80%, the number of Fos-positive neurons DRAGUNOW
1988). Morphine has also been shown to reduce, by up to
80%, the number of Fos-positive neurons induced in DRAGUNOW
1988). Morphine has also been shown to reduce, by up to
80%, the number of Fos-positive neurons induced in
spinal cord dorsal horn after peripheral noxious stimu-DRAGUNOW
1988). Morphine has also been shown to reduce, by up
80%, the number of Fos-positive neurons induced
spinal cord dorsal horn after peripheral noxious stimuation (Tolle et al., 1990). 1988). Morphine has also b
80%, the number of Fos-
spinal cord dorsal horn aft
lation (Tolle et al., 1990). 80%, the number of Fosspinal cord dorsal horn a
lation (Tolle et al., 1990).
G. Adenosine Receptors
Blockade of central ade Spinal cord dorsal horn after peripheral noxious stimu-
lation (Tolle et al., 1990).
G. Adenosine Receptors
Blockade of central adenosine receptors with the adenosine-receptor antagonist caffeine can transiently in-

lation (Tolle et al., 1990).

G. Adenosine Receptors

Blockade of central adenosine receptors with the adenosine-receptor antagonist caffeine can transiently in-

duce c-fos mRNA in mouse brain. Caffeine, at a subcon-G. Adenosine Receptors
Blockade of central adenosine receptors with the a
enosine-receptor antagonist caffeine can transiently
duce c-fos mRNA in mouse brain. Caffeine, at a subco
vulsive dose (100 mg/kg i.p.), caused a si G. Adenosine Receptors
Blockade of central adenosine receptors with the ad-
enosine-receptor antagonist caffeine can transiently in-
duce c-fos mRNA in mouse brain. Caffeine, at a subcon-
vulsive dose (100 mg/kg i.p.), cau vulsive dose (100 mg/kg i.p.), caused a significant rise in
the levels of *c-fos* mRNA in caudate-putamen and olfac-
tory tubercle. Coadministration of the adenosine A₁ reenosine-receptor antagonist caffeine can transiently in-
duce c-fos mRNA in mouse brain. Caffeine, at a subcon-
vulsive dose (100 mg/kg i.p.), caused a significant rise in
the levels of c-fos mRNA in caudate-putamen and o duce c-*fos* mRNA in mouse brain. Caffeine, at a subconvulsive dose (100 mg/kg i.p.), caused a significant rise in the levels of c-*fos* mRNA in caudate-putamen and olfactory tubercle. Coadministration of the adenosine A vulsive dose (100 mg/kg i.p.), caused a significant rise in
the levels of c-*fos* mRNA in caudate-putamen and olfac-
tory tubercle. Coadministration of the adenosine A_1 re-
ceptor agonist, N^6 -cyclohexyladenosine, di the levels of c-*fos* mRNA in caudate-putamen and of tory tubercle. Coadministration of the adenosine A-ceptor agonist, N^6 -cyclohexyladenosine, did not b C-*fos* stimulated by caffeine administration, how the selective tory tubercle. Coadministration of the adenosine A_1 receptor agonist, N^6 -cyclohexyladenosine, did not block C-*fos* stimulated by caffeine administration, however the selective adenosine A_2 receptor agonist, 5'-N ceptor agonist, N^6 -cyclohexyladenosine, did not block C-*fos* stimulated by caffeine administration, however the selective adenosine A_2 receptor agonist, 5'-N-ethyl-carboxamide adenosine (0.1 mg/kg i.p.), significan C-fos stimulated by caffeine administration, however
the selective adenosine A_2 receptor agonist, 5'-N-ethyl-
carboxamide adenosine (0.1 mg/kg i.p.), significantly re-
versed c-fos expression induced by caffeine. These the selective adenosine A_2 receptor agonist, 5'-N-ethyl-
carboxamide adenosine (0.1 mg/kg i.p.), significantly re-
versed c-*fos* expression induced by caffeine. These re-
sults suggest that blockade of central adenosi carboxamide adenosine (0.1 mg/kg i.p.), significantly reversed c-*fos* expression induced by caffeine. These results suggest that blockade of central adenosine A_2 receptors by caffeine results in c-*fos* mRNA expressio versed c-fos expression induced by caffeine. These results suggest that blockade of central adenosine A_2 receptors by caffeine results in c-fos mRNA expression in mouse brain (Nakajima et al., 1989b), although recent w receptors by caffeine results in c-fos mRNA expression in

H. Neuropeptide and *Hormone Receptors*

Various neuropeptide and hormone systems seem able
to regulate the expression of IEGs. For example, an al., 1992).
 H. Neuropeptide and Hormone Receptors

Various neuropeptide and hormone systems seem able

to regulate the expression of IEGs. For example, an

estrogen-responsive element exists in the c-*fos* gene, and H. Neuropeptide and Hormone Receptors
Various neuropeptide and hormone systems seem able
to regulate the expression of IEGs. For example, an
estrogen-responsive element exists in the c-fos gene, and
estrogen (0.375 mg/kg s μ . Neuropeptude and *Hormone* Receptors
Various neuropeptide and hormone systems seem able
to regulate the expression of IEGs. For example, an
estrogen-responsive element exists in the c-fos gene, and
estrogen (0.375 m Various neuropeptide and hormone systems seem able
to regulate the expression of *IEGs*. For example, an
estrogen-responsive element exists in the c-fos gene, and
estrogen (0.375 mg/kg s.c.) has been shown to increase
the to regulate the expression of IEGs. For example, an estrogen-responsive element exists in the c -*fos* gene, and estrogen $(0.375 \text{ mg/kg s.c.})$ has been shown to increase the expression of c -*fos* mRNA in ovariectomised ra estrogen-responsive element exists in the c-fos gene, and
estrogen (0.375 mg/kg s.c.) has been shown to increase
the expression of c-fos mRNA in ovariectomised rats in
midbrain and hippocampus, but not in cerebellum. In
du estrogen $(0.375 \text{ mg/kg s.c.})$ has been shown to increase
the expression of c-*fos* mRNA in ovariectomised rats in
midbrain and hippocampus, but not in cerebellum. In-
duction of c-*fos* mRNA was maximal at 30 min in mid-
bra the expression of c-*fos* mRNA in ovariectomised rats
midbrain and hippocampus, but not in cerebellum. I
duction of c-*fos* mRNA was maximal at 30 min in mi
brain and at 60 min in hippocampus (Cattaneo a
Maggi, 1990). A si midorain and mppocampus, but not in cerebenium. In
duction of c-fos mRNA was maximal at 30 min in mid
brain and at 60 min in hippocampus (Cattaneo an
Maggi, 1990). A single subcutaneous injection of estra
diol (0.1 mg/kg) duction of c-fos mRNA was maximal at 30 min in mid-
brain and at 60 min in hippocampus (Cattaneo and
Maggi, 1990). A single subcutaneous injection of estra-
diol (0.1 mg/kg) also induces Fos-like immunoreactivity
in noradr brain and at 60 min in hippocampus (Cattaneo and Maggi, 1990). A single subcutaneous injection of estradiol (0.1 mg/kg) also induces Fos-like immunoreactivity in noradrenergic neurons of the A2 cell group of the nucleus tr Maggi, 199
diol (0.1 mg
in noradren
nucleus tra
al., 1992).
Administ ol (0.1 mg/kg) also induces Fos-like immunoreactivity
noradrenergic neurons of the A2 cell group of the
incleus tractus solitarius 3 h after injection (Jennes et
., 1992).
Administration of recombinant growth hormone (1.33 in noradrenergic neurons of the A2 cell group of the
nucleus tractus solitarius 3 h after injection (Jennes et
al., 1992).
Administration of recombinant growth hormone (1.33
mg i.v. = 4 units) to hypophysectomised rats re al., 1992).
Administration of recombinant growth hormone (1.33)

nucleus tractus solitarius 3 h after injection (Jennes et al., 1992).
 c-fosiling i.v. = 4 units) to hypophysectomised rats results in c-fos expression in specific brain regions. Induction of c-fos gene expression occurs Administration of recombinant growth hormone $(1.33 \text{ mg i.v.} = 4 \text{ units})$ to hypophysectomised rats results in c-*fos* expression in specific brain regions. Induction of c -*fos* gene expression occurs in the arcuate nucleus mg i.v. $=$ 4 units) to hypophysectomised rats results in c -*fos* expression in specific brain regions. Induction of c -*fos* gene expression occurs in the arcuate nucleus of the hypothalamus after a single dose of gro c-fos expression in specific brain regions. Induction of c-fos gene expression occurs in the arcuate nucleus of the hypothalamus after a single dose of growth hormone. After a second dose of growth hormone, c-fos induction c-fos gene expression occurs in the arcuate nucleus of the hypothalamus after a single dose of growth hormone After a second dose of growth hormone, c-fos induction also occurs within the periventricular nucleus of the hyp After a second dose of growth hormone, c-fos induction
also occurs within the periventricular nucleus of the
hypothalamus. Induction in both areas was transient,
being maximal at 60 min and decreasing thereafter until
bas also occurs within the periventricular nucleus of the 1992). pothalamus. Induction in both areas was transient,
ing maximal at 60 min and decreasing thereafter until
isal levels were reached at 120 min (Minami et al.,
92).
Peripheral administration of CCK (8 μ g/kg i.p.) in-
ices being maximal at 60 min and decreasing thereafter until
basal levels were reached at 120 min (Minami et al.,
1992).
Peripheral administration of CCK (8 μ g/kg i.p.) in-
duces c-*fos* expression in rostral and caudal par

basal levels were reached at 120 min (Minami et al., 1992).

Peripheral administration of CCK (8 μ g/kg i.p.) induces c-fos expression in rostral and caudal parts of the nucleus of the solitary tract and in the PVN of t 1992).

Peripheral administration of CCK $(8 \mu g/kg \text{ i.p.})$ induces c-fos expression in rostral and caudal parts of the nucleus of the solitary tract and in the PVN of the hypothalamus. Because induction was blocked by admin Peripheral administration of CCK $(8 \mu g/kg \text{ i.p.})$ in duces c-*fos* expression in rostral and caudal parts of the nucleus of the solitary tract and in the PVN of the hypothalamus. Because induction was blocked by administra duces c-fos expression in rostral and caudal parts of the nucleus of the solitary tract and in the PVN of the hypothalamus. Because induction was blocked by administration of the peripheral CCK-A antagonist, Devazepide (L3 nucleus of the solitary tract and in the PVN of the
hypothalamus. Because induction was blocked by ad-
ministration of the peripheral CCK-A antagonist,
Devazepide (L364, 718), it is likely that CCK induces
Fos-like immunor hypothalamus. Because induction was blocked by administration of the peripheral CCK-A antagonist, Devazepide (L364, 718), it is likely that CCK induces Fos-like immunoreactivity in CNS regions by activating peripheral syst ministration of the peripheral CCK-A antagonist,
Devazepide (L364, 718), it is likely that CCK induces
Fos-like immunoreactivity in CNS regions by activating
peripheral systems that project to these areas (Chen et
al., 199

Shown to reduce seizure-mediated (pentylenetetrazole, mg/kg i.p.) induction of c-*fos* and *zif* 268 mRN. IMMEDIATE-EARLY GENES AND
50 mg/kg i.p.) induction of c-fos and zif268 mRNA in it h
hippocampus and dentate gyrus, but not in piriform unit IMMEDIATE-EARLY GENES AND C
shown to reduce seizure-mediated (pentylenetetrazole, and h
50 mg/kg i.p.) induction of c-fos and zif 268 mRNA in it has
hippocampus and dentate gyrus, but not in piriform unifor
cortex (Miyoshi shown to reduce seizure-medi
50 mg/kg i.p.) induction of c-
hippocampus and dentate gy
cortex (Miyoshi et al., 1992).
Peripheral bombesin, like CO For the vertex correction of the entrylene tetrazole, and $\frac{p}{k}$ i.p.) induction of c-*fos* and $\frac{z}{f}$ 268 mRNA in it ppocampus and dentate gyrus, but not in piriform und the cCK (Miyoshi et al., 1992). K Peripheral

50 mg/kg i.p.) induction of c-*fos* and $zif 268$ mRNA in hippocampus and dentate gyrus, but not in piriform cortex (Miyoshi et al., 1992). Peripheral bombesin, like CCK, results in induction of Fos-like immunoreactivity i hippocampus and dentate gyrus, but not in piriform un
cortex (Miyoshi et al., 1992). Kr
Peripheral bombesin, like CCK, results in induction of we
Fos-like immunoreactivity in area postrema, medial por-
tion of the nucleus cortex (Miyoshi et al., 1992).
Peripheral bombesin, like CCK, results in inductifulners.
Fos-like immunoreactivity in area postrema, medial
tion of the nucleus tractus solitarius, and in the PVN of
hypothalamus. Smaller in Peripheral bombesin, like CCK, results in induction of Fos-like immunoreactivity in area postrema, medial pot tion of the nucleus tractus solitarius, and in the PVN of the hypothalamus. Smaller increases in Fos-like immuno Fos-like immunoreactivity in area postrema, medial portion of the nucleus tractus solitarius, and in the PVN of the hypothalamus. Smaller increases in Fos-like immunoreactivity were seen in the central part of the amygdala tion of the nucleus tractus solitarius, and in the PVN of the
hypothalamus. Smaller increases in Fos-like immunoreac-
tivity were seen in the central part of the amygdala, para-
brachial nucleus, and supraoptic nucleus (B Aypothalamus. Smaller increases in Fos-like immunoreactivity is dependent on NMDA receptor activation and
tivity were seen in the central part of the amygdala, paractivity calcium/calmodulin kinase II, induction in non-ne brachial nucleus, and supraoptic nucleus (Bonaz et al., 1993a). Furthermore, peripheral administration of Peptide YY (300 μ g/kg i.p.) increases fos-like immunoreactivity in area postrema, nucleus tractus solitarius, ce 1993a). Furthermore, peripheral administration of Peptide 93a). Furthermore, peripheral administration of Peptide \overline{Y} (300 μ g/kg i.p.) increases fos-like immunoreactivity in ea postrema, nucleus tractus solitarius, central amyglia, and thalamus (Bonaz et al., 1993b). Int

YY (300 μ g/kg i.p.) increases fos-like immunoreactivity in non area postrema, nucleus tractus solitarius, central amyg- 198 dala, and thalamus (Bonaz et al., 1993b). we Intracerebroventricular injection of somatostatin area postrema, nucleus tractus solitarius, central amyg-
dala, and thalamus (Bonaz et al., 1993b). www.
Intracerebroventricular injection of somatostatin or va-
sopressin leads to increased expression of c-fos mRNA in por dala, and thalamus (Bonaz et al., 1993b). we
Intracerebroventricular injection of somatostatin or va-
sopressin leads to increased expression of c-*fos* mRNA in
granule cells of the cerebellum but not in cortex or limbic
 Intracerebroventricular injection of somatostatin or vasopressin leads to increased expression of c-*fos* mRNA in pos
granule cells of the cerebellum but not in cortex or limbic nas
brain regions such as the hippocampus. I sopressin leads to increased expression of c -*fos* mRNA in paranule cells of the cerebellum but not in cortex or limbic normal brain regions such as the hippocampus. It is not known T whether this transient induction of granule cells of the cerebellum but not in cortex or limbi
brain regions such as the hippocampus. It is not know
whether this transient induction of c -*fos* in cerebellum is
direct effect of the two neuropeptides on gra brain regions such as the hippocampus. It is not known
whether this transient induction of c-fos in cerebellum is a
direct effect of the two neuropeptides on granule cells or
lwhether induction is secondary to the phenome whether this transient induction of c-*fos* in cerebellum is a direct effect of the two neuropeptides on granule cells or whether induction is secondary to the phenomenon of "bar-
rel rotation" that both drugs produce in r direct effect of the two neuropeptides on granule cells or
whether induction is secondary to the phenomenon of "bar-
rel rotation" that both drugs produce in rats (Kamegai et
Hal., 1993). Central injection of vasopressin a whether induction is secondary to the phenomenon of "bar-
rel rotation" that both drugs produce in rats (Kamegai et H
al., 1993). Central injection of vasopressin also increases ce
Fos-like immunoreactivity in the central rel rotation" that both drugs produce in rats (Kamegai et Hu al., 1993). Central injection of vasopressin also increases cell Fos-like immunoreactivity in the central nucleus of the produny any any damage and tuberal septu al., 1993). Central injection of vasa
Fos-like immunoreactivity in the
amygdala, ventrolateral septum, pa
the PVN of the hypothalamus, dors
LC (Andreae and Herbert, 1993).
Intraventricular administration S-like immunoreactivity in the central nucleus
nygdala, ventrolateral septum, parvocellular divis
e PVN of the hypothalamus, dorsal tuberal nucleu
C (Andreae and Herbert, 1993).
Intraventricular administration of corticot

amygdala, ventrolateral septum, parvocellular divisions of
the PVN of the hypothalamus, dorsal tuberal nucleus, and
LC (Andreae and Herbert, 1993).
Intraventricular administration of corticotropin-re-
leasing hormone (100 ally in several cerebral cortical structures, most predom-LC (Andreae and Herbert, 1993).

Intraventricular administration of corticotropin-re-

leasing hormone (100 μ g) induces c-*fos* mRNA unilater-

ally in several cerebral cortical structures, most predom-

inantly in the Intraventricular administration of corticotropin-re-
leasing hormone (100 μ g) induces c-*fos* mRNA unilater-
ally in several cerebral cortical structures, most predom-
inantly in the dorsal endopiriform nucleus and in leasing hormone (100 μ g) induces c-*fos* mRNA unilate
ally in several cerebral cortical structures, most predon
inantly in the dorsal endopiriform nucleus and in th
piriform and insular cortices (Clark et al., 1991b). ally in several cerebral cortical structures, most predominantly in the dorsal endopiriform nucleus and in the piriform and insular cortices (Clark et al., 1991b). Another report has shown that corticotropin-releasing horm inantly in the dorsal endopiriform nucleus and in the
piriform and insular cortices (Clark et al., 1991b). An-
other report has shown that corticotropin-releasing hor-
mone also induces c -*fos* mRNA in limbic structures piriform and insular cortices (Clark et al., 1991b).
other report has shown that corticotropin-releasing l
mone also induces c-fos mRNA in limbic structures,
cluding the cingulate cortex, lateral septal nucle
hippocampus, other report has shown that corticotropin-releasing hor-
mone also induces c-*fos* mRNA in limbic structures, in-
cluding the cingulate cortex, lateral septal nucleus,
hippocampus, amygdala (i.e., central nucleus), hypotha mone also induces c-*fos* mRNA in limbic structures, in-
cluding the cingulate cortex, lateral septal nucleus, th
hippocampus, amygdala (i.e., central nucleus), hypotha-
lamic PVN, supraoptic nucleus, dorsomedial nucleus, cluding the cingulate cortex, lateral septal nucleus,
hippocampus, amygdala (i.e., central nucleus), hypotha-
lamic PVN, supraoptic nucleus, dorsomedial nucleus,
pontine nucleus, Barrington's nucleus, and LC. The
granule c hippocampus, amygdala (i.e., central nucleus), hypothalamic PVN, supraoptic nucleus, dorsomedial nucleus, pontine nucleus, Barrington's nucleus, and LC. The granule cells of the cerebellum, some thalamic nuclei, the bed nu lamic PVN, supraoptic nucleus, dorsomedial nucleus, discontine nucleus, Barrington's nucleus, and LC. The mear granule cells of the cerebellum, some thalamic nuclei, ally the bed nucleus of the stria terminalis, and the ha pontine nucleus, Barrington's nucleus, and LC. Th
granule cells of the cerebellum, some thalamic nucle
the bed nucleus of the stria terminalis, and the habenul
nuclei also showed increases (Imaki et al., 1993). I
addition, granule cells of the cerebellum, some thalamic n
the bed nucleus of the stria terminalis, and the habe
nuclei also showed increases (Imaki et al., 1993
addition, the dorsal tuberal nucleus and parabra
nucleus show increase the bed nucleus of the stria terminalis, and the habe
nuclei also showed increases (Imaki et al., 1993
addition, the dorsal tuberal nucleus and parabra
nucleus show increased levels of Fos-like immuno
tivity after corticot addition, the dorsal tuberal nucleus and parabrachial nucleus show increased levels of Fos-like immunoreactivity after corticotropin-releasing hormone administration (Andreae and Herbert, 1993). **where the interest of Immediate in the immediate dividends in the interest dividends in the interest of Immediate-early Genes in Non-
IV. Expression of Immediate-early Genes in Non-
nerve Cells of the Central Nervous Syst**

nerve Cells of the Central Nervous System

N_i
 **Expression of Immediate-early Genes in Non-

nerve Cells of the Central Nervous System

is was discovered a number of years ago that mechan-**

It Expression of Immediate-early Genes in Networks.

It was discovered a number of years ago that mech

It was discovered a number of years ago that mech

It injury to the brain induces Fos in non-nerve cell: IV. Expression of Immediate-early Genes in Non-
nerve Cells of the Central Nervous System
it was discovered a number of years ago that mechan-logi
ical injury to the brain induces Fos in non-nerve cells in Jun
white matter IV. Expression of Immediate-early Genes in Non-
nerve Cells of the Central Nervous System
It was discovered a number of years ago that mechan-
ical injury to the brain induces Fos in non-nerve cells in
white matter tracts nerve Cens of the Central Nervous System
It was discovered a number of years ago that mechan-
ical injury to the brain induces Fos in non-nerve cells in
white matter tracts (corpus callosum, fornix-fimbria, in-
ternal caps It was discovered a number of years ago that mechical injury to the brain induces Fos in non-nerve cells
white matter tracts (corpus callosum, fornix-fimbria,
ternal capsule), grey matter (hippocampus, cortex, s
atum, thal ical injury to the brain induces Fos in non-nerve cells in Ju
white matter tracts (corpus callosum, fornix-fimbria, in-
ternal capsule), grey matter (hippocampus, cortex, stri-
contum, thalamus), lateral and third ventricl white matter tracts (corpus callosum, fornix-fimbria, in-
ternal capsule), grey matter (hippocampus, cortex, stri-
atum, thalamus), lateral and third ventricles in ependy-
condicials, and on the pial surfaces of the brain
 ternal capsule), grey matter (hippocampus, cortex, striatum, thalamus), lateral and third ventricles in ependymal cells, and on the pial surfaces of the brain (Dragunow and Robertson, 1988b). Similar effects were lobserved

IMMEDIATE-EARLY GENES AND GENE EXPRESSION 155
d (pentylenetetrazole, and heat-shock (Dragunow et al., 1989c). More recently,
and zif 268 mRNA in it has been shown that this induction does not occur uniformly in non-nerve cells with Fos/Fras, c-Jun, and 155
and heat-shock (Dragunow et al., 1989c). More recently,
it has been shown that this induction does not occur
uniformly in non-nerve cells with Fos/Fras, c-Jun, and
Krox-24 being strongly induced, Jun-B and Jun-D and heat-shock (Dragunow et al., 1989c). More recently,
it has been shown that this induction does not occur
uniformly in non-nerve cells with Fos/Fras, c-Jun, and
Krox-24 being strongly induced, Jun-B and Jun-D
weakly ind and heat-shock (Dragunow et al., 1989c). More recently,
it has been shown that this induction does not occur
uniformly in non-nerve cells with Fos/Fras, c-Jun, and
Krox-24 being strongly induced, Jun-B and Jun-D
weakly ind it has been shown that this induction does not occur
uniformly in non-nerve cells with Fos/Fras, c-Jun, and
Krox-24 being strongly induced, Jun-B and Jun-D
weakly induced, and Fos-B and Krox-20 not induced
(Dragunow, 1990; uniformly in non-nerve cells with Fos/Fras, c-Jun, and
Krox-24 being strongly induced, Jun-B and Jun-D
weakly induced, and Fos-B and Krox-20 not induced
(Dragunow, 1990; Dragunow and Hughes, 1993). Al-
though induction in Krox-24 being strongly induced, Jun-B and Jun-D
weakly induced, and Fos-B and Krox-20 not induced
(Dragunow, 1990; Dragunow and Hughes, 1993). Al-
though induction in neurons after mechanical brain in-
jury is dependent on weakly induced, and Fos-B and Krox-20 not induced
(Dragunow, 1990; Dragunow and Hughes, 1993). Al-
though induction in neurons after mechanical brain in-
jury is dependent on NMDA receptor activation and
calcium/calmodulin (Dragunow, 1990; Dragunow and Hughes, 1993). Al-
though induction in neurons after mechanical brain in-
jury is dependent on NMDA receptor activation and
calcium/calmodulin kinase II, induction in non-nerve
cells is not (D though induction in neurons after mechanical brain in-
jury is dependent on NMDA receptor activation and
calcium/calmodulin kinase II, induction in non-nerve
cells is not (Dragunow et al., 1990b, c). Cyclic AMP
seems to be jury is dependent on NMDA receptor activation and calcium/calmodulin kinase II, induction in non-nerve cells is not (Dragunow et al., 1990b, c). Cyclic AMP seems to be an important signal for IEGP induction in non-nerve ce ealciding amodul in Kinase 11, induction in non-nerve cells is not (Dragunow et al., 1990b, c). Cyclic AMP seems to be an important signal for IEGP induction in non-nerve cells of the brain (Dragunow and Faull, 1989b). Fur non-nerve cells of the brain (Dragunow and Faull, 1989b). Furthermore, using double-labeling methods, we have discovered that most of the non-nerve cells expressing IEGPs are not glial fibrillary acidic proteinpositive astrocytes or glycerol phosphate dehydroge-nase-posit we have discovered that most of the non-nerve cells
expressing IEGPs are not glial fibrillary acidic protein-
positive astrocytes or glycerol phosphate dehydroge-
nase-positive oligodendrocytes (Dragunow et al., 1990c).
Th expressing IEGPs are not glial fibrillary acidic protein-
positive astrocytes or glycerol phosphate dehydroge-
nase-positive oligodendrocytes (Dragunow et al., 1990c).
Thus, at present, the identity of the non-nerve cells
 positive astrocytes or glycerol phosphate dehydrogepositive astrocytes or glycerol phosphate dehydrogenase-positive oligodendrocytes (Dragunow et al., 1990c).
Thus, at present, the identity of the non-nerve cells expressing IEGPs in white and grey matter is unclear.
Howeve nase-positive oligodendrocytes (Dragunow et al., 1990c).
Thus, at present, the identity of the non-nerve cells
expressing IEGPs in white and grey matter is unclear.
However, a number of these cells seem, from their do-
nut Thus, at present, the identity of the non-nerve cells expressing IEGPs in white and grey matter is unclear.
However, a number of these cells seem, from their do-
nut-shaped morphology, to be dividing (Dragunow and
Hughes, expressing IEGPs in white and grey matter is unclear.
However, a number of these cells seem, from their do-
nut-shaped morphology, to be dividing (Dragunow and
Hughes, 1993). Thus, IEGP expression in non-nerve
cells after However, a number of these cells seem, from their do-
nut-shaped morphology, to be dividing (Dragunow and
Hughes, 1993). Thus, IEGP expression in non-nerve
cells after traumatic stimuli may be involved in the
proliferation nut-shaped morphology, to be dividing (Dragunow and Hughes, 1993). Thus, IEGP expression in non-nerve cells after traumatic stimuli may be involved in the proliferation of these cells in response to injury, as has been dem Hughes, 1993). Thus, IEGP expres
cells after traumatic stimuli may b
proliferation of these cells in respons
been demonstrated in other cell ty
Bravo, 1991; Riabowol et al., 1988). **Present demonstrated in other cell types (Kovary and Bravo, 1991; Riabowol et al., 1988).**
 V. Specificity of Immediate-early Gene Induction
 in Adult Neurons

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 i Immediate-early C
 in Adult Neurons

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Specificity of Immediate-early Gene Induction
in Adult Neurons
Because of the apparently widespread inducibility of
e Fos IEG (Morgan and Curran, 1991b), many re-V. Specificity of Immediate-early Gene Induction
in Adult Neurons
Because of the apparently widespread inducibility of
the Fos IEG (Morgan and Curran, 1991b), many re-
searchers initially questioned the specificity and imp in Adult Neurons
Because of the apparently widespread inducibility of
the Fos IEG (Morgan and Curran, 1991b), many re-
searchers initially questioned the specificity and impor-
tance of this molecule to neuronal function. In Adult Neurons
Because of the apparently widespread inducibility of
the Fos IEG (Morgan and Curran, 1991b), many re-
searchers initially questioned the specificity and impor-
tance of this molecule to neuronal function. Because of the apparently widespread inducibility of
the Fos IEG (Morgan and Curran, 1991b), many re-
searchers initially questioned the specificity and impor-
tance of this molecule to neuronal function. However,
the DNA the Fos IEG (Morgan and Curran, 1991b), many re-
searchers initially questioned the specificity and impor-
tance of this molecule to neuronal function. However,
the DNA binding activity of IEGPs is complex, inasmuch
as the searchers initially questioned the specificity and importance of this molecule to neuronal function. However, the DNA binding activity of IEGPs is complex, inasmuch as they interact with many other TFs (see previous discus tance of this molecule to neuronal function. Howe
the DNA binding activity of IEGPs is complex, inasm
as they interact with many other TFs (see previ
discussion in I.F.3). Therefore, the induction of I
measured in isolatio the DNA binding activity of IEGPs is complex, inasmuch
as they interact with many other TFs (see previous
discussion in I.F.3). Therefore, the induction of Fos,
measured in isolation by a variety of stimuli, is function-
a as they interact with many other TFs (see previous discussion in I.F.3). Therefore, the induction of Fos, measured in isolation by a variety of stimuli, is functionally meaningless, because members of the Fos (c-fos, Fos-B discussion in I.F.3). Therefore, the induction of Fos,
measured in isolation by a variety of stimuli, is function-
ally meaningless, because members of the Fos (c-fos,
Fos-B, Fra-1, Fra-2, Fras) and Jun (c-Jun, Jun-B,
Junally meaningless, because members of the Fos (c-fos, Fos-B, Fra-1, Fra-2, Fras) and Jun (c-Jun, Jun-B, Jun-D) family of TFs must form homodimers (Jun family only) and heterodimers (e.g., Fos/Jun-D) for transcriptional acti Jun-D) family of TFs must form homodimers (Jun family only) and heterodimers (e.g., Fos/Jun-D) for transcriptional activity (Morgan and Curran, 1991b). Further-
more, a naturally occurring truncated form of Fos-B can Fos-B, Fra-1, Fra-2, Fras) and Jun (c-Jun, Jun-B,
Jun-D) family of TFs must form homodimers (Jun family
only) and heterodimers (e.g., Fos/Jun-D) for transcrip-
tional activity (Morgan and Curran, 1991b). Further-
more, a n Jun-D) family of TFs must form homodimers (Jun family
only) and heterodimers (e.g., Fos/Jun-D) for transcrip-
tional activity (Morgan and Curran, 1991b). Further-
more, a naturally occurring truncated form of Fos-B can
inh only) and heterodimers (e.g., Fos/Jun-D) for transcrip-
tional activity (Morgan and Curran, 1991b). Further-
more, a naturally occurring truncated form of Fos-B can
inhibit Fos/Jun transcriptional activity (Nakabeppu and
N tional activity (Morgan and Curran, 1991b). Furthermore, a naturally occurring truncated form of Fos-B can inhibit Fos/Jun transcriptional activity (Nakabeppu and Nathans, 1991), increasing the possible interactions betwee more, a naturally occurring truncated form of Fos-B can
inhibit Fos/Jun transcriptional activity (Nakabeppu and
Nathans, 1991), increasing the possible interactions be-
tween these various TFs. Also, recent studies have fo inhibit Fos/Jun transcriptional activity (Nakabeppu an Nathans, 1991), increasing the possible interactions be
tween these various TFs. Also, recent studies have foun
that Fos/Jun and Jun/Jun dimers bend DNA in opposit
dir Nathans, 1991), increasing the possible interactions be-
tween these various TFs. Also, recent studies have found
that Fos/Jun and Jun/Jun dimers bend DNA in opposite
directions (Kerpolla and Curran, 1991) and form topo-
l tween these various TFs. Also, recent studies have found
that Fos/Jun and Jun/Jun dimers bend DNA in opposite
directions (Kerpolla and Curran, 1991) and form topo-
logically distinct DNA-protein complexes. Also, Fos and
Ju that Fos/Jun and Jun/Jun dimers bend DNA in opposite
directions (Kerpolla and Curran, 1991) and form topo-
logically distinct DNA-protein complexes. Also, Fos and
Jun act cooperatively with the glucocorticoid receptor
but directions (Kerpolla and Curran, 1991) and form
logically distinct DNA-protein complexes. Also, For
Jun act cooperatively with the glucocorticoid rec
but have opposite effects on transcriptional activi
combination with the logically distinct DNA-protein complexes. Also, Fos and Jun act cooperatively with the glucocorticoid recept but have opposite effects on transcriptional activity combination with the glucocorticoid and mineralocort coid r In act cooperatively with the glucocorticoid receptor
it have opposite effects on transcriptional activity in
mbination with the glucocorticoid and mineralocorti-
id receptors (Diamond et al., 1990, Funder, 1993).
Fos and

but have opposite effects on transcriptional activity in combination with the glucocorticoid and mineralocorticoid receptors (Diamond et al., 1990, Funder, 1993). Fos and Jun also interact with other members of the ligandcombination with the glucocorticoid and mineralocorticoid receptors (Diamond et al., 1990, Funder, 1993).
Fos and Jun also interact with other members of the ligand-dependent family of TFs such as the thyroid hor-
mone rec Downloaded from pharmrev.aspetjournals.org at Thammasart University on December 8, 2012

noic acid is a negative regulator of AP-1-responsive
genes (Schüle et al., 1991), and a phosphorylation-mod-HU
noic acid is a negative regulator of AP-1-res
genes (Schüle et al., 1991), and a phosphorylation-model inhibitor of Fos/Jun activity called IP-1 HUGHES ANI
noic acid is a negative regulator of AP-1-responsive
genes (Schüle et al., 1991), and a phosphorylation-mod-
ulated inhibitor of Fos/Jun activity called IP-1 has re-
cently been identified (Auwerx and Sassone-Co noic acid is a negative regulator of AP-1-responsingenes (Schüle et al., 1991), and a phosphorylation-moulated inhibitor of Fos/Jun activity called IP-1 has rently been identified (Auwerx and Sassone-Cors 1991). Regulation genes (Schüle et al., 1991), and a phosphorylation-mod-
ulated inhibitor of Fos/Jun activity called IP-1 has re-
cently been identified (Auwerx and Sassone-Corsi, ca
1991). Regulation by methylation has also been reported cently been identified (Auwerx and Sassone-Corsi, 1991). Regulation by methylation has also been reported for the Egr-1 IEG (Seyfert et al., 1990), and this gene is also regulated by protein phosphorylation and dephos-
pho cently been identified (Auwerx and Sassone-Corsi, can
1991). Regulation by methylation has also been reported
for the Egr-1 IEG (Seyfert et al., 1990), and this gene is
malso regulated by protein phosphorylation and dephos 1991). Regulation by methylation has also been reported
for the Egr-1 IEG (Seyfert et al., 1990), and this gene is
also regulated by protein phosphorylation and dephos-
phorylation (Cao et al., 1992). Also, phosphorylation also regulated by protein phosphorylation and dephos-
phorylation (Cao et al., 1992). Also, phosphorylation of
Jun protein by MAP-serine kinases positively regulates
its transactivating activity (Pulverer et al., 1991),
wh phorylation (Cao et al., 1992). Also, phosphorylation of phorylation (Cao et al., 1992). Also, phosphory
Jun protein by MAP-serine kinases positively r
its transactivating activity (Pulverer et al.
whereas phosphorylation of Jun by casein kina
hibits Jun activity (Hunter and Kar In protein by MAP-serine kinases positively regulates

Intransactivating activity (Pulverer et al., 1991), locations are phosphorylation of Jun by case

in kinase II in-

bits Jun activity (Hunter and Karin, 1992).

