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 Atrial Natriuretic Factor Receptors and Signal
 Transduction Mechanisms* for Pharmacology and Experimental Therapeutics
 Transduction Mechanisms*

NDHU B. ANAND-SRIVASTAVA¹† AND GEORGE J. TRACHTE⁴ Transduction Mechanisms*
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Quebec, Canada, and 2Department of Pharmacology, University of Minnesota-Duluth, School of Medicine, Duluth, Minnesota

5. Atrial natriuretic factor effects on eicosanoid and endothelium-derived relaxing factor
production in the vasculature
* The research in the authors' laboratories has been supported by grants from the Quebec Heart Founda the research in the authors' laboratories has been supported by grants from the Quebec Heart Foundation and Medical Research Council of Canada (MRC MT 11024) to M. B. A.-S. and grant HL42525 from the National Institutes of Faculty of Medicine, University of Montreal, C. P. 6128, Succursale A, Montréal, Québec, Canada H3C 3J7.

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I. Introduction M
ANF[†] was discovered by de Bold et al. (1981, 1982) as ^{su}
endogenous diuretic stored in atrial granules. It ini-I. Introduction
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ANF‡ was discovered by de Bold et al. (1981, 1982) as
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ANF‡ was discovered by de Bold et al. (1981, 1982) as
an endogenous diuretic stored in atrial granules. It ini-
tially was heralded as the long sought after plasma na-
triuretic substance; however, an in ANF \ddagger was discovered by de Bold et al. (1981, 1982) an endogenous diuretic stored in atrial granules. It in tially was heralded as the long sought after plasma nutriuretic substance; however, an in depth analysis of in an endogenous diuretic stored in atrial granules. It initially was heralded as the long sought after plasma natriuretic substance; however, an in depth analysis of its matricins indicated that ANF has diverse biological a Fully was heralded as the long sought after plasma na-
triuretic substance; however, an in depth analysis of its
actions indicated that ANF has diverse biological activities at both renal and extrarenal sites. Its role in actions indicated that ANF has diverse biological activactions indicated that ANF has diverse biological activities at both renal and extrarenal sites. Its role in kidney function was reviewed by Goetz (1990) who questioned its physiological significance as an endogenous diure ities at both renal and extrarenal sites. Its role in kidney
function was reviewed by Goetz (1990) who questioned
its physiological significance as an endogenous diuretic,
and Richards (1990) reviewed the literature suppor function was reviewed by Goetz (1990) who questioned
its physiological significance as an endogenous diuretic,
and Richards (1990) reviewed the literature supporting
a physiological renal function for ANF. This review wil its physiological significance as an endogenous diuretic,

and Richards (1990) reviewed the literature supporting

a physiological renal function for ANF. This review will

focus on the signal transduction mechanisms medi and Richards (1990) reviewed the literature supportively physiological renal function for ANF. This review w
focus on the signal transduction mechanisms mediatio
biological actions of ANF. We shall emphasize AN
receptors w focus on the signal transduction mechanisms mediating
biological actions of ANF. We shall emphasize ANF
receptors with their associated intracellular signal trans-
duction mechanisms. Some of the major biological activ-
it focus on the signal transduction mechanisms mediating
biological actions of ANF. We shall emphasize ANF
receptors with their associated intracellular signal trans-
duction mechanisms. Some of the major biological activ-
it duction mechanisms. Some of the major biological activities of ANF will be matched to causative transduction mechanisms in the instances where adequate experimental evidence is available to make this assessment. Finally, p receptors with their associated intracellular signal trans-
duction mechanisms. Some of the major biological activ-
ities of ANF will be matched to causative transduction
mechanisms in the instances where adequate experime duction mechanisms. Some of the major biological activities of ANF will be matched to causative transduction
mechanisms in the instances where adequate experimental evidence is available to make this assessment. Finally,
p mechanisms will be covered.
The perception of ANF signal transduction pathways echanisms in the instances where adequate experimendevidence is available to make this assessment. Finally, thophysiological alterations in these transduction echanisms will be covered.
The perception of ANF signal transdu

the evolution of ANF signal transduction and photophysiological alterations in these transduction The perception of ANF signal transduction pathways has evolved recently away from the concept that GC and partivation accoun pathophysiological alterations in these transduction \overline{a} actime accounts will be covered.
The perception of ANF signal transduction pathways kidnes evolved recently away from the concept that GC and activation accoun mechanisms will be covered.

The perception of ANF signal transduction pathways

has evolved recently away from the concept that GC an

activation accounts for all biological effects of ANF. In

keeping with this principl The perception of ANF signal transduction pathways
has evolved recently away from the concept that GC and
activation accounts for all biological effects of ANF. In
the so-called "clearance") receptor mediates at least som has evolved recently away from the concept that GC
activation accounts for all biological effects of ANF. In
keeping with this principle, it appears that the R_2 (the
so-called "clearance") receptor mediates at least so activation accounts for all biological effects of ANF. In keeping with this principle, it appears that the R_2 (the so-called "clearance") receptor mediates at least some of the biological activities of ANF. These two p keeping with this principle, it appears that the R_2 (the so-called "clearance") receptor mediates at least some of the biological activities of ANF. These two points rep-
resent major deviations from the widely held be so-called "clearance") receptor mediates at least some of
the biological activities of ANF. These two points rep-
resent major deviations from the widely held beliefs that
ANF acts solely by stimulating the synthesis of c the biological activities of ANF. These two portogent major deviations from the widely held be ANF acts solely by stimulating the synthesis and that the R_2 receptor is merely a binding promoting the clearance of ANF fr Superty may be via tions from the widely held beliefs
NF acts solely by stimulating the synthesis of cG
d that the R_2 receptor is merely a binding pro
omoting the clearance of ANF from plasma.
ANF is synthesized primar

and that the R_2 receptor is merely a binding protein G(
promoting the clearance of ANF from plasma. 18
ANF is synthesized primarily in atria as a preprohor-
affinione that is cleaved to a prohormone of 126 amino acids promoting the clearance of ANF from plasma. 180

ANF is synthesized primarily in atria as a preprohor-

affin

mone that is cleaved to a prohormone of 126 amino acids

al.,

(Gardner et al., 1991). The carboxy-terminal 28 ANF is synthesized primarily in atria as a preprohemone that is cleaved to a prohormone of 126 amino ac (Gardner et al., 1991). The carboxy-terminal 28 amino acids represent the principal circulating form of Al (Thibault e mone that is cleaved to a prohormone of 126 amino acids
(Gardner et al., 1991). The carboxy-terminal 28 amino
acids represent the principal circulating form of ANF
(Thibault et al., 1985; Glembotski et al., 1988). Deriva-
 (Gardner et al., 1991). The carboxy-terminal 28 amino
acids represent the principal circulating form of ANF
(Thibault et al., 1985; Glembotski et al., 1988). Deriva-
tives of ANF will be presented in this review by their
 acids represent the principal circulating form of AN
(Thibault et al., 1985; Glembotski et al., 1988). Derive
tives of ANF will be presented in this review by the
correspondence with the prohormone molecule, such tha
the c rrespondence with the prohormone molecule, such t
e circulating form of ANF is designated ANF(99–12

[†] Abbreviations: ANF, atrial natriuretic factor; ACTH, adreno

otropin; ATP, adenosine triphosphate; BNP, brain natriur

Many other designations for ANF are commonly used, Many other designations for ANF are commonly used,
such as atriopeptins, cardionatrin, auriculin, and atrial
natriuretic peptide. The amino terminal ANF(1-98) frag-Many other designations for ANF are commonly used
such as atriopeptins, cardionatrin, auriculin, and atria
natriuretic peptide. The amino terminal ANF(1-98) frag
ment is processed into ANF(1-30) and ANF(31-67) frag Many other designations for ANF are commonly used
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ment is processed into ANF(1–30) and ANF(31–67) frag-
ments, which also possess biological activity, but inf natriuretic peptide. The amino terminal ANF(1-98) fragment is processed into ANF(1-30) and ANF(31-67) fragments, which also possess biological activity, but information regarding their biological significance is limited to ment is processed into ANF(1–30) and ANF(31–67) fragments, which also possess biological activity, but information regarding their biological significance is limited to the fact that they activate GC, promote hypotension a 1988). ation regarding their biological significance is limited
the fact that they activate GC, promote hypotension
d natriuresis, and are vasodilators (Winters et al.,
88).
Other natriuretic peptides also have been discovered.
h

to the fact that they activate GC, promote hypotension
and natriuresis, and are vasodilators (Winters et al.,
1988).
Cher natriuretic peptides also have been discovered.
They include BNP (Sudoh et al., 1988), CNP (Sudoh et and natriuresis, and are vasodilators (Winters et al., 1988).

Other natriuretic peptides also have been discovered.

They include BNP (Sudoh et al., 1988), CNP (Sudoh et

al., 1990), and urodilatin (ANF 95-126) (Schulz-Kn 1988).

Other natriuretic peptides also have been discovered.

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al., 1990), and urodilatin (ANF 95-126) (Schulz-Knappe

et al., 1988). A full discussion of their biologi Other natriuretic peptides also have been discovered.
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al., 1990), and urodilatin (ANF 95–126)
et al., 1988). A full discussion of their bis
is precluded by an absence of studies e
other than GC activation and diuresis.
ANF promotes biolog , 1990), and urodilatin (ANF 95–126) (Schulz-Knappe
al., 1988). A full discussion of their biological activities
precluded by an absence of studies examining effects
her than GC activation and diuresis.
ANF promotes biolog

et al., 1988). A full discussion of their biological activities
is precluded by an absence of studies examining effects
other than GC activation and diuresis.
ANF promotes biological responses by interacting with
receptors is precluded by an absence of studies examining effects
other than GC activation and diuresis.
ANF promotes biological responses by interacting with
receptors on the plasma membrane either to generate
second-messenger mole other than GC activation and diuresis.
ANF promotes biological responses by interacting with
receptors on the plasma membrane either to generate
second-messenger molecules or to influence ion channels.
The primary effects ANF promotes biological responses by interacting with
receptors on the plasma membrane either to generat
second-messenger molecules or to influence ion channels
The primary effects of ANF are perceived to involve
actions o receptors on the plasma membrane either to generate second-messenger molecules or to influence ion channels.
The primary effects of ANF are perceived to involve actions on the following organs or systems: vasculature, kidn second-messenger molecules or to influence ion channel. The primary effects of ANF are perceived to investions on the following organs or systems: vasculat kidney, adrenal, heart, lung, endocrine organs, neurand platelets. actions on the following organs or systems: vasculature, kidney, adrenal, heart, lung, endocrine organs, neurons, and platelets. The ANF receptors and signal transduction mechanisms for these areas will be presented.
II. A kidney, adrenal, heart, lung, endocrine organs, neurons, and platelets. The ANF receptors and signal transduction mechanisms for these areas will be presented.
II. Atrial Natriuretic Factor Receptors
A. Overview tion mechanisms for these areas will be presented.