Anothe

its transactivating activity (Pulverer et al., 1991), lowhereas phosphorylation of Jun by casein kinase II inhibits Jun activity (Hunter and Karin, 1992). potention and the regulated has more recently been described (Baich whereas phosphorylation of Jun by casein kinase II in-
hibits Jun activity (Hunter and Karin, 1992).
Another level at which c-Jun can be regulated has
recently been described (Baichwal et al., 1991). These
authors demonstr hibits Jun activity (Hunter and Karin, 1992). pot

Another level at which c-Jun can be regulated has

recently been described (Baichwal et al., 1991). These

rend authors demonstrated the existence of a cell-specific in-
 Another level at which c-Jun can be regulated has mer et recently been described (Baichwal et al., 1991). These rons a authors demonstrated the existence of a cell-specific incell desibitor of c-Jun activity that was overc recently been described (Baichwal et al., 1991). These
authors demonstrated the existence of a cell-specific in-
hibitor of c-Jun activity that was overcome by Src and
Ras proteins. A factor called Ref-1 stimulates AP-1 DN authors demonstrated the existence of a cell-specific in-
hibitor of c-Jun activity that was overcome by Src and
Ras proteins. A factor called Ref-1 stimulates AP-1 DNA
binding activity of Fos and Jun without altering thei hibitor of c-Jun activity that was overcome by Src and A
Ras proteins. A factor called Ref-1 stimulates AP-1 DNA $diff$
binding activity of Fos and Jun without altering their tern
DNA binding specificity via a novel reductio Ras proteins. A factor called Ref-1 stimulates AP-1 DNA
binding activity of Fos and Jun without altering their
DNA binding specificity via a novel reduction-oxidation
mechanism (Xanthoudakis and Curran, 1992). Jun can
als binding activity of Fos and Jun without altering their *teri*
DNA binding specificity via a novel reduction-oxidation *reg*
mechanism (Xanthoudakis and Curran, 1992). Jun can
diffuls and Curran, 1991) and fig.
binding pro DNA binding specificity via a novel reduction-oxida
mechanism (Xanthoudakis and Curran, 1992). Jun
also form dimers with $Ca^{2+}/cAMP$ response elem
binding protein and ATFs (Hai and Curran, 1991)
bind to other cis-acting ele mechanism (Xanthoudakis and Curran, 1992). Ju
also form dimers with $Ca^{2+}/cAMP$ response ele
binding protein and ATFs (Hai and Curran, 1991
bind to other cis-acting elements (e.g., CRE, ATF
ing sites). Fos can also interact also form dimers with $Ca^{2+}/cAMP$ response element
binding protein and ATFs (Hai and Curran, 1991) and
bind to other cis-acting elements (e.g., CRE, ATF-bind-
ing sites). Fos can also interact with a helix-loop-helix-
zippe binding protein and ATFs (Hai and Curran, 1991) and
bind to other cis-acting elements (e.g., CRE, ATF-bind-
ing sites). Fos can also interact with a helix-loop-helix-
zipper protein (Blanar and Rutter, 1992). Another level bind to other cis-acting elements (e.g., CRE, ATF-bind-
ing sites). Fos can also interact with a helix-loop-helix-
zipper protein (Blanar and Rutter, 1992). Another level deg
of regulation of b-zip proteins has recently b ing sites). Fos can also interact with a helix-loop-helix-
zipper protein (Blanar and Rutter, 1992). Another level de
of regulation of b-zip proteins has recently been de-
scribed (Wagner and Green, 1993), showing that th zipper protein (Blanar and Rutter, 1992). Another level
of regulation of b-zip proteins has recently been de-
scribed (Wagner and Green, 1993), showing that the Tax
protein promotes dimerisation of c-Jun and other b-zip
pr of regulation of b-zip proteins has recently been described (Wagner and Green, 1993), showing that the Tax protein promotes dimerisation of c-Jun and other b-zip proteins, thereby facilitating the DNA binding reaction. Th scribed (Wagner and Green, 1993), showing that the Tax
protein promotes dimerisation of c-Jun and other b-zip
proteins, thereby facilitating the DNA binding reaction.
Thus, the complexity of these interactions suggests th protein promotes dimerisation of c-Jun and other b-zip
proteins, thereby facilitating the DNA binding reaction.
Thus, the complexity of these interactions suggests that
the IEGPs could potentially mediate a vast array of
b oteins, thereby facilitating the DNA binding reaction. 199

nus, the complexity of these interactions suggests that

e IEGPs could potentially mediate a vast array of san

ological processes in neurons. Kr

To understand t

Thus, the complexity of these interactions suggests that antathe IEGPs could potentially mediate a vast array of sam biological processes in neurons. Kro
To understand the functions of these molecules, we old must determin the IEGPs could potentially mediate a vast array of
biological processes in neurons.
To understand the functions of these molecules, we
must determine the expression of a range of IEGPs in
neurons and uncover the biochemic biological processes in neurons. K
To understand the functions of these molecules, we
must determine the expression of a range of IEGPs in
to
neurons and uncover the biochemical pathways of their
induction. However, the sp To understand the functions of these molecules, we olmust determine the expression of a range of IEGPs in to neurons and uncover the biochemical pathways of their dinduction. However, the specificity and function of IEGPs must determine the expression of a range of IEGPs in to
neurons and uncover the biochemical pathways of their di
induction. However, the specificity and function of
IEGPs may be determined not only by the pattern of a
IEGP neurons and uncover the biochemical pathways of their
induction. However, the specificity and function of
IEGPs may be determined not only by the pattern of
IEGPs induced but also by their temporal profile of
induction (es induction. However, the specificity and function of IEGPs may be determined not only by the pattern of after IEGPs induced but also by their temporal profile of guinduction (especially for Fos and Jun family members quinta IEGPs may be determined not only by the pattern of IEGPs induced but also by their temporal profile of induction (especially for Fos and Jun family members that form dimers for transcriptional activity) and by the biochem induction (especially for Fos and Jun family members quency electrical stimulation (leading to LTP) will in-
that form dimers for transcriptional activity) and by the duce Krox-24 but not c-Fos, c-Jun, Jun-B, or Krox-20 in induction (especially for Fos and Jun family member
that form dimers for transcriptional activity) and by th
biochemical pathway through which they are induce
For example, the induction of the c-myc IEG in th
presence of that form dimers for transcriptional activity) and by the biochemical pathway through which they are induced.
For example, the induction of the c-*myc* IEG in the presence of growth factors leads to cell proliferation, whe biochemical pathway through which they are induced.
For example, the induction of the c- myc IEG in the cress of growth factors leads to cell proliferation, 1
whereas c- myc induction in growth-arrested cells in-
duces ap For example, the induction of the c- myc IEG in the presence of growth factors leads to cell proliferation, whereas c- myc induction in growth-arrested cells induces apoptosis (programmed cell death) Bissonnette et al., 1 i992). ne eas c-myc induction in growth-arrested cells in-
ical ces apoptosis (programmed cell death) Bissonnette et to i
, 1992; Evan et al., 1992; Fanidi et al., 1992; Shi et al., hig
92).
Presumably, the biochemical environmen duces apoptosis (programmed cell death) Bissonnette e
al., 1992; Evan et al., 1992; Fanidi et al., 1992; Shi et al
1992). Presumably, the biochemical environment in which
particular IEGP is induced will influence its DNA b

al., 1992; Evan et al., 1992; Fanidi et al., 1992; Shi et al., 1992).

Presumably, the biochemical environment in which a

particular IEGP is induced will influence its DNA bind-

ing activity and its biological effect. Fo 1992).

Presumably, the biochemical environment in which a

particular IEGP is induced will influence its DNA bind-

ing activity and its biological effect. For this reason,

multiple biochemical induction pathways in neur Presumably, the biochemical environment in which a
particular IEGP is induced will influence its DNA bind-
ing activity and its biological effect. For this reason,
multiple biochemical induction pathways in neurons
may not particular IEGP is induced will influence its DNA bind-
ing activity and its biological effect. For this reason,
multiple biochemical induction pathways in neurons a
may not be solely a redundancy mechanism (Lerea et al., ing activity and its biological effect. For this reason, T
multiple biochemical induction pathways in neurons a paray not be solely a redundancy mechanism (Lerea et al., dep
1992) but may confer specificity and a wide rang multiple biochemical induction pathways in neurom
ay not be solely a redundancy mechanism (Lerea et a
1992) but may confer specificity and a wide range
functions to IEGPs. For example, Krox-24 is induced
CA1 pyramidal cell may not be solely a redundancy mechanism (Lerea et al., dep
1992) but may confer specificity and a wide range of mer
functions to IEGPs. For example, Krox-24 is induced in gran
CA1 pyramidal cells by tonic activation of NM 1992) but may conier specificity and a wide range of motions to IEGPs. For example, Krox-24 is induced in gr CA1 pyramidal cells by tonic activation of NMDA receptors (Morley et al., 1991; Richardson et al., 1992) and by i

genes (Schüle et al., 1991), and a phosphorylation-mod-
ulated inhibitor of Fos/Jun activity called IP-1 has re-
ulated inhibitor of Fos/Jun activity called IP-1 has re-
activation will be different from that existing aft DRAGUNOW
Dragunow, 1994). Because the biochemical environmen
into which Krox-24 is induced after NMDA recepto DRAGUNOW
Dragunow, 1994). Because the biochemical environment
into which Krox-24 is induced after NMDA receptor
activation will be different from that existing after mus-DRAGUNOW
Dragunow, 1994). Because the biochemical environmen
into which Krox-24 is induced after NMDA recepto
activation will be different from that existing after mus
carinic receptor activation (e.g., cellular pH, ions, Dragunow, 1994). Because the biochemical environment
into which Krox-24 is induced after NMDA receptor
activation will be different from that existing after mus-
carinic receptor activation (e.g., cellular pH, ions, pro-
t into which Krox-24 is induced after NMDA receptor
activation will be different from that existing after mus-
carinic receptor activation (e.g., cellular pH, ions, pro-
tein kinase activation, other TFs), the biological eff activation will be different from that existing after mus-
carinic receptor activation (e.g., cellular pH, ions, pro-
tein kinase activation, other TFs), the biological effect
may be quantitatively and/or qualitatively dif carinic receptor activation (e.g., cellular pH, ions, p.
tein kinase activation, other TFs), the biological eff
may be quantitatively and/or qualitatively differe:
Furthermore, because the microenvironment of neuro
in diff tein kinase activation, other TFs), the biological effect
may be quantitatively and/or qualitatively different.
Furthermore, because the microenvironment of neurons
in different brain regions differs (growth factors, neuro may be quantitatively antion quantatively unter-
Furthermore, because the microenvironment of neur-
in different brain regions differs (growth factors, neu
transmitters, TFs, etc.), IEGPs may have different l
logical effec in different brain regions differs (growth factors, neuro-
transmitters, TFs, etc.), IEGPs may have different bio-
logical effects in different brain regions. Thus, expres-
sion of c-Jun in dentate granule cells after long in different brain regions differs (growth factors, neur
transmitters, TFs, etc.), IEGPs may have different bi
logical effects in different brain regions. Thus, expre
sion of c-Jun in dentate granule cells after long-ter
p transmitters, TFs, etc.), IEGPs may have different biological effects in different brain regions. Thus, expression of c-Jun in dentate granule cells after long-term potentiation may be involved in LTP stabilisation (Demmer logical effects in different brain regions. Thus, expres-
sion of c-Jun in dentate granule cells after long-term
potentiation may be involved in LTP stabilisation (Dem-
mer et al., 1993), whereas c-Jun induction in CA1 neu sion of c-Jun in dentate granule cells after lon
potentiation may be involved in LTP stabilisation
mer et al., 1993), whereas c-Jun induction in CA
rons after hypoxia-ischaemia and SE may be invo
cell death (Dragunow et al tentiation may be involved in LTP stabilisation (Dem-
er et al., 1993), whereas c-Jun induction in CA1 neu-
ns after hypoxia-ischaemia and SE may be involved in
ll death (Dragunow et al., 1993c) (see VII.G.).
As detailed i

different neurotransmitter receptors induction different neurotransmitter receptors induces specific pat-
different neurotransmitter receptors induces specific pat-
terns of IEG expression in anatomically distinct b regions. This suggests that different neurotransmitter receptors induces specific patterns of *IEG* expression in anatomically distinct brain regions. This suggests that different IEGs are linked to different neurotransmit As detailed in section III of this review., activation of
different neurotransmitter receptors induces specific pat-
terns of IEG expression in anatomically distinct brain
regions. This suggests that different IEGs are lin different neurotransmitter receptors induces specific pat-
terns of IEG expression in anatomically distinct brain
regions. This suggests that different IEGs are linked to
different neurotransmitter receptors (e.g., muscari regions. This suggests that different IEGs are linked to different neurotransmitter receptors (e.g., muscarinic activation induces Jun-B but not c-Jun: see table 2 and fig. 2). This is clearly an important determinant of t regions. This suggests that different IEGs are linked to different neurotransmitter receptors (e.g., muscarinic activation induces Jun-B but not c-Jun: see table 2 and fig. 2). This is clearly an important determinant of t different neurotransmitter receptors (e.g., muscarinic activation induces Jun-B but not c-Jun: see table 2 and fig. 2). This is clearly an important determinant of the specificity of action of IEGs. However, not only are d *decivation mattes Jun-B but not c-Jun: see table 2 and* fig. 2). This is clearly an important determinant of the specificity of action of IEGs. However, not only are different IEGs linked to different receptors, but also specificity of action of IEGs. However, not only are different IEGs linked to different receptors, but also *the*
degree of activation of the same receptor can influence
which IEGs are expressed. For example, Krox-24 is ex ferent IEGs linked to different receptors, but also the degree of activation of the same receptor can influence which IEGs are expressed. For example, Krox-24 is expressed at high levels in CA1 pyramidal cells of the hippo degree of activation of the same receptor can influence
which IEGs are expressed. For example, Krox-24 is ex-
pressed at high levels in CA1 pyramidal cells of the
hippocampus under basal conditions (Hughes et al.,
1992), which IEGs are expressed. For example, Krox-24 is expressed at high levels in CA1 pyramidal cells of the hippocampus under basal conditions (Hughes et al., 1992), and this induction can be abolished by NMDA antagonists (Wo cell death (Dragunow et al., 1993c) (see VII.G.).
As detailed in section III of this review, activation of
different neurotransmitter receptors induces specific pat-
terns of IEG expression in anatomically distinct brain
 1992), and this induction can be abolished by NMDA 1992), and this induction can be abolished by NMDA
antagonists (Worley et al., 1991). However, under the
same basal conditions, Fos, c-Jun, Jun-B, Jun-D, and
Krox-20 are not expressed, suggesting that their thresh-
old for antagonists (Worley et al., 1991). However, under the same basal conditions, Fos, c-Jun, Jun-B, Jun-D, and Krox-20 are not expressed, suggesting that their threshold for induction via NMDA receptors is higher. Thus, tonic same basal conditions, Fos, c-Jun, Jun-B, Jun-D, and
Krox-20 are not expressed, suggesting that their thresh-
old for induction via NMDA receptors is higher. Thus,
tonic activation of NMDA receptors is sufficient to in-
du Fox-20 are not expressed, suggesting that their thresh-

d for induction via NMDA receptors is higher. Thus,

inc activation of NMDA receptors is sufficient to in-

ce Krox-24 but not the other IEGPs in CA1 neurons.

CA1 tonic activation of NMDA receptors is sufficient to induce Krox-24 but not the other IEGPs in CA1 neurons.
CA1 neurons can express c-Fos, c-Jun, and Jun-B
after SE, and this is NMDA receptor-mediated (Dra-

tonic activation of NMDA receptors is sufficient to
duce Krox-24 but not the other IEGPs in CA1 neuro
CA1 neurons can express c-Fos, c-Jun, and Jurafter SE, and this is NMDA receptor-mediated (L
gunow et al., 1993c). Simil duce Krox-24 but not the other IEGPs in CA1 neurons.
CA1 neurons can express c-Fos, c-Jun, and Jun-B
after SE, and this is NMDA receptor-mediated (Dra-
gunow et al., 1993c). Similarly, 10 bursts of high-fre-
quency electri CA1 neurons can express c-Fos, c-Jun, and Jun-B
after SE, and this is NMDA receptor-mediated (Dra-
gunow et al., 1993c). Similarly, 10 bursts of high-fre-
quency electrical stimulation (leading to LTP) will in-
duce Kroxafter SE, and this is NMDA receptor-mediated (Dragunow et al., 1993c). Similarly, 10 bursts of high-frequency electrical stimulation (leading to LTP) will induce Krox-24 but not c-Fos, c-Jun, Jun-B, or Krox-20 in dentate g quency electrical stimulation (leading to LTP) will induce Krox-24 but not c-Fos, c-Jun, Jun-B, or Krox-20 in duce Krox-24 but not c-Fos, c-Jun, Jun-B, or Krox-20 in
dentate granule cells, whereas 50 bursts will induce all
of these genes via NMDA receptors (Demmer et al.,
1993; Abraham et al., 1992, 1993). Thus, low (physiolog-
ic dentate granule cells, whereas 50 bursts will induce all
of these genes via NMDA receptors (Demmer et al.,
1993; Abraham et al., 1992, 1993). Thus, low (physiolog-
ical?) levels of activation of NMDA receptors is sufficien of these genes via NMDA receptors (Demmer et al., 1993; Abraham et al., 1992, 1993). Thus, low (physiological?) levels of activation of NMDA receptors is sufficient to induce Krox-24 in CA1 and dentate granule cells, but h 1993; Abraham et al., 1992, 1993). Thus, low (physiolog-
ical?) levels of activation of NMDA receptors is sufficient
to induce Krox-24 in CA1 and dentate granule cells, but
higher (pathological?) levels are required for in ical?) levels of activation of NMDA receptors is sufficed to induce Krox-24 in CA1 and dentate granule cells higher (pathological?) levels are required for induction related genes. Perhaps this differential sensitivit NMDA to induce Krox-24 in CA1 and dentate granule cells, b
higher (pathological?) levels are required for induction
related genes. Perhaps this differential sensitivity
NMDA receptor activation reflects different second-me
seng gher (pathological?) levels are required for induction of
lated genes. Perhaps this differential sensitivity to
MDA receptor activation reflects different second-mes-
nger induction pathways for these different IEGs.
The n

related genes. Perhaps this differential sensitivity to NMDA receptor activation reflects different second-messenger induction pathways for these different IEGs.
The neurotransmitter receptor-mediated induction of a partic NMDA receptor activation reflects different second-mes-
senger induction pathways for these different IEGs.
The neurotransmitter receptor-mediated induction of
a particular IEG in the same sets of neurons can vary,
dependi senger induction pathways for these different IEGs.
The neurotransmitter receptor-mediated induction of
a particular IEG in the same sets of neurons can vary,
depending upon the nature of the inducing stimulus. As
mentione The neurotransmitter receptor-mediated induction of
a particular IEG in the same sets of neurons can vary,
depending upon the nature of the inducing stimulus. As
mentioned above, LTP induction of Krox-24 in dentate
granule a particular 1EG in the same sets of neurons can vary,
depending upon the nature of the inducing stimulus. As
mentioned above, LTP induction of Krox-24 in dentate
granule cells occurs via NMDA receptor activation
(Abraham mentioned above, LTP induction of Krox-24 in dentate
granule cells occurs via NMDA receptor activation
(Abraham et al., 1992). Similarly, induction of Krox-24
in these same neurons by injury is via NMDA receptors
(Hughes e

PHARMACOLOGICAL REVIEWS

Notice that c-jun gene expression is only increased strongly following activation of NMDA glutamate receptors.

Entate granule cells, after brief hippocampal seizures, **VII. Functions of Immediate-early Genes in**

depending upon area
Notice that c-jun gene expression is only increased strongly follow
dentate granule cells, after brief hippocampal seizures,
is not NMDA receptor-mediated, whereas c-Fos induc-Notice that c-jun gene expression is only increased strongly for
dentate granule cells, after brief hippocampal seizure
is not NMDA receptor-mediated, whereas c-Fos indu
tion *is* (Hughes et al., 1994). dentate granule cells, after brief hippocampal seizures,
is not NMDA receptor-mediated, whereas c-Fos induc-
tion *is* (Hughes et al., 1994). ntate granule cells, after brief hippocampal seizures,
not NMDA receptor-mediated, whereas c-Fos induc-
n is (Hughes et al., 1994).
This complexity of regulation may be an important
terminant of the specificity of action o

dentate granule cells, after brief hippocampal seizures,
is not NMDA receptor-mediated, whereas c-Fos induc-
tion is (Hughes et al., 1994).
This complexity of regulation may be an important
determinant of the specificity o is not NMDA receptor-mediated, whereas c-Fos induction is (Hughes et al., 1994).

This complexity of regulation may be an important \overline{S} determinant of the specificity of action of IEGPs. Another potential factor that tion *is* (Hughes et al., 1994).

This complexity of regulation may be an important S

determinant of the specificity of action of IEGPs. An-

other potential factor that may regulate IEG specificity

is the time-course This complexity of regulation may be an important S_u
determinant of the specificity of action of IEGPs. An-
other potential factor that may regulate IEG specificity
is the time-course of IEGP expression. Recently, it ha determinant of the specificity of action of IEGPs. Another potential factor that may regulate IEG specificity
is the time-course of IEGP expression. Recently, it has
been demonstrated that prolonged, but not brief, c-Jun
 other potential factor that may regulate IEG specificies is the time-course of IEGP expression. Recently, it helds been demonstrated that prolonged, but not brief, c-Junduction was required for transactivation by Jun (Tree is the time-course of IEGP expression. Recently, it has cal still
been demonstrated that prolonged, but not brief, c-Jun
induction was required for transactivation by Jun (Trejo
et al., 1992). Thus, the temporal profile o been demonstrated that prolonged, but not brief, c-Jun induction was required for transactivation by Jun (Trejo et al., 1992). Thus, the temporal profile of IEGP induction may also regulate biological activity. IEGPs show induction was requinet al., 1992). Thus,
tion may also regul
different profiles of
tion of this review. *Fremaxy also regulate biological activity.* Extrs show
fferent profiles of induction as shown in the next sec-
on of this review.
VI. Temporal Profile of Immediate-early Gene
Protein Induction in Adult Neurons

Protein Induction as shown in the heads.
 Protein Induction in Adult Neurons
 Protein Induction in Adult Neurons
 So show different time-courses of expression

ISS

VI. Temporal Profile of Immediate-early Gene in 1

Protein Induction in Adult Neurons era

IEGPs show different time-courses of expression and dep

cay after various treatments with Fos, Jun-B, and **VI. Temporal Profile of Immediate-early Gene** in $\begin{array}{c} \n\text{I} \\
\text{I} \\
\text{I} \\
\text{EGPs} \\
\text{flow} \\
\text{d} \\
\text{decay} \\
\text{after} \\
\text{various treatments} \\
\text{with} \\
\begin{array}{c} \n\text{Fos, Jun-B,} \\
\text{J} \\
\text{Gm} \\
\text{S} \\
\text{Gm} \\
\text{Hm} \\
\text$ **VI. Temporal Profile of Immediate-early Gene** in learning and memory, and pathologically in drug tol-
Protein Induction in Adult Neurons erance/supersensitivity, epileptogenesis, development of
IEGPs show different tim FIGPs show different time-courses of expression and
decay after various treatments with Fos, Jun-B, and
Krox-24 being induced first (within 1 h) and falling away B .
rapidly to baseline (within 4 h). Induction of Fos-B a IEGPs show different time-courses of expression and
decay after various treatments with Fos, Jun-B, and
Krox-24 being induced first (within 1 h) and falling away B
rapidly to baseline (within 4 h). Induction of Fos-B and decay after various treatments with Fos, Jun-B, and
Krox-24 being induced first (within 1 h) and falling away
rapidly to baseline (within 4 h). Induction of Fos-B and
Jun-D is more delayed (4 h), but these IEGPs remain
ele Krox-24 being induced first (within 1 h) and falling away
rapidly to baseline (within 4 h). Induction of Fos-B and
Jun-D is more delayed (4 h), but these IEGPs remain
elevated for longer periods of time (up to 24 h) (Demme rapidly to baseline (within 4 h). Induction of Fos-B and
Jun-D is more delayed (4 h), but these IEGPs remain
elevated for longer periods of time (up to 24 h) (Demmer
et al., 1993; Dragunow et al., 1992; MacGibbon et al.,
1 Jun-D is more delayed (4 h), but these IEGPs remain
elevated for longer periods of time (up to 24 h) (Demmer
et al., 1993; Dragunow et al., 1992; MacGibbon et al.,
1994; Dragunow et al., 1993c). This suggests that Fos/
Jun elevated for longer periods of time (up to 24 h) (Demmer
et al., 1993; Dragunow et al., 1992; MacGibbon et al.,
1994; Dragunow et al., 1993c). This suggests that Fos/
Jun-B and Fos-B/Jun-D dimers are formed in neurons.
Kr et al., 1993; Dragunow et al., 1992; MacGibboon et al., $\frac{1}{2}$ ing of synaptic efficacy that may be involved in memory
1994; Dragunow et al., 1993c). This suggests that Fos/
Jun-B and Fos-B/Jun-D dimers are formed in n 1994; Dragunow et al., 1993c). This suggests that Fos/
Jun-B and Fos-B/Jun-D dimers are formed in neurons.
Krox-20 is induced rapidly after LTP, but levels remain
elevated for over 24 h (Williams et al., 1995). c-Jun (J
i Jun-B and Fos-B/Jun-D dimers are formed in neurons.
Krox-20 is induced rapidly after LTP, but levels remain
elevated for over 24 h (Williams et al., 1995). c-Jun
induction is delayed (3 to 6 h) and prolonged (24 to 72 h)
a Krox-20 is induced rapidly after LTP, but levels remain
elevated for over 24 h (Williams et al., 1995). c-Jun
induction is delayed (3 to 6 h) and prolonged (24 to 72 h)
after SE and HI (Dragunow et al., 1993c). After axot elevated for over 24 h (Williams et al., 1995). c-Jun (J_d
induction is delayed (3 to 6 h) and prolonged (24 to 72 h) wis
after SE and HI (Dragunow et al., 1993c). After axotomy, de
c-Jun induction is more delayed (48 h) after SE and HI (Dragunow et al., 1993c). After axotomy, c-Jun induction is more delayed (48 h) and very prolonged (weeks to months) depending upon the brain region affected (Dragunow, 1992; Leah et al., 1993).

Neurons

VII. Functions of Immediate-early Genes in A. Immediate-early Genes as Plasticity/Sensitisation
A. Immediate-early Genes as Plasticity/Sensitisation Switches

Neurons

Immediate-early Genes as Plasticity/Sensitisation

uitches

The nervous system is dynamic in that it changes in

sponse to pharmacological/environmental/pathologi-A. Immediate-early Genes as Plasticity/.
Switches
The nervous system is dynamic in the
response to pharmacological/environmental stimuli. From the time of the initial di Example 1.1 Interactive dentry Genes as Fusticity exposition.
Switches
The nervous system is dynamic in that it changes in
response to pharmacological/environmental/pathologi-
cal stimuli. From the time of the initial disc Suttenes
The nervous system is dynamic in that it changes in
response to pharmacological/environmental/pathologi-
cal stimuli. From the time of the initial discovery of IEGs
and associated proteins in brain neurons (Goelet The nervous system is dynamic in that it changes in
response to pharmacological/environmental/pathologi-
cal stimuli. From the time of the initial discovery of IEGs
and associated proteins in brain neurons (Goelet et al.,
 cal stimuli. From the time of the initial discovery of IEGs
and associated proteins in brain neurons (Goelet et al.,
1986; Morgan et al., 1987; Dragunow et al., 1987) to the
present, investigators have hypothesised that th cal stimuli. From the time of the initial discovery of IEGs
and associated proteins in brain neurons (Goelet et al.,
1986; Morgan et al., 1987; Dragunow et al., 1987) to the
present, investigators have hypothesised that th and associated proteins in brain neurons (Goelet et al. 1986; Morgan et al., 1987; Dragunow et al., 1987) to the present, investigators have hypothesised that these proteins may be involved in this plasticity by linking ne 1986; Morgan et al., 1987; Dragunow et al., 1987) to the present, investigators have hypothesised that these proteins may be involved in this plasticity by linking nerve cell membrane events to the neuronal genome and lead present, investigators have hypothesised that these proteins may be involved in this plasticity by linking nerve
cell membrane events to the neuronal genome and lead-
ing to neuronal phenotype changes (Dragunow et al.,
198 teins may be involved in this plasticity by linking nerve
cell membrane events to the neuronal genome and lead-
ing to neuronal phenotype changes (Dragunow et al.,
1989b). Physiologically, this plasticity may be involved
i ing to neuronal phenotype changes (Dragunow et al., 1989b). Physiologically, this plasticity may be involved drugs, etc., as described in the next section. depression, development of side effects to antipsychotic

*Memory B. Immediate-early Gene Proteins in Learning and Memory
Memory
1. Krox-20 and Krox-24 as stabilisers of long-term*

ugs, etc., as described in the next section.
 Immediate-early Gene Proteins in Learning and
 2. Krox-20 and Krox-24 as stabilisers of long-term
 tentiation. LTP is an activity-dependent strengthenis immediate-early Gene Proteins in Learning and
Memory
1. Krox-20 and Krox-24 as stabilisers of long-term
potentiation. LTP is an activity-dependent strengthen-
ing of synaptic efficacy that may be involved in memory
stor Memory
1. Krox-20 and Krox-24 as stabilisers of long-term
potentiation. LTP is an activity-dependent strengthen-
ing of synaptic efficacy that may be involved in memory
storage in the brain (Bliss and Collingridge, 1993). 1. Krox-20 and Krox-24 as stabilisers of long-term
potentiation. LTP is an activity-dependent strengthen-
ing of synaptic efficacy that may be involved in memory
storage in the brain (Bliss and Collingridge, 1993). Re-
ce potentiation. LTP is an activity-dependent strengthen-
ing of synaptic efficacy that may be involved in memory
storage in the brain (Bliss and Collingridge, 1993). Re-
cent studies suggest that there are at least three typ ing of synaptic efficacy that may be involved in memory
storage in the brain (Bliss and Collingridge, 1993). Re-
cent studies suggest that there are at least three types of
LTP that can be distinguished on the basis of dec storage in the brain (Bliss and Collingridge, 1993). Recent studies suggest that there are at least three types of LTP that can be distinguished on the basis of decay rates (Jeffery et al., 1990; Abraham et al., 1993): LTP cent studies suggest that there are at least three types of
LTP that can be distinguished on the basis of decay rates
(Jeffery et al., 1990; Abraham et al., 1993): LTP1 decays
with an average decay constant of about 2 h; L LTP that can be distinguished on the basis of decay rates
(Jeffery et al., 1990; Abraham et al., 1993): LTP1 decays
with an average decay constant of about 2 h; LTP2
decays with a decay constant of about 4 days, and LTP3
d (Jeffery et al., 1990; Abraham et al., 1993): LTP1 decays
with an average decay constant of about 2 h; LTP2
decays with a decay constant of about 4 days, and LTP3
decays with a decay constant of about 23 days (Jeffery et
a with an average decay constant of about 2 h; LTP2
decays with a decay constant of about 4 days, and LTP3
decays with a decay constant of about 23 days (Jeffery et
al., 1990). These various types of LTP can be generated
in

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tive muscarinic agonist pilocarpine (25 mg/kg i.p.) results in in-FIG. 2. Differential induction of Jun family members within the
CNS. Activation of neuronal muscarinic receptors with the nonselec-
tive muscarinic agonist pilocarpine (25 mg/kg i.p.) results in in-
creased expression of J FIG. 2. Differential induction of Jun-family members within the
CNS. Activation of neuronal muscarinic receptors with the nonselec-
tive muscarinic agonist pilocarpine (25 mg/kg i.p.) results in in-
creased expression of J after muscarinic agonist pilocarpine (25 mg/kg i.p.) results in increased expression of Jun-B but not c-Jun protein in hippocampa CA1 pyramidal neurons. (a) c-Jun protein expression in a rat 2 lafter distilled water (cont creased expression of Jun-B but not c-Jun protein in hippocampal
CA1 pyramidal neurons. (a) c-Jun protein expression in a rat 2 h
after distilled water (control) injection; 2 h after injection of pilo-
carpine solution, Ju CA1 pyramidal neurons. (a) c-Jun protein expression in a rat 2 h after distilled water (control) injection; 2 h after injection of pilocarpine solution, Jun-B (c) but not c-Jun (b) or Jun-D proteins are produced in CA1 py after distilled water (control) injection; 2 h after injection of pilocarpine solution, Jun-B (c) but not c-Jun (b) or Jun-D proteins are produced in CA1 pyramidal neurons. Twenty-four hours after SE produced by electri carpine solution, Jun-B (c) but not c-Jun (b) or Jun-D proteins
are produced in CA1 pyramidal neurons. Twenty-four hours after
SE produced by electrical stimulation of the hippocampus (see
Dragunow et al., 1993), c-Jun pr are produced in CA1 pyramidal neurons. Twenty-four hours after SE produced by electrical stimulation of the hippocampus (see Dragunow et al., 1993), c-Jun protein is strongly expressed in hippocampal CA1 pyramidal neurons SE produced by electrical stimulation of the hippocampus (see
Dragunow et al., 1993), c-Jun protein is strongly expressed in hip-
pocampal CA1 pyramidal neurons (d), whereas the expression of
Jun-B and Jun-D proteins occur Dragunow et al., 1993), c-Jun protein is strongly expressed in hip-
pocampal CA1 pyramidal neurons (d) , whereas the expression of
Jun-B and Jun-D proteins occurs weakly. Closed arrows show CA1.
Eight to 24 h after hippoc pocampal CA1 pyramidal neurons (d), whereas the expression Jun-B and Jun-D proteins occurs weakly. Closed arrows show χ Eight to 24 h after hippocampal SE or after a single hippocal kindling AD, Jun-D protein is strong pal interneurons (open arrows), *inclued arrows* show CA1.
Eight to 24 h after hippocampal SE or after a single hippocampal
kindling AD, Jun-D protein is strongly expressed within hippocam-
pal interneurons (open arrows), Eight to 24 h after hippocampal SE or after a single hippocampal
kindling AD, Jun-D protein is strongly expressed within hippocam-
pal interneurons (open arrows), (e) although c-Jun and Jun-B protein
are not significantly

are not significantly expressed within these neurons. Scale I
 300μ m.
numbers of bursts of pulses (Jeffery et al., 1990).
thermore, anaesthetising rats with sodium pentob
tal prevents LTP3 expression (Jeffery et al., 19 soo μ m.

numbers of bursts of pulses (Jeffery et al., 1990). F

thermore, anaesthetising rats with sodium pentobar

tal prevents LTP3 expression (Jeffery et al., 1990).

We have recently shown that stimulation that gen umbers of bursts of pulses (Jeffery et al., 1990). Furthermore, anaesthetising rats with sodium pentobarl
I prevents LTP3 expression (Jeffery et al., 1990).
We have recently shown that stimulation that generals LTP3, but n numbers of bursts of pulses (Jeffery et al., 1990). Fur-
thermore, anaesthetising rats with sodium pentobarbi-
tal prevents LTP3 expression (Jeffery et al., 1990).
We have recently shown that stimulation that gener-
ates

thermore, anaesthetising rats with sodium pentobarbital prevents LTP3 expression (Jeffery et al., 1990).
We have recently shown that stimulation that gener-
LT
ates LTP3, but not LTP2, will produce a strong induction
of Kr tal prevents LTP3 expression (Jeffery et al., 1990).
We have recently shown that stimulation that generates LTP3, but not LTP2, will produce a strong induction
of Krox-20 and Krox-24 in dentate granule cells v:
NMDA-recept We have recently shown that stimulation that generates LTP3, but not LTP2, will produce a strong induction tion of Krox-20 and Krox-24 in dentate granule cells via the NMDA-receptor activation (Williams et al., 1995; Abraates LTP3, but not LTP2, will produce a strong induction of Krox-20 and Krox-24 in dentate granule cells v.
NMDA-receptor activation (Williams et al., 1995; Abram et al., 1993), although stimulation inducing LTF
will produ of Krox-20 and Krox-24 in dentate granule cells via
NMDA-receptor activation (Williams et al., 1995; Abra-
ham et al., 1993), although stimulation inducing LTP2
will produce a weak induction of Krox-24 but not Krox-
20. Kr NMDA-receptor activation (Williams et al., 1993), Abra-
ham et al., 1993), although stimulation inducing LTP2
will produce a weak induction of Krox-24 but not Krox-
20. Krox-24 expression does not correlate with LTP in-
du will produce a weak induction of Krox-24 but not Krox-
20. Krox-24 expression does not correlate with LTP in-
duction (Richardson et al., 1992; Schreiber et al., 1991a) ind
but correlates with LTP maintenance (Richardson e 20. Krox-24 expression does not correlate with LTP in duction (Richardson et al., 1992; Schreiber et al., 1991a
but correlates with LTP maintenance (Richardson et al. 1992). Members of the Fos and Jun families are also
ind duction (Richardson et al., 1992; Schreiber et al., 1991a)
but correlates with LTP maintenance (Richardson et al.,
1992). Members of the Fos and Jun families are also
induced in these situations (Nikolaev et al., 1991; Kac but correlates with LTP maintenance (Richardson et al., 1992). Members of the Fos and Jun families are also induced in these situations (Nikolaev et al., 1991; Kaczmarek, 1992, 1993a, b; Demmer et al., 1993), but their ind 1992). Members of the Fos and Jun families are also induced in these situations (Nikolaev et al., 1991; Kaczmarek, 1992, 1993a, b; Demmer et al., 1993), but their induction does not correlate with LTP induction or stabilis induced in these situations (Nikolaev et al., 1991; Kac-
zmarek, 1992, 1993a, b; Demmer et al., 1993), but their
induction does not correlate with LTP induction or sta-
bilisation (Demmer et al., 1993). These results sugge zmarek, 1992, 1993a, b; Demmer et al., 1993), but their
induction does not correlate with LTP induction or sta-
bilisation (Demmer et al., 1993). These results suggest
that Krox-20 and Krox-24 may be involved in the
NMDA-r induction does not correlate with LTP induction or stabilisation (Demmer et al., 1993). These results suggest more that Krox-20 and Krox-24 may be involved in the 198 NMDA-receptor-mediated *stabilisation* of the synaptic

DRAGUNOW
the generation of LTP3. Both of these zinc-finger TFs
recognise the *cis*-acting element *GCGTGGGGCG* (Le-DRAGUNOW
the generation of LTP3. Both of these zinc-finger TF_S
recognise the *cis-*acting element *GCGTGGGCG* (Le-
maire et al., 1988; Christy and Nathans, 1989). DRAGUNOW
the generation of LTP3. Both of these zinc-fing
recognise the *cis*-acting element GCGTGGGCC
maire et al., 1988; Christy and Nathans, 1989).
Krox-24 is expressed at very high levels basally e generation of LTP3. Both of these zinc-finger TFs
cognise the *cis*-acting element *GCGTGGGCG* (Le-
aire et al., 1988; Christy and Nathans, 1989).
Krox-24 is expressed at very high levels basally in the
ocortex, hippocam

CA1 destruction (Kubo et al., 1993) and NMDA antagonists injected into the hippocampus (Ohno et al., 1992)
CNS. Activation of neuronal muscarinic receptors with the nonselec-
CNS. Activation of neuronal muscarinic receptor the generation of LTP3. Both of these zinc-finger TFs
recognise the *cis*-acting element *GCGTGGGGCG* (Le-
maire et al., 1988; Christy and Nathans, 1989).
Krox-24 is expressed at very high levels basally in the
neocortex, recognise the *cis*-acting element *GCGTGGGCG* (Le-
maire et al., 1988; Christy and Nathans, 1989).
Krox-24 is expressed at very high levels basally in the
neocortex, hippocampus, striatum, and limbic system
regions (Hughe maire et al., 1988; Christy and Nathans, 1989).
Krox-24 is expressed at very high levels basally in the
neocortex, hippocampus, striatum, and limbic system
regions (Hughes et al., 1992), and this basal expression
can be ab Krox-24 is expressed at very high levels basally in the
neocortex, hippocampus, striatum, and limbic system
regions (Hughes et al., 1992), and this basal expression
can be abolished by blocking NMDA receptors (Worley et
al regions (Hughes et al., 1992), and this basal expression
can be abolished by blocking NMDA receptors (Worley et
al., 1991; Gass et al., 1993) and by sodium pentobarbital
anaesthesia (Richardson et al., 1992). Basal expres in the neocortex is also reduced after noradrenaline depletion (Bhat and Baraban, 1992) and by block of D_1 -dopamine receptors (Mailleux et al., 1992). As NMDA. al., 1991; Gass et al., 1993) and by sodium pentobarbital anaesthesia (Richardson et al., 1992). Basal expression
in the neocortex is also reduced after noradrenaline de-
pletion (Bhat and Baraban, 1992) and by block of D_1 -
dopamine receptors (Mailleux et al., 1992). As NMDA, anaesthesia (Richardson et al., 1992). Basal expression
in the neocortex is also reduced after noradrenaline de-
pletion (Bhat and Baraban, 1992) and by block of D_1 -
dopamine receptors (Mailleux et al., 1992). As NMDA, in the neocortex is also reduced after noradrenaline de
pletion (Bhat and Baraban, 1992) and by block of D_1
dopamine receptors (Mailleux et al., 1992). As NMDA
noradrenaline, and D_1 -dopamine receptors are all in
vol pletion (Bhat and Baraban, 1992) and by block of D_1 -
dopamine receptors (Mailleux et al., 1992). As NMDA,
noradrenaline, and D_1 -dopamine receptors are all in-
volved in learning and memory (Ohno et al., 1992; Mat-
t dopamine receptors (Mailleux et al., 1992). As NMDA,
noradrenaline, and D_1 -dopamine receptors are all in-
volved in learning and memory (Ohno et al., 1992; Mat-
thies, 1989), basally expressed Krox-24 may be involved
i noradrenaline, and D_1 -dopamine receptors are all in-
volved in learning and memory (Ohno et al., 1992; Mat-
thies, 1989), basally expressed Krox-24 may be involved
in these actions. In particular, basal expression of
K volved in learning and memory (Ohno et al., 1992; Matthies, 1989), basally expressed Krox-24 may be involved
in these actions. In particular, basal expression of
Krox-24 in CA1 pyramidal cells (Hughes et al., 1992),
which thies, 1989), basally expressed Krox-24 may be involved
in these actions. In particular, basal expression of
Krox-24 in CA1 pyramidal cells (Hughes et al., 1992),
which is largely NMDA-receptor mediated (Worley et
al., 199 in these actions. In particular, basal expression
Krox-24 in CA1 pyramidal cells (Hughes et al., 199
which is largely NMDA-receptor mediated (Worley
al., 1991), may be involved in new learning, inasmuch
CA1 destruction (Ku Krox-24 in CA1 pyramidal cells (Hughes et al., 1992),
which is largely NMDA-receptor mediated (Worley et
al., 1991), may be involved in new learning, inasmuch as
CA1 destruction (Kubo et al., 1993) and NMDA antago-
nists i which is largely NMDA-receptor mediated (Worley al., 1991), may be involved in new learning, inasmuch CA1 destruction (Kubo et al., 1993) and NMDA antag mists injected into the hippocampus (Ohno et al., 1993) impair new le impair new learning (similar to deficits seen in Alzhei-A1 destruction (Kubo et al., 1993) and NMDA antagosts injected into the hippocampus (Ohno et al., 1992)
ppair new learning (similar to deficits seen in Alzhei-
er's disease).
All of the work on LTP and IEGs has been perfor

nists injected into the hippocampus (Ohno et al., 1992
impair new learning (similar to deficits seen in Alzhe
mer's disease).
All of the work on LTP and IEGs has been performe
in dentate granule cells. LTP also occurs in C impair new learning (similar to deficits seen in Alzheimer's disease).

All of the work on LTP and IEGs has been performed

in dentate granule cells. LTP also occurs in CA1 pyra-

midal cells, although the induction of IEG mer's disease).

All of the work on LTP and IEGs has been performed

in dentate granule cells. LTP also occurs in CA1 pyra-

midal cells, although the induction of IEGs after LTP in

these neurons has not been investigated in dentate granule cells. LTP also occurs in CA1 pyra-
midal cells, although the induction of IEGs after LTP in
these neurons has not been investigated. However, al-
though dentate granule cells express low levels of Kroxin dentate granule cells. LTP also occurs in CA1 pyra-
midal cells, although the induction of IEGs after LTP in
these neurons has not been investigated. However, al-
though dentate granule cells express low levels of Kroxmidal cells, although the induction of IEGs after LTP in
these neurons has not been investigated. However, al-
though dentate granule cells express low levels of Krox-
24, CA1 neurons show very high constitutive expression though dentate granule cells express low levels of Krox-
24, CA1 neurons show very high constitutive expression
that is mediated by activation of NMDA receptors
(Hughes et al., 1992; Worley et al., 1991). NMDA antagthough dentate granule cells express low levels of Krox-
24, CA1 neurons show very high constitutive expression
that is mediated by activation of NMDA receptors
(Hughes et al., 1992; Worley et al., 1991). NMDA antag-
onist 24, CA1 neurons show very high constitutive expression
that is mediated by activation of NMDA receptors
(Hughes et al., 1992; Worley et al., 1991). NMDA antag-
onists also block LTP production in granule cells and
CA1 neur that is mediated by activation of NMDA receptors (Hughes et al., 1992; Worley et al., 1991). NMDA antagonists also block LTP production in granule cells and CA1 neurons (reviewed in Bliss and Collingridge, 1993). Thus, ass (Hughes et al., 1992; Worley et al., 1991). NMDA antagonists also block LTP production in granule cells and
CA1 neurons (reviewed in Bliss and Collingridge, 1993).
Thus, assuming that Krox-24 is also involved in CA1
LTP, t onists also block LTP production in granule cells and CA1 neurons (reviewed in Bliss and Collingridge, 1993).
Thus, assuming that Krox-24 is also involved in CA1
LTP, this NMDA-mediated high basal expression suggests that CA1 neurons (reviewed in Bliss and Collingridge, 19:
Thus, assuming that Krox-24 is also involved in (
LTP, this NMDA-mediated high basal expression s
gests that LTP may be occurring in CA1 neurons un
physiological conditi Thus, assuming that Krox-24 is also involved in CA1
LTP, this NMDA-mediated high basal expression sug-
gests that LTP may be occurring in CA1 neurons under
physiological conditions and that Krox-24 is a constitu-
tively ex LTP, this NMDA-mediated high basal expression suggests that LTP may be occurring in CA1 neurons under physiological conditions and that Krox-24 is a constitutively expressed *plasticity switch*. Alternatively, Krox-24 expr gests that LTP may be occurring in CA1 neurons uncepty physiological conditions and that Krox-24 is a constitively expressed *plasticity switch*. Alternatively, Krox-expression may be necessary, but not sufficient, LTP3 pr physiological conditions and that Krox-24 is a constitu-
tively expressed *plasticity switch*. Alternatively, Krox-24
expression may be necessary, but not sufficient, for
LTP3 production, inasmuch as NMDA receptor activa-
 tively expressed *plasticity switch*. Alternatively, Krox-24 expression may be necessary, but not sufficient, for LTP3 production, inasmuch as NMDA receptor activation alone is not sufficient to induce LTP but requires the expression may be necessary, but not sufficient, for
LTP3 production, inasmuch as NMDA receptor activa-
tion alone is not sufficient to induce LTP but requires
the co-activation of metabotropic glutamate receptors
(Musgrav LTP3 production, inasmuch as NMDA receptor activation alone is not sufficient to induce LTP but require
the co-activation of metabotropic glutamate receptor
(Musgrave et al., 1993; Behnisch et al., 1991). It will
important tion alone is not sufficient to induce LTP but requires
the co-activation of metabotropic glutamate receptors
(Musgrave et al., 1993; Behnisch et al., 1991). It will be
important to determine the second-messenger/protein
k the co-activation of metabotropic glutamate receptors
(Musgrave et al., 1993; Behnisch et al., 1991). It will be
important to determine the second-messenger/protein
kinases regulating NMDA-receptor-mediated basal ex-
press (Musgrave et al., 1993; Behnisch et al., 1991). It will be
important to determine the second-messenger/protein
kinases regulating NMDA-receptor-mediated basal ex-
pression of Krox-24 in CA1. NMDA receptor activation
induce important to determine the second-messenger/protein
kinases regulating NMDA-receptor-mediated basal ex-
pression of Krox-24 in CA1. NMDA receptor activation
induces cAMP and tyrosine kinases in CA1 neurons
(Bading and Gree nases regulating NMDA-receptor-mediated basal ession of Krox-24 in CA1. NMDA receptor activation
duces cAMP and tyrosine kinases in CA1 neuro
ading and Greenberg, 1991; Chetkovich et al., 199
Recent studies have shown that

induces cAMP and tyrosine kinases in CA1 neurons
(Bading and Greenberg, 1991; Chetkovich et al., 1991).
Recent studies have shown that a number of second-
messenger/protein kinase systems are involved in LTP
production (e. induces cAMP and tyrosine kinases in CA1 neurons
(Bading and Greenberg, 1991; Chetkovich et al., 1991).
Recent studies have shown that a number of second-
messenger/protein kinase systems are involved in LTP
production (e. (Bading and Greenberg, 1991; Chetkovich et al., 1991).
Recent studies have shown that a number of second-
messenger/protein kinase systems are involved in LTP
production (e.g., tyrosine kinases, cAMP/PKA, PKC, ca-
sein kin Recent studies have shown that a number of second-
messenger/protein kinase systems are involved in LTP
production (e.g., tyrosine kinases, cAMP/PKA, PKC, ca-
sein kinase II, calmodulin kinase II, nitric oxide/carbon
monox messenger/protein kinase systems are involved in LTP
production (e.g., tyrosine kinases, cAMP/PKA, PKC, ca-
sein kinase II, calmodulin kinase II, nitric oxide/carbon
monoxide, Stevens and Wang, 1993; Reymann et al.,
1988; production (e.g., tyrosine kinases, cAMP/PKA, PKC, casein kinase II, calmodulin kinase II, nitric oxide/carbon
monoxide, Stevens and Wang, 1993; Reymann et al.,
1988; Silva et al., 1992; Ben-Ari et al., 1992; Frey et al.,
 sein kinase II, calmodulin kinase II, nitric oxide/carbon
monoxide, Stevens and Wang, 1993; Reymann et al.,
1988; Silva et al., 1992; Ben-Ari et al., 1992; Frey et al.,
1993; Matthies and Reymann, 1993; Slack and Pockett,

PHARMACOLOGICAL REVIEWS

1991; Charriaut-Marlangue et al., 1991; Zhuo et al., thalamus (Dragunow and Faull, 1990; Hughes et al., 1993), and in particular, LTP maintenance may involve 1993b). The pattern of IEG expression produced in the IMMEDIATE-EARLY GENES A
1991; Charriaut-Marlangue et al., 1991; Zhuo et al., tl
1993), and in particular, LTP maintenance may involve
PKA activation. It will be interesting to determine the n IMMEDIATE-EARLY GENES AN

1991; Charriaut-Marlangue et al., 1991; Zhuo et al., the

1993), and in particular, LTP maintenance may involve

PKA activation. It will be interesting to determine the neeffects of blocking these 1991; Charriaut-Marlangue et al., 1991; Zhuo et al., thal
1993), and in particular, LTP maintenance may involve 199
PKA activation. It will be interesting to determine the neoe
effects of blocking these second-messenger pa 1991; Charriaut-Marlangue et al., 1991; Zhuo et al., t
1993), and in particular, LTP maintenance may involve
PKA activation. It will be interesting to determine the
effects of blocking these second-messenger pathways on
LT 1993), and in particular, LTP maintenance may involve PKA activation. It will be interesting to determine the effects of blocking these second-messenger pathways on LTP-induction of IEGs, especially cAMP and tyrosine kinas PKA activation. It will be interesting to determine the effects of blocking these second-messenger pathways or LTP-induction of IEGs, especially cAMP and tyrosine kinases, both of which are turned on by NMDA receptor activ effects of blocking these second-messenger pathways on
LTP-induction of IEGs, especially cAMP and tyrosine
kinases, both of which are turned on by NMDA receptor
activation in CA1 neurons, (Bading and Greenberg, t
1991; Che kinases, both of which are turned on by NMDA receptor
activation in CA1 neurons, (Bading and Greenberg,
1991; Chetkovich et al., 1991) as is Krox-24 (Worley et
al., 1991). Long-lasting LTP produced by cAMP is pro-
tein-syn activation in CA1 neurons, (Bading and Greenbe
1991; Chetkovich et al., 1991) as is Krox-24 (Worley
al., 1991). Long-lasting LTP produced by cAMP is p
tein-synthesis dependent (Frey et al., 1993), suggesti
that it might in 1991; Chetkovich et al., 1991) as is Krox-24 (Worley et NML
al., 1991). Long-lasting LTP produced by cAMP is pro-
tein-synthesis dependent (Frey et al., 1993), suggesting migh
that it might involve IEG and late-response g al., 1991). Long-lasting LTP produced by cAMP is present-
tein-synthesis dependent (Frey et al., 1993), suggestir
that it might involve IEG and late-response gene expre
sion. It will be interesting to elucidate the role of tein-synthesis dependent (Frey et al., 1993), suggesting muth that it might involve IEG and late-response gene expression. It will be interesting to elucidate the role of CREB happlosphorylation in IEG expression in this c that it might involve IEG and late-response gene expression. It will be interesting to elucidate the role of CREB $\,$ ¹ phosphorylation in IEG expression in this cyclic AMP-
inducible form of LTP, because CREB is involv sion. It will
phosphoryla
inducible fo
strengtheni
al., 1990).
Many stu have shown in IEG expression in this cyclic A ducible form of LTP, because CREB is involved in rengthening of synaptic efficacy in Aplysia (Das., 1990).
Many studies have shown that various neurotiters, such as acetylchol

inducible form of LTP, because CREB is involved in the strengthening of synaptic efficacy in Aplysia (Dash e al., 1990).

Many studies have shown that various neurotrans mitters, such as acetylcholine, serotonin, glutamate strengthening of synaptic efficacy in Aplysia (Dash et al., 1990).

Many studies have shown that various neurotrans

mitters, such as acetylcholine, serotonin, glutamate

platelet-activating factor, noradrenaline, dynorphi al., 1990).
Many studies have shown that various neurotrans-
mitters, such as acetylcholine, serotonin, glutamate,
platelet-activating factor, noradrenaline, dynorphin,
adenosine, and benzodiazepines (Del Cerro et al., 199 Many studies have shown that various neurotrans-
mitters, such as acetylcholine, serotonin, glutamate,
platelet-activating factor, noradrenaline, dynorphin,
adenosine, and benzodiazepines (Del Cerro et al., 1992;
Wagner et mitters, such as acetylcholine, serotonin, glutamate, platelet-activating factor, noradrenaline, dynorphin, adenosine, and benzodiazepines (Del Cerro et al., 1992; Wagner et al., 1993; Weisskopf et al., 1993; Dunwiddie et platelet-activating factor, noradrenaline, dynorphin,
adenosine, and benzodiazepines (Del Cerro et al., 1992;
Wagner et al., 1993; Weisskopf et al., 1993; Dunwiddie
et al., 1992; Wieraszko et al., 1993; Corradetti et al.,
 adenosine, and benzodiazepines (Del Cerro et al., 1992; Wagner et al., 1993; Weisskopf et al., 1993; Dunwiddie (Minduction. 1992; Wieraszko et al., 1993; Corradetti et al., 1992; Stanton and Sarvey, 1985; Sekino et al., 1 Wagner et al., 1993; Weisskopf et al., 1993; Dunwiddie
et al., 1992; Wieraszko et al., 1993; Corradetti et al.
1992; Stanton and Sarvey, 1985; Sekino et al., 1991
Sirviö et al., 1992), regulate LTP induction. It will be
fa et al., 1992; Wieraszko et al., 1993; Corradetti et al., 1992; Stanton and Sarvey, 1985; Sekino et al., 1991; Sirviö et al., 1992), regulate LTP induction. It will be fascinating to investigate whether any of these compou 1992; Stanton and Sarvey, 1985; Sekino et al., 1991;
Sirviö et al., 1992), regulate LTP induction. It will be
fascinating to investigate whether any of these com-
pounds also alter IEG expression in the same direction
as Sirviö et al., 1992), regulate LTP induction. It will be fascinating to investigate whether any of these compounds also alter IEG expression in the same direction as LTP processes. Noradrenaline facilitates LTP and learnin pounds also alter IEG expression in the same direction
as LTP processes. Noradrenaline facilitates LTP and
learning and induces Fos/Fras in the cortex (Bing et al.,
1992a) and in subcortical structures (Tsujino et al.,
199 pounds also alter IEG expression in the same direction (H
as LTP processes. Noradrenaline facilitates LTP and (H
learning and induces Fos/Fras in the cortex (Bing et al., ph
1992a) and in subcortical structures (Tsujino e as LTP processes. Noradrenaline facilitates LTP and
learning and induces Fos/Fras in the cortex (Bing et al.,
1992a) and in subcortical structures (Tsujino et al.,
1992). IEG expression may someday provide a rapid
method o learning and induces Fos/Fras in the cortex (Bing et al., 1992a) and in subcortical structures (Tsujino et al., 1992). IEG expression may someday provide a rapid of method of screening drugs with potential to influence le 1992a) and in subcortical structures (Tsujino et 1992). IEG expression may someday provide a ramethod of screening drugs with potential to influe
learning and memory. In this regard, a recent students shows that apamin, wh 1992). IEG expression may someday provide a rapid
method of screening drugs with potential to influence
learning and memory. In this regard, a recent study
shows that apamin, which blocks a class of calcium-
activated pota method of screening drugs with potential to influence
learning and memory. In this regard, a recent study
shows that apamin, which blocks a class of calcium-
activated potassium channels and which improves
learning, facili learning and memory. In this regard, a recent study
shows that apamin, which blocks a class of calcium-
activated potassium channels and which improves
learning, facilitates c-Fos and c-Jun expression in hip-
pocampus (Heu activated potassium channels and which improves
learning, facilitates c-Fos and c-Jun expression in hip-
pocampus (Heurteaux et al., 1993). These authors sug-
gested that this action of apamin on IEGs might account
for its activated potassium channels a
learning, facilitates c-Fos and c-Ju
pocampus (Heurteaux et al., 1993)
gested that this action of apamin or
for its memory-enhancing effects.
Tetanisation of pathways genera arning, facilitates c-Fos and c-Jun expression in hicampus (Heurteaux et al., 1993). These authors substed that this action of apamin on IEGs might accourt its memory-enhancing effects.
Tetanisation of pathways generating

Tetanisation of pathways generating LTP also generates LTD of synaptic transmission (Abraham and Goddard, 1983). Thus, expression of IEGs might be involved gested that this action of apamin on IEGs might account
for its memory-enhancing effects. The involved area ITD of synaptic transmission (Abraham and Goddard, 1983). Thus, expression of IEGs might be involved
in this proc for its memory-enhancing effects.
Tetanisation of pathways generating LTP also gener-
ates LTD of synaptic transmission (Abraham and God-
dard, 1983). Thus, expression of IEGs might be involved
in this process, although we Tetanisation of pathways generating LTP also generates LTD of synaptic transmission (Abraham and Goddard, 1983). Thus, expression of IEGs might be involved
in this process, although we have recently found in pre-
liminary ates LTD of synaptic transmission (Abraham and Goodard, 1983). Thus, expression of IEGs might be involve
in this process, although we have recently found in pr
liminary studies that, although blockers of L-type ca
cium cha dard, 1983). Thus, expression of IEGs might be involved
in this process, although we have recently found in pre-
liminary studies that, although blockers of L-type cal-
cium channels block LTD induction (Wickens and Abra-
 in this process, although we have recently found in pre-
liminary studies that, although blockers of L-type cal-
cium channels block LTD induction (Wickens and Abra-
ham, 1991), they do not affect IEG expression after stu liminary studies that, although blockers of L-type calcium channels block LTD induction (Wickens and Abra-
ham, 1991), they do not affect IEG expression after
tetanisation. Thus, IEGs are probably not involved in
LTD induc cium channels block LTD induction (Wickens and Abra-
ham, 1991), they do not affect IEG expression after st
tetanisation. Thus, IEGs are probably not involved in fe
LTD induction but could play a role in LTD persistence
(A ham, 1991), they do not affect IEG expression aftetanisation. Thus, IEGs are probably not involved LTD induction but could play a role in LTD persister (Abraham et al., 1994). A recent report suggests that F and Jun-B may tetanisation. Thus,
LTD induction but c
(Abraham et al., 1993).
zawa et al., 1993).
Studies on LTP a (Abraham et al., 1994). A recent report suggests that Fos
and Jun-B may be involved in cerebellar LTD (Naka-
zawa et al., 1993).
Studies on LTP as well as in many other paradigms
show that IEGs are induced in hippocampal a

(Abraham et al., 1994). A recent report suggests that F
and Jun-B may be involved in cerebellar LTD (Nak
zawa et al., 1993).
Studies on LTP as well as in many other paradig
show that IEGs are induced in hippocampal and neo and Jun-B may be involved in cerebellar LTD (Naka-
zawa et al., 1993).
Studies on LTP as well as in many other paradigms
show that IEGs are induced in hippocampal and neocor-
tical neurons via NMDA-receptor activation. How zawa et al., 1993). ces

Studies on LTP as well as in many other paradigms

show that IEGs are induced in hippocampal and neocor-

mical neurons via NMDA-receptor activation. However, sh

NMDA receptor antagonists, such as Studies on LTP as well as in many other paradigms
show that IEGs are induced in hippocampal and neocor-
tical neurons via NMDA-receptor activation. However,
NMDA receptor antagonists, such as MK801, which
block IEG inducti show that IEGs are induced in hippocampal and neocor-
tical neurons via NMDA-receptor activation. However, shows that theta rhythm induced by the muscarinic
NMDA receptor antagonists, such as MK801, which agonist carbachol

kinases, both of which are turned on by NMDA receptor with atropine (Hughes et al., 1993b). Other NMDA an-
activation in CA1 neurons, (Bading and Greenberg, tagonists, such as CGS19755, produce similar effects.
1991; Chetk 1993b). The pattern of IEG expression produced in the AND GENE EXPRESSION 159

1593b). The pattern of IEG expression produced in the

1993b). The pattern of IEG expression produced in the

neocortex by MK801 is similar to that produced by the neof The EXPRESSION

159

1993b). The pattern of IEG expression produced in the

1993b). The pattern of IEG expression produced in the

1993b). The pattern of IEG expression produced by the

1993b muscarinic agonist piloca muscaria muscariic and Faull, 1990; Hughes et al.
1993b). The pattern of IEG expression produced in the
neocortex by MK801 is similar to that produced by the
muscarinic agonist pilocarpine (Hughes and Dragunow
1993) and in thalamus (Dragunow and Faull, 1990; Hughes et al., 1993b). The pattern of IEG expression produced in the neocortex by MK801 is similar to that produced by the muscarinic agonist pilocarpine (Hughes and Dragunow, 1993) and 1993b). The pattern of IEG expression produced in the neocortex by MK801 is similar to that produced by the muscarinic agonist pilocarpine (Hughes and Dragunow, 1993) and induction in the neocortex can be prevented with at muscarinic agonist pilocarpine (Hughes and Dragunow, 1993) and induction in the neocortex can be prevented with atropine (Hughes et al., 1993b). Other NMDA antagonists, such as CGS19755, produce similar effects. muscarinic agonist pilocarpine (Hughes and Draguno
1993) and induction in the neocortex can be prevent
with atropine (Hughes et al., 1993b). Other NMDA
tagonists, such as CGS19755, produce similar effec
NMDA antagonists in 1993) and induction in the neocortex can be prevented
with atropine (Hughes et al., 1993b). Other NMDA an-
tagonists, such as CGS19755, produce similar effects.
NMDA antagonists interfere with learning tasks involv-
ing hi with atropine (Hughes et al., 1993b). Other NMDA antagonists, such as CGS19755, produce similar effects.
NMDA antagonists interfere with learning tasks involving hippocampal function (Ohno et al., 1992), and this
might be tagonists, such as CGS19755, produce similar effects.
NMDA antagonists interfere with learning tasks involving hippocampal function (Ohno et al., 1992), and this
might be caused by suppression of hippocampal IEG
expression NMDA antagonists interfere with learning tasks involving hippocampal function (Ohno et al., 1992), and this might be caused by suppression of hippocampal IEG expression. However, these drugs might be expected to have memor ing hippocampal function (Ohno et al., 1992), and this
might be caused by suppression of hippocampal IEG
expression. However, these drugs might be expected to
have memory-enhancing effects on learning involving
neocortical might be caused by suppression of hippocampal IEG
expression. However, these drugs might be expected to
have memory-enhancing effects on learning involving
neocortical regions. Although MK801 and pilocarpine
induce a simil expression. However, these drugs might be expected have memory-enhancing effects on learning involved neocortical regions. Although MK801 and pilocarpine induce a similar pattern of IEG expression in the neocrtex, only pil have memory-enhancing effects on learning involvine
ocortical regions. Although MK801 and pilocarpi
induce a similar pattern of IEG expression in the ne
cortex, only pilocarpine induces IEGs in the hippoca
pus (Hughes and neocortical regions. Although MK801 and pilocarpine
induce a similar pattern of IEG expression in the neo-
cortex, only pilocarpine induces IEGs in the hippocam-
pus (Hughes and Dragunow, 1994). Thus, in the neocor-
tex, m induce a similar pattern of IEG expression in the neo-
cortex, only pilocarpine induces IEGs in the hippocam-
pus (Hughes and Dragunow, 1994). Thus, in the neocor-
tex, muscarinic and NMDA receptors seem to be
negatively c cortex, only pilocarpine induces IEGs in the hippocam-
pus (Hughes and Dragunow, 1994). Thus, in the neocor-
tex, muscarinic and NMDA receptors seem to be
negatively coupled, whereas this is not the case in the
hippocampus pus (Hughes and Dragunow, 1994). Thus, in the neocortex, muscarinic and NMDA receptors seem to be negatively coupled, whereas this is not the case in the hippocampus. Indeed, in the hippocampus, muscarinic and NMDA recepto tex, muscarinic and NMDA receptors seem to be
negatively coupled, whereas this is not the case in the
hippocampus. Indeed, in the hippocampus, muscarinic
and NMDA receptors may be positively coupled
(Markram and Segal, 199 1993). Procampus. Indeed, in the hippocampus, muscarinic
2. IMDA receptors may be positively coupled
1931).
2. *Immediate-early gene proteins and the mnemonic*
2. *Immediate-early gene proteins and the mnemonic*
fects of acetyl

effects of acetylcholine: role of hippocampal theta
 effects of acetylcholine: role of hippocampal theta
 rhythm. Activation of muscarinic receptors in the brain
 effects of acetylcholine: role of hippocampal thet 1993).