ANF acts solely by stimulating the synthesis of cGMP those that activate GC (R_1) and that do not (R_2) . The and that the R_2 receptor is merely a binding protein GC-coupled receptors have a molecular mass of 130 to p ANF receptors are divided into two major categories: **H. Atrial Natriuretic Factor Receptors**
A. Overview
ANF receptors are divided into two major categories:
those that activate GC (R_1) and that do not (R_2) . The
GC-coupled receptors have a molecular mass of 130 to A. Overview
ANF receptors are divided into two major categories:
those that activate GC (R_1) and that do not (R_2) . The
GC-coupled receptors have a molecular mass of 130 to
180 kDa and can be subdivided based on high o ANF receptors are divided into two major categories:

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af ANF receptors are divided into two major categories:
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GC-coupled receptors have a molecular mass of 130 to
180 kDa and can be subdivided based on high or low
affini those that activate GC (R_1) and that do not (R_2) . The GC-coupled receptors have a molecular mass of 130 to 180 kDa and can be subdivided based on high or low affinities for the ANF-related peptides, BNP (Chang et al., GC-coupled receptors have a molecular mass of 130 to 180 kDa and can be subdivided based on high or low affinities for the ANF-related peptides, BNP (Chang et al., 1989) or CNP (Sudoh et al., 1990). Receptors with a higher 180 kDa and can be subdivided based on high or low
affinities for the ANF-related peptides, BNP (Chang et
al., 1989) or CNP (Sudoh et al., 1990). Receptors with a
higher affinity for ANF have been designated GC-A, and
thos affinities for the ANF-related peptides, BNP (Chang et al., 1989) or CNP (Sudoh et al., 1990). Receptors with a higher affinity for ANF have been designated GC-A, and those possessing a greater affinity for CNP or BNP are al., 1989) or CNP (Sudoh et al., 1990). Receptors with a higher affinity for ANF have been designated GC-A, and those possessing a greater affinity for CNP or BNP are known as GC-B (Chang et al., 1989); Schultz et al., 19 higher affinity for ANF have been designated GC-A, and
those possessing a greater affinity for CNP or BNP are
known as GC-B (Chang et al., 1989; Schultz et al., 1989).
The R₂ receptor has been promoted as a "clearance
r those possessing a greater affinity for CNP or BNP are
known as GC-B (Chang et al., 1989; Schultz et al., 1989).
The R_2 receptor has been promoted as a "clearance
receptor," as indicated above. The R_2 receptor exist known as GC-B (Chang et al., 1989; Schultz et al., 1989).
The R_2 receptor has been promoted as a "clearance
receptor," as indicated above. The R_2 receptor exists as
a monomer (66 kDa) and as a dimer (130 kDa) (Leitm receptor," as indicated above. The R_2 receptor exists as
a monomer (66 kDa) and as a dimer (130 kDa) (Leitman
et al., 1986). The following discussion will summarize the
evidence from radioligand-binding, autoradiograph receptor," as indicated above. The R_2 receptor exists as
a monomer (66 kDa) and as a dimer (130 kDa) (Leitman
et al., 1986). The following discussion will summarize the
evidence from radioligand-binding, autoradiograph a monomer (66 kDa) and as a dimer (130 kDa) (I
et al., 1986). The following discussion will summa
evidence from radioligand-binding, autoradiogra
gand-cross-linking, and cloning studies which
for our present understanding evidence from radioligand-binding, autoradiographic, li-
gand-cross-linking, and cloning studies which account
for our present understanding of ANF receptors.
B. Radioligand-binding Studies
1. Vasculature. Vascular tissu

nd-cross-linking, and cloning studies which account

¹. Our present understanding of ANF receptors.
 Radioligand-binding Studies
 1. Vasculature. Vascular tissues bound labeled ANF

th relatively high affinities. The for our present understanding of ANF receptors.
 B. Radioligand-binding Studies

1. Vasculature. Vascular tissues bound labeled ANF

with relatively high affinities. The concentration of ANF

producing half-maximal bind *B. Radioligand-binding Studies*
1. Vasculature. Vascular tissues bound labeled ANF
with relatively high affinities. The concentration of ANF
producing half-maximal binding (K_d) was 129 pM in
aortic membranes, identifying B. Kaatougana-binding Studies

1. Vasculature. Vascular tissues bound labeled ANF

with relatively high affinities. The concentration of ANF

producing half-maximal binding (K_d) was 129 pM in

aortic membranes, identifyi producing half-maximal binding (K_d) was 129 pM in aortic membranes, identifying only one binding site (Napier et al., 1984). The affinities for other vascular smooth

the circulating form of ANF is designated ANF(99–126)

⁺ Abbreviations: ANF, atrial natriuretic factor; ACTH, adrenocor

ticotropin; ATP, adenosine triphosphate; BNP, brain natriuretic pep

tide; cANF, des[Gln¹⁸, Ser¹ ^t Abbreviations: ANF, atrial natriuretic factor; ACTH, adrenocor-
ticotropin; ATP, adenosine triphosphate; BNP, brain natriuretic pep-
tide; cANF, des[Gln¹⁸, Ser¹⁹, Gln²⁰, Leu²¹, Gly²²]ANF₄₋₂₃; CNP, C-type
na [†] Abbreviations: ANF, atrial natriuretic factor; ACTH, adrenocorticotropin; ATP, adenosine triphosphate; BNP, brain natriuretic pep-
tide; cANF, des[Gln¹⁸, Ser¹⁹, Gln²⁹, Leu²¹, Gly²²]ANF₄₋₂₃; CNP, C-type
natr Education: CANF, des[Gln¹⁸, Ser¹⁹, Gln²⁹, Leu²¹, Gly²²]ANF₄₋₂₅; CNP, C-type inatriuretic peptide; cAMP, cyclic adenoaine monophosphate; cGMP, cyclic guanosine monophosphate; DOCA, deoxycorticosterone acetate; E tide; cANF, des[Gln¹⁸, Ser¹⁹, Gln²⁰, Leu²¹, Gly²²]ANF₄₋₂₅; CNP, C-type
natriuretic peptide; cAMP, cyclic adenosine monophosphate; cGMP,
cyclic guanosine monophosphate; DOCA, deoxycorticosterone acetate;
EDRF, e GUAR's endothelium-derived relaxing factor; GC, guanylyl cycles.

FLPRF, endothelium-derived relaxing factor; GC, guanylyl cycles

protein; G_u, inhibitory G-protein; G_o, G-protein of unknown further

GTP, guanosine tri protein; G_u, inhibitory G-protein; G_o, G-protein of unknown functions;
GTP, guanosine triphosphate; GTP₇S, guanosine 5'-(O-thiotriphos-
phate); IP_s, inositol trisphosphate; K_d , dissociation constant; K_i , inhi-
 GTP, guanosine triphosphate; GTP γ S, guanosine 5'-(O-thiotriphosphate); IP₃, inositol trisphosphate; K_d , dissociation constant; K_i , inhibition constant; PT, pertussis toxin; SHR, spontaneously hypertensive rat; WK

⁴⁵⁸ **ANAND-SRIVASTAVA AND TRACHTE** muscles varied from 12 to 102 pM in rat mesenteric ARAND-SRIVASTAVA
muscles varied from 12 to 102 pM in rat mesenteric in
arteries (Schiffrin et al., 1985, 1986b), 600 pM in bovine
pulmonary vascular smooth muscle (Redmond et al., 19 ANAND-SRIVASTAV.

muscles varied from 12 to 102 pM in rat mesenteric

arteries (Schiffrin et al., 1985, 1986b), 600 pM in bovine

pulmonary vascular smooth muscle (Redmond et al.,

1990), and 1000 pM in bovine aortic smoot muscles varied from 12 to 102 pM in rat mesenteric in arteries (Schiffrin et al., 1985, 1986b), 600 pM in bovine p
pulmonary vascular smooth muscle (Redmond et al., 1990), and 1000 pM in bovine aortic smooth muscle w
(Scar muscles varied from 12 to 102 pM in rat mesenteric interies (Schiffrin et al., 1985, 1986b), 600 pM in bovine pulmonary vascular smooth muscle (Redmond et al., 1990), and 1000 pM in bovine aortic smooth muscle (Scarbouroug arteries (Schiffrin et al., 1985, 1986b), 600 pM in bovine papulmonary vascular smooth muscle (Redmond et al., 1990), and 1000 pM in bovine aortic smooth muscle with a generally higher affinity variant species also bound pulmonary vascular smooth muscle (Redmond et al., 1990), and 1000 pM in bovine aortic smooth muscle w
(Scarbourough et al., 1986). Endothelial cells of various age
species also bound ANF with a generally higher affinity va 1990), and 1000 pM in bovine aortic smooth muscle wi
(Scarbourough et al., 1986). Endothelial cells of various age
species also bound ANF with a generally higher affinity va
than smooth muscle cells. The K_d values for A (Scarbourough et al., 1986). Endothelial cells of various species also bound ANF with a generally higher affinity than smooth muscle cells. The K_d values for ANF binding to endothelium from various vascular segments wer species also bound ANF with a generally higher affinity vas
than smooth muscle cells. The K_d values for ANF binding tiss
to endothelium from various vascular segments were the
following: 100 pM for bovine aorta (Leitman than smooth muscle cells. The K_d values for ANF binding tis
to endothelium from various vascular segments were the
following: 100 pM for bovine aorta (Leitman and Murad,
1986), 400 pM for bovine brain (Smith et al., 198 to endothelium from various vascular segments were the following: 100 pM for bovine aorta (Leitman and Murad, vertilized), 400 pM for bovine brain (Smith et al., 1988), and behinding site was identified in all of these stu following: 100 pM for bovine aorta (Leitman and Murad, ves
1986), 400 pM for bovine brain (Smith et al., 1988), and bov
230 pM for rat brain (Ermisch et al., 1991). Only one Th
binding site was identified in all of these s 1986), 400 pM for bovine brain (Smith et al., 1988), and bo
230 pM for rat brain (Ermisch et al., 1991). Only one Th
binding site was identified in all of these studies utilizing for
radioligand-binding techniques, but la 230 pM for rat brain (Ermisch et al., 1991). Only one The
binding site was identified in all of these studies utilizing for
radioligand-binding techniques, but later studies with Sug
selective ligands and cross-linking ag binding site was identificated
radioligand-binding technologies
selective ligands and crossistence of both R_1 -
(Leitman et al., 1986).
Most of the ANF bin dioligand-binding techniques, but later studies with lective ligands and cross-linking agents established the istence of both R_1 - and R_2 -binding sites for ANF eitman et al., 1986).
Most of the ANF binding to vascula

selective ligands and cross-linking agents established the existence of both R_1 - and R_2 -binding sites for ANF (Leitman et al., 1986).
Most of the ANF binding to vascular tissue was displaced by truncated derivatives existence of both R_1 - and R_2 -binding sites for ANF b.
(Leitman et al., 1986). the ANF binding to vascular tissue was dis-
placed by truncated derivatives selective for the R_2 re-
ceptor. Leitman et al. (1986) fou (Leitman et al., 1986).

Most of the ANF binding to vascular tissue was dis-

placed by truncated derivatives selective for the R_2 re-

ceptor. Leitman et al. (1986) found a truncated peptide

selective for the R_2 r Most of the ANF binding to vascular tissue was dis-
placed by truncated derivatives selective for the R_2 re-
ceptor. Leitman et al. (1986) found a truncated peptide
selective for the R_2 receptor, ANF(103-123), to di placed by truncated derivatives selective for the R_2 re-
ceptor. Leitman et al. (1986) found a truncated peptide et al., 1
selective for the R_2 receptor, ANF(103–123), to displace dominar
 $>94\%$ of the ANF binding ceptor. Leitman et al. (1986) found a truncated peptide et a
selective for the R_2 receptor, ANF(103-123), to displace dor
 $>94\%$ of the ANF binding in bovine aortic endothelial tors
cells, suggesting that the R_2 re selective for the R_2 receptor, ANF(103-123), to displace dom $>94\%$ of the ANF binding in bovine aortic endothelial tors cells, suggesting that the R_2 receptor accounts for 94% The of the ANF receptors present. $>94\%$ of the ANF binding in bovine aortic endothelial the cells, suggesting that the R_2 receptor accounts for 94% of the ANF receptors present. The R_2 receptor also the accounted for 93% of the ANF receptors cells, suggesting that the R_2 receptor accounts for 94%
of the ANF receptors present. The R_2 receptor also
accounted for 93% of the ANF receptors present in
bovine pulmonary arterial smooth muscle (Redmond et
al., 1 of the ANF receptors present. The R_2 receptor also the accounted for 93% of the ANF receptors present in abovine pulmonary arterial smooth muscle (Redmond et al., 1990) and rat aortic smooth muscle (Cahill et al., 1990 accounted for 93% of the ANF receptors present in
bovine pulmonary arterial smooth muscle (Redmond et
al., 1990) and rat aortic smooth muscle (Cahill et al.,
1990) based on the ability of cANF, a selective R₂-binding
ag bovine pulmonary arterial smooth muscle (Redmond
al., 1990) and rat aortic smooth muscle (Cahill et a
1990) based on the ability of cANF, a selective R₂-bindin
agent (Maack et al., 1987), to displace binding. Rabk
renal al., 1990) and rat aortic smooth muscle (Cahill et al., rep
1990) based on the ability of cANF, a selective R₂-binding AN
agent (Maack et al., 1987), to displace binding. Rabbit a s
renal arteriole smooth muscle contain 1990) based on the ability of cANF, a selective R_2 -binding agent (Maack et al., 1987), to displace binding. Rabbit renal arteriole smooth muscle contained 90% R_2 receptors as indicated by the displacement of bind agent (Maack et al., 1987)
renal arteriole smooth mu
tors as indicated by the dise
(Bea et al., 1991). Thus, v
tain the R_2 ANF receptor.
Autoradiographic studie

tors as indicated by the displacement of binding by cANF

(Bea et al., 1991). Thus, vascular tissues primarily con-

tain the R_2 ANF receptor.