2. Immediate-early gene proteins and the mnemonic

effects of acetylcholine: role of hippocampal theta

rhythm. Activation of muscarinic receptors in the brain

enhances learning and memory and facilitates LTP

(H 2. Immediate-early gene proteins and the mnemonic
effects of acetylcholine: role of hippocampal theta
rhythm. Activation of muscarinic receptors in the brain
enhances learning and memory and facilitates LTP
(Hughes and Dra effects of acetylcholine: role of hippocampal theta
rhythm. Activation of muscarinic receptors in the brain
enhances learning and memory and facilitates LTP
(Hughes and Dragunow, 1993). Muscarinic receptor ac-
tivation can rhythm. Activation of muscarinic receptors in the brain
enhances learning and memory and facilitates LTP
(Hughes and Dragunow, 1993). Muscarinic receptor ac-
tivation can also produce LTP in the cortex (Lin and
Phillis, 19 enhances learning and memory and facilitates LTP
(Hughes and Dragunow, 1993). Muscarinic receptor ac-
tivation can also produce LTP in the cortex (Lin and
Phillis, 1991). Recent studies have shown that activation
of centra (Hughes and Dragunow, 1993). Muscarinic receptor activation can also produce LTP in the cortex (Lin and Phillis, 1991). Recent studies have shown that activation of central pirenzepine-sensitive muscarinic receptors induce cortex, only pilocarpine induces IEGs in the hippocam-
pus (Hughes and Dragunow, 1994). Thus, in the necocricex, muscarinic and NMDA receptors seem to be
negatively coupled, whereas this is not the case in the
negatively c of central pirenzepine-sensitive muscarinic receptors inof central pirenzepine-sensitive muscarinic receptors in-
duces c-Fos (Hughes and Dragunow, 1993; Pombo-Villar
et al., 1992), Jun-B, Krox-20, and Krox-24 (Hughes and
Dragunow, 1994) in hippocampal (mainly CA1), limbic
syst duces c-Fos (Hughes and Dragunow, 1993; Pombo-Villar
et al., 1992), Jun-B, Krox-20, and Krox-24 (Hughes and
Dragunow, 1994) in hippocampal (mainly CA1), limbic
system, and neocortical neurons. This action on IEG
expression et al., 1992), Jun-B, Krox-20, and Krox-24 (Hughes and
Dragunow, 1994) in hippocampal (mainly CA1), limbic
system, and neocortical neurons. This action on IEG
expression in parts of the brain implicated in learning
and mem Dragunow, 1994) in hippocampal (mainly CA1), limbic
system, and neocortical neurons. This action on IEG
expression in parts of the brain implicated in learning
and memory suggests that the effects of muscarinic
drugs on LT expression in parts of the brain implicated in learning
and memory suggests that the effects of muscarinic
drugs on LTP, learning, and memory may be mediated
by IEG expression (Hughes and Dragunow, 1993).
Therefore, the ef and memory suggests that the effects of muscarinic and memory suggests that the enects of muscarinic
drugs on LTP, learning, and memory may be mediated
by IEG expression. (Hughes and Dragunow, 1993).
Therefore, the effects of tacrine to improve cognition in
Alzheimer's di by IEG expression (Hughes and Dragunow, 1993).
Therefore, the effects of tacrine to improve cognition in
Alzheimer's disease (Holford and Peace, 1992) may also
be mediated by IEG expression. Because muscarinic M_1
recep Therefore, the effects of tacrine to improve cognition in Alzheimer's disease (Holford and Peace, 1992) may also be mediated by IEG expression. Because muscarinic M_1 receptors are spared, whereas glutamate receptors ar Alzheimer's disease (Holford and Peace, 1992) may also
be mediated by IEG expression. Because muscarinic M₁
receptors are spared, whereas glutamate receptors are
lost, in the hippocampus of Alzheimer's patients (Jansen
 be mediated by IEG expression. Because muscarinic M
receptors are spared, whereas glutamate receptors are
lost, in the hippocampus of Alzheimer's patients (Janse
et al., 1990), the muscarinic M_1 receptor will remain an receptors are spared, whereas glutamate receptors are
lost, in the hippocampus of Alzheimer's patients (Jansen
et al., 1990), the muscarinic M_1 receptor will remain an
important target for anti-Alzheimer's drug develop lost, in the hippocampus of Alzheimet al., 1990), the muscarinic M_1 rectimportant target for anti-Alzheimer studies of the role of IEGs in M_1 -rects may be vital to these actions.
One important role for choliner al., 1990), the muscarinic M_1 receptor will remain an portant target for anti-Alzheimer's drug development;
udies of the role of IEGs in M_1 -receptor-mediated ef-
ts may be vital to these actions.
One important role

important target for anti-Alzheimer's drug development;
studies of the role of IEGs in M_1 -receptor-mediated ef-
fects may be vital to these actions.
One important role for cholinergic neurons in the
brain is to generat studies of the role of IEGs in M_1 -receptor-mediated effects may be vital to these actions.
One important role for cholinergic neurons in the brain is to generate hippocampal theta rhythm in the hippocampus, and this ma fects may be vital to these actions.

One important role for cholinergic neurons in the

brain is to generate hippocampal theta rhythm in the

hippocampus, and this may be involved in memory pro-

cessing (Huerta and Lisma One important role for cholinergic neurons in the
brain is to generate hippocampal theta rhythm in the
hippocampus, and this may be involved in memory pro-
cessing (Huerta and Lisman, 1993). Learning, arousal,
exploration, brain is to generate hippocampal theta rhythm in the
hippocampus, and this may be involved in memory pro-
cessing (Huerta and Lisman, 1993). Learning, arousal,
exploration, etc., induce hippocampal theta rhythm via
muscari hippocampus, and this may be involved in memory processing (Huerta and Lisman, 1993). Learning, arousal, exploration, etc., induce hippocampal theta rhythm via muscarinic receptor activation, and a recent study shows that exploration, etc., induce hippocampal theta rhythm via exploration, etc., induce hippocampal theta rhythm via
muscarinic receptor activation, and a recent study
shows that theta rhythm induced by the muscarinic
agonist carbachol induces synapses to a state of height-
ened plas muscarinic receptor activation, and a recent study
shows that theta rhythm induced by the muscarinic
agonist carbachol induces synapses to a state of height-
ened plasticity so that even weak stimulation will induce
LTP in

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may be the physiological mechanism whereby musca-

permaneter physiological mechanism whereby musca-

permaneter physiological mechanism whereby musca-

permaneter permaneter permaneter permaneter ringth act in the physiological mechanism whereby muscarinic activation facilitates and muscarinic antagonists
impair new learning and memory. Furthermore, this **incept 160**

imay be the physiological mechanism whereby musca-
 \overline{L}

impair new learning and memory. Furthermore, this

may account for the learning problems in patients with may be the physiological mechanism whereby musca-
rinic activation facilitates and muscarinic antagonists Dej
impair new learning and memory. Furthermore, this
may account for the learning problems in patients with
Alzhe rinic activation facilitates and muscarinic antagonists Dependence

impair new learning and memory. Furthermore, this

may account for the learning problems in patients with

Alzheimer's disease, who experience an early lo rinic activation facilitates and muscarinic antagonists
impair new learning and memory. Furthermore, this
may account for the learning problems in patients with
Alzheimer's disease, who experience an early loss of
choliner impair new learning and memory. Furthermore, this may account for the learning problems in patients with (M
Alzheimer's disease, who experience an early loss of CN
cholinergic systems (Hughes and Dragunow, 1993). Be-
caus may account for the learning problems in patients with
Alzheimer's disease, who experience an early loss of
cholinergic systems (Hughes and Dragunow, 1993). Be-
cause activation of muscarinic receptors induces both
hippoca Alzheimer's disease, who experience an early loss of
cholinergic systems (Hughes and Dragunow, 1993). Be-
cause activation of muscarinic receptors induces both
hippocampal theta rhythm and IEGs in CA1 neurons
induced the cholinergic systems (Hughes and Dragunow, 1993). Be-
cause activation of muscarinic receptors induces both III.E).
hippocampal theta rhythm and IEGs in CA1 neurons involve
(Hughes and Dragunow, 1993, 1994), the facilitator cause activation of muscarinic receptors induces both
hippocampal theta rhythm and IEGs in CA1 neurons
in (Hughes and Dragunow, 1993, 1994), the facilitatory
effects of cholinergically induced theta activity on new
learni hippocampal theta rhythm and IEGs in CA1 neurons
(Hughes and Dragunow, 1993, 1994), the facilitatory
effects of cholinergically induced theta activity on new
learning might be mediated by IEG expression. This
hypothesis wo (Hughes and Dragunow, 1993, 1994), the facilitato effects of cholinergically induced theta activity on nelearning might be mediated by IEG expression. The hypothesis would predict that other treatments that is duce hippoca learning might be mediated by IEG expression. This
hypothesis would predict that other treatments that in-
duce hippocampal theta (e.g., exploration, stress, learn-
ing, urethane anaesthesia) should also lead to IEG ex-
p hypothesis would predict that other treatments that in-
duce hippocampal theta (e.g., exploration, stress, learn-
ing, urethane anaesthesia) should also lead to IEG ex-
pression in an atropine-sensitive manner. Stress and
 duce hippocampal theta (e.g., exploration, stress, learning, urethane anaesthesia) should also lead to IEG expression in an atropine-sensitive manner. Stress and pexposure to a novel environment is known to be a potent in mg, urenanc anacsuresha) should also icad to fire car-
pression in an atropine-sensitive manner. Stress and
inducer of IEGs in the hippocampus and neocortex
(Schreiber et al., 1991b; Handa et al., 1993; Papa et al.,
1993; exposure to a novel environment is known to be a potent
inducer of IEGs in the hippocampus and neocortex
(Schreiber et al., 1991b; Handa et al., 1993; Papa et al.,
1993; Kinney and Routtenberg, 1993), supporting this
hypot inducer of IEGs in the hippot(Schreiber et al., 1991b; Handa (1993; Kinney and Routtenberg, hypothesis. It will be important IEG induction is atropine-sensit 3. Behavioural learning and chreiber et al., 1991b; Handa et al., 1993; Papa et al., 193; Kinney and Routtenberg, 1993), supporting this pothesis. It will be important to determine whether G induction is atropine-sensitive.
3. *Behavioural learning a*

1993; Kinney and Routtenberg, 1993), supporting this close
hypothesis. It will be important to determine whether adr
IEG induction is atropine-sensitive.
3. Behavioural learning and immediate-early genes.
As reviewed prev hypothesis. It will be important to determine whether

IEG induction is atropine-sensitive.

3. Behavioural learning and immediate-early genes.

As reviewed previously, a number of studies have shown

that c-Fos is induced IEG induction is atropine-sensitive.
3. Behavioural learning and immediate-early genes.
As reviewed previously, a number of studies have shown
that c-Fos is induced in situations where an animal is
learning a behavioural t that c-Fos is induced in situations where an animal is
learning a behavioural task. It has yet to be definitively
demonstrated, however, that the c-fos expression is
causally related to learning. Furthermore, as suggested, that c-Fos is induced in situations where an animal is
learning a behavioural task. It has yet to be definitively (K
demonstrated, however, that the c-fos expression is NI
causally related to learning. Furthermore, as sugg demonstrated, however, that the c-fos expression is Networks, however, that the c-fos expression is Networks and the caused by stress and/or the arousal state of the animal (Nikolaev et al., 1992a, b). As discussed in cau demonstrated, however, that the c-fos expression is NM
causally related to learning. Furthermore, as suggested, and
learning-induced increases in Fos expression in the tion
brain might be caused by stress and/or the arousa learning-induced increases in Fos expression in the tibrain might be caused by stress and/or the arousal state P-
of the animal (Nikolaev et al., 1992a, b). As discussed in cate
the previous section, stress/arousal may ind brain might be caused by stress and/or the arousal state
of the animal (Nikolaev et al., 1992a, b). As discussed in
the previous section, stress/arousal may induce IEGs via
cholinergically mediated theta activation. The ro in learning processes. **Change 12 In Fourning and Internety presences as presently inclear, however, they are likely to serve important roles**
in learning processes.
C. Immediate-early Gene Proteins as Transducers of
Stress into Psychopatholo

Stress into Processes.
Stress into Psychopathology
It was suggested in a requ

Immediate-early Gene Proteins as Transducers of
ress into Psychopathology
It was suggested in a recent review that sensitisation
psychosocial stressors may be encoded at the level of C. Immediate-early Gene Proteins as Transducers of $\frac{1}{w}$
Stress into Psychopathology
It was suggested in a recent review that sensitisation $\frac{1}{w}$
to psychosocial stressors may be encoded at the level of be
gene ex gene expression and that IEGPs may play a role in this difference of the psychopathology
that sensitisation with psychosocial stressors may be encoded at the level of began expression and that IEGPs may play a role in thi It was suggested in a recent review that sensitisation where the psychosocial stressors may be encoded at the level of begene expression and that IEGPs may play a role in this (H) process (Post, 1992). Eventually, these ge to psychosocial stressors may be encoded at the level of gene expression and that IEGPs may play a role in thi
process (Post, 1992). Eventually, these genetically encoded stressful events may manifest themselves in the
for gene expression and that IEGPs may play a role in this (Heilig et al., 1993). Whether it also blocks the reward-
process (Post, 1992). Eventually, these genetically en-
coded stressful events may manifest themselves in the process (Post, 1992). Eventually, these genetically
coded stressful events may manifest themselves in
form of a major affective disorder. One important t
apeutic implication of this hypothesis is that there
be a justificat coded stressful events may manifest themselves in the form of a major affective disorder. One important ther-
apeutic implication of this hypothesis is that there may
be a justification for the prophylactic use of antidepr form of a major affective disorder. One important therapeutic implication of this hypothesis is that there may
be a justification for the prophylactic use of antidepressant drugs to prevent this sensitisation phenomenon
(P apeutic implication of this hypothesis is that there may
be a justification for the prophylactic use of antidepres-
sant drugs to prevent this sensitisation phenomenon
(Post, 1992). A number of studies show that stress insant drugs to prevent this sensitisation phenomenon (Post, 1992). A number of studies show that stress induces IEGPs in brain neurons (Post, 1992; Deutch et al., 1991). This intriguing hypothesis must await experimental ve sant drugs to prevent this sensitisation phenomenon er
(Post, 1992). A number of studies show that stress in-
duces IEGPs in brain neurons (Post, 1992; Deutch et al., 19
1991). This intriguing hypothesis must await experi-(Post, 1992). A number of studies show that stress induces IEGPs in brain neurons (Post, 1992; Deutch et al., 1991). This intriguing hypothesis must await experimental verification. Furthermore, it might be argued that bec 1991). This intriguing hypothesis must await experimental verification. Furthermore, it might be argued that because seizures induce IEGPs (Dragunow et al., 1992), the therapeutic effects of electroconvulsive ther-1991). This intriguing hypothesis must await experimental verification. Furthermore, it might be argued that because seizures induce IEGPs (Dragunow et al., 1992), the therapeutic effects of electroconvulsive therapy might mental verification. Furthermore, it might be antidate that because seizures induce IEGPs (Dragunow of 1992), the therapeutic effects of electroconvulsive apy might be mediated through this action. Thus, I
might be antidep

D. Role oflmmediate-early Gene Proteins in Drug Dependence

Framing might be mediated by IEG expression. This ing schedule, repeated administration of stimulants hypothesis would predict that other treatments that in-
duce hippocampal theta (e.g., exploration, stress, learn-
ing, A number of drugs of abuse, such as morphine, ecstasy D. Role of Immediate-early Gene Proteins in Drug
Dependence
A number of drugs of abuse, such as morphine, ecstasy
(MDMA), amphetamine, and cocaine, induce IEGPs in
CNS neurons, principally the striatum, but also cortical Dependence

A number of drugs of abuse, such as morphine, ecstasy

(MDMA), amphetamine, and cocaine, induce IEGPs in

CNS neurons, principally the striatum, but also cortical

regions (see references in section on dopamine *A* number of drugs of abuse, such as morphine, ecstasy (MDMA), amphetamine, and cocaine, induce IEGPs in CNS neurons, principally the striatum, but also cortical regions (see references in section on dopamine receptors, I A number of drugs of abuse, such as morphine, ecstasy
(MDMA), amphetamine, and cocaine, induce IEGPs in
CNS neurons, principally the striatum, but also cortical
regions (see references in section on dopamine receptors,
III (MDMA), amphetamine, and cocaine, induce IEGPs in
CNS neurons, principally the striatum, but also cortical
regions (see references in section on dopamine receptors,
III.E). It has been suggested that this action may be
inv CNS neurons, principally the striatum, but also cortical
regions (see references in section on dopamine receptors,
III.E). It has been suggested that this action may be
involved in the dependence-inducing properties of the regions (see references in section on dopamine receptors,
III.E). It has been suggested that this action may be
involved in the dependence-inducing properties of these
drugs (for reviews see Nestler, 1992 and Mackler and
E involved in the dependence-inducing properties of these drugs (for reviews see Nestler, 1992 and Mackler and Eberwine, 1992). In particular, depending upon the dosinvolved in the dependence-inducing properties of these
drugs (for reviews see Nestler, 1992 and Mackler and
Eberwine, 1992). In particular, depending upon the dos
ing schedule, repeated administration of stimulant
such as drugs (for reviews see Nestler, 1992 and Mackler and Eberwine, 1992). In particular, depending upon the dosing schedule, repeated administration of stimulants such as amphetamine can lead to either behavioural tolerance or Eberwine, 1992). In particular, depending upon the dosing schedule, repeated administration of stimulants such as amphetamine can lead to either behavioural tolerance or sensitisation (Post, 1980). Normally, drugs such as ing schedule, repeated administration of stimulants
such as amphetamine can lead to either behavioural
tolerance or sensitisation (Post, 1980). Normally, drugs
such as cocaine and amphetamine, which augment do-
paminergic such as amphetamine can lead to either behavioural
tolerance or sensitisation (Post, 1980). Normally, drugs
such as cocaine and amphetamine, which augment do-
paminergic transmission, would be expected to decrease
neuroche tolerance or sensitisation (Post, 1980). Normally, drugs
such as cocaine and amphetamine, which augment do-
paminergic transmission, would be expected to decrease
neurochemical and behavioural sensitivity; indeed, be-
havi such as cocaine and amphetamine, which augment do-
paminergic transmission, would be expected to decrease
neurochemical and behavioural sensitivity; indeed, be-
havioural (Post, 1980) and biochemical (Hope et al.,
1992) to panniergic transmission, would be expected to decrease
neurochemical and behavioural sensitivity; indeed, be-
havioural (Post, 1980) and biochemical (Hope et al.,
1992) tolerance occurs with drug administration at
closely havioural (Post, 1980) and bioch
1992) tolerance occurs with dru
closely spaced intervals. Howeven
administered at longer intertrial is
sensitisation occurs (Post, 1980).
Recently, it has been shown that closely spaced intervals. However, if these drugs are
administered at longer intertrial intervals, behavioural
sensitisation occurs (Post, 1980).
Recently, it has been shown that the behavioural sen-

As reviewed previously, a number of studies have shown sitisation to cocaine, methamphetamine, and amphet-
that c-Fos is induced in situations where an animal is amine can be blocked by inhibitors of protein synthesis
lear learning-induced increases in Fos expression in the tion is produced by NMDA-receptor-activated genes.

brain might be caused by stress and/or the arousal state Previous studies have shown that c-Fos induction in

of the a the previous section, stress/arousal may induce IEGs via NMDA-receptor mediated (Torres and Rivier, 1993; Dracholinergically mediated theta activation. The role of gunow et al., 1991b). These results suggest that IEGPs IEG closely spaced intervals. However, if these drugs
administered at longer intertrial intervals, behaviou
sensitisation occurs (Post, 1980).
Recently, it has been shown that the behavioural s
sitisation to cocaine, methamphe administered at longer intertrial intervals, behavioural
sensitisation occurs (Post, 1980).
Recently, it has been shown that the behavioural sen-
sitisation to cocaine, methamphetamine, and amphet-
amine can be blocked by sensitisation occurs (Post, 1980).

Recently, it has been shown that the behavioural sensitisation to cocaine, methamphetamine, and amphetamine can be blocked by inhibitors of protein synthesis

(Karler et al., 1993; Shimo Recently, it has been shown that the behavioural sensitisation to cocaine, methamphetamine, and amphetamine can be blocked by inhibitors of protein synthesis (Karler et al., 1993; Shimosato and Saito, 1993) and by NMDA rec (Karler et al., 1993; Shimosato and Saito, 1993) and by amine can be blocked by inhibitors of protein synthesis (Karler et al., 1993; Shimosato and Saito, 1993) and by NMDA receptor antagonists (Karler et al., 1989; Wolf and Jeziorski, 1993). This suggests that the sensitisatio (Karler et al., 1993; Shimosato and Saito, 1993) and by

NMDA receptor antagonists (Karler et al., 1989; Wolf

and Jeziorski, 1993). This suggests that the sensitisa-

tion is produced by NMDA-receptor-activated genes.

Pr NMDA receptor antagonists (Karler et al., 1989; Wolf
and Jeziorski, 1993). This suggests that the sensitisa-
tion is produced by NMDA-receptor-activated genes.
Previous studies have shown that c-Fos induction in
caudate ne and Jeziorski, 1993). This suggests that the sensitisation is produced by NMDA-receptor-activated genes
Previous studies have shown that c-Fos induction in
caudate neurons by cocaine or ecstasy (MDMA) is
NMDA-receptor medi tion is produced by NMDA-receptor-activated genes.
Previous studies have shown that c-Fos induction in
caudate neurons by cocaine or ecstasy (MDMA) is
NMDA-receptor mediated (Torres and Rivier, 1993; Dra-
gunow et al., 199 Previous studies have shown that c-Fos induction is
caudate neurons by cocaine or ecstasy (MDMA) is
NMDA-receptor mediated (Torres and Rivier, 1993; Dragunow et al., 1991b). These results suggest that IEGP
may be involved caudate neurons by cocaine or ecstasy (MDMA) is
NMDA-receptor mediated (Torres and Rivier, 1993; Dragunow et al., 1991b). These results suggest that IEGPs
may be involved in the behavioural sensitisation to stim-
ulant dru NMDA-receptor mediated (Torres and Rivier, 1993; Digunow et al., 1991b). These results suggest that IEG may be involved in the behavioural sensitisation to still ulant drugs. Evidence for this hypothesis is provided result gunow et al., 1991b). These results suggest that IEGPs
may be involved in the behavioural sensitisation to stim-
ulant drugs. Evidence for this hypothesis is provided by
results that show that amphetamine induces signifi-
 may be involved in the behavioural sensitisation to stim-
ulant drugs. Evidence for this hypothesis is provided by
results that show that amphetamine induces signifi-
cantly greater expression of c-Fos in the striatum of r ulant drugs. Evidence for this hypothesis is provided by
results that show that amphetamine induces signifi-
cantly greater expression of c-Fos in the striatum of rats
injected 3 days previously with amphetamine compared
w cantly greater expression of c-Fos in the striatum of rats
injected 3 days previously with amphetamine compared
with saline-pretreated rats (Norman et al., 1993). Fur-
thermore, a recent study shows that c-fos antisense, cantly greater expression of c-Fos in the striatum of rainjected 3 days previously with amphetamine compare with saline-pretreated rats (Norman et al., 1993). Futhermore, a recent study shows that c-fos antisens which prev injected 3 days previously with amphetamine compared
with saline-pretreated rats (Norman et al., 1993). Fur-
thermore, a recent study shows that c-fos antisense,
which prevents c-fos induction in the nucleus accum-
bens, b with saline-pretreated rats (Norman et al., 1993). F
thermore, a recent study shows that c-fos antisen
which prevents c-fos induction in the nucleus accu
bens, blocks the locomotor stimulant action of coca
(Heilig et al., thermore, a recent study shows that c-fos antises
which prevents c-fos induction in the nucleus acc
bens, blocks the locomotor stimulant action of coca
(Heilig et al., 1993). Whether it also blocks the rews
ing effects of which prevents c-fos induction in the nucleus accum-
bens, blocks the locomotor stimulant action of cocaine
(Heilig et al., 1993). Whether it also blocks the reward-
ing effects of cocaine is unclear. Similarly, the sensit bens, blocks the locomotor stimulant action of cocaine (Heilig et al., 1993). Whether it also blocks the reward-
ing effects of cocaine is unclear. Similarly, the sensitisa-
tion to amphetamine, which might be involved in tion to amphetamine, which might be involved in amg effects of cocaine is unclear. Similarly, the sensitisa-
on to amphetamine, which might be involved in am-
netamine-induced psychosis, might be mediated at the
ne level by the IEGPs.
A recent study has shown that morphin

tion to amphetamine, which might be involved in am-
phetamine-induced psychosis, might be mediated at the
gene level by the IEGPs.
A recent study has shown that morphine-induced tol-
erance and dependence can be inhibited phetamine-induced psychosis, might be mediated at the
gene level by the IEGPs.
A recent study has shown that morphine-induced tol-
erance and dependence can be inhibited by the NMDA
antagonist MK801 (Trujillo and Akil, 199 gene level by the IEGPs.

A recent study has shown that morphine-induced

erance and dependence can be inhibited by the NM

antagonist MK801 (Trujillo and Akil, 1991; Marek et

1990) and by a nitric oxide synthase inhibito A recent study has shown that morphine-induced tolerance and dependence can be inhibited by the NMDA antagonist MK801 (Trujillo and Akil, 1991; Marek et al., 1990) and by a nitric oxide synthase inhibitor (Kolesnikov et al erance and dependence can be inhibited by the NMDA
antagonist MK801 (Trujillo and Akil, 1991; Marek et al.,
1990) and by a nitric oxide synthase inhibitor (Kolesni-
kov et al., 1992). Because MK801 potentiates the re-
ward antagonist MK801 (Trujillo and Akil, 1991; Marek et al., 1990) and by a nitric oxide synthase inhibitor (Kolesni-
kov et al., 1992). Because MK801 potentiates the re-
warding effects of morphine (Carlezon and Wise, 1993),
 1990) and by a nitric oxide synthase inhibitor (Kolesni-
kov et al., 1992). Because MK801 potentiates the re-
warding effects of morphine (Carlezon and Wise, 1993),
this action of MK801 on morphine-induced dependence
canno kov et al., 1992). Because MK801 potentiates the re-
warding effects of morphine (Carlezon and Wise, 1993),
this action of MK801 on morphine-induced dependence
cannot be caused by block of the rewarding effects of
morphine warding effects of morphine (Carlezon and Wise, 1993),
this action of MK801 on morphine-induced dependence
cannot be caused by block of the rewarding effects of
morphine. Morphine induces c-Fos in the striatum and
other br

PHARMACOLOGICAL REVIEWS

IMMEDIATE-EARLY GENES
1992), and this action is inhibited by MK801 (Krylova et
al., 1992), suggesting that morphine tolerance and de-IMMEDIATE-EARLY GENE
1992), and this action is inhibited by MK801 (Krylova et
al., 1992), suggesting that morphine tolerance and de-
pendence may involve an NMDA receptor-activated Fos mMEDIATE-EARLY GENES ALLET CHARRENT CENTER AND MEDIATE-EARLY GENES AN ALL., 1992), suggesting that morphine tolerance and dependence may involve an NMDA receptor-activated Fos Inexpression. expression.

pendence may involve an NMDA receptor-activated Fos
expression.
IEGPs may also be involved in the chronic effects of
opiates in the LC (Nestler, 1992). Acutely, opiates de-
crease the firing of LC neurons and inhibit adeny pendence may involve an NMDA receptor-activated Fos
expression.
IEGPs may also be involved in the chronic effects of
opiates in the LC (Nestler, 1992). Acutely, opiates de-
crease the firing of LC neurons and inhibit adeny expression.
IEGPs may also be involved in the chronic effects of
opiates in the LC (Nestler, 1992). Acutely, opiates de-
crease the firing of LC neurons and inhibit adenylate
cyclase. However, chronic administration of opi IEGPs may also be involved in the chronic effects of
opiates in the LC (Nestler, 1992). Acutely, opiates de-
crease the firing of LC neurons and inhibit adenylate
cyclase. However, chronic administration of opiates pro-
du opiates in the LC (Nestler, 1992). Acutely, opiates de-
crease the firing of LC neurons and inhibit adenylate
cyclase. However, chronic administration of opiates pro-
duces tolerance to the inhibitory action on LC neurons, duces tolerance to the inhibitory action on LC neurons,
an upregulation of the cAMP system, and an increase in cyclase. However, chronic administration of opiates produces tolerance to the inhibitory action on LC neurons, an upregulation of the cAMP system, and an increase in tyrosine hydroxylase (Nestler, 1992). Opiate withdrawal tyrosine hydroxylase (Nestler, 1992). Opiate withdrawal
leads to overactivity of LC neurons, suggesting that
these effects on the LC may be involved in opiate with-
drawal and dependence.
Recent studies have implicated the drawal and dependence. rosine hydroxylase (Nestler, 1992). Opiate withdrawal
ads to overactivity of LC neurons, suggesting that
ese effects on the LC may be involved in opiate with-
awal and dependence.
Recent studies have implicated the IEGPs i

these effects on the LC may be involved in opiate with-
drawal and dependence.
Recent studies have implicated the IEGPs in the mo-
lecular mechanism by which chronic opiates up-regulate
the cAMP system in LC neurons (Haywa Nestler, 1992). Opiate withdrawal after chronic treatdrawal and dependence.
Recent studies have implicated the IEGPs in the m
lecular mechanism by which chronic opiates up-regulat
the cAMP system in LC neurons (Hayward et al., 199
Nestler, 1992). Opiate withdrawal after chro Recent studies have implicated the IEGPs in the mo-
lecular mechanism by which chronic opiates up-regulate
the cAMP system in LC neurons (Hayward et al., 1990;
Nestler, 1992). Opiate withdrawal after chronic treat-
ment in lecular mechanism by which chronic opiates up-regulate
the cAMP system in LC neurons (Hayward et al., 1990)
Nestler, 1992). Opiate withdrawal after chronic treat
ment induces c-fos in the LC in rats (Hayward et al.
1990). the cAMP system in LC neurons (Hayward et al., 19
Nestler, 1992). Opiate withdrawal after chronic tre
ment induces c-fos in the LC in rats (Hayward et a
1990). Morphine withdrawal responses of rat LC no
rons can be blocked Nestler, 1992). Opiate withdrawal after chronic treat-
ment induces c-fos in the LC in rats (Hayward et al., per
1990). Morphine withdrawal responses of rat LC neu-
rons can be blocked by excitatory amino-acid antago-
mist ment induces c-fos in the LC in rats (Hayward et al., perhaps c-Fos induction is part of the cascade that me-
1990). Morphine withdrawal responses of rat LC neu-
rons can be blocked by excitatory amino-acid antago-
mists 1990). Morphine withdrawal responses of rat LC neu-
rons can be blocked by excitatory amino-acid antago-
nists (Tung et al., 1990), and it will be interesting to see
what effects these drugs have on Fos expression in LC
ne diated by CREB-like TFs (Guitart et al., 1992).
Another aspect of the effects of drugs, such as cocaine sts (Tung et al., 1990), and it will be interesting to see
hat effects these drugs have on Fos expression in LC
rurons. These effects of opiates on IEGPs may be me-
ated by CREB-like TFs (Guitart et al., 1992).
Another asp

what effects these drugs have on Fos expression in LC ER neurons. These effects of opiates on IEGPs may be me-
diated by CREB-like TFs (Guitart et al., 1992). close and morphine, that relates to drug dependence is the pre diated by CREB-like TFs (Guitart et al., 1992).