Autoradiographic studies demonstrated ANF binding

to vascular endothelium (Bea et al., 1991). Thus, vascular tissues primarily con-
tain the R_2 ANF receptor. the constrated ANF binding m
to vascular endothelium and smooth muscle in the rat of
(Bianchi et al., 1985; vonSchroeder et al, 1985; tain the R_2 ANF receptor. It also the Microsofted ANF binding m
to vascular endothelium and smooth muscle in the rat on
(Bianchi et al., 1985; vonSchroeder et al, 1985; Tjalve ie
and Wilander, 1988) after intravenous i Autoradiographic studies demonstrated ANF bindito vascular endothelium and smooth muscle in the r (Bianchi et al., 1985; vonSchroeder et al, 1985; Tjaland Wilander, 1988) after intravenous injection. The data are consisten to vascular endothelium and smooth muscle in the rat (Bianchi et al., 1985; vonSchroeder et al., 1985; Tjalve and Wilander, 1988) after intravenous injection. These data are consistent with the hypothesis that ANF receptor (Bianchi et al., 1985; vonSchroeder et al., 1985; Tjalv
and Wilander, 1988) after intravenous injection. Thes
data are consistent with the hypothesis that ANF recep
tors in vascular tissue have a physiological function
How and Wilander, 1988) after intravenous injection. These
data are consistent with the hypothesis that ANF recep-
tors in vascular tissue have a physiological function.
However, they provide no evidence concerning the iden-
t data are consistors
tors in vascul
However, they
tity or physiol
types present.
Cross-linkin rs in vascular tissue have a physiological function.

Owever, they provide no evidence concerning the iden-

y or physiological relevance of the ANF receptor sub-

pes present.

Cross-linking of ANF to its receptors with s

However, they provide no evidence concerning the itity or physiological relevance of the ANF receptor types present.
Cross-linking of ANF to its receptors with separa
by sodium dodecyl sulfate-polyacrylamide gel electrop
r tity or physiological relevance of the ANF receptor sub-
types present. st
cross-linking of ANF to its receptors with separation sites with molecular weights of
resis yielded two binding sites with molecular weights of
66, types present.
Cross-linking of ANF to its receptors with separation
by sodium dodecyl sulfate-polyacrylamide gel electropho-
resis yielded two binding sites with molecular weights of
66,000 and 130,000 (Leitman et al., 19 Cross-linking of ANF to its receptors with separation
by sodium dodecyl sulfate-polyacrylamide gel electropho-
resis yielded two binding sites with molecular weights of
66,000 and 130,000 (Leitman et al., 1986). The relati by sodium dodecyl sulfate-polyacrylamide gel electrophoresis yielded two binding sites with molecular weights of 66,000 and 130,000 (Leitman et al., 1986). The relative proportions of these two binding sites were 94 and 6 resis yielded two binding sites with molecular weights 66,000 and 130,000 (Leitman et al., 1986). The relative proportions of these two binding sites were 94 and 69. Bovine pulmonary artery endothelial cells demonstrate t 66,000 and 130,000 (Leitman et al., 1986). The relation-proportions of these two binding sites were 94 and 6 Bovine pulmonary artery endothelial cells demonstrat the same abundance of R_2 receptors relative to R_1 rec proportions of these two binding sites were 94 and 69.
Bovine pulmonary artery endothelial cells demonstrate
the same abundance of R_2 receptors relative to R_1 receptors,
but this tissue contained R_2 receptors wit Bovine pulmonary artery endothelial cells demonstrated glor
the same abundance of R_2 receptors relative to R_1 recep-
tors, but this tissue contained R_2 receptors with molec-
ular weights of 60,000 and 70,000, sug tors, but this tissue contained R_2 receptors with molec-
ular weights of 60,000 and 70,000, suggesting the exist-
and Healy and Fanestil (1986) demonstrated ANF-bind-
ence of multiple R_2 -binding sites (Kato et al., tors, but this tissue contained R_2 receptors with molecular weights of 60,000 and 70,000, suggesting the existence of multiple R_2 -binding sites (Kato et al., 1991). In contrast, ultraviolet irradiation of rat aorta ular weights of 60,000 and 70,000, suggesting the existence of multiple R₂-binding sites (Kato et al., 1991). In contrast, ultraviolet irradiation of rat aorta primarily yielded a 130,000 molecular weight receptor with a ence of multiple R₂-binding sites (Kato et al., 1991). In contrast, ultraviolet irradiation of rat aorta primarily yielded a 130,000 molecular weight receptor with a minority of 65,000 molecular weight sites (Koseki et a contrast, ultraviolet irradiation of rat aorta primarily covided a 130,000 molecular weight receptor with a mi-
mority of 65,000 molecular weight sites (Koseki et al., the
1986). This irradiation with ultraviolet light ma

in an overestimation of adrenal R_1 **receptors when com-
pared to other cross-linking procedures (Larose et al.** A AND TRACHTE
in an overestimation of adrenal R_1 receptors when com-
pared to other cross-linking procedures (Larose et al.,
1990). The cross-linking data are in general agreement 14 AND TRACHTE
in an overestimation of adrenal R_1 receptors when com-
pared to other cross-linking procedures (Larose et al.,
1990). The cross-linking data are in general agreement
with binding data using selective rec in an overestimation of adrenal R_1 receptors when compared to other cross-linking procedures (Larose et al., 1990). The cross-linking data are in general agreement with binding data using selective receptor-binding age in an overestimation of adrenal R_1 receptors when compared to other cross-linking procedures (Larose et al., 1990). The cross-linking data are in general agreement with binding data using selective receptor-binding age pared to other cross-linking procedures (Larose et al., 1990). The cross-linking data are in general agreement with binding data using selective receptor-binding agents, indicating a predominance of the R_2 receptor in 1990). The cross-linking data are in general age with binding data using selective receptor-
agents, indicating a predominance of the R_2 rec
vascular tissue. A diversity of R_2 -binding sites in
tissue also was sugges th binding data using selective receptor-binding
ents, indicating a predominance of the R_2 receptor in
scular tissue. A diversity of R_2 -binding sites in vascular
sue also was suggested by Kato et al. (1991).
Analysi

agents, indicating a predominance of the R_2 receptor in vascular tissue. A diversity of R_2 -binding sites in vascular tissue also was suggested by Kato et al. (1991).
Analysis of mRNA expression of ANF receptors reve vascular tissue. A diversity of R_2 -binding sites in vascular tissue also was suggested by Kato et al. (1991).
Analysis of mRNA expression of ANF receptors revealed the predominant expression of the R_2 receptor in bo tissue also was suggested by Kato et al. (1991).

Analysis of mRNA expression of ANF receptors re-

vealed the predominant expression of the R_2 receptor in

bovine aortic endothelial cells (Katafuchi et al., 1992).

Th Analysis of mRNA expression of ANF receptors revealed the predominant expression of the R_2 receptor in bovine aortic endothelial cells (Katafuchi et al., 1992). The R_1 receptor also was expressed. The message coded vealed the predominant expression of the R_2 receptor in
bovine aortic endothelial cells (Katafuchi et al., 1992).
The R_1 receptor also was expressed. The message coded
for the GC-A type of R_1 receptor (Katafuchi bovine aortic endothelial cells (Katafuchi et al., 1992).
The R_1 receptor also was expressed. The message coded
for the GC-A type of R_1 receptor (Katafuchi et al., 1992;
Suga et al., 1992). No message for GC-B was d The R_1 receptor also was expressed. The message code
for the GC-A type of R_1 receptor (Katafuchi et al., 199
Suga et al., 1992). No message for GC-B was detectabl
and the absence of the GC-B receptor also was confir for the GC-A type of R_1 receptor (Katafuchi et al., 1992;
Suga et al., 1992). No message for GC-B was detectable,
and the absence of the GC-B receptor also was confirmed
by the inability of CNP to generate cGMP in the Suga et al., 1992). No message for GC-B was detectable,
and the absence of the GC-B receptor also was confirmed
by the inability of CNP to generate cGMP in the endo-
thelium. In contrast, rat aortic smooth muscle expresse and the absence of the GC-B receptor also was confirmed
by the inability of CNP to generate cGMP in the endo-
thelium. In contrast, rat aortic smooth muscle expressed
only the GC-B form of the R_1 receptor with both CNP by the inability of CNP to generate cGMP in the endo-
the lium. In contrast, rat aortic smooth muscle expressed
only the GC-B form of the R₁ receptor with both CNP
and BNP activating GC more potently than ANF (Suga
et al the ium. In contrast, rat aortic smooth muscle express
only the GC-B form of the R_1 receptor with both CN
and BNP activating GC more potently than ANF (Su
et al., 1992). Collectively, these studies indicate a pr
domina only the GC-B form of the R_1 receptor with both CNP
and BNP activating GC more potently than ANF (Suga
et al., 1992). Collectively, these studies indicate a pre-
dominant expression and production of ANF R_2 recep-
t and BNP activating GC more potently than ANF (Suget al., 1992). Collectively, these studies indicate a prodominant expression and production of ANF R_2 receptors in both vascular endothelium and smooth muscle The ANF R dominant expression and production of ANF R_2 receptors in both vascular endothelium and smooth muscle.
The ANF R_1 receptor is present in much smaller quantities than the R_2 receptor, and the subtypes present appe tors in both vascular endothelium and smooth muscle. For a single to research in much smaller quan-
ies $ANF R_1$ receptor is present in much smaller quan-
ies than the R_2 receptor, and the subtypes present
pear to vary with the cell type analyzed.
2. *Kidney*. ANF b

renal arteriole smooth muscle contained 90% R₂ recep-490 pM in rabbit kidneys, indicating two binding sites.
tors as indicated by the displacement of binding by cANF In contrast, ANF bound to rat renal membranes with The ANF R_1 receptor is present in much smaller quantities than the R_2 receptor, and the subtypes present appear to vary with the cell type analyzed.
2. Kidney. ANF binding to renal receptor sites was reported initia tities than the R_2 receptor, and the subtypes present
appear to vary with the cell type analyzed.
2. Kidney. ANF binding to renal receptor sites was
reported initially by Napier et al. (1984). Radiolabeled
ANF bound to appear to vary with the cell type analyzed.
2. Kidney. ANF binding to renal receptor sites was
reported initially by Napier et al. (1984). Radiolabeled
ANF bound to renal membranes from rabbit and rat in
a saturable and sp 2. Kidney. ANF binding to renal receptor sites was
reported initially by Napier et al. (1984). Radiolabeled
ANF bound to renal membranes from rabbit and rat in
a saturable and specific manner. K_d values were 52 and
490 p reported initially by Napier et al. (1984). Radiolabeled
ANF bound to renal membranes from rabbit and rat in
a saturable and specific manner. K_d values were 52 and
490 pM in rabbit kidneys, indicating two binding sites. ANF bound to renal membranes from rabbit and rat is
a saturable and specific manner. K_d values were 52 an
490 pM in rabbit kidneys, indicating two binding site
In contrast, ANF bound to rat renal membranes with
 K_d of a saturable and specific manner. K_d values were 52 and 490 pM in rabbit kidneys, indicating two binding sites In contrast, ANF bound to rat renal membranes with K_d of 49 pM, demonstrating only one binding site. Additi 490 pM in rabbit kidneys, indicating two binding sites.
In contrast, ANF bound to rat renal membranes with a K_d of 49 pM, demonstrating only one binding site. Additional studies in a variety of species usually found hal K_d of 49 pM, demonstrating only one binding site. Additional studies in a variety of species usually found half-
maximal ANF binding in the range of 40 to 600 pM with
only one site identified by Scatchard analysis. Five tional studies in a variety of species usually found halftional studies in a variety of species usually found half-
maximal ANF binding in the range of 40 to 600 pM with
only one site identified by Scatchard analysis. Five stud-
ies reported multiple renal receptors based on dif maximal ANF binding in the range of 40 to 600 pM with
only one site identified by Scatchard analysis. Five stud-
ies reported multiple renal receptors based on differential
affinities of the receptors for ANF. The rabbit k only one site identified by Scatchard analysis. Five studies reported multiple renal receptors based on differential affinities of the receptors for ANF. The rabbit kidney (Napier et al., 1984), canine renal cortex (DeLean ies reported multiple renal receptors based on differential
affinities of the receptors for ANF. The rabbit kidney
(Napier et al., 1984), canine renal cortex (DeLean et al.,
1985), rat inner medulla (Maeda et al., 1990; Ko affinities of the receptors for ANF. The rabbit kidney
(Napier et al., 1984), canine renal cortex (DeLean et al.,
1985), rat inner medulla (Maeda et al., 1990; Koseki et
al., 1986), and rat kidney (Michel et al., 1991) hav (Napier et al., 1984), canine renal cortex (DeLean et al., 1985), rat inner medulla (Maeda et al., 1990; Koseki et al., 1986), and rat kidney (Michel et al., 1991) have been reported to display two binding sites for ANF b 1985), rat inner medulla (Maeda et al., 1990; Koseki et al., 1986), and rat kidney (Michel et al., 1991) have been reported to display two binding sites for ANF based strictly on affinity for the ligand. Low-affinity-bindi reported to display two binding sites for ANF based
strictly on affinity for the ligand. Low-affinity-binding
sites possess K_d values in the range of 490 to 30,000 pM.
The differential sensitivities of these ANF recepto strictly on affinity for the ligand. Low-affinity-binding kidney. To manimal NNF binding or between evolver in the endow
and BMP action and DNF and the R₁ receptor with both CNP
and BNP activity of CC-B form of the R₁ receptor with both CNP
and BNP activity the GC-B form of the R₁

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The differential sensitivities of these ANF receptors have
not been related to any functional effects of ANF in the
kidney.
The ANF receptor binding was subsequently shown in
glomeruli, ascending limb of the loop of Henle, not been related to any functional effects of ANF in the kidney.