Another aspect of the effects of drugs, such as cocaine

and morphine, that relates to drug dependence is the

classical conditioning of their behavioural effects with

spec Another aspect of the effects of drugs, such as cocaine
and morphine, that relates to drug dependence is the
classical conditioning of their behavioural effects with
specific environmental stimuli, leading to conditioned
c and morphine, that relates to drug dependence is the classical conditioning of their behavioural effects with specific environmental stimuli, leading to conditioned cravings. This action of these drugs is of major clinical classical conditioning of their behavioural effects with
specific environmental stimuli, leading to conditioned
cravings. This action of these drugs is of major clinical
significance, because it can result in abstinent ab specific environmental stimuli, leading to conditioned generavings. This action of these drugs is of major clinical his significance, because it can result in abstinent abusers E resuming drug use (Brown et al., 1992). In cravings. This action of these drugs is of major clinical hals ignificance, because it can result in abstinent abusers EP resuming drug use (Brown et al., 1992). Induction of the IEGPs in the brain by drugs of abuse might significance, because it can result in abstinent abusers
resuming drug use (Brown et al., 1992). Induction of
IEGPs in the brain by drugs of abuse might be involved
in this classical conditioning via their role in LTP and
 suming drug use (Brown et al., 1992). Induction of the GPs in the brain by drugs of abuse might be involved here this classical conditioning via their role in LTP and parming phenomena (see sections V and VI). Phencyclidi IEGPs in the brain by drugs of abuse might be involved has
in this classical conditioning via their role in LTP and pron
learning phenomena (see sections V and VI). pyr:
Phencyclidine, ketamine, and MK801 also induce
IEGP

in this classical conditioning via their role in LTP and
learning phenomena (see sections V and VI).
Phencyclidine, ketamine, and MK801 also induce
IEGPs in neocortical and thalamic neurons (Dragunow
and Faull, 1990; Sharp 1993b; Gass et al., 1993), although this action may be the Thencyclidine, ketamine, and MK801 also induce IEGPs in neocortical and thalamic neurons (Dragunow and Faull, 1990; Sharp et al., 1991a; Hughes et al., 1993b; Gas Phencyclidine, ketamine, and MK801 also induce IEGPs in neocortical and thalamic neurons (Dragunow and Faull, 1990; Sharp et al., 1991a; Hughes et al., 1993b; Gass et al., 1993), although this action may be more involved IEGPs in neocortical and thalamic neurons (Dragunow
and Faull, 1990; Sharp et al., 1991a; Hughes et al., $F.$ I
1993b; Gass et al., 1993), although this action may be
more involved in the psychotomimetic effects of these and Faull, 1990; Sharp et al., 1991a; Hughes et al., P
1993b; Gass et al., 1993), although this action may be
more involved in the psychotomimetic effects of these
drugs, rather than to their abuse potential (Dragunow
a 1993b; Gass et al., 1993), although this action may be more involved in the psychotomimetic effects of these drugs, rather than to their abuse potential (Dragunow and Faull, 1990). Indeed, phencyclidine and related drugs c more involved in the psychotomimetic effects of these
drugs, rather than to their abuse potential (Dragunow nand Faull, 1990). Indeed, phencyclidine and related et
drugs can produce a prolonged psychosis in normal hu-
mans drugs, rather than to their abuse potential (Dragunow net and Faull, 1990). Indeed, phencyclidine and related et drugs can produce a prolonged psychosis in normal humans and can greatly exacerbate the symptoms of an schizo and Faull, 1990). Indeed, phencyclidine and related et a drugs can produce a prolonged psychosis in normal humans and can greatly exacerbate the symptoms of an schizophrenia in schizophrenics (Snyder, 1980), and we suggec drugs can produce a prolonged psychosis in normal humans and can greatly exacerbate the symptoms of also schizophrenia in schizophrenics (Snyder, 1980), and we superculate that perhaps the induction of IEGs in deep tile la mans and car
schizophrenia is
peculate that
layers of the ne
in this action.
Clearly, IEG speculate that perhaps the induction of IEGs in deep

layers of the neocortex and in the thalamus is involved in this action.
Clearly, IEGPs are very important molecules in that
action of drugs of abuse. This area of research promit
to provide major insights into the molecula in this action.
Clearly, IEGPs are very important n
action of drugs of abuse. This area of rea
to provide major insights into the monisms of drug tolerance/sensitisation/de action of drugs of abuse. This area of research prom
to provide major insights into the molecular me
nisms of drug tolerance/sensitisation/dependence.
E. C-Fos as a Regulator of Basal Ganglia Motor
Function

Function

Simum of drug tolerance/sensitisation/dependence.

C-Fos as a Regulator of Basal Ganglia Motor

unction

As reviewed previously in the section on dopamine

ceptors (section III.E.), IEGPs are induced in striatal E. C-Fos as a Regulator of Basal Ganglia Motor
Function
As reviewed previously in the section on dopamine
receptors (section III.E.), IEGPs are induced in striatal

1992), and this action is inhibited by MK801 (Krylova et neurons by direct-acting agonists on supersensitive D_1 -
al., 1992), suggesting that morphine tolerance and de-
pendence may involve an NMDA receptor-activated Fo AND GENE EXPRESSION 161
neurons by direct-acting agonists on supersensitive D_1 -
receptors and by indirect agonists on intact receptors. AND GENE EXPRESSION 161
neurons by direct-acting agonists on supersensitive D_1 -
receptors and by indirect agonists on intact receptors.
Induction of c-Fos in dopamine-depleted striatum does AND GENE EXPRESSION 161
neurons by direct-acting agonists on supersensitive D_1 -
receptors and by indirect agonists on intact receptors.
Induction of c-Fos in dopamine-depleted striatum does
not require any turning resp neurons by direct-acting agonists on supersensitive D_1 -
receptors and by indirect agonists on intact receptors.
Induction of c-Fos in dopamine-depleted striatum does
not require any turning responses. However, a recent neurons by direct-acting agonists on supersensitive D_1 -
receptors and by indirect agonists on intact receptors.
Induction of c-Fos in dopamine-depleted striatum does
not require any turning responses. However, a recent receptors and by indirect agonists on intact recepto
Induction of c-Fos in dopamine-depleted striatum do
not require any turning responses. However, a rece
study has shown that c-fos antisense DNA injected in
the nucleus a Induction of c-Fos in dopamine-depleted striatum does
not require any turning responses. However, a recent
study has shown that c-fos antisense DNA injected into
the nucleus accumbens can block the locomotor stimu-
lant ac not require any turning responses. However, a recent
study has shown that c-fos antisense DNA injected into
the nucleus accumbens can block the locomotor stimu-
lant action of cocaine (Heilig et al., 1993). We have found
t study has shown that c-fos antisense DNA injected
the nucleus accumbens can block the locomotor s
lant action of cocaine (Heilig et al., 1993). We have if
that injection of c-fos antisense and sense DNA
opposing striata le the nucleus accumbens can block the locomotor stimu
lant action of cocaine (Heilig et al., 1993). We have found
that injection of c-*fos* antisense and sense DNA into
opposing striata leads 10 hours later to apomorphine
an lant action of cocaine (Heilig et al., 1993). We have found that injection of c-*fos* antisense and sense DNA into opposing striata leads 10 hours later to apomorphine-
and amphetamine-induced turning toward the antisensethat injection of c-*fos* antisense and sense DNA intopposing striata leads 10 hours later to apomorphine
and amphetamine-induced turning toward the ant
sense-injected side of the brain (Dragunow et al., 1993b
Others have opposing striata leads 10 hours later to apomorphine-
and amphetamine-induced turning toward the anti-
sense-injected side of the brain (Dragunow et al., 1993b).
Others have also recently shown amphetamine-induced
turning and amphetamine-induced turning toward the anti-
sense-injected side of the brain (Dragunow et al., 1993b).
Others have also recently shown amphetamine-induced
turning toward the c-fos antisense side after striatal
injecti sense-injected side of the brain (Dragunow et al., 1993b).
Others have also recently shown amphetamine-induced
turning toward the c-fos antisense side after striatal
injection (Sommer et al., 1993). These results suggest
t Others have also recently shown amphetamine-induced
turning toward the c-*fos* antisense side after striatal
injection (Sommer et al., 1993). These results suggest
that c-Fos regulates a gene in the striatum that is im-
p turning toward the c-fos antisense side after striatal
injection (Sommer et al., 1993). These results suggest
that c-Fos regulates a gene in the striatum that is im-
portant for the actions of direct- and indirect-acting injection (Sommer et al., 1993). These results suggest
that c-Fos regulates a gene in the striatum that is im-
portant for the actions of direct- and indirect-acting do-
pamine agonists, perhaps the D_1 - or D_2 -recept that c-Fos regulates a gene in the striatum that is important for the actions of direct- and indirect-acting do-
pamine agonists, perhaps the D_1 - or D_2 -receptor, or for a
neuropeptide such as dynorphin (Lucas et al. portant for the actions of direct- and indirect-acting do-
pamine agonists, perhaps the D_1 - or D_2 -receptor, or for a
neuropeptide such as dynorphin (Lucas et al., 1993)—or
perhaps c-Fos induction is part of the casc neuropeptide such as dynorphin (Lucas et al., 1993)—or uropeptide such as dynorphin (Lucas et al., 1993)—or
rhaps c-Fos induction is part of the cascade that me-
ates D_1 -receptor-mediated motor activity, probably a
ngenetic effect because of its rapid onset.
Antipsychoti

diated by CREB-like TF's (Guitart et al., 1992). clozapine, a neuroleptic that does not produce EPSs,
Another aspect of the effects of drugs, such as cocaine does not induce c-Fos (MacGibbon et al., 1994). Thus, the
and mo perhaps c-Fos induction is part of the cascade that me-
diates D_1 -receptor-mediated motor activity, probably a
nongenetic effect because of its rapid onset.
Antipsychotic drugs, such as haloperidol, that produce
EPSs diates D_1 -receptor-mediated motor activity, probably a
nongenetic effect because of its rapid onset.
Antipsychotic drugs, such as haloperidol, that produce
EPSs, induce c-Fos and Jun-B (as well as Jun-D and
Krox-24) in nongenetic effect because of its rapid onset.

Antipsychotic drugs, such as haloperidol, that produce

EPSs, induce c-Fos and Jun-B (as well as Jun-D and

Krox-24) in striatal pallidal-projecting neurons, whereas

clozapin Antipsychotic drugs, such as haloperidol, that produce EPSs, induce c-Fos and Jun-B (as well as Jun-D and Krox-24) in striatal pallidal-projecting neurons, whereas clozapine, a neuroleptic that does not produce EPSs, does EPSs, induce c-Fos and Jun-B (as well as Jun-D and
Krox-24) in striatal pallidal-projecting neurons, whereas
clozapine, a neuroleptic that does not produce EPSs,
does not induce c-Fos (MacGibbon et al., 1994). Thus, the
pr Krox-24) in striatal pallidal-projecting neurons, whereas
clozapine, a neuroleptic that does not produce EPSs,
does not induce c-Fos (MacGibbon et al., 1994). Thus, the
production of Fos/Jun-B dimers by haloperidol may ini clozapine, a neuroleptic that does not produce EPSs,
does not induce c-Fos (MacGibbon et al., 1994). Thus, the
production of Fos/Jun-B dimers by haloperidol may ini-
tiate long-lasting changes in gene expression that could does not induce c-Fos (MacGibbon et al., 1994). Thus, the
production of Fos/Jun-B dimers by haloperidol may ini-
tiate long-lasting changes in gene expression that could
generate the EPSs. It will be interesting to test wh production of Fos/Jun-B dimers by haloperidol may
tiate long-lasting changes in gene expression that c
generate the EPSs. It will be interesting to test whe
haloperidol-induced behavioural sensitivity, a mod
EPSs in rats (tiate long-lasting changes in gene expression that could
generate the EPSs. It will be interesting to test whether
haloperidol-induced behavioural sensitivity, a model of
EPSs in rats (Marin and Chase, 1993), is protein-sy generate the EPSs. It will be interesting to test whether
haloperidol-induced behavioural sensitivity, a model of
EPSs in rats (Marin and Chase, 1993), is protein-syn-
thesis-dependent and what effects c-fos antisense DNA
 haloperidol-induced behavioural sensitivity, a model
EPSs in rats (Marin and Chase, 1993), is protein-sy
thesis-dependent and what effects c-fos antisense DN
has on this process. Fos expression in striatal neuro
promises t EPSs in rats (Marin and Chase, 1993), is p
thesis-dependent and what effects c-*fos* anti
has on this process. Fos expression in striat
promises to be a sensitive screening method
pyramidal side effects of neuroleptic drug *F. Role of this process. Fos expression in striatal neurons* promises to be a sensitive screening method for extra-
pyramidal side effects of neuroleptic drugs.
F. Role of Immediate-early Genes in Epileptogenesis:
Proc pyramidal side effects of neuroleptic drugs.

schizophrenia in schizophrenics (Snyder, 1980), and we suggested that c-Fos may be involved in this sensitisa-
speculate that perhaps the induction of IEGs in deep tion phenomenon and hence in the development of epi-
layer The first two studies to show c-Fos expression in CNS F. Role of Immediate-early Genes in Epileptogenesis:
Proconvulsive or Anticonvulsive?
The first two studies to show c-Fos expression in CNS
neurons used seizures as the inducing stimulus (Morgan
et al., 1987; Dragunow and r. Role of Immediate-early Genes in Epiteplogenesis:
Proconvulsive or Anticonvulsive?
The first two studies to show c-Fos expression in CNS
neurons used seizures as the inducing stimulus (Morgan
et al., 1987; Dragunow and neurons used seizures as the inducing stimulus (Morgan et al., 1987; Dragunow and Robertson, 1987b). Because the brain sensitises to seizures after repeated elicitation, an effect called kindling (Goddard et al., 1969), it The first two studies to show c-Fos expression in CNS
neurons used seizures as the inducing stimulus (Morgan
et al., 1987; Dragunow and Robertson, 1987b). Because
the brain sensitises to seizures after repeated elicitation neurons used seizures as the inducing stimulus (Moret al., 1987; Dragunow and Robertson, 1987b). Because the brain sensitises to seizures after repeated elicitation an effect called kindling (Goddard et al., 1969), it sugg et al., 1987; Dragunow and Robertson, 1987b). Because
the brain sensitises to seizures after repeated elicitation,
an effect called kindling (Goddard et al., 1969), it was
suggested that c-Fos may be involved in this sensi the brain sensitises to seizures after repeated elicitation,
an effect called kindling (Goddard et al., 1969), it was
suggested that c-Fos may be involved in this sensitisa-
tion phenomenon and hence in the development of an effect called kindling (Goddard et al., 1969), it was
suggested that c-Fos may be involved in this sensitisa-
tion phenomenon and hence in the development of epi-
lepsy in the brain (i.e., epileptogenesis) (Dragunow et
 suggested that c-Fos may be involved in this sensitisation phenomenon and hence in the development of epilepsy in the brain (i.e., epileptogenesis) (Dragunow et al., 1989b, 1992). As discussed later in the section on targe tion phenomenon and hence in the development of epi-
lepsy in the brain (i.e., epileptogenesis) (Dragunow et
al., 1989b, 1992). As discussed later in the section on
target genes (VIII. Potential IEGP Target Genes within
th lepsy in the brain (i.e., epileptogenesis) (Dragunow et al., 1989b, 1992). As discussed later in the section on target genes (VIII. Potential IEGP Target Genes within the CNS), c-Fos and other IEGPs may regulate the expres al., 1989b, 1992). As discussed later in the section on target genes (VIII. Potential IEGP Target Genes within the CNS), c-Fos and other IEGPs may regulate the expression of neuropeptides and growth factors after brief sei target genes (VIII. Potential IEGP Target Genes within
the CNS), c-Fos and other IEGPs may regulate the ex-
pression of neuropeptides and growth factors after brief
seizures and may be responsible for the neuronal or
nerve the CNS), c-Fos and other IEGPs may regulate the expression of neuropeptides and growth factors after brief seizures and may be responsible for the neuronal or nerve terminal sprouting that occurs after brief seizures. The pression of neuropeptides and growth factors after biseizures and may be responsible for the neuronal
nerve terminal sprouting that occurs after brief s
zures. These effects may be epileptogenic and contrib
to the developm seizures and may be responsible for the neuronal or
nerve terminal sprouting that occurs after brief sei-
zures. These effects may be epileptogenic and contribute
to the development of epilepsy in the brain. Alterna-
tivel nerve terminal sprouting that occurs after brief sequences. These effects may be epileptogenic and contributo the development of epilepsy in the brain. Alternatively, IEGPs may induce expression of molecules (e.g. thyrotro

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(Post and Weiss, 1992) and may be responsible for post
- seizure anticonvulsant effects (Dragunow, 1986). HUGH
(Post and Weiss, 1992) and may be responsible for
seizure anticonvulsant effects (Dragunow, 1986).
The NMDA receptor is critical for the developm

(Post and Weiss, 1992) and may be responsible for post-
seizure anticonvulsant effects (Dragunow, 1986). in
The NMDA receptor is critical for the development of
kindling (Sato et al., 1988), and NMDA receptors are m
involv Fost and weiss, 1992) and may be responsible for post-
seizure anticonvulsant effects (Dragunow, 1986).
The NMDA receptor is critical for the development of
kindling (Sato et al., 1988), and NMDA receptors are
involved in gerative anticonvulsant enects (Dragunow, 1560).
The NMDA receptor is critical for the development of
kindling (Sato et al., 1988), and NMDA receptors are
involved in inducing c-Fos, but not Krox-24, in dentate
granule cel The NMDA receptor is critical for the development of
kindling (Sato et al., 1988), and NMDA receptors are
involved in inducing c-Fos, but not Krox-24, in dentate
granule cells after brief seizures (Labiner et al., 1993;
Hu kinding (Saw et al., 1566), and NMDA receptors are
involved in inducing c-Fos, but not Krox-24, in dentate
granule cells after brief seizures (Labiner et al., 1993;
Hughes and Dragunow, 1994). However, we have re-
cently f myolved in inducing c-r os, but not Krox-24, in dental
granule cells after brief seizures (Labiner et al., 199.
Hughes and Dragunow, 1994). However, we have reently found that the induction of IEGPs in the piriform
amygdal granue cens after brief seizures (Labiner et al., 1993),
Hughes and Dragunow, 1994). However, we have recently found that the induction of IEGPs in the piriform/
amygdala region after a brief amygdala seizure (Dragunow et ringnes and Dragunow, 1994). However, we have re-
cently found that the induction of IEGPs in the piriform/
amygdala region after a brief amygdala seizure (Dra-
gunow et al., 1988) is not blocked by an NMDA receptor
antago entry found that the mudction of EG1 s in the printime
amygdala region after a brief amygdala seizure (Dragunow et al., 1988) is not blocked by an NMDA receptor
antagonist (Hughes et al., 1994) at a dose that blocks
amygda amyguala region after a brief amyguala seizure (Dra-
gunow et al., 1988) is not blocked by an NMDA receptor sy.
antagonist (Hughes et al., 1994) at a dose that blocks cel
amygdala kindling. This suggests that IEGP expressi antagomst (rugnes et al., 1994) at a dose that blocks
amygdala kindling. This suggests that IEGP expression
is not sufficient for amygdala kindling but could still be
a necessary component of the sensitisation process.
Thu unclear. *A* necessary component of the sensitisation process.
Thus, the role of IEGPs in epileptogenesis is currently
unclear.
G. Immediate-early Genes in Brain Injury:
Regeneration or Suicide Genes?

Regeneration or Suicide Genes?

clear.
*Immediate-early Genes in Brain Injury:
generation or Suicide Genes?*
Recent studies have begun to unravel the mechanisms
sponsible for nerve cell death in the infant and adult G. Immediate-early Genes in Brain Injury:

Regeneration or Suicide Genes?

Recent studies have begun to unravel the mechanisms

responsible for nerve cell death in the infant and adult

brain (Choi, 1990; Pulsinelli, 1992) Recent studies have begun to unravel the mechanisms
responsible for nerve cell death in the infant and adult
brain (Choi, 1990; Pulsinelli, 1992). Brief ischaemia or
SE produce a delayed nerve cell death in vulnerable
stru Recent studies have begun to unraver the mechanisms
responsible for nerve cell death in the infant and adult
brain (Choi, 1990; Pulsinelli, 1992). Brief ischaemia or
SE produce a delayed nerve cell death in vulnerable
stru responsible for nerve cell death in the miant and addit in
brain (Choi, 1990; Pulsinelli, 1992). Brief ischaemia or sl
SE produce a delayed nerve cell death in vulnerable (I
structures such as the hippocampus. Severe ischa SE produce a delayed herve cent death in vulnerable
structures such as the hippocampus. Severe ischaemic in
insults result in quick-onset neuronal and glial death
is leading to infarction, although around this infarcted
pr structures such as the hippocampus. Severe ischaemic
insults result in quick-onset neuronal and glial death
leading to infarction, although around this infarcted
region, neurons die via a delayed mechanism. Based
upon stud the ading to infarction, although around this infarcted pregion, neurons die via a delayed mechanism. Based the region, neurons die via a delayed mechanism. Based the idea has arisen that some types of nerve cell death in that some types of nerves of a delayed mechanism. Based
that some types of growth factor-dependent neurons in culture and during brain development, the idea has arisen
that some types of nerve cell death in the brain may b region, neurons die via a delayed mechanism. Dased
upon studies of growth factor-dependent neurons in culture and during brain development, the idea has arise
that some types of nerve cell death in the brain may b
genetica ture and during brain development, the idea has arisen Not all reports, however, have shown neuroprotective
that some types of nerve cell death in the brain may be effects of protein synthesis inhibitors. Cycloheximide
gen Oppenheim, 1991; Raff, 1992; Schwartz, 1991). However, before we discuss these data, we will review the metrically programmed (Martin et al., 1988; Altmann, do
1992; Johnson et al., 1989; Lockshin and Zakeri, 1990; co
Oppenheim, 1991; Raff, 1992; Schwartz, 1991). How-
ev 1992; Johnson et al., 1989; Lockshin and Zakeri, 1990; Coppenheim, 1991; Raff, 1992; Schwartz, 1991). How-
ever, before we discuss these data, we will review the mevidence for and against the hypothesis that delayed 1
neur Oppenheim, 1991; Kail, 1992; Wever, before we discuss these davidence for and against the h
neuronal death in the brain is p
expression and protein synthesis.
If nerve cell death in the adult er, before we discuss these data, we will review the
idence for and against the hypothesis that delayed
uronal death in the brain is produced by active gene
pression and protein synthesis.
If nerve cell death in the adult

neuronal death in the brain is produced by active gene
expression and protein synthesis. The interverse cell death in the adult brain is caused by PCD, p
then drugs that interfere with protein synthesis should A
block nerv expression and protein synthesis.
If nerve cell death in the adult brain is caused by PCD,
then drugs that interfere with protein synthesis should
block nerve cell death, as has been demonstrated for
sympathetic neurons in If herve cen death in the adult brain is caused by FCD ,
then drugs that interfere with protein synthesis should block nerve cell death, as has been demonstrated for
sympathetic neurons in culture (Martin et al., 1988); I then artigs that interfere with protein synthesis should block nerve cell death, as has been demonstrated for appropathetic neurons in culture (Martin et al., 1988); lex-
however, it should be remembered that it is possib sympathetic heurons in culture (what the et al., 1966),
however, it should be remembered that it is possible for expressed proteins activated post-translationally, e.g., o
 Ca^{2+} -dependent endonucleases). Initial reports α ²⁺-dependent endonucleases). Initial reports showed in
that inhibition of protein synthesis with either cyclohex-
timide or anisomycin reduced HI-induced DND in vivo in res
rat and gerbil hippocampus (Goto et al., 1 pressed proteins activated post-transiationally, e.g., Ca^{2+} -dependent endonucleases). Initial reports showed that inhibition of protein synthesis with either cycloheximide or anisomycin reduced HI-induced DND in vivo in Ca^{2+} -dependent endonucleases). Initial reports showed inhibitors is that their peripheral administration pro-
that inhibition of protein synthesis with either cyclohex-
imide or anisomycin reduced HI-induced DND in viv that infinition of protein synthesis with either cyclonex-
imide or anisomycin reduced HI-induced DND in vivo in
rat and gerbil hippocampus (Goto et al., 1990; Pappas et tha
al., 1992; Shigeno et al., 1990) and in vitro in rat and gerbil hippocampus (Goto et al., 1990; Pappas et al., 1992; Shigeno et al., 1990) and in vitro in cultured
cerebellar neurons after anoxia (Dessi et al., 1992). In
rats, administration of cycloheximide 12 h after H rat and geron mppocampus (God
al., 1992; Shigeno et al., 1990) a
cerebellar neurons after anoxia
rats, administration of cyclohexii
duces the strongest neuroprotect
These results suggest that the $(1992, 1992)$, suggest that (1990) and in virro in cultum rebellar neurons after anoxia (Dessi et al., 1992).

ts, administration of cycloheximide 12 h after HI process the strongest neuroprotection.

These results sug rats, administration of cycloheximide 12 h after HI produces the strongest neuroprotection.
These results suggest that there are proteins synthesised after HI that may be involved in the subsequent

rats, administration of cycloheximide 12 h after HI produces the strongest neuroprotection. Check contracts contract the subsequent that there are proteins synthesized after HI that may be involved in the subsequent to DND duces the strongest neuroprotection.
These results suggest that there are proteins synthe-
sised after HI that may be involved in the subsequent
DND (so-called "killer proteins"). Moreover, providing
trophic support for hi Inese results suggest that there are proteins synthe
sised after HI that may be involved in the subsequen
DND (so-called "killer proteins"). Moreover, providing
trophic support for hippocampal neurons with NGF in
fusions p

HUGHES AND DRAGUNOW
(Post and Weiss, 1992) and may be responsible for post-
seizure anticonvulsant effects (Dragunow, 1986). interfere with PCD. Protein synthesis inhibitors also
The NMDA receptor is critical for the devel DRAGUNOW
fect (Shigeno et al., 1991) after transient HI that may
interfere with PCD. Protein synthesis inhibitors also DRAGUNOW
fect (Shigeno et al., 1991) after transient HI that may
interfere with PCD. Protein synthesis inhibitors also
prevent the neurotoxic effects of methamphetamine in DRAGUNOW
fect (Shigeno et al., 1991) after transient HI that may
interfere with PCD. Protein synthesis inhibitors also
prevent the neurotoxic effects of methamphetamine in
mice and rats (Finnegan and Karler, 1992), and the fect (Shigeno et al., 1991) after transient HI that may
interfere with PCD. Protein synthesis inhibitors also
prevent the neurotoxic effects of methamphetamine in
mice and rats (Finnegan and Karler, 1992), and the
neurotox interfere with PCD. Protein synthesis inhibitors also
prevent the neurotoxic effects of methamphetamine in
mice and rats (Finnegan and Karler, 1992), and the
neurotoxicity of calcium-channel antagonists in cultured
cortica prevent the neurotoxic effects of methamphetamine in
mice and rats (Finnegan and Karler, 1992), and the
neurotoxicity of calcium-channel antagonists in cultured
cortical neurons (Koh and Cotman, 1992). Cyclohexi-
mide also prevent the heurotoxic enects of methamphetamine
mice and rats (Finnegan and Karler, 1992), and t
neurotoxicity of calcium-channel antagonists in cultur
cortical neurons (Koh and Cotman, 1992). Cyclohe
mide also prevents S iffering and Fats (Fillingan and Karler, 1992), and the
neurotoxicity of calcium-channel antagonists in cultur
cortical neurons (Koh and Cotman, 1992). Cyclohe
mide also prevents SE-induced neuronal damage (Schi
iber et al neurotoxicity of calcium-channel antagonists in cultured
cortical neurons (Koh and Cotman, 1992). Cyclohexi-
mide also prevents SE-induced neuronal damage (Schre-
iber et al., 1992a). Also, bcl-2, which blocks PCD (Hock-
e cortical neurons (Kon and Cotman, 1992). Cyclonexi-
mide also prevents SE-induced neuronal damage (Schre-
iber et al., 1992a). Also, bcl-2, which blocks PCD (Hock-
enberry et al., 1990), prevents apoptosis in cultured
symp mine also prevents SE-induced neuro
iber et al., 1992a). Also, bcl-2, which
enberry et al., 1990), prevents ap
sympathetic neurons (Garcia et al.,
cell lines (Zhong et al., 1993a, b).
Furthermore, calcium can activat Furthermore, calcium can activate endonucleases re-
herry et al., 1990), prevents apoptosis in cultured
mpathetic neurons (Garcia et al., 1992) and in neural
ll lines (Zhong et al., 1993a, b).
Furthermore, calcium can acti

emberry et al., 1990), prevents apoptosis in cultured
sympathetic neurons (Garcia et al., 1992) and in neural
cell lines (Zhong et al., 1993a, b).
Furthermore, calcium can activate endonucleases re-
sulting in DNA fragment sympathetic heurons (cartra et al., 1992) and in heuroleal lines (Zhong et al., 1993a, b).
Furthermore, calcium can activate endonucleases sulting in DNA fragmentation in PC12 cells (Joseph
al., 1993) and in rat brain afte cen mies (zhong et al., 1993a, b).
Furthermore, calcium can activate endonucleases resulting in DNA fragmentation in PC12 cells (Joseph e
al., 1993) and in rat brain after focal ischaemia (Tomi
naga et al., 1993). DNA frag Furthermore, calcium can activate endonucleases resulting in DNA fragmentation in PC12 cells (Joseph et al., 1993) and in rat brain after focal ischaemia (Tominaga et al., 1993). DNA fragmentation is an important character sulting in DNA fragmentation in $\text{F}\text{C12}$ cens (Joseph et al., 1993) and in rat brain after focal ischaemia (Tominaga et al., 1993). DNA fragmentation is an important characteristic of PCD/apoptosis (Cohen, 1993). Als all, 1993) and in rat brain after local ischaemia (10mm-
naga et al., 1993). DNA fragmentation is an important
characteristic of PCD/apoptosis (Cohen, 1993). Also, glu-
tamate infusions into the hippocampus of rats produce fragmentation is an important
characteristic of PCD/apoptosis (Cohen, 1993). Also, glu-
tamate infusions into the hippocampus of rats produces
DNA fragmentation (Kure et al., 1991), and a β -amyloid
fragment also causes characteristic of PCD/apoptosis (Cohen, 1993). Also, glu-
tamate infusions into the hippocampus of rats produces
DNA fragmentation (Kure et al., 1991), and a β -amyloid
fragment also causes DNA fragmentation in cultured calliate infusions into the inppocal
news of rates produces
DNA fragmentation (Kure et al., 1991), and a β -amyloid
fragment also causes DNA fragmentation in cultured
hippocampal neurons (Forloni et al., 1993). Further-DNA Iragmentation (Kure et al., 1991), and a p-amyloid
fragment also causes DNA fragmentation in cultured
hippocampal neurons (Forloni et al., 1993). Further-
more, aurintricarboxylic acid, a drug that has been
shown to pr ragment also causes DNA fragmentation in culture
hippocampal neurons (Forloni et al., 1993). Furthe
more, aurintricarboxylic acid, a drug that has bee
shown to prevent PCD of sympathetic neurons in culture
(Bastistou and G more, aurintricarboxylic acid, a drug that has
shown to prevent PCD of sympathetic neurons in cul
(Bastistou and Greene, 1991), protects hippocan
neurons from NMDA- and ischemia-induced neurot
ity in vivo and in vitro (Rob more, aurintricarboxylic acid, a drug that has bee
shown to prevent PCD of sympathetic neurons in cultur
(Bastistou and Greene, 1991), protects hippocampi
neurons from NMDA- and ischemia-induced neurotoxic
ity in vivo and shown to prevent PCD of sympathetic heurons in culture
(Bastistou and Greene, 1991), protects hippocampal
neurons from NMDA- and ischemia-induced neurotoxic-
ity in vivo and in vitro (Robert-Lewis et al., 1993; Sam-
ples a neurons from NMDA- and ischemia-induced neurotoxicity in vivo and in vitro (Robert-Lewis et al., 1993; Samples and Dubinsky, 1993; Zeevalk et al., 1993), although this effect may be because of direct NMDA receptor effects edrons from NMDA- and iscribity in vivo and in vitro (Rober
ples and Dubinsky, 1993; Zeev
this effect may be because (
effects (Zeevalk et al., 1993).
Not all reports, however, ha In vivo and in vitro (Kobert-Lewis et al., 1993, Sammes and Dubinsky, 1993; Zeevalk et al., 1993), although is effect may be because of direct NMDA recepto fects (Zeevalk et al., 1993).
Not all reports, however, have shown

neuronal death in the brain is produced by active gene culture is not PCD (Dessi et al., 1993). Furthermore, expression and protein synthesis. injections of kainic acid or quinolinic acid into the hip-
If nerve cell death ples and Dublisky, 1993, Zeevalk et al., 1993), althought
this effect may be because of direct NMDA receptor
effects (Zeevalk et al., 1993).
Not all reports, however, have shown neuroprotective
effects of protein synthesis does not block, and seems to potentiate, excitotoxicity in cortical cultured neurons (Koh and Cotman, 1992), and cortical cultured neurons (Koh and Cotman, 1992), and enects (zeevant et al., 1993).
Not all reports, however, have shown neuroprotective
effects of protein synthesis inhibitors. Cycloheximide
does not block, and seems to potentiate, excitotoxicity in
cortical cultured neuron Not an reports, nowever, nave shown heuroprotectieffects of protein synthesis inhibitors. Cycloheximidoes not block, and seems to potentiate, excitotoxicity cortical cultured neurons (Koh and Cotman, 1992), a anisomycin is enects of protein synthesis inhibitors. Cycloneximide
does not block, and seems to potentiate, excitotoxicity in
cortical cultured neurons (Koh and Cotman, 1992), and
anisomycin is not neuroprotective in vivo after gluta-
 does not block, and seems to potentiate, excitotoxicity in cortical cultured neurons (Koh and Cotman, 1992), and anisomycin is not neuroprotective in vivo after glutamate receptor-mediated neurotoxicity (Leppin et al., 199 cortical cultured neurons (Koh and Cotman, 1992), at anisomycin is not neuroprotective in vivo after glut mate receptor-mediated neurotoxicity (Leppin et a
1992). Glutamate-induced nerve cell death in cerebell.
culture is anisomycin is not neuroprotective in vivo after giuta-
mate receptor-mediated neurotoxicity (Leppin et al.,
1992). Glutamate-induced nerve cell death in cerebellar
culture is not PCD (Dessi et al., 1993). Furthermore,
inje mate receptor-mediated neurotoxicity (Leppin et an., 1992). Glutamate-induced nerve cell death in cerebellar culture is not PCD (Dessi et al., 1993). Furthermore, injections of kainic acid or quinolinic acid into the hippo 1992). Giutamate-induced nerve cen death in cerebenar
culture is not PCD (Dessi et al., 1993). Furthermore,
injections of kainic acid or quinolinic acid into the hip-
pocampus does not induce PCD (Ignatowicz et al., 1991). culture is not PCD (Dessi et al., 1993). Furthermore,
injections of kainic acid or quinolinic acid into the hip-
pocampus does not induce PCD (Ignatowicz et al., 1991).
Also, HI brain damage is not reduced by actinomycin D injections of kainic acid or quinolinic acid into the hip-
pocampus does not induce PCD (Ignatowicz et al., 1991).
Also, HI brain damage is not reduced by actinomycin D,
anisomycin, or cycloheximide (Deshpande et al., 1992 pocampus does not mudde FCD (ignatowicz et al., 1991).
Also, HI brain damage is not reduced by actinomycin D,
anisomycin, or cycloheximide (Deshpande et al., 1992).
Indeed, it has been suggested that the neuroprotective
ef anisomycin, or cycloheximide (Deshpande et al., 1992).
Indeed, it has been suggested that the neuroprotective
effects of protein synthesis inhibitors on hypoxia may be
caused by hypothermia (Keissling et al., 1991). Thus,
 Indeed, it has been suggested that the neuroprotective indeed, it has been suggested that the heuroprotective
effects of protein synthesis inhibitors on hypoxia may b
caused by hypothermia (Keissling et al., 1991). Thu
one major problem with the studies of protein synthes
inhi enects of protein synthesis inhibitors on hypoxia may be
caused by hypothermia (Keissling et al., 1991). Thus,
one major problem with the studies of protein synthesis
inhibitors is that their peripheral administration procaused by hypothermia (heissing et al., 1991). Inus,
one major problem with the studies of protein synthesis
inhibitors is that their peripheral administration pro-
duces hypothermia, confounding interpretation of these
re one major problem with the studies of protein synthesis
inhibitors is that their peripheral administration pro-
duces hypothermia, confounding interpretation of these
results. Another problem with these previous studies is minotors is that their peripheral administration produces hypothermia, confounding interpretation of these
results. Another problem with these previous studies is
that none have monitored protein or RNA synthesis, so
that duces hypothermia, confounding interpretation of the
results. Another problem with these previous studies
that none have monitored protein or RNA synthesis,
that some of the negative results might be caused by
lack of prot results. Another problem with these previous studies is
that none have monitored protein or RNA synthesis, so
that some of the negative results might be caused by a
lack of protein synthesis block at the appropriate time-
 characterised by endomoreal protein or KNA synthesis
that some of the negative results might be caused lack of protein synthesis block at the appropriate ti
point. Furthermore, although PCD and apoptosis
characterised by e that some of the negative results might be caused by a
lack of protein synthesis block at the appropriate time-
point. Furthermore, although PCD and apoptosis are
characterised by endonuclease-mediated DNA fragmen-
tation, point. Furthermore, although PCD and apoptosis are characterised by endonuclease-mediated DNA fragmentation, it is possible for de novo gene transcription and translation in neurons to contribute to nerve cell death withou characterised by endonuclease-mediated DNA fragmentation, it is possible for de novo gene transcription and translation in neurons to contribute to nerve cell death without necessarily producing "classic" PCD/apoptosis; in characterised by endonuclease-mediated DNA fragmen-
tation, it is possible for de novo gene transcription and
translation in neurons to contribute to nerve cell death
without necessarily producing "classic" PCD/apoptosis;
 cation, it is possible for de novo gene transcription and
translation in neurons to contribute to nerve cell death
without necessarily producing "classic" PCD/apoptosis;
indeed, DNA fragmentation cannot be used as a sole
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IMMEDIATE-EARLY GENES AN
effects of protein synthesis inhibitors on cell survival are gueromplicated by the injury-induced stimulation of endog-IMMEDIATE-EARLY GI
effects of protein synthesis inhibitors on cell survival a
complicated by the injury-induced stimulation of endo
enous neuroprotective mechanisms, i.e., insulin-li $IMMEDIATE-EARLY GENES$
effects of protein synthesis inhibitors on cell survival are
complicated by the injury-induced stimulation of endog-
enous neuroprotective mechanisms, i.e., insulin-like
growth factor-1, transforming growth f effects of protein synthesis inhibitors on cell survival are gun complicated by the injury-induced stimulation of endog-
enous neuroprotective mechanisms, i.e., insulin-like this
growth factor-1, transforming growth factor effects of protein synthesis inhibitors on cell survival are
complicated by the injury-induced stimulation of endog-
enous neuroprotective mechanisms, i.e., insulin-like
growth factor-1, transforming growth factor β 1, complicated by the injury-induced stimulation of endog-

enous neuroprotective mechanisms, i.e., insulin-like

this growth factor-1, transforming growth factor β 1, and

tec

BDNF (Gluckman et al., 1992, 1993; Beilharz growth factor-1, transforming growth factor β 1, and BDNF (Gluckman et al., 1992, 1993; Beilharz et al., 1993; Hughes et al., 1993a), which are also RNA- and protein synthesis-dependent (Favaron et al., 1993). With this growth factor-1, transforming growth factor β 1, and te BDNF (Gluckman et al., 1992, 1993; Beilharz et al., (K
1993; Hughes et al., 1993a), which are also RNA- and
protein synthesis-dependent (Favaron et al., 1993). H
W BDNF (Gluckman et al., 1992, 1993; Beilharz et al., (1993; Hughes et al., 1993a), which are also RNA- and protein synthesis-dependent (Favaron et al., 1993). In With this proviso in mind, it is still clear that if "death t 1993; Hughes et al., 1993a), which are also RNA- and Oth protein synthesis-dependent (Favaron et al., 1993). Hence With this proviso in mind, it is still clear that if "death traum genes" exist in neurons and if these gen protein synthesis-dependent (Favaron et al., 1993). Howith this proviso in mind, it is still clear that if "death transpeares" exist in neurons and if these genes are required by for nerve cell death, then their suppressio injury. nes" exist in neurons and if these genes are required by

r nerve cell death, then their suppression with RNA NI

d protein-synthesis inhibitors should reduce brain et

jury. may

In contrast to these results, other studie

for nerve cell death, then their suppression with RNA
and protein-synthesis inhibitors should reduce brain
injury.
In contrast to these results, other studies have shown
a progressive loss of mRNA during DND in the hip-
po and protein-synthesis inhibitors should reduce brain et
injury. In contrast to these results, other studies have shown et
a progressive loss of mRNA during DND in the hip-
pocampus (Maruno and Yanagihara, 1990), and it has injury.
In contrast to these results, other studies have shown
a progressive loss of mRNA during DND in the hip-
pocampus (Maruno and Yanagihara, 1990), and it has
been suggested that this suppression of RNA and pro-
tein In contrast to these results, other studies have shown et
a progressive loss of mRNA during DND in the hip-
pocampus (Maruno and Yanagihara, 1990), and it has
aft
been suggested that this suppression of RNA and pro-
su tei a progressive loss of mRNA during DND in the h
pocampus (Maruno and Yanagihara, 1990), and it h
been suggested that this suppression of RNA and p
tein synthesis may cause DND. Furthermore, SE, whi
induces neuronal death, i pocampus (Maruno and Yanagihara, 1990), and it has
been suggested that this suppression of RNA and pro-
tein synthesis may cause DND. Furthermore, SE, which
induces neuronal death, is also characterised by inhibi-
tion of been suggested that this suppression of RNA and pro-
tein synthesis may cause DND. Furthermore, SE, which neu
induces neuronal death, is also characterised by inhibi-
inducon of protein synthesis (Dwyer and Wasterlain, 198 tein synthesis may cause DND. Furthermore, SE, which
induces neuronal death, is also characterised by inhibi-
tion of protein synthesis (Dwyer and Wasterlain, 1983).
At first appraisal, these two areas of research seem to
 induces neuronal death, is also characterised by inhibition of protein synthesis (Dwyer and Wasterlain, 1983).
At first appraisal, these two areas of research seem to contradict each other, however, it is possible for over tion of protein synthesis (Dwyer and Wasterlain, 1983). ma
At first appraisal, these two areas of research seem to 199
contradict each other, however, it is possible for overall al.,
RNA and protein synthesis to be inhibit At first appraisal, these two areas of research seem to 1
contradict each other, however, it is possible for overall
RNA and protein synthesis to be inhibited by transient
HI and SE but for specific mRNAs and proteins to b contradict each other, however, it is possible for overall RNA and protein synthesis to be inhibited by transient HI and SE but for specific mRNAs and proteins to be strongly expressed. Furthermore, a recent study shows th RNA and protein synthesis to be inhibited by transient
HI and SE but for specific mRNAs and proteins to be
strongly expressed. Furthermore, a recent study shows
that in rat hippocampal slices, anoxia produces an in-
crease 1992).

rist in Fat inppocampar sites, anoxia produces an in-
crease in protein synthesis (Charriaut-Marlangue et al.,
1992).
The identity of the genes and protein(s) that may give
wrise to delayed neuronal death is unknown. Possi 1992). The identity of the genes and protein(s) that may give where to delayed neuronal death is unknown. Possible c-1 candidate molecules that may be either directly involved For part of the cascade that generates "neuro The identity of the genes and protein(s) that may give
rise to delayed neuronal death is unknown. Possible
candidate molecules that may be either directly involved
or part of the cascade that generates "neuron death
protei rise to delayed neuronal death is unknown. Possible
candidate molecules that may be either directly involved
or part of the cascade that generates "neuron death
proteins" are the IEGPs (e.g., c-Fos, Fras, Fos-B, c-Jun,
Jun candidate molecules that may be either directly involved
or part of the cascade that generates "neuron death
inproteins" are the IEGPs (e.g., c-Fos, Fras, Fos-B, c-Jun,
Jun-B, Jun-D, Krox-20, Krox-24, Nur77, c-Myc). Recent or part of the cascade that generates "neuron death in
proteins" are the IEGPs (e.g., c-Fos, Fras, Fos-B, c-Jun, d
Jun-B, Jun-D, Krox-20, Krox-24, Nur77, c-Myc). Recent p
studies have shown that c-fos and c-myc are induced proteins" are the IEGPs (e.g., c-Fos, Fras, Fos-B, c-Jun-Dum-B, Jun-D, Krox-20, Krox-24, Nur77, c-Myc). Recentiaties have shown that c-fos and c-myc are induced during PCD/apoptosis in prostate and in liver (Lockshing and studies have shown that c-fos and c-myc are induced
during PCD/apoptosis in prostate and in liver (Lockshin
and Zakeri, 1990); c-Myc is involved in fibroblast apop-
tosis (Evan et al., 1992). Also, block of c-Myc expressio during PCD/apoptosis in prostate and in liver (Lockshin during PCD/apoptosis in prostate and in liver (Lockshin
and Zakeri, 1990); c-Myc is involved in fibroblast apop-
tosis (Evan et al., 1992). Also, block of c-Myc expression
by antisense oligonucleotides in T-cells blocks ac and Zakeri, 1990); c-Myc is involved in fibroblast apoptosis (Evan et al., 1992). Also, block of c-Myc expression
by antisense oligonucleotides in T-cells blocks activa-
tion-induced apoptosis (Shi et al., 1992). Bcl-2 may tosis (Evan et al., 1992). Also, block of c-Myc expression tio
by antisense oligonucleotides in T-cells blocks activa-
tion-induced apoptosis (Shi et al., 1992). Bcl-2 may in-
bionit apoptosis by inhibiting the actions of by antisense oligonucleotides in T-cells blocks activa- (You
tion-induced apoptosis (Shi et al., 1992). Bcl-2 may in-
hibit apoptosis by inhibiting the actions of c-Myc (Fanidi mat
et al., 1992; Bissonnette et al., 1992). hibit apoptosis by inhibiting the actions of c-Myc (Fanidi matches the pattern seen in human brain after SE (De-
et al., 1992; Bissonnette et al., 1992). A recent study Giorgio et al., 1992; Young and Dragunow, 1993). Howet al., 1992; Bissonnette et al., 1992). A recent study et al., 1992; Bissonnette et al., 1992). A recent study G
shows that prolonged c-*fos* expression precedes PCD in evivo and in vitro (Smeyne et al., 1993). The protein c-Jun bl
is induced in astrocytoma cell lines (*a*) af shows that prolonged c-*fos* expression precedes PCD in ever
vivo and in vitro (Smeyne et al., 1993). The protein c-Jun
is induced in astrocytoma cell lines (*a*) after DNA dam-
thes
age produced by chemotherapeutic drugs vivo and in vitro (Smeyne et al., 1993). The protein c-Jun
is induced in astrocytoma cell lines (a) after DNA dam-
age produced by chemotherapeutic drugs and ionising et
radiation (Manome et al., 1993) and (b) in resp is induced in astrocytoma cell lines (
age produced by chemotherapeutic cradiation (Manome et al., 1993) and
etoposide-induced DNA damage and
leukemia cells (Rubin et al., 1991).
The first report of the effects of bi reproduced by chemotherapeutic drugs and ionising
diation (Manome et al., 1993) and (*b*) in response to (
oposide-induced DNA damage and PCD in myeloid the
diatemia cells (Rubin et al., 1991).
The first report of the effe radiation (Manome et al., 1993) and (b) in response to (exposide-induced DNA damage and PCD in myeloid that leukemia cells (Rubin et al., 1991).
The first report of the effects of brain injury on c-fos summers demonstrat

etoposide-induced DNA damage and PCD in myeloid
leukemia cells (Rubin et al., 1991).
The first report of the effects of brain injury on c-fos
demonstrated that cerebellar injury induced c-fos
mRNA in neonatal—but not adult leukemia cells (Rubin et al., 1991). It

The first report of the effects of brain injury on c-fos

demonstrated that cerebellar injury induced c-fos

mRNA in neonatal—but not adult—rat brain (Ruppert w

and Wille, 1987). I The first report of the effects of brain injury on c-fos sitements demonstrated that cerebellar injury induced c-fos mRNA in neonatal—but not adult—rat brain (Ruppert was exsubsequently shown that a stab-wound injury to t demonstrated that cerebellar injury induced c-form RNA in neonatal—but not adult—rat brain (Rupper and Wille, 1987). In contrast to this earlier study, it we subsequently shown that a stab-wound injury to the adult brain i mRNA in neonatal—but not adult—rat brain (Ruppert
and Wille, 1987). In contrast to this earlier study, it was
subsequently shown that a stab-wound injury to the
adult brain induces c-Fos in neocortical neurons (Dra-
gunow and Wille, 1987). In contrast to this earlier study, it was because the production of the production of adult brain induces c-Fos in neocortical neurons (D gunow and Robertson, 1988b; Dragunow et al., 1990a c) and that thi subsequently shown that a stab-wound injury to the adult brain induces c-Fos in neocortical neurons (Dragunow and Robertson, 1988b; Dragunow et al., 1990a, le c) and that this was because of the production of spreading dep

AND GENE EXPRESSION
gunow et al., 1990a, b, c). Neocortical neurons do not die
after this type of insult, and a recent study suggests that AND GENE EXPRESSION 163
gunow et al., 1990a, b, c). Neocortical neurons do not die
after this type of insult, and a recent study suggests that
this may be because of the production of the neuropro-163
gunow et al., 1990a, b, c). Neocortical neurons do not die
after this type of insult, and a recent study suggests that
this may be because of the production of the neuropro-
tective growth factor BDNF after spreading d gunow et al., 1990a, b,
after this type of insult
this may be because of
tective growth factor E
(Kokaia et al., 1993).
Other studies have ter this type of insult, and a recent study suggests that
is may be because of the production of the neuropro-
ctive growth factor BDNF after spreading depression
okaia et al., 1993).
Other studies have confirmed these ini

this may be because of the production of the neuroprotective growth factor BDNF after spreading depression (Kokaia et al., 1993).

Cther studies have confirmed these initial results.

Hence, c-Fos is induced in CNS neurons tective growth factor BDNF after spreading depression
(Kokaia et al., 1993).
Other studies have confirmed these initial results.
Hence, c-Fos is induced in CNS neurons by a number of
traumatic stimuli, such as mechanical b (Kokaia et al., 1993).

Other studies have confirmed these initial results.

Hence, c-Fos is induced in CNS neurons by a number of

traumatic stimuli, such as mechanical brain injury, and

by neurotoxins such as lindane an Other studies have confirmed these initial results.
Hence, c-Fos is induced in CNS neurons by a number of
traumatic stimuli, such as mechanical brain injury, and
by neurotoxins such as lindane and quinolinic acid, via
NMDA Hence, c-Fos is induced in CNS neurons by a number extraumatic stimuli, such as mechanical brain injury, an
by neurotoxins such as lindane and quinolinic acid, vi
NMDA-receptor activation (Aronin et al., 1991; Ballari
et a traumatic stimuli, such as mechanical brain injury, and
by neurotoxins such as lindane and quinolinic acid, via
NMDA-receptor activation (Aronin et al., 1991; Ballarin
et al., 1991; Herrera and Robertson, 1989, 1990; Kaczby neurotoxins such as imuatie and quinoninc acid, NMDA-receptor activation (Aronin et al., 1991; Ballar
et al., 1991; Herrera and Robertson, 1989, 1990; Kaa
marek et al., 1988; Sequier and Lazdunski, 1990; Sha
et al., 198 rumba-recepton activation (Aronni et al., 1991, Banarin
et al., 1991; Herrera and Robertson, 1989, 1990; Kacz-
marek et al., 1988; Sequier and Lazdunski, 1990; Sharp
et al., 1989, 1990; Vendrell et al., 1991). NMDA recep-
 et al., 1989, 1990; Vendrell et al., 1991). NMDA receptors are involved in producing the neuronal damage after traumatic brain injury (Faden et al., 1989). This suggests that c-Fos induction may be involved in the neurotox et al., 1989, 1990; Vendrell et al., 1991). NMDA receptors are involved in producing the neuronal damage after traumatic brain injury (Faden et al., 1989). This suggests that c-Fos induction may be involved in the neurotox tors are involved in producing the neuronal damage
after traumatic brain injury (Faden et al., 1989). This
suggests that c-Fos induction may be involved in the
neurotoxic effects of NMDA-receptor activation; c-Fos
inductio after traumatic brain injury (Faden et al., 1989). This suggests that c-Fos induction may be involved in the neurotoxic effects of NMDA-receptor activation; c-Fos induction has also been associated with survival and/or mat suggests that c-Fos induction may be involved in the
neurotoxic effects of NMDA-receptor activation; c-Fos
induction has also been associated with survival and/or
maturation of nerve cells in culture (Didier et al., 1989,
 neurotoxic effects of NMDA-receptor activation; c-Fos
induction has also been associated with survival and/or
maturation of nerve cells in culture (Didier et al., 1989,
1992), although this has been questioned (Bardoscia e induction has also been associated with survival and/or
maturation of nerve cells in culture (Didier et al., 1989,
1992), although this has been questioned (Bardoscia et
al., 1992; Graham and Burgoyne, 1991). Thus, c-Fos m maturation of nerve cells in culture (Didier e
1992), although this has been questioned (B
al., 1992; Graham and Burgoyne, 1991). Thus
be involved in neuronal injury/repair after
administration and traumatic brain injury.
 al., 1992; Graham and Burgoyne, 1991). Thus, c-Fos may
be involved in neuronal injury/repair after neurotoxin
administration and traumatic brain injury.

strongly expressed. Furthermore, a recent study shows c-Fos has been implicated in PCD during development
that in rat hippocampal slices, anoxia produces an in-
of the rat cortex (Gonzalez-Martin et al., 1992). Addi-
crea an, 1992, Graniam and Burgoyne, 1991). Thus, c-ros may
be involved in neuronal injury/repair after neurotoxin
administration and traumatic brain injury.
c-Fos has been implicated in PCD during development
of the rat cortex administration and traumatic brain injury.

c-Fos has been implicated in PCD during development

of the rat cortex (Gonzalez-Martin et al., 1992). Addi-

tionally, in rats before postnatal day 13, kainic acid

seizures do e-Fos has been implicated in FCD during development
of the rat cortex (Gonzalez-Martin et al., 1992). Addi-
tionally, in rats before postnatal day 13, kainic acid
seizures do not lead to c-Fos induction or brain damage
whe of the rat cortex (contzaiez-martin et al., 1992). Additionally, in rats before postnatal day 13, kainic acid
seizures do not lead to c-Fos induction or brain damage,
whereas in older rats, kainic acid produces seizures,
c seizures do not lead to c-Fos induction or brain dama,
whereas in older rats, kainic acid produces seizur
c-Fos induction, and brain damage, suggesting that
Fos may be involved in brain damage after kainic acid-
induced SE whereas in older rats, kainic acid produces seizures,
c-Fos induction, and brain damage, suggesting that c-
Fos may be involved in brain damage after kainic acid-
induced SE (Schreiber et al., 1992b). Kainic acid-in-
duced c-Fos induction, and brain damage, suggesting that c-Fos may be involved in brain damage after kainic acid-induced SE (Schreiber et al., 1992b). Kainic acid-induced SE in adult mice has been associated with prolonged c-fos is may be involved in brain damage after kainic acid-
duced SE (Schreiber et al., 1992b). Kainic acid-in-
iced SE in adult mice has been associated with
olonged c-fos expression (Smeyne et al., 1993).
We have also been stu

induced SE (Schreiber et al., 1992b). Kainic acid-in-
duced SE in adult mice has been associated with
prolonged c-fos expression (Smeyne et al., 1993).
We have also been studying the role of IEGs in nerve
cell death occurr duced SE in adult mice has been associated w
prolonged c-fos expression (Smeyne et al., 1993).
We have also been studying the role of IEGs in necell death occurring after SE (Dragunow et al., 1993)
Our model of SE involves prolonged c-fos expression (Smeyne et al., 1993).
We have also been studying the role of IEGs in nerve
cell death occurring after SE (Dragunow et al., 1993c).
Our model of SE involves delivering electrical stimula-
tion fo We have also been studying the role of IEGs in nerve
cell death occurring after SE (Dragunow et al., 1993c).
Our model of SE involves delivering electrical stimula-
tion for 1 h to the dorsal hippocampus of rat brain
(Youn cell death occurring after SE (Dragunow et al., 1993c).
Our model of SE involves delivering electrical stimulation for 1 h to the dorsal hippocampus of rat brain
(Young and Dragunow, 1994). This mainly leads to lim-
bic SE Our model of SE involves delivering electrical stimulation for 1 h to the dorsal hippocampus of rat brain (Young and Dragunow, 1994). This mainly leads to limbic SE that results in hippocampal injury and exactly matches th tion for 1 h to the dorsal hippocampus of rat brait (Young and Dragunow, 1994). This mainly leads to lim
bic SE that results in hippocampal injury and exactle matches the pattern seen in human brain after SE (De
Giorgio et (Young and Dragunow, 1994). This mainly leads to lim-
bic SE that results in hippocampal injury and exactly
matches the pattern seen in human brain after SE (De-
Giorgio et al., 1992; Young and Dragunow, 1993). How-
ever, bic SE that results in hippocampal injury and exactly
matches the pattern seen in human brain after SE (De-
Giorgio et al., 1992; Young and Dragunow, 1993). How-
ever, if SE is induced in the presence of MK801, a
blocker o matches the pattern seen in human brain after SE (De-
Giorgio et al., 1992; Young and Dragunow, 1993). How-
ever, if SE is induced in the presence of MK801, a
blocker of NMDA-type glutamate receptors (block of
these recept Giorgio et al., 1992; Young and Dragunow, 1993). How-
ever, if SE is induced in the presence of MK801, a
blocker of NMDA-type glutamate receptors (block of
these receptors does not terminate limbic SE) (Hughes
et al., 1993 ever, if SE is induced in the presence of MKS01, a
blocker of NMDA-type glutamate receptors (block of
these receptors does not terminate limbic SE) (Hughes
et al., 1993c), hippocampal cell death does not occur
(Dragunow et these receptors does not terminate limbic SE) (Hughet al., 1993c), hippocampal cell death does not occ (Dragunow et al., 1993c). Thus, although NMDA rectors do not maintain seizures during SE (Hughes et al., 1993c), activa et al., 1993c), hippocampal cell deat
(Dragunow et al., 1993c). Thus, althor
tors do not maintain seizures during S
1993c), activation of these receptors du
sible for killing hippocampal neurons.
We recently discovered tha ragunow et al., 1993c). Thus, although NMDA receptra do not maintain seizures during SE (Hughes et al., 993c), activation of these receptors during SE is respon-
ble for killing hippocampal neurons.
We recently discovered

was a massive expression of the Jun and a smaller
was a massive expression of the Jun and a smaller
expression of the Fos TFs in hippocampal neurons des-
tined to die and (b) this expression was blocked in sible for killing hippocampal neurons.
We recently discovered that (a) 24 h after SE, there
was a massive expression of the Jun and a smaller
expression of the Fos TFs in hippocampal neurons des-
tined to die and (b) th We recently discovered that (a) 24 h after SE, there was a massive expression of the Jun and a smaller expression of the Fos TFs in hippocampal neurons destined to die and (b) this expression was blocked in MK801-treate was a massive expression of the Jun and a smaller expression of the Fos TFs in hippocampal neurons destined to die and (b) this expression was blocked in MK801-treated rats undergoing SE (Dragunow et al., 1993c). Because expression of the Fos TFs in hippocampal neurons destined to die and (b) this expression was blocked in MK801-treated rats undergoing SE (Dragunow et al., 1993c). Because Jun and Fos are TFs, we speculated that they may be tined to die and (b) this expression was blocked in MK801-treated rats undergoing SE (Dragunow et al., 1993c). Because Jun and Fos are TFs, we speculated that they may be involved in the regulation of genes involved in kil

hypothesis is supported by other studies we have under-taken. For example, c-Jun is selectively expressed in the HUGHES A
hypothesis is supported by other studies we have under
taken. For example, c-Jun is selectively expressed in th
nucleus of axotomised medial septal neurons (Dra-
gunow, 1992). After axotomy, these cholinergic medi hypothesis is supported by other studies we have under-
taken. For example, c-Jun is selectively expressed in the
nucleus of axotomised medial septal neurons (Dra-
gunow, 1992). After axotomy, these cholinergic medial
sept taken. For example, c-Jun is selectively expressed in the nucleus of axotomised medial septal neurons (Dragunow, 1992). After axotomy, these cholinergic medial septal neurons undergo atrophy and lose their cholintaken. For example, c-Jun is selectively expressed in the nucleus of axotomised medial septal neurons (Dra
gunow, 1992). After axotomy, these cholinergic media
septal neurons undergo atrophy and lose their cholinergic mark mucleus of axotomised methal septar heurons (Dra-
gunow, 1992). After axotomy, these cholinergic medial the
septal neurons undergo atrophy and lose their cholin-
hergic markers (Fischer and Björklund, 1991). This atro-
phy gunow, 1992). After axotomy, these cholinergic medial
septal neurons undergo atrophy and lose their cholin-
ergic markers (Fischer and Björklund, 1991). This atro-
phy can be prevented by NGF infusions (Fischer and
Björklu septal neurons undergo atrophy and lose their cholinergic markers (Fischer and Björklund, 1991). This atrophy can be prevented by NGF infusions (Fischer and in Björklund, 1991); these infusions also inhibit c-Jun expressio phy can be prevented by NGF infusions (Fischer and Björklund, 1991); these infusions also inhibit c-Jun expression in peripheral neurons after axotomy (Gold et al., 1993).
Although many investigators have speculated that c phy can be prevented by NGF infusions (Fischer and ischere)
Björklund, 1991); these infusions also inhibit c-Jun ex-
pression in peripheral neurons after axotomy (Gold et ingl
al., 1993).
Although many investigators have s

pression in peripheral neurons after axotomy (Gold et ing
al., 1993). Lor
Mithough many investigators have speculated that c-
Jun expression is involved in axonal regeneration in em
peripheral neurons (Leah et al., 1991; J al., 1993).