The ANF receptor binding was subsequently shown in

glomeruli, ascending limb of the loop of Henle, and

collecting ducts but not in proximal tubule in the kidney.

The ANF receptor binding was subsequently shown in

glomeruli, ascending limb of the loop of Henle, and

collecting ducts but not in proximal tubule in the dog

(DeLean et al., 1985). However, Yamamoto et al. (198 The ANF receptor binding was subsequently show
glomeruli, ascending limb of the loop of Henle,
collecting ducts but not in proximal tubule in the
(DeLean et al., 1985). However, Yamamoto et al. (14
and Healy and Fanestil (glomeruli, ascending limb of the loop of Henle, and
collecting ducts but not in proximal tubule in the dog
(DeLean et al., 1985). However, Yamamoto et al. (1987)
and Healy and Fanestil (1986) demonstrated ANF-bind-
ing sit collecting ducts but not in proximal tubule in the dog (DeLean et al., 1985). However, Yamamoto et al. (1987) and Healy and Fanestil (1986) demonstrated ANF-bind-
ing sites in proximal tubules in rat kidney. Rat mesangial (DeLean et al., 1985). However, Yamamoto et al. (1987)
and Healy and Fanestil (1986) demonstrated ANF-bind-
ing sites in proximal tubules in rat kidney. Rat mesangial
cells also bound ANF with a K_d of 220 pM (Ballerman and Healy and Fanestil (1986) demonstrated ANF-bind-
ing sites in proximal tubules in rat kidney. Rat mesangial
cells also bound ANF with a K_d of 220 pM (Ballerman et
al., 1985). Radioligand binding of ANF predominated ing sites in proximal tubules in rat kidney. Rat mesangial
cells also bound ANF with a K_d of 220 pM (Ballerman et
al., 1985). Radioligand binding of ANF predominated in
the renal cortex of rats, whereas the papilla acco cells also bound ANF with a K_d of 220 pM (Ballerman et al., 1985). Radioligand binding of ANF predominated in the renal cortex of rats, whereas the papilla accounted for only 2% of the total renal binding sites (Suzuki

(Mantyh et al., 1986; Mendelsohn et al., 1987).

ANF RECEPTORS AND SIGNA

g in the glomerulus, medulla, and arterial segments

fantyh et al., 1986; Mendelsohn et al., 1987).

Most of these early studies found a homogeneous pop-

ation of binding sites for ANF. The introd ing in the glomerulus, medulla, and arterial segments in (Mantyh et al., 1986; Mendelsohn et al., 1987). A Most of these early studies found a homogeneous poppeution of binding sites for ANF. The introduction of setruncate ing in the glomerulus, medulla, and arterial segments in (Mantyh et al., 1986; Mendelsohn et al., 1987). A Most of these early studies found a homogeneous population of binding sites for ANF. The introduction of struncated (Mantyh et al., 1986; Mendelsohn et al., 1987).
Most of these early studies found a homogeneous pop-
ulation of binding sites for ANF. The introduction of
truncated derivatives of ANF provided a mechanism for
discriminati Most of these early studies found a homogeneous pop-
ulation of binding sites for ANF. The introduction of set-
truncated derivatives of ANF provided a mechanism for net
discriminating binding sites into two types of rece ulation of binding sites for ANF. The introduction of seg
truncated derivatives of ANF provided a mechanism for nat
discriminating binding sites into two types of receptors, rea
labeled B (R_1) for biologically active an truncated derivatives of ANF provided a mechanism for nifical discriminating binding sites into two types of receptors, relabeled B (R₁) for biologically active and C (R₂) for all clearance (Maack et al., 1987). These discriminating binding sites into two types of receptors, reader also labeled B (R₁) for biologically active and C (R₂) for also clearance (Maack et al., 1987). These investigators found GC a truncated ANF derivative, labeled B (R_1) for biologically active and C (R_2) for all
clearance (Maack et al., 1987). These investigators found G
a truncated ANF derivative, cANF, to displace 99% of th
ANF binding from the rat renal cortex but t clearance (Maack et al., 1987). These investigators found G
a truncated ANF derivative, cANF, to displace 99% of the
ANF binding from the rat renal cortex but to have no
teffect on renal function or the renal actions of in a truncated ANF derivative, cANF, to displace 99% of
ANF binding from the rat renal cortex but to have no
effect on renal function or the renal actions of infused
ANF in the isolated rat kidney. The cANF increased
plasma c ANF binding from the rat renal cortex but to have no
effect on renal function or the renal actions of infused sect
ANF in the isolated rat kidney. The cANF increased exp
plasma concentrations of ANF when infused in vivo, effect on renal function or the renal actions of infused
ANF in the isolated rat kidney. The cANF increased
plasma concentrations of ANF when infused in vivo,
leading Maack et al. (1987) to the conclusion that cANF lintera ANF in the isolated rat kidney. The cANF increased explasma concentrations of ANF when infused in vivo, deleading Maack et al. (1987) to the conclusion that cANF butteracts with a specific receptor to prevent the clearance plasma concentrations of ANF when infused in vivo,
leading Maack et al. (1987) to the conclusion that cANF
interacts with a specific receptor to prevent the clearance
of ANF from the circulation. Since this study, cANF has leading Maack et al. (1987) to the conclusion that cANF b
interacts with a specific receptor to prevent the clearance
of ANF from the circulation. Since this study, cANF has
been commonly used to identify the type of rece interacts with a specific receptor to prevent the clearance of ANF from the circulation. Since this study, cANF has bind been commonly used to identify the type of receptor Lear
present in various tissues. Rat renal papil of ANF from the circulation. Since this study, cANF has bind been commonly used to identify the type of receptor Leapresent in various tissues. Rat renal papilla possessed 198 either 40% (Maack et al., 1987) or 100% been commonly used to identify the type of receptor
present in various tissues. Rat renal papilla possessed
either 40% (Maack et al., 1987) or 100% of the R_1
subtype, as defined by the inability of the truncated present in various tissues. Rat renal papilla possessed
either 40% (Maack et al., 1987) or 100% of the R₁
subtype, as defined by the inability of the truncated ANF
derivatives, cANF (Nuglozeh et al., 1990; Martin et al., either 40% (Maack et al., 1987) or 100% of the R_1
subtype, as defined by the inability of the truncated ANF
derivatives, cANF (Nuglozeh et al., 1990; Martin et al.,
1989) or ANF(103-123) (Fethiere and De Lean, 1991),
t subtype, as defined by the inability of the truncated ANF (i.derivatives, cANF (Nuglozeh et al., 1990; Martin et al., Le 1989) or ANF(103-123) (Fethiere and De Lean, 1991), va to displace ANF binding. Rat renal medullary i derivatives, cANF (Nuglozeh et al., 1990; Martin et al., Land 1989) or ANF (103-123) (Fethiere and De Lean, 1991), value displace ANF binding. Rat renal medullary interstitial in cells contained primarily R₁-binding site 1989) or ANF(103–123) (Fethiere and De Lean, 199
to displace ANF binding. Rat renal medullary interstit
cells contained primarily R₁-binding sites inasmuch
cANF failed to compete with 90% of the ANF bindi
(Fontoura et a to displace ANF binding. Rat renal medullary interstitial
cells contained primarily R_1 -binding sites inasmuch as
cANF failed to compete with 90% of the ANF binding
(Fontoura et al., 1990). A novel ANF R_1 receptor an cells contained primarily R_1 -binding sites inasmuch as cANF failed to compete with 90% of the ANF binding (Fontoura et al., 1990). A novel ANF R_1 receptor antagonist, HS-142-1, displaced 60% of ANF binding in rabbit cANF failed to compete with 90% of the ANF binding
(Fontoura et al., 1990). A novel ANF R_1 receptor antag-
onist, HS-142-1, displaced 60% of ANF binding in rabbit
kidney cortex (Morishita et al., 1991a,b), suggesting t (Fontoura et al., 1990). A novel ANF R_1 receptor antag-
onist, HS-142-1, displaced 60% of ANF binding in rabbit
kidney cortex (Morishita et al., 1991a,b), suggesting that
the R_1 receptor predominates in the rabbit. onist, HS-142-1, displaced 60% of ANF binding in rabbit lations, havenum kidney cortex (Morishita et al., 1991a,b), suggesting that (vor the R_1 receptor predominates in the rabbit. This has not Her been confirmed with kidney cortex (Morishita et al., 1991a,b), suggesting that (ve
the R₁ receptor predominates in the rabbit. This has not Ho
been confirmed with cANF at this point. These binding zo
studies have identified ANF receptors i the R₁ receptor predominates in the rabbit. This has not been confirmed with cANF at this point. These binding z studies have identified ANF receptors in the kidney in the most sections of the nephron. Cortical binding been confirmed with cANF at this
studies have identified ANF recept
most sections of the nephron. Cortic
primarily of the R_2 variety, when
predominated in papillary regions.
The binding of ANF to renal mem In the kidney in the kidney in the sections of the nephron. Cortical binding sites were given in a papillary regions. In the binding of ANF to renal membranes was classified rether utilizing disuccinimidyl suberate to cov

most sections of the nephron. Cortical binding sites were
primarily of the R_2 variety, whereas the R_1 subtype
predominated in papillary regions.
The binding of ANF to renal membranes was classified
further utilizing primarily of the R_2 variety, whereas the R_1 subtyperedominated in papillary regions.
The binding of ANF to renal membranes was classified further utilizing disuccinimidyl suberate to covalently link labeled ANF to r predominated in papillary regions.
The binding of ANF to renal membranes was cla
further utilizing disuccinimidyl suberate to cove
link labeled ANF to receptors. The ANF-recepto:
plex was subjected to sodium dodecyl sulfat The binding of ANF to renal membranes was classified
further utilizing disuccinimidyl suberate to covalently
link labeled ANF to receptors. The ANF-receptor com-
plex was subjected to sodium dodecyl sulfate-polyacryl-
amid further utilizing disuccinimidyl suberate to covalently
link labeled ANF to receptors. The ANF-receptor com-
plex was subjected to sodium dodecyl sulfate-polyacryl-
amide gel electrophoresis to determine the molecular
weig link labeled ANF to receptors. The ANF-receptor com-
plex was subjected to sodium dodecyl sulfate-polyacryl-
amide gel electrophoresis to determine the molecular weight of the receptors under reducing conditions. Rat diglo plex was subjected to sodium dodecyl sulfate-polyacryl-
amide gel electrophoresis to determine the molecular
weight of the receptors under reducing conditions. Rat
glomeruli contained receptors with molecular weights of
13 amide gel electrophoresis to determine the molecular weight of the receptors under reducing conditions. Rat glomeruli contained receptors with molecular weights of 130,000 and 64,000. The binding to the lower molecular we weight of the receptors under reducing conditions. Rat
glomeruli contained receptors with molecular weights of
130,000 and 64,000. The binding to the lower molecular
weight receptor was displaced by the R₂-selective lig glomeruli contained receptors with molecular weights of et a
130,000 and 64,000. The binding to the lower molecular disp
weight receptor was displaced by the R_2 -selective ligand, ishit
cANF, indicating that it represen 130,000 and 64,000. The binding to the lower molecular diverght receptor was displaced by the R_2 -selective ligand, is cANF, indicating that it represented the R_2 receptor R_3 (Martin et al., 1989). The R_2 recep weight receptor was displaced by the R_2 -selective ligand,
cANF, indicating that it represented the R_2 receptor
(Martin et al., 1989). The R_2 receptor accounted for 50
to 80% (Brown et al., 1990; Martin et al., 19 cANF, indicating that it represented the R_2 receptor 80%
(Martin et al., 1989). The R_2 receptor accounted for 50 T
to 80% (Brown et al., 1990; Martin et al., 1989; DeLean sued
and Garcia, 1991) of the binding sites (Martin et al., 1989). The R_2 receptor accounted for 50
to 80% (Brown et al., 1990; Martin et al., 1989; DeLean
and Garcia, 1991) of the binding sites in the glomeruli. m
In contrast, rat papilla only expressed the lar to 80% (Brown et al., 1990; Martin et al., 1989; DeLean
and Garcia, 1991) of the binding sites in the glomeruli.
In contrast, rat papilla only expressed the larger R_1
receptor (Martin et al., 1989). Another receptor wa and Garcia, 1991) of the binding sites in the glomerul
In contrast, rat papilla only expressed the larger Freceptor (Martin et al., 1989). Another receptor was
identified in the rat kidney exhibiting a molecular weight
of In contrast, rat papilla only expressed the larger R_1 b
receptor (Martin et al., 1989). Another receptor was ridentified in the rat kidney exhibiting a molecular weight
of 180,000 (Ballerman et al., 1988). This recepto receptor (Martin et al., 1989). Another receptor was raidentified in the rat kidney exhibiting a molecular weight as of 180,000 (Ballerman et al., 1988). This receptor probably represents another R_1 receptor subtype in identified in the rat kidney exhibiting a molecular weight
of 180,000 (Ballerman et al., 1988). This receptor prob-
ably represents another R_1 receptor subtype inasmuch
as it was retained on a GTP-affinity column. Thes of 180,000 (Ballerman et al., 1988). The above presents another R_1 receptor s as it was retained on a GTP-affinity results are consistent with the presence types of ANF receptors in the kidney. The final proof for the