Although many investigators have speculated that c-

Jun expression is involved in axonal regeneration in

peripheral neurons (Leah et al., 1991; Jenkins and

Hunt, 1991), it has been suggested that in the med Although many investigators have speculated that J un expression is involved in axonal regeneration is peripheral neurons (Leah et al., 1991; Jenkins an Hunt, 1991), it has been suggested that in the media septum at leas Jun expression is involved in axonal regeneration in en
peripheral neurons (Leah et al., 1991; Jenkins and side
Hunt, 1991), it has been suggested that in the medial
septum at least the expression may be neurotoxic (Dra-
g peripheral heurons (Lean et al., 1991, Jenkins and sidentified, Hunt, 1991), it has been suggested that in the medial septum at least the expression may be neurotoxic (Dragunow, 1992; Dragunow et al., 1993c). This hypothes septum at least the expression may be neurotoxic (Dragunow, 1992; Dragunow et al., 1993c). This hypothesis is
strengthened by our SE studies and by our other studies
showing that ischaemic brain injury also induces c-Jun
i gunow, 1992; Dragunow et al., 1993c). This hypothesis is are
strengthened by our SE studies and by our other studies ter
showing that ischaemic brain injury also induces c-Jun
in dying neurons (Dragunow et al., 1993c). In showing that ischaemic brain injury also induces c-Jun
in dying neurons (Dragunow et al., 1993c). In other
studies, we have found that colchicine, which causes a
at
selective degeneration of hippocampal dentate granule
roo studies, we have found that colchicine, which causes a atselective degeneration of hippocampal dentate granule rol
cells (Goldschmidt and Steward, 1980), also induces c-
Jun in these neurons (Leah et al., 1993). Also, c-Ju selective degeneration of hippocampal dentate granule
cells (Goldschmidt and Steward, 1980), also induces c-
Jun in these neurons (Leah et al., 1993). Also, c-Jun is
induced in dopaminergic neurons after injections of the
 cells (Goldschmidt and Steward, 1980), also induces c-

Jun in these neurons (Leah et al., 1993). Also, c-Jun is

induced in dopaminergic neurons after injections of the

dopamine neurotoxin 6-hydroxydopamine (Jenkins et
 Jun in these neurons (Leah induced in dopaminergic neurotoxin 6-hydial., 1993) and after axoton bundle (Leah et al., 1993).
EGs may also play roles duced in dopaminergic neurons after injections of the
pamine neurotoxin 6-hydroxydopamine (Jenkins et
, 1993) and after axotomy of the medial forebrain
ndle (Leah et al., 1993).
IEGs may also play roles in brain injury ass

dopamine neurotoxin 6-hydroxydopamine (Jenkins et al., 1993) and after axotomy of the medial forebrain bundle (Leah et al., 1993).

IEGs may also play roles in brain injury associated with ischaemia. HI in adult rat and ge al., 1993) and after axotomy of the medial forebrain

bundle (Leah et al., 1993).

IEGs may also play roles in brain injury associated

with ischaemia. HI in adult rat and gerbil brain induces

c-fos, c-jun and zif 268 mRN bundle (Leah et al., 1993).

IEGs may also play roles in brain injury associated

with ischaemia. HI in adult rat and gerbil brain induces

c-fos, c-jun and zif 268 mRNA and c-Fos protein (Abe et

al., 1991b; Blumenfeld et IEGs may also play roles in brain injury associated
with ischaemia. HI in adult rat and gerbil brain induces
c-fos, c-jun and zif 268 mRNA and c-Fos protein (Abe et
al., 1991b; Blumenfeld et al., 1992; Jørgensen et al.,
19 with ischaemia. HI in adult rat and gerbil brain induces nerc-fos, c-jun and zif 268 mRNA and c-Fos protein (Abe et stin al., 1991b; Blumenfeld et al., 1992; Jørgensen et al., does 1989; Onodera et al., 1989; Wessel et al. c-fos, c-jun and zif 268 mRNA and c-Fos protein (Abe et sal., 1991b; Blumenfeld et al., 1992; Jørgensen et al., d
1989; Onodera et al., 1989; Wessel et al., 1991; Nowak et ed., 1990; Gass et al., 1992b; Gubits et al., 1993 al., 1991b; Blumenfeld et al., 1992; Jørgensen et al., 1989; Onodera et al., 1989; Wessel et al., 1991; Nowak et al., 1990; Gass et al., 1992b; Gubits et al., 1993). In contrast, other studies have found either weak induct 1989; Onodera et al., 1989; Wessel et al., 1991; Nowak e
al., 1990; Gass et al., 1992b; Gubits et al., 1993). In
contrast, other studies have found either weak induction
of c-Fos after ischaemia (Ikeda et al., 1990; Popovi al., 1990; Gass et al., 1992b; Gubits et al., 1993). I contrast, other studies have found either weak inductio
of c-Fos after ischaemia (Ikeda et al., 1990; Popovici e
al., 1990), or induction in areas surrounding the isch contrast, other studies have found either weak induction
of c-Fos after ischaemia (Ikeda et al., 1990; Popovici et
al., 1990), or induction in areas surrounding the isch-
aemic core (Uemura et al., 1991a) or in neurons res

al., 1990), or induction in areas surrounding the isch-
aemic core (Uemura et al., 1991a) or in neurons resis-
tant to injury (Uemura et al., 1991b). by
We have also investigated the regulation of IEGPs
vafter HI and foun neuronal core (Uemura et al., 1991a) or in neurons resisted that to injury (Uemura et al., 1991b). bries we have also investigated the regulation of IEGPs vational and found that neurons undergoing delayed *differ* neurona tant to injury (Uemura et al., 1991b). bries

We have also investigated the regulation of IEGPs vatiater HI and found that neurons undergoing delayed difficient

meuronal death show prolonged c-jun and c-fos mRNA surre

a we have also investigated the regulation of HEGPs
after HI and found that neurons undergoing delayed
neuronal death show prolonged c-jun and c-fos mRNA
and protein expression (24 to 48 h), whereas neurons in
infarcted tiss neuronal death show prolonged c-jun and c-fos mRNA surviving neurons may be critical in determining its
and protein expression (24 to 48 h), whereas neurons in biological effects.
infarcted tissue did not express IEGPs (D short-lasting IEGP expression (1 to 4 h).
Although these different results may be because of Although these differences of $(24 \text{ to } 48 \text{ h})$, whereas neurons in bifarcted tissue did not express IEGPs (Dragunow et al., (94)). Neurons surviving moderate HI showed only in ort-lasting IEGP expression $(1 \text{ to } 4 \text{$

miarcted ussue did not express iEGrs (Dragunow et al.,
1994). Neurons surviving moderate HI showed only in
short-lasting IEGP expression (1 to 4 h). F
Although these different results may be because of e
differences in spe previously proposed that the results obtained reflect
differences in species or to technical differences, we have
differences in species or to technical differences, we have
increviously proposed that the results obtained Although these different results may be because of differences in species or to technical differences, we have previously proposed that the results obtained reflect differences in the severity of the ischaemic insult, with differences in species or to technical differences, we have
previously proposed that the results obtained reflect
differences in the severity of the ischaemic insult, with
milder insults leading to c-Fos expression in isch previously proposed that the results obtained reflect
differences in the severity of the ischaemic insult, with
milder insults leading to c-Fos expression in ischaemic
neurons undergoing DND and more severe insults re-
sul differences in the severity of the ischaemic insult, with needled milder insults leading to c-Fos expression in ischaemic (H
neurons undergoing DND and more severe insults re-
sulting in rapid neuronal failure, infarction, milder insults leading to c-Fos expression in ischaemic (Hughes et al., 1993a; Dragunow et al., 1993a). Because
neurons undergoing DND and more severe insults re-
BDNF is neuroprotective (Sendtner et al., 1992; Shimo-
sult neurons undergoing DND and more severe insults re-
sulting in rapid neuronal failure, infarction, and death, hat
thereby obscuring any potential c-Fos expression (Gunn nee
et al., 1990). This possibility is supported by a thereby obscuring any potential c-Fos expression (Gunn
et al., 1990). This possibility is supported by a study
showing that mild traumatic brain injury produces a
stronger induction of c-Fos in CA1 hippocampal neurons
than

DRAGUNOW
However, in contrast to these reports, hyperglycemia
suppresses c-*fos* mRNA expression after transient cere-BRAGUNOW
However, in contrast to these reports, hyperglycemia
suppresses c-*fos* mRNA expression after transient cere-
bral ischemia in gerbils (Combs et al., 1992), suggesting
that c-Fos may be protective of neurons, inas However, in contrast to these reports, hyperglycemia
suppresses c-fos mRNA expression after transient cere-
bral ischemia in gerbils (Combs et al., 1992), suggesting
that c-Fos may be protective of neurons, inasmuch as
hyp suppresses c -*fos* mRNA expression after transient cere-
bral ischemia in gerbils (Combs et al., 1992), suggesting
that c -Fos may be protective of neurons, inasmuch as
hyperglycemia enhances brain injury after ischemi suppresses c-fos mRNA expression after transient cere-
bral ischemia in gerbils (Combs et al., 1992), suggesting
that c-Fos may be protective of neurons, inasmuch as
hyperglycemia enhances brain injury after ischemia. A
re bral ischemia in gerbils (Combs et al., 1992), suggesting
that c-Fos may be protective of neurons, inasmuch as
hyperglycemia enhances brain injury after ischemia. A
recent study in adult rat brain showed that 30-min
ischae that c-ros may be protective of heurons, mashfuct
hyperglycemia enhances brain injury after ischemi
recent study in adult rat brain showed that 30-
ischaemia strongly induced c-*fos* and *jun*-B but
weakly induced c-*jun* ingly, 30-min emiances brain injury aiter ischemia. A
recent study in adult rat brain showed that 30-min
ischaemia strongly induced c-fos and jun-B but only
weakly induced c-jun mRNA (An et al., 1993). Interest-
ingly, 30ischaemia strongly induced c-*fos* and *jun*-B but only weakly induced c-*jun* mRNA (An et al., 1993). Interestingly, 30-min ischemia did not cause any damage. Longer ischaemia (90 min) caused a reduced expression of thes weakly induced c-jun mRNA (An et al., 1993). Interestingly, 30-min ischemia did not cause any damage.
Longer ischaemia (90 min) caused a reduced expression
of these genes, but the anatomical distribution of isch-
emia did not correspond to the pattern of IEG expres-
sion.
Pe sion. mger ischaemia (90 min) caused a reduced expressio
these genes, but the anatomical distribution of isch
ia did not correspond to the pattern of IEG expres
n.
Permanent middle cerebral artery occlusion in spon-
neously hype

of these genes, but the anatomical distribution of isch-
emia did not correspond to the pattern of IEG expres-
sion.
Permanent middle cerebral artery occlusion in spon-
taneously hypertensive rats induces c-Fos in the zone taneously hypertensive rats induces c-Fos in the zone around the infarct but not in the infarct itself (Chris-
tensen et al., 1993). This induction in the peri-infarct sion.

Permanent middle cerebral artery occlusion in spon-

taneously hypertensive rats induces c-Fos in the zone

around the infarct but not in the infarct itself (Chris-

tensen et al., 1993). This induction in the pericalled the infarct but not in the infarct itself (Christensen et al., 1993). This induction in the peri-infarct zone was blocked by MK801 but not by a non-NMDA antagonist, indicating that it is NMDA-receptor mediated. Tiss tensen et al., 1993). This induction in the peri-infarct
zone was blocked by MK801 but not by a non-NMDA
antagonist, indicating that it is NMDA-receptor medi-
ated. Tissue in the peri-infarct zone shows selective neu-
rona zone was blocked by MK801 but not by a non-NMDA
antagonist, indicating that it is NMDA-receptor medi-
ated. Tissue in the peri-infarct zone shows selective neu-
ronal loss that can be prevented by MK801, suggesting
that th antagomst, mulcating that it is NMDA-receptor medi-
ated. Tissue in the peri-infarct zone shows selective neu-
ronal loss that can be prevented by MK801, suggesting
that the c-Fos expression may be involved in cell death.
 ronar loss that
that the c-Fos
Furthermore,
tion that c-Fo
et al., 1990).
These stud at the c-Fos expression may be involved in cent death.
Intribermore, this study confirms the previous observa-
in that c-Fos is not induced in infarcted tissue (Gunn
al., 1990).
These studies suggest that perhaps c-Jun and

c-Fos after ischaemia (Ikeda et al., 1990; Popovici et induction in dying neurons is prolonged $(24 \text{ to } 72 \text{ h})$
 (1990) , or induction in areas surrounding the isch-
 (1990) , or induction in areas surrounding the isc ruiterinore, this study commiss the previous observa-
tion that c-Fos is not induced in infarcted tissue (Gunn
et al., 1990).
These studies suggest that perhaps c-Jun and c-Fos
are involved in killing neurons during delaye death; c-Jun expression is death perhaps c-Jun and c-Fos are involved in killing neurons during delayed cell death; c-Jun expression is clearly not sufficient to cause nerve cell death, because it is induced in neurons by et an., 1990).
These studies suggest that perhaps c-Jun and c-Fos
are involved in killing neurons during delayed cell
death; c-Jun expression is clearly not sufficient to cause
nerve cell death, because it is induced in ne death; c-Jun expression is clearly not sufficient to cause
nerve cell death, because it is induced in neurons by
stimulation (LTP, saline infusion, brief seizures) that
does not lead to cell death. However, the duration of death; c-Jun expression is clearly not sufficient to cause
nerve cell death, because it is induced in neurons by
stimulation (LTP, saline infusion, brief seizures) that
does not lead to cell death. However, the duration of merve cen death, because it is induced in neurons b
stimulation (LTP, saline infusion, brief seizures) tha
does not lead to cell death. However, the duration of it
expression after these types of stimulation is brief (2 t
 stimulation (LTP, saline infusion, brief seizures) that
does not lead to cell death. However, the duration of its
expression after these types of stimulation is brief (2 to
4 h) (Demmer et al., 1993; Abraham et al., 1992; does not lead to cell death. However, the duration of its
expression after these types of stimulation is brief (2 to
4 h) (Demmer et al., 1993; Abraham et al., 1992; Dra-
gunow et al., 1992; Hughes et al., 1993a), whereas expression after these types of stimulation is brief (2 t
4 h) (Demmer et al., 1993; Abraham et al., 1992; Dra
gunow et al., 1992; Hughes et al., 1993a), whereas it
induction in dying neurons is prolonged (24 to 72 h afte
 4 h) (Demmer et al., 1993; Abraham et al., 1992; Dragunow et al., 1992; Hughes et al., 1993a), whereas its induction in dying neurons is prolonged (24 to 72 h after hypoxia and SE and many days after axotomy) (Dragunow, 19 gunow et al., 1992; Hughes et al., 1993a), whereas
induction in dying neurons is prolonged (24 to 72 h a
hypoxia and SE and many days after axotomy) (I
gunow, 1992; Dragunow et al., 1993c). Prolonged but
brief expression o induction in dying neurons is prolonged (24 to 72 h after
hypoxia and SE and many days after axotomy) (Dra-
gunow, 1992; Dragunow et al., 1993c). Prolonged but not
brief expression of c-Jun was required for its DNA-acti-
v *different time-courses of its expression in dying versus surviving ability (Trejo et al., 1992), suggesting that the different time-courses of its expression in dying versus surviving neurons may be critical in determinin* gunow, 1332, Dragunow et al., 1333c). Prolonged but not
brief expression of c-Jun was required for its DNA-acti-
vating ability (Trejo et al., 1992), *suggesting that the*
different time-courses of its expression in dying **binerexpression dividends**
 bifferent time-cousarviving neuron
 biological effects.
 Post-translation ting ability (11ejo et al., 1992), suggesting that the
fferent time-courses of its expression in dying versus
rviving neurons may be critical in determining its
plogical effects.
Post-translational modifications may also b

different time-courses of its expression in dying versus
surviving neurons may be critical in determining its
biological effects.
Post-translational modifications may also be involved
in determining the biological activity buotogical effects.

Post-translational modifications may also be involved

in determining the biological activity of Jun (Hunter and

Karin, 1992). Also, in all the situations where c-Jun is

expressed and neurons do not In determining the biological activity of Jun (Hunter and
Karin, 1992). Also, in all the situations where c-Jun is
expressed and neurons do not die, we have detected an
induction of BDNF, which we have discovered is itself neurons and neurons do not die, we have detected an induction of BDNF, which we have discovered is itself an early-response gene (Hughes et al., 1993a), in the same neurons with a similar time-course of expression (Hughes expressed and neurons do not die, we nave detected an
induction of BDNF, which we have discovered is itself an
early-response gene (Hughes et al., 1993a), in the same
neurons with a similar time-course of expression
(Hughe early-response gene (Hughes et al., 1993a), in the same
neurons with a similar time-course of expression
(Hughes et al., 1993a; Dragunow et al., 1993a). Because
BDNF is neuroprotective (Sendtner et al., 1992; Shimo-
hama e neurons with a similar time-course of expressi (Hughes et al., 1993a; Dragunow et al., 1993a). Becau
BDNF is neuroprotective (Sendtner et al., 1992; Shim
hama et al., 1993), its expression may interfere with a
neurotoxic e (riughes et al., 1993a; Dragunow et al., 1993a). Because
BDNF is neuroprotective (Sendtner et al., 1992; Shimo-
hama et al., 1993), its expression may interfere with any
neurotoxic effects of c-Jun, perhaps in a fashion an BDNY IS heuroprotective (Sendther et al., 1992; Shimo-
hama et al., 1993), its expression may interfere with any
neurotoxic effects of c-Jun, perhaps in a fashion analo-
gous to the prevention of programmed cell death by
g hama et al., 1993), its expression may interfere with any
neurotoxic effects of c-Jun, perhaps in a fashion analo-
gous to the prevention of programmed cell death by
growth factors. Furthermore, although c-Jun is induced
b neurotoxic enects or c-Jun, pernaps in a rasmion analogous to the prevention of programmed cell death by growth factors. Furthermore, although c-Jun is induced by LTP, saline infusion into hippocampus and brief seizures, t

IMMEDIATE-EARLY GENES
tion occurs via glutamate receptors (Demmer et al.,
1993; Hughes et al., 1993a; Hughes and Dragunow, sub-IMMEDIATE-EARLY GEN
1993; Hughes et al., 1993a; Hughes and Dragunow, sub-
1993; Hughes et al., 1993a; Hughes and Dragunow, sub-
mitted). In contrast, activation of muscarinic receptors IMMEDIATE-EARLY GENES
tion occurs via glutamate receptors (Demmer et al.,
1993; Hughes et al., 1993a; Hughes and Dragunow, sub-
mitted). In contrast, activation of muscarinic receptors
or block of dopamine receptors, which or block of dopamine receptors (Demmer et al., strongly; Hughes et al., 1993a; Hughes and Dragunow, sub-
mitted). In contrast, activation of muscarinic receptors nor block of dopamine receptors, which strongly induce a
Jun tion occurs via glutamate receptors (Demmer et al., 1993; Hughes et al., 1993a; Hughes and Dragunow, sub-
mitted). In contrast, activation of muscarinic receptors
or block of dopamine receptors, which strongly induce
Jun-B 1993; Hughes et al., 1993a; Hughes and Dragunow, sumitted). In contrast, activation of muscarinic receptor block of dopamine receptors, which strongly indular-B, Krox-24 and Fos, do not induce c-Jun (Hugher and Dragunow, 1 mitted). In contrast, activation of muscarinic receptors
or block of dopamine receptors, which strongly induce
Jun-B, Krox-24 and Fos, do not induce c-Jun (Hughes
and Dragunow, 1994; Dragunow et al., 1993c; MacGib-
bon et or block of dopamine receptors, whi

Jun-B, Krox-24 and Fos, do not ind

and Dragunow, 1994; Dragunow et a

bon et al., 1994). Thus, *c*-Jun expres

pled to glutamate receptor activation

Glutamate receptors, particularly n-B, Krox-24 and Fos, do not induce c-Jun (Hugh
d Dragunow, 1994; Dragunow et al., 1993c; MacGi
n et al., 1994). Thus, *c-Jun expression is closely co*
ed to glutamate receptor activation.
Glutamate receptors, particularly

and Dragunow, 1994; Dragunow et al., 1993c; MacGibbon et al., 1994). Thus, *c*-Jun expression is closely coupled to glutamate receptor activation. the Cultamate receptors, particularly the NMDA receptor, play important rol bon et al., 1994). Thus, *c*-Jun expression is closely cou-
pled to glutamate receptor activation.
Glutamate receptors, particularly the NMDA recep-
tor, play important roles in brain plasticity and neuronal
injury (Choi, pled to glutamate receptor activation.

Glutamate receptors, particularly the NMDA recep-

tor, play important roles in brain plasticity and neuronal

injury (Choi, 1990). Jun expression occurs preferentially

in response Glutamate receptors, particularly the NMDA receptor, play important roles in brain plasticity and neuronal injury (Choi, 1990). Jun expression occurs preferentiall in response to glutamate receptor activation. Perhaplow-le tor, play important roles in brain plasticity and neuronal
injury (Choi, 1990). Jun expression occurs preferentially
in response to glutamate receptor activation. Perhaps
low-level glutamate receptor activation produces a injury (Choi, 1990). Jun expression occurs preferentially
in response to glutamate receptor activation. Perhaps
low-level glutamate receptor activation produces a tran-
sient induction of c-Jun (Demmer et al., 1993; Hughes in response to glutamate receptor activation. Perhalow-level glutamate receptor activation produces a transient induction of c-Jun (Demmer et al., 1993; Hughes al., 1993a), whereas activation of glutamate recepto producing sient induction of c-Jun (Demmer et al., 1993; Hughes et al., 1993a), whereas activation of glutamate receptors producing neurotoxicity leads to prolonged c-Jun expression. Thus, prolonged expression of c-Jun (and perhaps al., 1993a), whereas activation of glutamate receptors producing neurotoxicity leads to prolonged c-Jun expres-
sion. Thus, prolonged expression of c-Jun (and perhaps
c-Fos) may be necessary for nerve cell death (perhaps
n
PCD) in the brain. However, this hypothesis is based
e sion. Thus, prolonged expression of c-Jun (and perhaps c-Fos) may be necessary for nerve cell death (perhaps r
PCD) in the brain. However, this hypothesis is based centirely on correlational data, and direct tests of this PCD) in the brain. However, this hypothesis is based
entirely on correlational data, and direct tests of this
hypothesis await the use of antisense DNA technology
(Chiasson et al., 1992; Dragunow et al., 1993b).
In contras entirely on correlational data, and direct tests of this

entirely on correlational data, and direct tests of this neurothesis await the use of antisense DNA technology Sc (Chiasson et al., 1992; Dragunow et al., 1993b). ar In contrast to this cell death hypothesis, other represe hypothesis await the use of antisense DNA technology

(Chiasson et al., 1992; Dragunow et al., 1993b).

In contrast to this cell death hypothesis, other re-

searchers studying axotomy of peripheral neurons have

suggested (Chiasson et al., 1992; Dragunow et al., 1993b). arm
In contrast to this cell death hypothesis, other re-
searchers studying axotomy of peripheral neurons have
suggested that Jun proteins may play a role in initiating sy-
 In contrast to this cell death hypothesis, other re-
searchers studying axotomy of peripheral neurons have
suggested that Jun proteins may play a role in initiating
a regeneration program in neurons after axotomy (Leah
et searchers studying axotomy of peripheral neurons have
suggested that Jun proteins may play a role in initiating
a regeneration program in neurons after axotomy (Leah
et al., 1991; Jenkins and Hunt, 1991; Rutherford et al., suggested that Jun proteins may play a role in initiating
a regeneration program in neurons after axotomy (Leah
et al., 1991; Jenkins and Hunt, 1991; Rutherford et al.,
1992a; Jenkins et al., 1993; Hass et al., 1993) and t a regeneration program in neurons after axotomy (Leah
et al., 1991; Jenkins and Hunt, 1991; Rutherford et al.,
1992a; Jenkins et al., 1993; Hass et al., 1993) and that
c-Fos may be involved in survival of LC neurons after
 et al., 1991; Jenkins and Hunt, 1991; Rutherford et al., 1992a; Jenkins et al., 1993; Hass et al., 1993) and that c-Fos may be involved in survival of LC neurons after axotomy (Weiser et al., 1993b). Peripheral neurons reg 1992a; Jenkins et al., 1993; Hass et al., 1993) and that for c-Fos may be involved in survival of LC neurons after reaxotomy (Weiser et al., 1993b). Peripheral neurons regrow axons after axotomy, and this process may be i c-Fos may be involved
axotomy (Weiser et axo
grow axons after axo
tiated by Jun express
axotomised neurons.
Axotomy of facial a Axotomy (Weiser et al., 1993b). Peripheral neurons re-

ow axons after axotomy, and this process may be ini-

ated by Jun expression that occurs in the nuclei of the

otomised neurons.

Axotomy of facial and rubrospinal ne grow axons after axotomy, and this process may be initiated by Jun expression that occurs in the nuclei of the axotomised neurons.
Axotomy of facial and rubrospinal neurons causes increased expression of cytoskeletal prote

tiated by Jun expression that occurs in the nuclei of the experience axotomised neurons. upo
axotomy of facial and rubrospinal neurons causes in-
creased expression of cytoskeletal proteins and growth-
in n
associated prot axotomised neurons.
Axotomy of facial and rubrospinal neurons causes increased expression of cytoskeletal proteins and growth-
associated protein-43, which are likely to be involved in
the regenerative response (Tetzlaff e Axotomy of facial and rubrospinal neurons causes in-
creased expression of cytoskeletal proteins and growth-
associated protein-43, which are likely to be involved in
the regenerative response (Tetzlaff et al., 1991). Furcreased expression of cytoskeletal proteins and growth-
associated protein-43, which are likely to be involved in
the regenerative response (Tetzlaff et al., 1991). Fur-
thermore, other genes, such as calcitonin gene-relat associated protein-43, which are likely to be involved in
the regenerative response (Tetzlaff et al., 1991). Fur-
thermore, other genes, such as calcitonin gene-related
peptide (Herdegen et al., 1993b; Saika et al., 1991), the regenerative response (Tetzlaff et al., 1991). Fur-
thermore, other genes, such as calcitonin gene-related
peptide (Herdegen et al., 1993b; Saika et al., 1991), c
galanin (Rutherford et al., 1992a), and CCK (Saika et
a thermore, other genes, such as calcitonin gene-related
peptide (Herdegen et al., 1993b; Saika et al., 1991), de
galanin (Rutherford et al., 1992a), and CCK (Saika et roi
al., 1991) are also induced after axotomy. Calcitoni peptide (Herdegen et al.,
galanin (Rutherford et al.
al., 1991) are also induce
gene-related peptide seem
(Herdegen et al., 1993b).
Expression of c-Jun may

al., 1991) are also induced after axotomy. Calcitonin cause
gene-related peptide seems to be colocalised with c-Jun vati
(Herdegen et al., 1993b). inte
Expression of c-Jun may be involved in regulating the these
expression gene-related peptide seems to be colocalised with c-Jun (Herdegen et al., 1993b).

Expression of c-Jun may be involved in regulating the expression of the regenerative proteins and hence in axonal regeneration. CNS neurons (Herdegen et al., 1993b). in
Expression of c-Jun may be involved in regulating the the
expression of the regenerative proteins and hence in le
axonal regeneration. CNS neurons do not regrow after en
axotomy, and yet they d Expression of c-Jun may be involved in regulating the expression of the regenerative proteins and hence in axonal regeneration. CNS neurons do not regrow after axotomy, and yet they display a robust expression of c-Jun upo expression of the regenerative proteins and hence in axonal regeneration. CNS neurons do not regrow after axotomy, and yet they display a robust expression of c-Jun upon axotomy (Dragunow, 1992, Leah et al., 1993). If c-Ju axonal regeneration. CNS neurons do not regrow after axotomy, and yet they display a robust expression of c-Jun upon axotomy (Dragunow, 1992, Leah et al., 1993). If c-Jun is a crucial signal for the regenerative response, axotomy, and yet they display a robust expression of c-Jun upon axotomy (Dragunow, 1992, Leah et al., 1993). If c-Jun is a crucial signal for the regenerative response, then its expression in CNS neurons suggests that thes c-Jun upon axotomy (Dragunow, 1992, Leah
1993). If c-Jun is a crucial signal for the regen
response, then its expression in CNS neurons s
that these cells have the capacity to regrow axe
that some other factor may prohibit 93). If c-Jun is a crucial signal for the regenerative
sponse, then its expression in CNS neurons suggests
at these cells have the capacity to regrow axons but
at some other factor may prohibit regeneration.
Axotomy of nig

response, then its expression in CNS neurons suggests
that these cells have the capacity to regrow axons but
that some other factor may prohibit regeneration.
Axotomy of nigrostriatal neurons with 6-OHDA pro-
duces a stron that these cells have the capacity to regrow axons but
that some other factor may prohibit regeneration.
Axotomy of nigrostriatal neurons with 6-OHDA pro-
duces a strong but short (2 weeks) expression of c-Jun in
nigral do that some other factor may prohibit regeneration.
Axotomy of nigrostriatal neurons with 6-OHDA produces a strong but short (2 weeks) expression of c-Jun in
nigral dopamine neurons (Jenkins et al., 1993). Because
peripheral Axotomy of nigrostriatal neurons with 6-OHDA produces a strong but short (2 weeks) expression of c-Jun in nigral dopamine neurons (Jenkins et al., 1993). Because peripheral nerve transection produces a prolonged expression

AND GENE EXPRESSION 165
suggested that this shorter induction in CNS neurons
may be the result of other factors in the CNS that are AND GENE EXPRESSION 165
suggested that this shorter induction in CNS neurons
may be the result of other factors in the CNS that are
nonpermissive for regeneration. However, it might be 165
suggested that this shorter induction in CNS neurons
may be the result of other factors in the CNS that are
nonpermissive for regeneration. However, it might be
argued that because 6-OHDA kills dopamine neurons, suggested that this shorter induction in CNS neurons
may be the result of other factors in the CNS that are
nonpermissive for regeneration. However, it might be
argued that because 6-OHDA kills dopamine neurons,
the shortsuggested that this shorter induction in CNS neurons
may be the result of other factors in the CNS that are
nonpermissive for regeneration. However, it might be
argued that because 6-OHDA kills dopamine neurons,
the shortay be the result of other factors in the CNS that are
npermissive for regeneration. However, it might be
gued that because 6-OHDA kills dopamine neurons,
e short-lasting expression may be caused by cell death.
After transe

producing neurotoxicity leads to prolonged c-Jun expres-
sion. Thus, prolonged expression of c-Jun (and perhaps sible that induction of c-Jun after axotomy of peripheral
c-Fos) may be necessary for nerve cell death (perhap nonpermissive for regeneration. However, it might
argued that because 6-OHDA kills dopamine neuro
the short-lasting expression may be caused by cell des
After transection of the medial forebrain bundle
mamillary tract, we argued that because 6-OHDA kills dopamine neurons,
the short-lasting expression may be caused by cell death.
After transection of the medial forebrain bundle and
mamillary tract, we found that neurons in the substan-
tia n the short-lasting expression may be caused by cell death.
After transection of the medial forebrain bundle and
mamillary tract, we found that neurons in the substan-
tia nigra, mamillary nuclei, and ventral tegmentum ex-
p After transection of the medial forebrain bundle and
mamillary tract, we found that neurons in the substan-
tia nigra, mamillary nuclei, and ventral tegmentum ex-
pressed c-Jun (Leah et al., 1993). By 30 days after
transec mamillary tract, we found that neurons in the substantia nigra, mamillary nuclei, and ventral tegmentum expressed c-Jun (Leah et al., 1993). By 30 days after transection, levels had returned to baseline in the nigra and te tia nigra, mamillary nuclei, and ventral tegmentum ex-
pressed c-Jun (Leah et al., 1993). By 30 days after
transection, levels had returned to baseline in the nigra
and tegmentum but were still elevated in the mamillary
nu pressed c-Jun (Leah et al., 1993). By 30 days after
transection, levels had returned to baseline in the nigra
and tegmentum but were still elevated in the mamillary
nuclei. These results (apart from the mamillary nuclei)
w transection, levels had returned to baseline in the nigral tegmentum but were still elevated in the mamillary
nuclei. These results (apart from the mamillary nuclei
would support the previous hypothesis (Jenkins et al.
199 and tegmentum but were still elevated in the mamil
nuclei. These results (apart from the mamillary nu
would support the previous hypothesis (Jenkins et
1993). However, because the fate of the axotomised
rons was not determ nuclei. These results (apart from the mamillary nuclei) would support the previous hypothesis (Jenkins et al., 1993). However, because the fate of the axotomised neurons was not determined (Leah et al., 1993), interpretati would support the previous hypothesis (Jenkins et al., 1993). However, because the fate of the axotomised neurons was not determined (Leah et al., 1993), interpretation of these results is difficult. Furthermore, it is pos tion of these results is difficult. Furthermore, it is postion of these results is difficult. Furthermore, it is possible that induction of c-Jun after axotomy of peripheral
neurons is an attempt at cell suicide that is prevented by
other factors present in the peripheral (but no sible that induction of c-Jun after axotomy of peripheral
neurons is an attempt at cell suicide that is prevented by
other factors present in the peripheral (but not central)
nervous system that overcomes the death pathway neurons is an attempt at cell suicide that is prevented by
other factors present in the peripheral (but not central)
nervous system that overcomes the death pathway.
Schwann cells are known to produce growth factors
around process. rvous system that overcomes the death pathway.

hwann cells are known to produce growth factors

ound injured axons and thus may be involved in this

ocess.