ing in the glomerulus, medulla, and arterial segments in the kidney involves the expression of mRNA encoding
(Mantyh et al., 1986; Mendelsohn et al., 1987). ANF receptors. The presence of mRNA encoding an R_1
Most of th FRANSDUCTION MECHANISMS 459
in the kidney involves the expression of mRNA encoding
ANF receptors. The presence of mRNA encoding an R_1 RANSDUCTION MECHANISMS 459
in the kidney involves the expression of mRNA encoding
ANF receptors. The presence of mRNA encoding an R₁
receptor (GC-A) was demonstrated in all rat nephron FRANSDUCTION MECHANISMS 459
in the kidney involves the expression of mRNA encoding
ANF receptors. The presence of mRNA encoding an R_1
receptor (GC-A) was demonstrated in all rat nephron
segments, including the proximal in the kidney involves the expression of mRNA encodi
ANF receptors. The presence of mRNA encoding an
receptor (GC-A) was demonstrated in all rat nephr
segments, including the proximal tubule, by the com
nation of reverse t in the kidney involves the expression of mRNA encoding
ANF receptors. The presence of mRNA encoding an R_1
receptor (GC-A) was demonstrated in all rat nephron
segments, including the proximal tubule, by the combi-
natio ANF receptors. The presence of mRNA encoding an R_1
receptor (GC-A) was demonstrated in all rat nephron
segments, including the proximal tubule, by the combi-
nation of reverse transcriptase and the polymerase chain
rea receptor (GC-A) was demonstrated in all rat nephron
segments, including the proximal tubule, by the combi-
nation of reverse transcriptase and the polymerase chain
reaction (Terada et al., 1991). Canaan-Kuhl et al. (1992) segments, including the proximal tubule, by the combi-
nation of reverse transcriptase and the polymerase chair
reaction (Terada et al., 1991). Canaan-Kuhl et al. (1992)
also detected the message for R_1 receptors (GC-A nation of reverse transcriptase and the polymerase chareaction (Terada et al., 1991). Canaan-Kuhl et al. (199
also detected the message for R_1 receptors (GC-A an
GC-B) and R_2 receptors in human kidney. Collectivel
t reaction (Terada et al., 1991). Canaan-Kuhl et al. (1992)
also detected the message for R_1 receptors (GC-A and
GC-B) and R_2 receptors in human kidney. Collectively,
these results establish the existence of renal ANF also detected the message for R_1 receptors (GC-A and GC-B) and R_2 receptors in human kidney. Collectively, these results establish the existence of renal ANF receptors with biological activity, as will be detailed i GC-B) and R_2 receptors in human kidney. Collectively, these results establish the existence of renal ANF receptors with biological activity, as will be detailed in later sections. Furthermore, specific renal regions se these results establish the existence of renal ANF receptors with biological activity, as will be detailed in later sections. Furthermore, specific renal regions selectively express certain ANF receptors with the R_2 re tors with biological activity, as will be d
sections. Furthermore, specific renal reg
express certain ANF receptors with the H
dominating in most of the kidney, particul
but being absent from papillary regions.
3. Adrenal express certain ANF receptors with the R_2 receptor pre-
dominating in most of the kidney, particularly the cortex,
but being absent from papillary regions.
 $3.$ *Adrenal gland*. The adrenal glomerulosa layer avidly
bin

express certain ANF receptors with the R₂ receptor pre-
dominating in most of the kidney, particularly the cortex,
but being absent from papillary regions.
3. Adrenal gland. The adrenal glomerulosa layer avidly
binds ANF dominating in most of the kidney, particularly the cortex,
but being absent from papillary regions.
3. Adrenal gland. The adrenal glomerulosa layer avidly
binds ANF with a K_d in the range of 30 to 1800 pM (De
Lean et al but being absent from papillary regions.

3. Adrenal gland. The adrenal glomerulosa layer avidly

binds ANF with a K_d in the range of 30 to 1800 pM (De

Lean et al., 1984a; Schiffrin et al., 1985; Hirose et al.,

1985. 3. Adrenal gland. The adrenal glomerulosa layer avidly
binds ANF with a K_d in the range of 30 to 1800 pM (De
Lean et al., 1984a; Schiffrin et al., 1985; Hirose et al.,
1985. Only one binding site was found in the majori binds ANF with a K_d in the range of 30 to 1800 pM (De
Lean et al., 1984a; Schiffrin et al., 1985; Hirose et al.,
1985. Only one binding site was found in the majority of
these binding studies, although a very low-affini Lean et al., 1984a; Schiffrin et al., 1985; Hirose et al., 1985. Only one binding site was found in the majority of these binding studies, although a very low-affinity site (i.e., 3000 pM) was observed in bovine glomerulos 1985. Only one binding site was found in the majority of these binding studies, although a very low-affinity site (i.e., 3000 pM) was observed in bovine glomerulosa (De Lean et al., 1984a). The majority of studies report (i.e., 3000 pM) was observed in bovine glomerulosa (De Lean et al., 1984a). The majority of studies report K_d values <100 pM, findings consistent with the potent inhibitory effect of ANF on aldosterone secretion (Atar-
 (i.e., 3000 pM) was
Lean et al., 1984a
values <100 pM,
inhibitory effect of
ashi et al., 1985).
Autoradiographi an et al., 1984a). The majority of studies report K_d
lues <100 pM, findings consistent with the potent
hibitory effect of ANF on aldosterone secretion (Atar-
hi et al., 1985).
Autoradiographic studies involving the inje

values <100 pM, findings consistent with the pot
inhibitory effect of ANF on aldosterone secretion (At
ashi et al., 1985).
Autoradiographic studies involving the injection
labeled ANF into animals uniformly report the accu inhibitory effect of ANF on aldosterone secretion (Atar-
ashi et al., 1985).
Autoradiographic studies involving the injection of
labeled ANF into animals uniformly report the accumu-
lation of label by the zona glomerulosa ashi et al., 1985).

Autoradiographic studies involving the injection of

labeled ANF into animals uniformly report the accumu-

lation of label by the zona glomerulosa of the adrenal

(von Schroeder et al., 1985; Tjalve a Autoradiographic studies involving the injection of labeled ANF into animals uniformly report the accumulation of label by the zona glomerulosa of the adrenal (von Schroeder et al., 1985; Tjalve and Wilander, 1988; Hersey labeled ANF into animals uniformly report the accumu-
lation of label by the zona glomerulosa of the adrenal
(von Schroeder et al., 1985; Tjalve and Wilander, 1988;
Hersey et al., 1989; Neuser et al., 1989). Thus, the adre lation of label by the zona glomerulosa of the adrenal
(von Schroeder et al., 1985; Tjalve and Wilander, 1988;
Hersey et al., 1989; Neuser et al., 1989). Thus, the adrenal
zona glomerulosa, the aldosterone-producing sectio Hersey et al., 1989; Neuser et al., 1989). Thus, the adrenal zona glomerulosa, the aldosterone-producing section of the adrenal gland, is a site of ANF accumulation, suggesting a physiological relevance for these receptors

Neither crude binding nor autoradiographic studies zona glomerulosa, the aldosterone-producing section of
the adrenal gland, is a site of ANF accumulation, sug-
gesting a physiological relevance for these receptors.
Neither crude binding nor autoradiographic studies
indic the adrenal gland, is a site of ANF accumulation, suggesting a physiological relevance for these receptors.
Neither crude binding nor autoradiographic studies
indicated the type of ANF receptors present in the ad-
renal; gesting a physiological relevance for these receptors.
Neither crude binding nor autoradiographic studies
indicated the type of ANF receptors present in the ad-
renal; therefore, selective R_1 - or R_2 -binding agents w Neither crude binding nor autoradiographic studies
indicated the type of ANF receptors present in the ad-
renal; therefore, selective R_1 - or R_2 -binding agents were
used to clarify the relative density of adrenal rec indicated the type of ANF receptors present in the adrenal; therefore, selective R_1 - or R_2 -binding agents were used to clarify the relative density of adrenal receptors.
The R_2 -selective ligand, cANF, displaced 2 renal; therefore, selective R_1 - or R_2 -binding agents were
used to clarify the relative density of adrenal receptors.
The R_2 -selective ligand, cANF, displaced 20% of ANF
binding in hamster adrenals (Bianchi et al. used to clarify the relative density of adrenal receptors.
The R₂-selective ligand, cANF, displaced 20% of ANF
binding in hamster adrenals (Bianchi et al., 1989),
whereas a linear ANF analog selective for R₂ receptors
 The R₂-selective ligand, cANF, displaced 20% of ANF
binding in hamster adrenals (Bianchi et al., 1989),
whereas a linear ANF analog selective for R₂ receptors
displaced 50% of ANF binding to rat adrenals (Sessions
et a binding in hamster adrenals (Bianchi et al., 1989
whereas a linear ANF analog selective for R_2 recepto
displaced 50% of ANF binding to rat adrenals (Session
et al., 1992). An R_1 -selective antagonist, HS-142-1, all
d whereas a linear ANF analog selective for R_2 receptors
displaced 50% of ANF binding to rat adrenals (Sessions
et al., 1992). An R_1 -selective antagonist, HS-142–1, also
displaced 65% of ANF binding to bovine adrenals displaced 50% of ANF binding to rat adrenated at al., 1992). An R₁-selective antagonist, HS displaced 65% of ANF binding to bovine adishita et al., 1992). Thus, R₁ receptors accouse 80% of adrenal glomerulosa ANF recep al., 1992). An R₁-selective antagonist, HS-142-1, also
splaced 65% of ANF binding to bovine adrenals (Mor-
nita et al., 1992). Thus, R₁ receptors account for 50 to
% of adrenal glomerulosa ANF receptors.
The distribut

as it was retained on a GTP-affinity column. These labeling was displaced by ANF but not by its truncated
results are consistent with the presence of multiple sub-
types of ANF receptors in the kidney.
The final proof for displaced 65% of ANF binding to bovine adrenals (Morishita et al., 1992). Thus, R_1 receptors account for 50 to 80% of adrenal glomerulosa ANF receptors.
The distribution of adrenal ANF receptors was pursued further by ishita et al., 1992). Thus, R_1 receptors account for 50 to 80% of adrenal glomerulosa ANF receptors.
The distribution of adrenal ANF receptors was pursued further by cross-linking labeled ANF to the adrenal membrane an 80% of adrenal glomerulosa ANF receptors.
The distribution of adrenal ANF receptors was pur-
sued further by cross-linking labeled ANF to the adrenal
membrane and determining the molecular weight of
binding sites, as descr The distribution of adrenal ANF receptors was pur-
sued further by cross-linking labeled ANF to the adrenal
membrane and determining the molecular weight of
binding sites, as described in the section concerning renal
radio sued further by cross-linking labeled ANF to the adrenal
membrane and determining the molecular weight of
binding sites, as described in the section concerning renal
radioligand-binding studies. The initial study used an
a membrane and determining the molecular weight of
binding sites, as described in the section concerning renal
radioligand-binding studies. The initial study used an
azido-benzene moiety of ANF to allow coupling upon
exposur binding sites, as described in the section concerning renal
radioligand-binding studies. The initial study used an
azido-benzene moiety of ANF to allow coupling upon
exposure to ultraviolet light (Misono et al., 1985). Onl radioligand-binding studies. The initial study used an azido-benzene moiety of ANF to allow coupling upon exposure to ultraviolet light (Misono et al., 1985). Only a 124,000 molecular weight band was labeled, and this labe azido-benzene moiety of ANF to allow coupling upo
exposure to ultraviolet light (Misono et al., 1985). On
a 124,000 molecular weight band was labeled, and th
labeling was displaced by ANF but not by its truncate
derivative exposure to ultraviolet light (Misono et al., 1985). Only
a 124,000 molecular weight band was labeled, and this
labeling was displaced by ANF but not by its truncated
derivative, ANF(103–126), a compound relatively selective for the ANF R_2 receptor. These data indicated the

aspet

ANAND-SRIVASTAVA AND TRACHTE

observation that was confirmed in rat adrenal as well. In receptor from bovir

contrast, Meloche et al. (1986) found both 67,000 and pM (Uchida et al., 1 ANAND-SRIVASTAVA AND TRACHTE
observation that was confirmed in rat adrenal as well. In receptor from bovine lung bound ANF with a K_d of 6.5
contrast, Meloche et al. (1986) found both 67,000 and pM (Uchida et al., 1989). ANAND-SRIVASTA

114,000 molecular weight receptors in bovine adrenal

114,000 molecular weight receptors in bovine adrenal

114,000 molecular weight receptors in bovine adrenal

1200 glomerulosa membranes. Furthermore, the contrast, Meloche et al. (1986) found both 67,000 and
114,000 molecular weight receptors in bovine adrenal
20na glomerulosa membranes. Furthermore, the lower
molecular weight receptor was the predominant receptor observation that was confirmed in rat adrenal as well. In contrast, Meloche et al. (1986) found both 67,000 and 114,000 molecular weight receptors in bovine adrenal zona glomerulosa membranes. Furthermore, the lower molecu contrast, Meloche et al. (1986) found both 67,000 and pM
114,000 molecular weight receptors in bovine adrenal tifi
zona glomerulosa membranes. Furthermore, the lower foll
molecular weight receptor was the predominant recep 114,000 molecular weight receptors in bovine adrenazona glomerulosa membranes. Furthermore, the low
molecular weight receptor was the predominant receptor
present. Unlike Misono et al. (1985), Meloche et al. use
labeled AN zona glomerulosa membranes. Furthermore, the lower foll
molecular weight receptor was the predominant receptor He
present. Unlike Misono et al. (1985), Meloche et al. used bov
labeled ANF and coupled it to membranes with s molecular weight receptor was the predominant receptor H
present. Unlike Misono et al. (1985), Meloche et al. used
labeled ANF and coupled it to membranes with sulfo-
succinimidyl suberate. Takayanagi et al. (1987) also tr present. Unlike Misono et al. (1985), Meloche et al. used
labeled ANF and coupled it to membranes with sulfo-
succinimidyl suberate. Takayanagi et al. (1987) also
found two ANF-binding sites in the porcine adrenal of
molec labeled ANF and coupled it to membranes with sulfo-
succinimidyl suberate. Takayanagi et al. (1987) also tru
found two ANF-binding sites in the porcine adrenal of (U
molecular weight 135,000 and 62,000, with the higher of
 succinimidyl suberate. Takayanagi et al. (1987) also tr
found two ANF-binding sites in the porcine adrenal of (U
molecular weight 135,000 and 62,000, with the higher of
molecular weight receptor accounting for 54% of th found two ANF-binding sites in the porcine adrenal of (1 molecular weight 135,000 and 62,000, with the higher of molecular weight receptor accounting for 54% of the stotal binding. Human membranes obtained at autopsy lip molecular weight 135,000 and 62,000, with the higher
molecular weight receptor accounting for 54% of the
total binding. Human membranes obtained at autopsy
primarily contained the 67,000 molecular weight form of
the ANF re molecular weight receptor accounting for 54% of the
total binding. Human membranes obtained at autopsy
primarily contained the 67,000 molecular weight form of
the ANF receptor (Ohashi et al., 1988). Rat adrenal (
membranes total binding. Human membranes obtained at autopsy lin
primarily contained the 67,000 molecular weight form of 66
the ANF receptor (Ohashi et al., 1988). Rat adrenal (L
membranes incubated with labeled ANF and irradiated primarily contained the 67,000 molecular weight form of
the ANF receptor (Ohashi et al., 1988). Rat adrenal
membranes incubated with labeled ANF and irradiated
with ultraviolet light only exhibited labeling of the
130,000 the ANF receptor (Ohashi et al., 1988). Rat adrenal (Lemembranes incubated with labeled ANF and irradiated lun with ultraviolet light only exhibited labeling of the R_2 130,000 molecular weight binding site (Larose et a with ultraviolet light only exhibited labeling of the 130,000 molecular weight binding site (Larose et al., with ultraviolet light only exhibited labeling of the 130,000 molecular weight binding site (Larose et al., 1990). The variability in these reports complicates any conclusions regarding the proportion of ANF receptor subt 130,000 molecular weight binding site (Larose et a 1990). The variability in these reports complicates a conclusions regarding the proportion of ANF recepsubtypes in adrenal glomerulosa tissue. It appears the R_1 subtyp conclusions regarding the proportion of ANF receptor
subtypes in adrenal glomerulosa tissue. It appears that
the R_1 subtype predominates in rodent adrenal glomer-
ulosa, whereas bovine glomerulosa contains similar
amou subtypes in adrenal glomerulosa tissue. It appears that 90% of the total binding sites. These results clearly
the R_1 subtype predominates in rodent adrenal glomer-
ulosa, whereas bovine glomerulosa contains similar subtypes in adrenal glomerulosa tissue. It appears that
the R_1 subtype predominates in rodent adrenal glomer-
ulosa, whereas bovine glomerulosa contains similar
amounts of each receptor subtype. Studies examining the
e the R_1 subtype predominates in rodent adrenal glomer-
ulosa, whereas bovine glomerulosa contains similar the
amounts of each receptor subtype. Studies examining the
expression of ANF receptors at mRNA levels in adrenal ulosa, whereas bovine glomerulosa contains amounts of each receptor subtype. Studies examinexpression of ANF receptors at mRNA levels in a tissue have not appeared yet, but this information clarify the adrenal distribution nounts of each receptor subtype. Studies examining the
pression of ANF receptors at mRNA levels in adrenal 6
sue have not appeared yet, but this information may but
parify the adrenal distribution of ANF receptors.
4. Hear

expression of ANF receptors at mRNA levels in adrenal
tissue have not appeared yet, but this information may
clarify the adrenal distribution of ANF receptors.
4. Heart. Rat cardiac sarcolemma bound ANF in a
glumanner con tissue have not appeared yet, but this information may
clarify the adrenal distribution of ANF receptors.
4. Heart. Rat cardiac sarcolemma bound ANF in a
manner consistent with the existence of two binding
sites with K_d clarify the adrenal distribution of ANF receptors. ture
4. Heart. Rat cardiac sarcolemma bound ANF in a glamanner consistent with the existence of two binding (Lu
sites with K_d values of 11 and 1200 pM (Rugg et al., rad 4. *Heart*. Rat cardiac sarcolemma bound ANF in a manner consistent with the existence of two binding sites with K_d values of 11 and 1200 pM (Rugg et al., 1989). ANF bound to rat ventricular myocardium with a K_d of 12 sites with K_d values of 11 and 1200 pm (Rugg et al., radiographic studies revealed ANF-binding sites in the 1989). ANF bound to rat ventricular myocardium with a anterior pituitary (von Schroeder et al. 1985) but not in sites with K_d values of 11 and 1200 pM (Rugg et al., 1989). ANF bound to rat ventricular myocardium with a K_d of 12 (Neyses and Vetter, 1989) and 72 pM (Bastagli et al., 1990) and bovine ventricular sarcolemma with a 1989). ANF bound to rat ventricular myocardium wit K_d of 12 (Neyses and Vetter, 1989) and 72 pM (Bastet al., 1990) and bovine ventricular sarcolemma with K_d of 43 pM (McCartney et al., 1990). Many other stud found ANF K_d of 12 (Neyses and Vetter, 1989) and 72 pM (Bastagli
et al., 1990) and bovine ventricular sarcolemma with a
 K_d of 43 pM (McCartney et al., 1990). Many other studies
found ANF binding to endocardium, coronary vascula et al., 1990) and bovine ventricular sarcolemma with K_d of 43 pm (McCartney et al., 1990). Many other studies found ANF binding to endocardium, coronary vasculature endothelium, or mesenchyme but not to myocytes (Hirata K_d of 43 pm (McCartney et al., 1990). Many other studies A
found ANF binding to endocardium, coronary vascula-
ture endothelium, or mesenchyme but not to myocytes ao
(Hirata et al., 1985a; Currie et al., 1989; Oehlensch found ANF binding to endocardium, coronary vascula-
ture endothelium, or mesenchyme but not to myocytes adt
(Hirata et al., 1985a; Currie et al., 1989; Oehlenschlager rec
et al., 1989; Rutherford et al., 1992). The K_d o ture endothelium, or mesenchyme but not to myocytes (Hirata et al., 1985a; Currie et al., 1989; Oehlenschlagenet al., 1989; Rutherford et al., 1992). The K_d of binding to human endocardium was 36 pM with evidence of onl (Hirata et al., 1985a; Currie et al., 1989; Oehlenschlager
et al., 1989; Rutherford et al., 1992). The K_d of binding
to human endocardium was 36 pM with evidence of only
one high-affinity site (Rutherford et al., 1992). et al., 1989; Rutherford et al., 1992). The K_d of binding human thyroid cells (Tseng et al., 1990) and rat testis
to human endocardium was 36 pM with evidence of only (Pandey et al., 1986a; Leitman et al., 1988; Marala to human endocardium was 36 pM with evidence of only (Pa (Pa (Pa endocardium was 36 pM with evidence of only (Pa endotional tricular binding sites were characterized in cross-linking 70, studies and identified two receptor one high-affinity site (Rutherford et al., 1992). The ven-
tricular binding sites were characterized in cross-linking
studies and identified two receptors of 65,000 and 120,000
Da (McCartney et al., 1990). Binding of ANF t tricular binding sites were characterized in cross-linking 70
studies and identified two receptors of 65,000 and 120,000 tes
Da (McCartney et al., 1990). Binding of ANF to both mo
binding sites was attenuated by cANF, sugg studies and identified two receptors of 65,000 and 120,4
Da (McCartney et al., 1990). Binding of ANF to b
binding sites was attenuated by cANF, suggesting they were R₂-binding sites. The ANF-binding sites w
also found in Da (McCartney et al., 1990). I
binding sites was attenuated by
they were R₂-binding sites. The
also found in the conduction sys
Srivastava et al., 1989).
Autoradiographic studies inve nding sites was attenuated by cANF, suggesting that
ey were R_2 -binding sites. The ANF-binding sites were
so found in the conduction system of the heart (Anand-
ivastava et al., 1989).
Autoradiographic studies investiga

they were R₂-binding sites. The ANF-binding sites were 19
also found in the conduction system of the heart (Anand-
Srivastava et al., 1989).
Autoradiographic studies investigating the localization see
of injected ANF oft also found in the conduction system of the heart (Anand-Srivastava et al., 1989).

Autoradiographic studies investigating the localization

of injected ANF often found ANF accumulation in the

heart but usually in the endo Srivastava et al., 1989).

Autoradiographic studies investigating the localization

of injected ANF often found ANF accumulation in the

heart but usually in the endocardium (Bianchi et al.,

1985; Tjalve and Wilander, 198 Autoradiographic studies investigating the localization
of injected ANF often found ANF accumulation in the
heart but usually in the endocardium (Bianchi et al.,
1985; Tjalve and Wilander, 1988; Ou et al., 1989; Neuser
et of injected ANF often found ANF accumulation in the heart but usually in the endocardium (Bianchi et al., 1985; Tjalve and Wilander, 1988; Ou et al., 1989; Neuser et al., 1989). Fetal rat hearts expressed R_2 receptors heart but usually in the endocardium (Bianchi et al., 1985; Tjalve and Wilander, 1988; Ou et al., 1989; Neuser et al., 1989). Fetal rat hearts expressed R_2 receptors (Porter et al., 1990), but cardiac ANF receptors hav 1985; Tjalve and V
et al., 1989). Feta
(Porter et al., 1990)
been characterized
mRNA expression
5. Lung. Rat lun (Porter et al., 1990), but cardiac ANF receptors have not 7. Neurons. ANF binding to neuronal tissue has been
been characterized further by investigating ANF receptor studied in brain, spinal cord, sympathetic ganglia, and