Production of c-Jun in axotomised peripheral nervous

stem and C Schwann cells are known to produce growth factors
around injured axons and thus may be involved in this
process.
Production of c-Jun in axotomised peripheral nervous
system and CNS neurons may be initiated by the ab-
sence

rons was not determined (Leah et al., 1993), interpretation of these results is difficult. Furthermore, it is possible that induction of c-Jun after axotomy of pripheral neurons is an attempt at cell suicide that is preve around injured axons and thus may be involve
process.
Production of c-Jun in axotomised peripheral
system and CNS neurons may be initiated by
sence of retrogradely transported growth/surviv
tenance factors (perhaps NGF/fib process.

Production of c-Jun in axotomised peripheral nervous

system and CNS neurons may be initiated by the ab-

sence of retrogradely transported growth/survival/main-

tenance factors (perhaps NGF/fibroblast growth fa Production of c-Jun in axotomised peripheral nervous
system and CNS neurons may be initiated by the ab-
sence of retrogradely transported growth/survival/main-
tenance factors (perhaps NGF/fibroblast growth factor
for medi system and CNS neurons may be initiated by the absence of retrogradely transported growth/survival/main-
tenance factors (perhaps NGF/fibroblast growth factor
for medial septal neurons) (Dragunow, 1992). NGF has
recently b sence of retrogradely transported growth/survival/main-
tenance factors (perhaps NGF/fibroblast growth factor
for medial septal neurons) (Dragunow, 1992). NGF has
recently been shown to reduce c-Jun expression in axo-
tomi tenance factors (perhaps NGF/fibroblast growth factor
for medial septal neurons) (Dragunow, 1992). NGF has
recently been shown to reduce c-Jun expression in axo-
tomised peripheral neurons (Gold et al., 1993). Thus,
growth for medial septal neurons) (Dragunow, 1992). NGF has
recently been shown to reduce c-Jun expression in axo-
tomised peripheral neurons (Gold et al., 1993). Thus,
growth factor deprivation may be the signal for c-Jun
expres recently been shown to reduce c-Jun expression in axotomised peripheral neurons (Gold et al., 1993). Thus, growth factor deprivation may be the signal for c-Jun expression. Because cultured neurons die via apoptosis upon g tomised peripheral neurons (Gold et al., 1993). Thus,
growth factor deprivation may be the signal for c-Jun
expression. Because cultured neurons die via apoptosis
upon growth factor deprivation (Martin et al., 1988),
these growth factor deprivation may be the signal for c-Jun
expression. Because cultured neurons die via apoptosis
upon growth factor deprivation (Martin et al., 1988),
these results support our hypothesis of the role of c-Jun
i expression. Because cultured neurons die via apoptosi
upon growth factor deprivation (Martin et al., 1988
these results support our hypothesis of the role of c-Ju
in nerve cell death (Dragunow et al., 1993c). Howeve
whethe upon growth fact
these results sup
in nerve cell deat
whether or not as
tosis is unknown.
Clearly, antise in nerve cell death (Dragunow et al., 1993c). However,
whether or not axotomised CNS neurons undergo apop-
tosis is unknown.
Clearly, antisense DNA studies are now required to

galanin (Rutherford et al., 1992a), and CCK (Saika et constant injury/repair/regeneration mechanisms. Also, be-
al., 1991) are also induced after axotomy. Calcitonin cause CNS axons can be induced to sprout after dener-
ge in nerve cell death (Dragunow et al., 1993c). However
whether or not axotomised CNS neurons undergo apop-
tosis is unknown.
Clearly, antisense DNA studies are now required to
determine the role of neuronal c-Jun expression whether or not axotomised CNS neurons undergo apoptosis is unknown.
Clearly, antisense DNA studies are now required to
determine the role of neuronal c-Jun expression in neu-
ronal injury/repair/regeneration mechanisms. Al tosis is unknown.
Clearly, antisense DNA studies are now required
determine the role of neuronal c-Jun expression in ne
ronal injury/repair/regeneration mechanisms. Also, l
cause CNS axons can be induced to sprout after de Clearly, antisense DNA studies are now required to
determine the role of neuronal c-Jun expression in neu-
ronal injury/repair/regeneration mechanisms. Also, be-
cause CNS axons can be induced to sprout after dener-
vation determine the role of neuronal c-Jun expression in neuronal injury/repair/regeneration mechanisms. Also, because CNS axons can be induced to sprout after denervation and seizures (Sutula et al., 1988), it will be interesti cause CNS axons can be induced to sprout after dener-
vation and seizures (Sutula et al., 1988), it will be
interesting to investigate the role of c-Jun expression in
these processes. For example, entorhinal cortex lesions cause CNS axons can be induced to sprout after dener-
vation and seizures (Sutula et al., 1988), it will be
interesting to investigate the role of c-Jun expression in
these processes. For example, entorhinal cortex lesions vation and seizures (Sutula et al., 1988), it will be
interesting to investigate the role of c-Jun expression in
these processes. For example, entorhinal cortex lesions
lead to a sprouting of medial septal axons into the d interesting to investigate the role of c-Jun expression in
these processes. For example, entorhinal cortex lesions
lead to a sprouting of medial septal axons into the den-
ervated hippocampus (Fagan and Gage, 1990). If c-J these processes. For example, entorhinal cortex lesions
lead to a sprouting of medial septal axons into the den-
ervated hippocampus (Fagan and Gage, 1990). If c-Jun
is involved in axonal growth rather than nerve cell
deat lead to a sprouting of medial septal axons into the denervated hippocampus (Fagan and Gage, 1990). If c-Jun is involved in axonal growth rather than nerve cell death, then it might be induced in these sprouting medial sept From the same and stage, 1999. If your involved in axonal growth rather than nerve cell
ath, then it might be induced in these sprouting me-
al septal neurons.
VIII. Potential Immediate-early Gene Protein
arget Genes wit In the Central Indian Section 2.1 and the Central death, then it might be induced in these sprouting medial septal neurons.
 Target Genes within the Central Nervous System

A number of potential target genes with AP-1-li

al septal neurons.
 VIII. Potential Immediate-early Gene Protein
 arget Genes within the Central Nervous System

A number of potential target genes with AP-1-like

quences have been described, including tyrosine hy-VIII. Potential Immediate-early Gene Protein
Target Genes within the Central Nervous System
A number of potential target genes with AP-1-like
sequences have been described, including tyrosine hy-
droxylase, thyrotropin-rel Target Genes within the Central Nervous System
A number of potential target genes with AP-1-like
sequences have been described, including tyrosine hy-
droxylase, thyrotropin-releasing hormone, CCK, glu-
tamic-acid decarbox A number of potential target genes with AP-1-like
sequences have been described, including tyrosine hy-
droxylase, thyrotropin-releasing hormone, CCK, glu-
tamic-acid decarboxylase, PENK, and NGF (White and
Gall, 1987; Hen

PHARMACOLOGICAL REVIEWS

Potential target genes for IEGF
Potential target genes for IEGF *ential target genes for I EGPs in CNS*

Selected References Gene potential Almost certain Prodynorphin Lucas et al., 1993 to be NGF; Tyrosine Hengerer et al., 1990; Strong hydroxylase possibility Gall and Isackson, Kilbourne et al., al., 1993; Nestler, 1992; Jehan et al., 1993; although see 1993 Possible Proenkephalin; TRH; CCK; GAD; GAP- Mar, et al., 1992; 43: Somatostatin: Konradi et al., 1993; Interleukins; Rosen et al., 1992a; $TNF\alpha$; TrkB; NPY; Olenik et al., 1991; h sp 70 ; NOS ; Najilerahim; Meberg galanin; CGRP et al., 1993; Pennypacker et al., 1993; Minami et al., 1991: Merlio et al., 1993; Kubek et al., 1993; Marksteiner et al., 1990; Dragunow	Potential target genes for IEGPs in CNS		
	Target gene		
			Mocchetti et al., 1989; 1989; Goc et al., 1992; 1992; Icard-Liepkalns et al., 1992; Weiser et Barbany and Persson,
Minet et al., 1993;			Sonnenberg et al., 1989; al., 1990; Wanscher et et al., 1992; Lanteri- Fiallos-Estrada et al., 1993; Herdegen et al.,
	Unlikelv	BDNF	Hughes et al., 1993a

Abbreviations: BDNF-Brain-derived neurotrophic factor, CCK-1993b

Unlikely BDNF Hughes et al., 1993a

Abbreviations: BDNF-Brain-derived neurotrophic factor, C

Cholecystokinin, CGRP-Calcitonin gene-related peptide, GAD-

tamic acid decarboxylase, GAP-Growth-associated protein, hsp Unlikely BDNF Hughes et al., 1993a
Abbreviations: BDNF-Brain-derived neurotrophic factor, CCK
Cholecystokinin, CGRP-Calcitonin gene-related peptide, GAD-Glu
tamic acid decarboxylase, GAP-Growth-associated protein, hsp-heat Abbreviations: BDNF-Brain-derived neurotrophic factor, CCF
Cholecystokinin, CGRP-Calcitonin gene-related peptide, GAD-Glutamic acid decarboxylase, GAP-Growth-associated protein, hsp-hes
shock protein, NGF-Nerve growth fact The Calcitonin gene-related peptide, GAD
tamic acid decarboxylase, GAP-Growth-associated protein, hsp
shock protein, NGF-Nerve growth factor, NOS-Nitric oxide synt
NPY-Neuropeptide Y, TNF-Tumor necrosis factor, TRH-T
tropi tramic acid decarboxylase, GAP-Growth-associated protein, hsp
shock protein, NGF-Nerve growth factor, NOS-Nitric oxide synt
NPY-Neuropeptide Y, TNF-Tumor necrosis factor, TRH-T
tropin-releasing hormone, Trk-Tyrosine kinase

NPY-Neuropeptide Y, TNF-Tumor necrosis factor, TRH-Thyro-
tropin-releasing hormone, Trk-Tyrosine kinase linked receptor.
Ballarin et al., 1991; Sonnenberg et al., 1989c; Gall and
Isaacson, 1989; Icard-Liepkalns et al., 199 tropin-releasing hormone, Trk-Tyrosine kinase linked receptor.
Ballarin et al., 1991; Sonnenberg et al., 1989c; Gall a
Isaacson, 1989; Icard-Liepkalns et al., 1992; Monst
1993; Rosen et al., 1992a; Olenik et al., 1991; Naj Ballarin et al., 1991; Sonnenberg et al., 1989c; Gall and
Isaacson, 1989; Icard-Liepkalns et al., 1992; Monstein,
1993; Rosen et al., 1992a; Olenik et al., 1991; Najilira-
him et al., 1991; Goc et al., 1992; Weiser et al., Ballarin et al., 1991; Sonnenberg et al., 1989c; Gall and Isaacson, 1989; Icard-Liepkalns et al., 1992; Monstein, 1993; Rosen et al., 1992a; Olenik et al., 1991; Najilirahim et al., 1991; Goc et al., 1992; Weiser et al., 1 Isaacson, 19
1993; Roser
him et al., .
Wessel and
(table 3).
Although

Wessel and Joh, 1992, although see Zhu et al., 1993)

(table 3).

Although the PENK gene has been proposed as an

IEGP target (late-response gene) (Sonnenberg et al., 1989c), we have recently found that although hippocam-Wessel and Joh, 1992, although see Zhu et al., 19

(table 3).

Although the PENK gene has been proposed as

IEGP target (late-response gene) (Sonnenberg et

1989c), we have recently found that although hippoc

pal injury i (table 3).

Although the PENK gene has been proposed as an

IEGP target (late-response gene) (Sonnenberg et al.,

1989c), we have recently found that although hippocam-

pal injury induces IEGPs in dentate granule cells,
 Although the PENK gene has been proposed as ar
IEGP target (late-response gene) (Sonnenberg et al.
1989c), we have recently found that although hippocam-
pal injury induces IEGPs in dentate granule cells
PENK mRNA is not i pal injury induces IEGPs in dentate granule cells, PENK mRNA is not induced (Hughes and Dragunow, unpublished observations). Also, a recent study demonstrates that PENK mRNA is induced in caudate neurons PENK mRNA is not induced (Hughes and Dragunow, regulated by Jun dimers.
unpublished observations). Also, a recent study demon-BDNF mRNA is induced in many situations where the
strates that PENK mRNA is induced in caudate n unpublished observations). Also, a recent study demonstrates that PENK mRNA is induced in caudate neurons after haloperidol injection via CREB phosphorylation, but c-Fos is not involved (Konradi et al., 1993). However, PENK mRNA is not induced (Hughes and Dragunow,
unpublished observations). Also, a recent study demon-
strates that PENK mRNA is induced in caudate neurons
after haloperidol injection via CREB phosphorylation,
but c-Fos is unpublished observations). Also, a recent study demonstrates that PENK mRNA is induced in caudate neurons
after haloperidol injection via CREB phosphorylation, l
but c-Fos is not involved (Konradi et al., 1993). However, strates that PENK mRNA is induced in caudate neurons
after haloperidol injection via CREB phosphorylation,
but c-Fos is not involved (Konradi et al., 1993). However,
in spinal cord cultures using antisense DNA methods, it
 after haloperidol injection via CREB phosphorylation,
but c-Fos is not involved (Konradi et al., 1993). However,
in spinal cord cultures using antisense DNA methods, it
has been demonstrated that $5HT_{1A}$ receptor agonist

DRAGUNOW
Fos expression (Lucas et al., 1993). This is the first
target gene to be unequivocally demonstrated in the DRAGUNOW
Fos expression (Lucas et al., 1993). This is the first
target gene to be unequivocally demonstrated in the
nervous system, although it will be important to dem-DRAGUNOW
Fos expression (Lucas et al., 1993). This is the first
arget gene to be unequivocally demonstrated in th
nervous system, although it will be important to dem
onstrate this action in vivo as well as in other brain Fos expression (Lucas et al., 1993). This is the first target gene to be unequivocally demonstrated in the nervous system, although it will be important to demonstrate this action in vivo as well as in other brain regions. target gene to be unequivocally demonstrated in the nervous system, although it will be important to demonstrate this action in vivo as well as in other brain regions. For example, cocaine induces IEGPs in striatal target gene to be unequivocally demonstrated in t
nervous system, although it will be important to de
onstrate this action in vivo as well as in other bra
regions. For example, cocaine induces IEGPs in striat
neurons and l nervous system, although it will be important to demonstrate this action in vivo as well as in other brain regions. For example, cocaine induces IEGPs in striatal neurons and leads to dynorphin gene expression (Graybiel et onstrate this action in vivo as well as in other brain regions. For example, cocaine induces IEGPs in striatal neurons and leads to dynorphin gene expression (Graybiel et al., 1990). Antisense DNA technology should be able regions. For example, cocaine in
neurons and leads to dynorphin
biel et al., 1990). Antisense DN
able to demonstrate any causa
1992; Dragunow et al., 1993b).
After brief and long seizures, biel et al., 1990). Antisense DNA technology should be able to demonstrate any causal link (Chiasson et al., 1992; Dragunow et al., 1993b). After brief and long seizures, induction of IEGPs in

dentate granule cells (Dragunow et al., 1992) may in-
duce axonal sprouting (Represa and Ben-Ari, 1992; able to demonstrate any causal link (Chiasson et al., 1992; Dragunow et al., 1993b).

After brief and long seizures, induction of IEGPs in dentate granule cells (Dragunow et al., 1992) may induce axonal sprouting (Represa 1992; Dragunow et al., 1993b).

After brief and long seizures, induction of IEGPs in

dentate granule cells (Dragunow et al., 1992) may in-

duce axonal sprouting (Represa and Ben-Ari, 1992;

Sutula et al., 1988, 1992) by After brief and long seizures, induction of IEGPs
dentate granule cells (Dragunow et al., 1992) may i
duce axonal sprouting (Represa and Ben-Ari, 199
Sutula et al., 1988, 1992) by regulating the expression
various growth-r dentate granule cells (Dragunow et al., 1992) may in-
duce axonal sprouting (Represa and Ben-Ari, 1992;
Sutula et al., 1988, 1992) by regulating the expression of
various growth-related genes: structural and/or micro-
tubu duce axonal sprouting (Represa and Ben-Ari, 1992;
Sutula et al., 1988, 1992) by regulating the expression of
various growth-related genes: structural and/or micro-
tubule proteins, growth-associated protein-43, NGFs
(Ernfo various growth-related genes: structural and/or micro-
tubule proteins, growth-associated protein-43, NGFs
(Ernfors et al., 1991; Gall and Isaacson, 1989; Meberg et
al., 1993), and/or growth factor receptors such as tran-
 various growth-related genes: structural and/or microtubule proteins, growth-associated protein-43, NGFs (Ernfors et al., 1991; Gall and Isaacson, 1989; Meberg et al., 1993), and/or growth factor receptors such as transket tubule proteins, growth-associated protein-43, NGFs (Ernfors et al., 1991; Gall and Isaacson, 1989; Meberg et al., 1993), and/or growth factor receptors such as transket
olaseB and transketblaseC (Bengzon et al., 1993).
Ex (Ernfors et al., 1991; Gall and Isaacson, 1989; Meberg et al., 1993), and/or growth factor receptors such as transketolaseB and transketolaseC (Bengzon et al., 1993).
Expression of Fos-Fra/Jun-D dimers in somatostatin neur sketolaseB and transketolaseC (Bengzon et al., 1993).
Expression of Fos-Fra/Jun-D dimers in somatostatin
neurons after seizures (Dragunow et al., 1992) may be
involved in regulation of the somatostatin gene after
seizure sketolaseB and transketolaseC (Bengzon et al., 1993).
Expression of Fos-Fra/Jun-D dimers in somatostatin
neurons after seizures (Dragunow et al., 1992) may be
involved in regulation of the somatostatin gene after
seizure a Expression of Fos-Fra/Jun-D dimers in somatostat
neurons after seizures (Dragunow et al., 1992) may
involved in regulation of the somatostatin gene aft
seizure activity. Seizures also induce (a) neuropeptid
PENK, neuropept neurons after seizures (Dragunow et al., 1992) may be
involved in regulation of the somatostatin gene after
seizure activity. Seizures also induce (a) neuropeptides
PENK, neuropeptide Y, preprodynorphin, and thyro-
tropi involved in regulation of the somatostatin gene after
seizure activity. Seizures also induce (a) neuropeptides
PENK, neuropeptide Y, preprodynorphin, and thyro-
tropin-releasing hormone and (b) glutamate receptors,
as w seizure activity. Seizures also induce (a) neuropeptides PENK, neuropeptide Y, preprodynorphin, and thyrotropin-releasing hormone and (b) glutamate receptors, as well as (c) interleukins and TNF α and transketolaseB PENK, neuropeptide Y, preprodynorphin, and thyro-
tropin-releasing hormone and (b) glutamate receptors,
as well as (c) interleukins and TNF α and transketolaseB
in dentate granule cells (Pennypacker et al., 1993; Ka-
mp tropin-releasing hormone and (b) glutamate receptors,
as well as (c) interleukins and TNF α and transketolaseB
in dentate granule cells (Pennypacker et al., 1993; Ka-
mphuis et al., 1992; Minami et al., 1991; Merlio e as well as (c) interleukins and TNF α and transketolaseB
in dentate granule cells (Pennypacker et al., 1993; Ka-
mphuis et al., 1992; Minami et al., 1991; Merlio et al.,
1993; Kubek et al., 1993; Rosen et al., 1992a, 1 in dentate granule cells (Pennypacker et al., 1993; Ka-
mphuis et al., 1992; Minami et al., 1991; Merlio et al.,
1993; Kubek et al., 1993; Rosen et al., 1992a, 1993;
Marksteiner et al., 1990); these may be controlled by th mphuis et al., 1992; Minami et al., 1991; Merlio et al., 1993; Kubek et al., 1993; Rosen et al., 1992a, 1993; Marksteiner et al., 1990); these may be controlled by the earlier IEGP expression that occurs selectively in the 1993; Kubek et al., 1993; Rosen et al., 1992a, 1993; Marksteiner et al., 1990); these may be controlled by the earlier IEGP expression that occurs selectively in these dentate granule cells after brief seizures (Dragunow a tubule proteins, growth-associated protein-43, NGFs
(Ernfors et al., 1991; Gall and Isaacson, 1988; Meberg et
al., 1993), and/or growth factor receptors such as tran-
sketolaseB and transketolaseC (Bengzon et al., 1993).

shock protein, NGF-Nerve growth factor, NOS-Nitric oxide synthase,

NPY-Neuropeptide Y, TNF-Tumor necrosis factor, TRH-Thyro-

te al., 1991). Furthermore, there is some evidence for a

tropin-releasing hormone, Trk-Tyrosin him et al., 1991; Goc et al., 1992; Weiser et al., 1993a; been proposed to be IEGP targets after axotomy, includ-
Wessel and Joh, 1992, although see Zhu et al., 1993) ing (a) heat-shock protein 70 (Lanteri-Minet et al.,
(earlier IEGP expression that occurs selectively in these
dentate granule cells after brief seizures (Dragunow and
Robertson, 1987b; Dragunow et al., 1992).
Injury to the neocortex can rapidly induce IEGPs in
neocortical ne dentate granule cells after brief seizures (Dragunow and Robertson, 1987b; Dragunow et al., 1992).
Injury to the neocortex can rapidly induce IEGPs in
neocortical neurons (Dragunow and Robertson, 1988b)
and cause a more de Robertson, 1987b; Dragunow et al., 1992).

Injury to the neocortex can rapidly induce IEGPs in

neocortical neurons (Dragunow and Robertson, 1988b)

and cause a more delayed expression of CCK (Olenik et

al., 1991) and glu Injury to the neocortex can rapidly induce IEGPs in
neocortical neurons (Dragunow and Robertson, 1988b)
and cause a more delayed expression of CCK (Olenik et
al., 1991) and glutamic-acid decarboxylase (Najilerahim
et al., relation and Robertson, 198
and cause a more delayed expression of CCK (Olenil
al., 1991) and glutamic-acid decarboxylase (Najileral
et al., 1991). Furthermore, there is some evidence fo
role for c-Fos in the regulation of and cause a more delayed expression of CCK (Olenik et al., 1991) and glutamic-acid decarboxylase (Najilerahim et al., 1991). Furthermore, there is some evidence for a role for c-Fos in the regulation of the tyrosine hydrox al., 1991) and glutamic-acid decarboxylase (Najilerahim

et al., 1991). Furthermore, there is some evidence for a

role for c-Fos in the regulation of the tyrosine hydroxy-

lase gene in LC neurons after axotomy (Weiser et et al., 1991). Furthermore, there is some evidence for a role for c-Fos in the regulation of the tyrosine hydroxy-
lase gene in LC neurons after axotomy (Weiser et al., 1993a). c-Fos may also be involved in the increase in lase gene in LC neurons after axotomy (Weiser et al., 1993a). c-Fos may also be involved in the increase in 1993a). c-Fos may also be involved in the increase in tyrosine hydroxylase expression that follows chronic opiate injection (Nestler, 1992). A number of genes have been proposed to be IEGP targets after axotomy, including tyrosine hydroxylase expression that follows chronic opi-
ate injection (Nestler, 1992). A number of genes have
been proposed to be IEGP targets after axotomy, includ-
ing (a) heat-shock protein 70 (Lanteri-Minet et al.,
1 ate injection (Nestler, 1992). A number of genes have
been proposed to be IEGP targets after axotomy, includ-
ing (a) heat-shock protein 70 (Lanteri-Minet et al.,
1993), which contains an ATF-binding site, (b) nitric
oxide been proposed to be IEGP targets after axotomy, includ-
ing (a) heat-shock protein 70 (Lanteri-Minet et al.,
1993), which contains an ATF-binding site, (b) nitric
oxide synthase (Fiallos-Estrada et al., 1993), (c) galanin, ing (a) heat-shock protein 70 (Lanteri-Minet et al., 1993), which contains an ATF-binding site, (b) nitric oxide synthase (Fiallos-Estrada et al., 1993), (c) galanin, and (d) calcitonin gene-related peptide (Herdegen oxide synthase (Fiallos-Estrada et al., 1993), (c) galanin, and (d) calcitonin gene-related peptide (Herdegen et al., 1993b; Rutherford et al., 1993; Saika et al., 1991), al-% oxide synthase (Fiallos-Es
and (d) calcitonin gene-rel
1993b; Rutherford et al.,
though there is no direct ϵ
regulated by Jun dimers.
BDNF mRNA is induced

BDNF mRNA is induced in many situations where the 1993b; Rutherford et al., 1993; Saika et al., 1991), although there is no direct evidence that any of these are regulated by Jun dimers.

BDNF mRNA is induced in many situations where the Fos, Jun and Krox families of IEGP though there is no direct evidence that any of these are
regulated by Jun dimers.
BDNF mRNA is induced in many situations where the
Fos, Jun and Krox families of IEGPs are induced; the
BDNF mRNA induction is delayed with r regulated by Jun dimers.

BDNF mRNA is induced in many situations where the

Fos, Jun and Krox families of IEGPs are induced; the

BDNF mRNA induction is delayed with respect to the

IEGP expression: after MK801 injection BDNF mRNA is induced in many situations where th
Fos, Jun and Krox families of IEGPs are induced; th
BDNF mRNA induction is delayed with respect to th
IEGP expression: after MK801 injection (Hughes et al
1993b), after LTP Fos, Jun and Krox families of IEGPs are induced; the
BDNF mRNA induction is delayed with respect to the
IEGP expression: after MK801 injection (Hughes et al.,
1993b), after LTP via NMDA receptor activation (Dra-
gunow et a BDNF mRNA induction is delayed with respect to the IEGP expression: after MK801 injection (Hughes et al., 1993b), after LTP via NMDA receptor activation (Dragunow et al., 1993a), and after hippocampal injury via NMDA recep

PHARMACOLOGICAL REVIEW!

 \mathbf{E}

IMMEDIATE-EARLY GEN
suggest that BDNF may be a target of IEGP expression
However, we (Hughes et al., 1993a) and others (Demelle IMMEDIATE-EARLY GENES AIR suggest that BDNF may be a target of IEGP expression. AIR However, we (Hughes et al., 1993a) and others (Demello et al., 1992) have found that BDNF expression after AI IMMEDIATE-EARLY GENES
suggest that BDNF may be a target of IEGP expression.
However, we (Hughes et al., 1993a) and others (Demello
et al., 1992) have found that BDNF expression after
hippocampal injury and seizures is not metally and suggest that BDNF may be a target of IEGP expression
However, we (Hughes et al., 1993a) and others (Demel
et al., 1992) have found that BDNF expression after
hippocampal injury and seizures is not blocked by cy suggest that BDNF may be a target of IEGP expression.
However, we (Hughes et al., 1993a) and others (Demello
et al., 1992) have found that BDNF expression after
hippocampal injury and seizures is not blocked by cyclo-
hexi However, we (Hughes et al., 1993a) and others (Demello
et al., 1992) have found that BDNF expression after
hippocampal injury and seizures is not blocked by cyclo-
heximide, a protein synthesis inhibitor that prevents
IEGP et al., 1992) have found that BDNF expression after
hippocampal injury and seizures is not blocked by cyclo-
heximide, a protein synthesis inhibitor that prevents
IEGP induction (Hughes et al., 1993a), suggesting that
BDNF ppocampal injury and seizures is not blocked by cyclo-
eximide, a protein synthesis inhibitor that prevents
GCP induction (Hughes et al., 1993a), suggesting that
DNF is not an IEGP target but is itself an IEG.
As an IEG, i

heximide, a protein synthesis inhibitor that prevents
IEGP induction (Hughes et al., 1993a), suggesting that
BDNF is not an IEGP target but is itself an IEG.
As an IEG, it seems to have both an interneuronal
signalling and IEGP induction (Hughes et al., 1993a), suggesting that
BDNF is not an IEGP target but is itself an IEG.
As an IEG, it seems to have both an interneurona
signalling and DNA binding capacity (Wetmore et al.
1991). Thus, BDNF BDNF is not an IEGP target but is itself an IEG.
As an IEG, it seems to have both an interneuronal
signalling and DNA binding capacity (Wetmore et al.,
1991). Thus, BDNF may also function as a TF in neu-
rons. Interestingl As an IEG, it seems to have both an interneuronal
signalling and DNA binding capacity (Wetmore et al.,
1991). Thus, BDNF may also function as a TF in neu-
rons. Interestingly, expression of BDNF after LTP cor-
relates with signalling and DNA binding capacity (Wetmore et al., 1991). Thus, BDNF may also function as a TF in neurons. Interestingly, expression of BDNF after LTP correlates with LTP maintenance (Dragunow et al., 1993a) and BDNF see 1991). Thus, BDNF may also function as a TF in neurons. Interestingly, expression of BDNF after LTP correlates with LTP maintenance (Dragunow et al., 1993a) and BDNF seems to be involved in spatial memory processes (Falke rons. Interestingly, expression of BDNF after LTP correlates with LTP maintenance (Dragunow et al., 1993a) and BDNF seems to be involved in spatial memory processes (Falkenberg et al., 1992). It may regulate both pre- and relates with LTP maintenance (Dragunow et al., 1993a)
and BDNF seems to be involved in spatial memory pro-
cesses (Falkenberg et al., 1992). It may regulate both
pre- and post-synaptic activity during LTP by acting as
both and BDNF seems to be involved in spatial memory processes (Falkenberg et al., 1992). It may regulate both Hermi
pre- and post-synaptic activity during LTP by acting as Hermi
both a retrograde messenger and as a TF cesses (Falkenberg et al., 1992). It may regulate both
pre- and post-synaptic activity during LTP by acting as
both a retrograde messenger and as a TF (Dragunow et
al., 1993a). Thus, it may play a crucial role in LTP
stabi pre- and post-synaptic activity during LTP by acting as
both a retrograde messenger and as a TF (Dragunow et
al., 1993a). Thus, it may play a crucial role in LTP
stabilisation. However, it is clearly not a target gene for
 both a retrograde messenger and as a TF (Dragunow et al., 1993a). Thus, it may play a crucial role in LTP stabilisation. However, it is clearly not a target gene for IEGPs. NGF may be a more likely candidate target gene, i al., 1993a). Thus, it may play a crucial role in LTP stabilisation. However, it is clearly not a target gene for IEGPs. NGF may be a more likely candidate target gene, in insmuch as it is induced by injury in dentate gran stabilisation. However, it is clearly not a target gene for IEGPs. NGF may be a more likely candidate target gene, inasmuch as it is induced by injury in dentate granule cells (Ballarin et al., 1991), although a recent stu IEGPs. NGF may be a more likely candidate target genes in
assmuch as it is induced by injury in dentate granul
cells (Ballarin et al., 1991), although a recent stud
indicates a clear dissociation between seizure-induce
c-F inasmuch as it is induced by injury in dentate granule

cells (Ballarin et al., 1991), although a recent study

indicates a clear dissociation between seizure-induced

c-Fos and NGF expression after adrenalectomy (Bar-

b cells (Ballarin et al., 1991), although a recent study
indicates a clear dissociation between seizure-induced
c-Fos and NGF expression after adrenalectomy (Bar-
bany and Persson, 1993). Therefore, apart from the
dynorphin indicates a clear dissociation between seizure-induced
c-Fos and NGF expression after adrenalectomy (Bar-
bany and Persson, 1993). Therefore, apart from the
dynorphin gene in spinal cord cultures, no other genes
have been c-Fos and NGF ex-
bany and Persson
dynorphin gene in
have been definitive
IEGPs in neurons.
Since their initimorphin gene in spinal cord cultures, no other genes Asinx
we been definitively demonstrated to be regulated by
it is in neurons.
Since their initial identification in brain neurons in x_0
87 (Dragunow et al., 1987; Mor

dynorphin gene in spinal cord cultures, no other genes
have been definitively demonstrated to be regulated by

IEGPs in neurons.

Since their initial identification in brain neurons in

1987 (Dragunow et al., 1987; Morgan have been definitively demonstrated to be regulated by

IEGPs in neurons.

Since their initial identification in brain neurons in

1987 (Dragunow et al., 1987; Morgan et al., 1987), a

wealth of studies have investigated IEGPs in neurons.
Since their initial identification in brain neurons in
1987 (Dragunow et al., 1987; Morgan et al., 1987), a
wealth of studies have investigated IEGPs in both the
peripheral nervous system and CNS. These s Since their initial identification in brain ne
1987 (Dragunow et al., 1987; Morgan et al.,
wealth of studies have investigated IEGPs in
peripheral nervous system and CNS. These stu
gest important roles for IEGPs in neurotr 1987 (Dragunow et al., 1987; Morgan et al., 1987), a
wealth of studies have investigated IEGPs in both the
peripheral nervous system and CNS. These studies sug-
gest important roles for IEGPs in neurotransmitter-reg-
ulate wealth of studies have investigated IEGPs in both the Axis
peripheral nervous system and CNS. These studies suggest important roles for IEGPs in neurotransmitter-reg-
ulated gene expression in the brain. However, the full fulfilled.

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