**AMD TRACHTE
receptor from bovine lung bound ANF with a** *K***_d of 6.5**
pM (Uchida et al., 1989). Autoradiographic studies iden-A AND TRACHTE
receptor from bovine lung bound ANF with a K_d of 6.
pM (Uchida et al., 1989). Autoradiographic studies iden
tified the lung as a major site of ANF accumulation A AND TRACHTE
receptor from bovine lung bound ANF with a K_d of 6.5
pM (Uchida et al., 1989). Autoradiographic studies iden-
tified the lung as a major site of ANF accumulation
following intravenous injection (Bianchi et Freeptor from bovine lung bound ANF with a K_d of 6.5
pM (Uchida et al., 1989). Autoradiographic studies iden-
tified the lung as a major site of ANF accumulation
following intravenous injection (Bianchi et al., 1985;
He receptor from bovine lung bound ANF with a K_d of 6.5 pm (Uchida et al., 1989). Autoradiographic studies identified the lung as a major site of ANF accumulation following intravenous injection (Bianchi et al., 1985; Hers pM (Uchida et al., 1989). Autoradiographic studies identified the lung as a major site of ANF accumulation following intravenous injection (Bianchi et al., 1985; Hersey et al., 1989; Ou et al., 1989). The receptors in the tified the lung as a major site of ANF accumulation
following intravenous injection (Bianchi et al., 1985;
Hersey et al., 1989; Ou et al., 1989). The receptors in the
bovine lung were characterized as R_2 receptors base following intravenous injection (Bianchi et al., 1985;
Hersey et al., 1989; Ou et al., 1989). The receptors in the
bovine lung were characterized as R_2 receptors based on
the potent displacement of binding by $ANF(103-1$ Hersey et al., 1989; Ou et al., 1989). The receptors in the bovine lung were characterized as R_2 receptors based on the potent displacement of binding by ANF(103-123), a truncated ANF derivative selective for R_2 rec bovine lung were characterized as R_2 receptors based on
the potent displacement of binding by ANF(103-123), a
truncated ANF derivative selective for R_2 receptors
(Uchida et al., 1989). The ANF(103-123) displaced 90% the potent displacement of binding by ANF(103-123)
truncated ANF derivative selective for R_2 receptor
(Uchida et al., 1989). The ANF(103-123) displaced 90
of ANF binding to bovine lung (Morishita et al., 199)
suggestin truncated ANF derivative selective for R_2 receptors (Uchida et al., 1989). The ANF(103–123) displaced 90% of ANF binding to bovine lung (Morishita et al., 1992), suggesting that the R_2 receptor predominates. Cross-
 (Uchida et al., 1989). The ANF(103-123) displaced 90% of ANF binding to bovine lung (Morishita et al., 1992), suggesting that the R_2 receptor predominates. Cross-
linking of ANF to receptors resulted in the labeling of of ANF binding to bovine lung (Morishita et al., 1992),
suggesting that the R_2 receptor predominates. Cross-
linking of ANF to receptors resulted in the labeling of
66,000- and 130,000-Da receptors in rat lung fibrobla suggesting that the R_2 receptor predominates. Cross-
linking of ANF to receptors resulted in the labeling of
66,000- and 130,000-Da receptors in rat lung fibroblasts
(Leitman et al., 1987) and a 70,000-Da receptor in b linking of ANF to receptors resulted in the labeling of 66,000- and 130,000-Da receptors in rat lung fibroblasts (Leitman et al., 1987) and a 70,000-Da receptor in bovine lung (Shimonaka et al., 1987; Uchida et al., 1989) 66,000- and 130,000-Da receptors in rat lung fibroblasts (Leitman et al., 1987) and a 70,000-Da receptor in bovine lung (Shimonaka et al., 1987; Uchida et al., 1989). The R_2 receptor accounted for 90% of the ANF-bindin lung (Shimonaka et al., 1987; Uchida et al., 1989). The R_2 receptor accounted for 90% of the ANF-binding sites in the fibroblast (Leitman et al., 1987). Morishita et al. (1992) found both the 60,000- and 135,000-Da rec lung (Shimonaka et al., 1987; Uchida et al., 1989). The R_2 receptor accounted for 90% of the ANF-binding sites
in the fibroblast (Leitman et al., 1987). Morishita et al.
(1992) found both the 60,000- and 135,000-Da rec R_2 receptor accounted for 90% of the ANF-binding sites
in the fibroblast (Leitman et al., 1987). Morishita et al.
(1992) found both the 60,000- and 135,000-Da receptors
in bovine lung; the lower molecular mass form mad in the fibroblast (Leitman et al., 1987). Morishita et al. (1992) found both the 60,000- and 135,000-Da receptors in bovine lung; the lower molecular mass form made up 90% of the total binding sites. These results clearly (1992) found both the 60,000- and 135,000-Da receptors
in bovine lung; the lower molecular mass form made up
90% of the total binding sites. These results clearly
indicate the preponderance of the ANF R_2 receptor in
th 90% of the total binding sites. These results clearly indicate the preponderance of the ANF R_2 receptor in
the lung, similar to the situation found in the renal cortex
and vasculature.
6. *Endocrine organs*. Endocrine tissues bound ANF,
but thorough studies of ANF binding

indicate the preponderance of the ANF R_2 receptor in
the lung, similar to the situation found in the renal cortex
and vasculature.
6. *Endocrine organs*. Endocrine tissues bound ANF,
but thorough studies of ANF binding the lung, similar to the situation found in the renal cortex
and vasculature.
6. Endocrine organs. Endocrine tissues bound ANF,
but thorough studies of ANF binding are lacking. Cul-
tured pituicytes bound ANF, as did whol and vasculature.
6. *Endocrine organs*. Endocrine tissues bound ANF,
but thorough studies of ANF binding are lacking. Cul-
tured pituicytes bound ANF, as did whole pituitary
glands, with K_d values of 125 and 9250 pM, res 6. *Endocrine organs*. Endocrine tissues bound ANI but thorough studies of ANF binding are lacking. Cutured pituicytes bound ANF, as did whole pituitar glands, with K_d values of 125 and 9250 pM, respective (Luckman and but thorough studies of ANF binding are lacking. Cultured pituicytes bound ANF, as did whole pituitary glands, with K_d values of 125 and 9250 pM, respectively (Luckman and Bicknell, 1991; Agui et al., 1989). Autoradiogr tured pituicytes bound ANF, as did whole pituitary
glands, with K_d values of 125 and 9250 pM, respectively
(Luckman and Bicknell, 1991; Agui et al., 1989). Auto-
radiographic studies revealed ANF-binding sites in the
an glands, with K_d values of 125 and 9250 pM, respectively (Luckman and Bicknell, 1991; Agui et al., 1989). Auto-radiographic studies revealed ANF-binding sites in the anterior pituitary (von Schroeder et al. 1985) but not (Luckman and Bicknell, 1991; Agui et al., 1989). Auto-radiographic studies revealed ANF-binding sites in the anterior pituitary (von Schroeder et al. 1985) but not in the posterior pituitary or testis (Pang et al., 1991) a radiographic studies revealed ANF-binding sites in the anterior pituitary (von Schroeder et al. 1985) but not ithe posterior pituitary or testis (Pang et al., 1991) after intravenous injection of ANF. These results indicat anterior pituitary (von Schroeder et al. 1985) but not in
the posterior pituitary or testis (Pang et al., 1991) after
intravenous injection of ANF. These results indicate that
ANF is not accumulated to a large extent in th intravenous injection of ANF. These results indicate that
ANF is not accumulated to a large extent in the endo-
crine organs examined except, as mentioned earlier, the
adrenal gland. Nevertheless, cross-linking of ANF to i lung (Shimonaka et al., 1987; Uchuda et al., 1989). The R₂ receptor accounted for 90% of the ANF-binding sites in the fibroblast (Leitman et al., 1987). Morishita et al. (1992) found both the 60,000- and 135,000-Da rece ANF is not accumulated to a large extent in the endo-
crine organs examined except, as mentioned earlier, the
adrenal gland. Nevertheless, cross-linking of ANF to its
receptors showed the presence of ANF-binding sites in
h crine organs examined except, as mentioned earlier, the
adrenal gland. Nevertheless, cross-linking of ANF to its
receptors showed the presence of ANF-binding sites in
human thyroid cells (Tseng et al., 1990) and rat testis adrenal gland. Nevertheless, cross-linking of ANF to its
receptors showed the presence of ANF-binding sites in
human thyroid cells (Tseng et al., 1990) and rat testis
(Pandey et al., 1986a; Leitman et al., 1988; Marala and receptors showed the presence of ANF-binding sites in
human thyroid cells (Tseng et al., 1990) and rat testis
(Pandey et al., 1986a; Leitman et al., 1988; Marala and
Sharma, 1991). The thyroid cells solely contained a
70,0 human thyroid cells (Tseng et al., 1990) and rat testis (Pandey et al., 1986a; Leitman et al., 1988; Marala and Sharma, 1991). The thyroid cells solely contained a 70,000-Da receptor (Tseng et al., 1990), whereas the testi (Pandey et al., 1986a; Leitman et al., 1988; Marala and Sharma, 1991). The thyroid cells solely contained a 70,000-Da receptor (Tseng et al., 1990), whereas the testicular cells only had the larger ANF receptor with molecu Sharma, 1991). The thyroid cells solely contained a 70,000-Da receptor (Tseng et al., 1990), whereas the testicular cells only had the larger ANF receptor with molecular masses of either 130,000 (Pandey et al., 1986a; Leit 70,000-Da receptor (Tseng et al., 1990), whereas the
testicular cells only had the larger ANF receptor with
molecular masses of either 130,000 (Pandey et al., 1986a;
Leitman et al., 1988) or 180,000 Da (Marala and Sharma,
 testicular cells only had the larger ANF receptor with
molecular masses of either 130,000 (Pandey et al., 1986a;
Leitman et al., 1988) or 180,000 Da (Marala and Sharma,
1991). The expression of these receptors has not been molecular masses of either 130,000 (Pandey et al., 1986a;
Leitman et al., 1988) or 180,000 Da (Marala and Sharma,
1991). The expression of these receptors has not been
studied in greater detail at this point. The work that Leitman et al., 1988) or 180,000 Da (Marala and Sharma, 1991). The expression of these receptors has not been studied in greater detail at this point. The work that has been performed indicates that endocrine tissue does 1991). The expression of these receptors has not been
studied in greater detail at this point. The work that has
been performed indicates that endocrine tissue does pos-
sess ANF receptors, but the subtypes present appear studied in greater detail at this point. The work that has
been performed indicates that endocrine tissue does pos-
sess ANF receptors, but the subtypes present appear to
be specific for the endocrine tissue studied. The been performed indicates that endocrine tissue does possess ANF receptors, but the subtypes present appear to be specific for the endocrine tissue studied. The R_2 receptor is the major subtype present in thyroid cells, tissue. specific for the endocrine tissue studied. The R_2
ceptor is the major subtype present in thyroid cells,
d the R_1 receptor is the major subtype in testicular
sue.
7. *Neurons*. ANF binding to neuronal tissue has been

(Porter et al., 1990), but cardiac ANF receptors have not 7. Neurons. ANF binding to neuronal tissue has been
been characterized further by investigating ANF receptor studied in brain, spinal cord, sympathetic ganglia, and receptor is the major subtype present in thyroid cells,
and the R_1 receptor is the major subtype in testicular
tissue.
7. Neurons. ANF binding to neuronal tissue has been
studied in brain, spinal cord, sympathetic gang and the R_1 receptor is the major subtype in testicular
tissue.
7. Neurons. ANF binding to neuronal tissue has been
studied in brain, spinal cord, sympathetic ganglia, and
pheochromocytoma tissue. ANF bounds to rat brai tissue.

7. Neurons. ANF binding to neuronal tissue has been

studied in brain, spinal cord, sympathetic ganglia, and

pheochromocytoma tissue. ANF bounds to rat brain with

a K_d of approximately 600 pM (Gibson et al., 1 7. Neurons. ANF binding to neuronal tissue has been
studied in brain, spinal cord, sympathetic ganglia, and
pheochromocytoma tissue. ANF bounds to rat brain with
a K_d of approximately 600 pM (Gibson et al., 1986;
Gutkow

PHARMACOLOGICAL REVIEWS

EXECT AND SIGNAL TRANSPARE AND SIGNAL TRANSPARE Characterized by a slightly higher affinity, with a K_d **of 250 pm (Levin et al., 1990), whereas glioma cells bound variable with a** K_d **of 15 pm (Eguchi et al., 1992). The** ANF RECEPTORS AND SIGNAL TR
characterized by a slightly higher affinity, with a K_d of
250 pM (Levin et al., 1990), whereas glioma cells bound
ANF with a K_d of 15 pM (Eguchi et al., 1992). The mouse et
spinal cord boun characterized by a slightly higher affinity, with a K_d of 250 pm (Levin et al., 1990), whereas glioma cells bound NNF with a K_d of 15 pm (Eguchi et al., 1992). The mouse espinal cord bound ANF with a K_d of 54 pm (Si characterized by a slightly higher affinity, with a K_d of 8.
250 pm (Levin et al., 1990), whereas glioma cells bound vary
ANF with a K_d of 15 pm (Eguchi et al., 1992). The mouse et a
spinal cord bound ANF with a K_d 250 pM (Levin et al., 1990), whereas glioma cells bound
ANF with a K_d of 15 pM (Eguchi et al., 1992). The mouse
spinal cord bound ANF with a K_d of 54 pM (Simonnet et
al., 1989). Rat superior cervical ganglia also boun ANF with a K_d of 15 pM (Eguchi et al., 1992). The mouse espinal cord bound ANF with a K_d of 54 pM (Simonnet et (al., 1989). Rat superior cervical ganglia also bound ANF havith K_d values of 160 to 330 pM (Gutkind et spinal cord bound ANF with a K_d of 54 pm (Simonnet et (Anand
al., 1989). Rat superior cervical ganglia also bound ANF human
with K_d values of 160 to 330 pm (Gutkind et al., 1987; ANF re
Torda et al., 1989). Pheochromo al., 1989). Rat superior cervical ganglia also bound ANF with K_d values of 160 to 330 pM (Gutkind et al., 1987; Torda et al., 1989). Pheochromocytoma-binding sites for ANF include a K_d in the range of 670 to 1000 pM (with K_d values of 160 to 330 pm (Gutkind et al., 1987; ANT orda et al., 1989). Pheochromocytoma-binding sites for 125
ANF include a K_d in the range of 670 to 1000 pm mol
(Shionoiri et al., 1987; Rathinavelu and Isom, Torda et al., 1989). Pheochromocytoma-binding sites for 12
ANF include a K_d in the range of 670 to 1000 pM most
(Shionoiri et al., 1987; Rathinavelu and Isom, 1988; Toki di
et al., 1992). Autoradiographic studies reveal ANF include a K_d in the range of 670 to 1000 p (Shionoiri et al., 1987; Rathinavelu and Isom, 1988; To et al., 1992). Autoradiographic studies revealed Ab binding to most areas of the brain with binding in to lifactory (Shionoiri et al., 1987; Rathinavelu and Isom, 1988; Toki diet al., 1992). Autoradiographic studies revealed ANF m
binding to most areas of the brain with binding in the redifactory bulb, pineal gland, choroid plexus, and et al., 1992). Autoradiographic studies revealed ANF motion in the state of the brain with binding in the repolfactory bulb, pineal gland, choroid plexus, and arachinoid mater predominating (Gibson et al., 1986; Mantyh al. binding to most areas of the brain with binding in the olfactory bulb, pineal gland, choroid plexus, and arach-
noid mater predominating (Gibson et al., 1986; Mantyh
et al., 1987). Binding sites for ANF in mouse spinal cor olfactory bulb, pineal gland, choroid plexus, and arach-tain
noid mater predominating (Gibson et al., 1986; Mantyh al.,
et al., 1987). Binding sites for ANF in mouse spinal cord plat
were on epithelial or glial cells and n noid mater predominating (Gibson et al., 1986; Mantyh alet al., 1987). Binding sites for ANF in mouse spinal cord powere on epithelial or glial cells and not on neurons variation (Simonnet et al., 1989). In superior cervic et al., 1987). Binding sites for ANF in mouse spinal cord
were on epithelial or glial cells and not on neurons
(Simonnet et al., 1989). In superior cervical ganglia, ANF
bound to glia, fibroblasts (James et al., 1990a,b), were on epithelial or glial cells and not on neurons (Simonnet et al., 1989). In superior cervical ganglia, ANF bound to glia, fibroblasts (James et al., 1990a,b), or ganglion cells (Gutkind et al., 1987). No binding to pr 1987). bound to glia, fibroblasts (James et al., 1990a,b), or ganglion cells (Gutkind et al., 1987). No binding to pre-
or postganglionic nerves was detected (Gutkind et al., 1987).
 R_2 -selective ligands failed to compete for m

or postganglionic nerves was detected (Gutkind et al., $\begin{array}{c} 1.46 \rightarrow 1.487 \end{array}$
1987).

R₂-selective ligands failed to compete for most central bin

nervous system ANF-binding sites with the exception of site

the ch 1987).
 R_2 -selective ligands failed to compete for most central

nervous system ANF-binding sites with the exception of

the choroid plexus and arachnoid mater (Brown and

Czarnecki, 1990; Konrad et al., 1991; Gutkowsk R_2 -selective ligands failed to compete for most central b
nervous system ANF-binding sites with the exception of site
the choroid plexus and arachnoid mater (Brown and fi
Czarnecki, 1990; Konrad et al., 1991; Gutkowska nervous system ANF-binding sites with the exception of site
the choroid plexus and arachnoid mater (Brown and frin
Czarnecki, 1990; Konrad et al., 1991; Gutkowska et al., stir
1991). Thus, most central nervous system bind the choroid plexus and arachnoid mater (Brown and Czarnecki, 1990; Konrad et al., 1991; Gutkowska et al., 1991). Thus, most central nervous system binding sites for ANF appear to be R_1 receptors. Curiously, CANF displa Czarnecki, 1990; Konrad et al., 1991; Gutkowska et a
1991). Thus, most central nervous system binding sit
for ANF appear to be R_1 receptors. Curiously, cAN
displaced 95% of the ANF binding to diencephalic cu
tures, sug 1991). Thus, most central nervous system binding sites
for ANF appear to be R_1 receptors. Curiously, cANF
displaced 95% of the ANF binding to diencephalic cul-
tures, suggesting that R_2 receptors predominate in astr for ANF appear to be R_1 receptors. Curiously, cAN displaced 95% of the ANF binding to diencephalic curres, suggesting that R_2 receptors predominate in astrepts from this section of the brain (Levin et al., 1990). Th displaced 95% of the ANF binding to diencephalic cultures, suggesting that R_2 receptors predominate in astrocytes from this section of the brain (Levin et al., 1990). The effect of R_1 - or R_2 -selective ligands was tures, suggesting that R_2 receptors predominate in astro-
cytes from this section of the brain (Levin et al., 1990). al., 19
The effect of R_1 - or R_2 -selective ligands was not inves-
tigated in the spinal cord or cytes from this section of the brain (Levin et al., 1990).
The effect of R_1 - or R_2 -selective ligands was not inves-
tigated in the spinal cord or sympathetic ganglia. Re-
cently, Sumners and Tang (1992) concluded th The effect of R_1 - or R_2 -selective ligands was not inves-
tigated in the spinal cord or sympathetic ganglia. Re-
tors but cently, Sumners and Tang (1992) concluded that GC-A
receptors predominate in fibroblasts, wher tigated in the spinal cord or sympathetic ganglia. Recently, Sumners and Tang (1992) concluded that GC-A 19 receptors predominate in fibroblasts, whereas GC-B receptors represent the major receptor in neurons from pletal cently, Sumners and Tang (1992) concluded that GC-A receptors predominate in fibroblasts, whereas GC-B receptors represent the major receptor in neurons from fetal rat brains. These results suggest that both forms of the ceptors predominate in fibroblasts, whereas GC-B reptors represent the major receptor in neurons from planet at brains. These results suggest that both forms of the R_1 receptor are present in the central nervous system

ceptors represent the major receptor in neurons from p
fetal rat brains. These results suggest that both forms of ti
the R_1 receptor are present in the central nervous system.
Cross-linking studies confirmed most of th the R_1 receptor are present in the central nervous system.
Cross-linking studies confirmed most of the above
observations. Rat olfactory bulb ANF receptors migrated
at molecular masses of $120,000$ and $180,000$ Da, su the R_1 receptor are present in the central nervous system.
Cross-linking studies confirmed most of the above
observations. Rat olfactory bulb ANF receptors migrated
at molecular masses of 120,000 and 180,000 Da, sugges Cross-linking studies confirmed most of the above
observations. Rat olfactory bulb ANF receptors migrated
at molecular masses of 120,000 and 180,000 Da, suggest-
ing the sole presence of R_1 receptor subtypes (Konrad et observations. Rat olfactory bulb ANF receptors migrated
at molecular masses of 120,000 and 180,000 Da, suggest-
ing the sole presence of R_1 receptor subtypes (Konrad et
al., 1991). Rat diencephalic cultures showed the at molecular masses of 120,000 and 180,000 Da, sugge
ing the sole presence of R_1 receptor subtypes (Konraa
al., 1991). Rat diencephalic cultures showed the existe
of ANF receptors with molecular masses of 66,0
102,000, al., 1991). Rat diencephalic cultures showed the existence
of ANF receptors with molecular masses of 66,000, bound to the 66,000-Da site, indicating that the GC-
102,000, and 130,000 Da, the smallest receptor account-
ing al., 1991). Rat diencephalic cultures showed the existence
of ANF receptors with molecular masses of 66,000,
102,000, and 130,000 Da, the smallest receptor account-
ing for 95% of the binding (Levin et al., 1990). Human
ph of ANF receptors with molecular masses of 66,000,
102,000, and 130,000 Da, the smallest receptor account-
ing for 95% of the binding (Levin et al., 1990). Human
pheochromocytomas contained only the 70,000-Da re-
ceptor pr 102,000, and 130,000 Da, the smallest receptor account-
ing for 95% of the binding (Levin et al., 1990). Human the
pheochromocytomas contained only the 70,000-Da re-
exptor present as a dimer (Shionoiri et al., 1987), whe ing for 95% of the binding (Levin et al., 1990). Human the pheochromocytomas contained only the 70,000-Da receptor present as a dimer (Shionoiri et al., 1987), whereas quant pheochromocytomas contained both the 70,000- an pheochromocytomas contained only the 70,000-Da receptor present as a dimer (Shionoiri et al., 1987), whereas quart pheochromocytomas contained both the 70,000- and it 130,000-Da receptors (Rathinavelu and Isom, 1988) with ceptor present as a dimer (Shionoiri et
rat pheochromocytomas contained bo
130,000-Da receptors (Rathinavelu an
the larger receptor accounting for 7
sites (Rathinavelu and Isom, 1991).
These studies indicate that neurol t pheochromocytomas contained both the 70,000- and it,
0,000-Da receptors (Rathinavelu and Isom, 1988) with
e larger receptor accounting for 70% of the binding en
es (Rathinavelu and Isom, 1991). et
These studies indicate

130,000-Da receptors (Rathinavelu and Isom, 1988) with get
the larger receptor accounting for 70% of the binding en
sites (Rathinavelu and Isom, 1991). et
These studies indicate that neuronal tissues contain an
ANF recep the larger receptor accounting for 70% of the binding
sites (Rathinavelu and Isom, 1991).
These studies indicate that neuronal tissues contain
ANF receptors, although the cell types expressing the
receptors may be nonneur sites (Rathinavelu and Isom, 1991).
These studies indicate that neuronal tissues contain
ANF receptors, although the cell types expressing the
receptors may be nonneuronal. The primary receptor
present in the central nerv These studies indicate that neuronal tissues contain and ANF receptors, although the cell types expressing the irreceptors may be nonneuronal. The primary receptor we present in the central nervous system is the R_1 sub ANF receptors, although the
receptors may be nonneur
present in the central nervo
The R_2 receptor is present
and diencephalic astrocytes.

ANF RECEPTORS AND SIGNAL TRANSDUCTION MECHANISMS 461
characterized by a slightly higher affinity, with a K_d of 8. Platelets. ANF binds to human platelets with a K_d 250 pm (Levin et al., 1990), whereas glioma cells bound varying from 3.5 to 28 pm (Schiffrin et al., 1986a; Duggan
ANF with a *K_d* of 15 pm (Eguchi et al., 1992). The mouse et al., 1991). This value in rat platelets was *8. Platelets.* ANF binds to human platelets with a *Kd* **EXANSDUCTION MECHANISMS** 461
8. Platelets. ANF binds to human platelets with a K_d
varying from 3.5 to 28 pM (Schiffrin et al., 1986a; Duggan
et al., 1991). This value in rat platelets was 135 pM FRANSDUCTION MECHANISMS 461
8. Platelets. ANF binds to human platelets with a K_d
varying from 3.5 to 28 pM (Schiffrin et al., 1986a; Duggan
et al., 1991). This value in rat platelets was 135 pM
(Anand-Srivastava et al., 8. Platelets. ANF binds to human platelets with a K_d varying from 3.5 to 28 pM (Schiffrin et al., 1986a; Duggan et al., 1991). This value in rat platelets was 135 pM (Anand-Srivastava et al., 1991). The receptor present 8. Platelets. ANF binds to human platelets with a K_d
varying from 3.5 to 28 pM (Schiffrin et al., 1986a; Duggan
et al., 1991). This value in rat platelets was 135 pM
(Anand-Srivastava et al., 1991). The receptor present varying from 3.5 to 28 pM (Schiffrin et al., 1986a; Duggan
et al., 1991). This value in rat platelets was 135 pM
(Anand-Srivastava et al., 1991). The receptor present in
human platelets was identified by cross-linking of t et al., 1991). This value in rat platelets was 135 pM
(Anand-Srivastava et al., 1991). The receptor present in
human platelets was identified by cross-linking of the
ANF receptor resulting in the labeling of two proteins o (Anand-Srivastava et al., 1991). The receptor present in
human platelets was identified by cross-linking of the
ANF receptor resulting in the labeling of two proteins of
 $125,000$ and $65,000$ Da (Schiffrin et al., 1991). human platelets was identified by cross-linking of the
ANF receptor resulting in the labeling of two proteins of
125,000 and 65,000 Da (Schiffrin et al., 1991). The lower
molecular mass receptor existed as a monomer or a
d ANF receptor resulting in the labeling of two proteins of 125,000 and 65,000 Da (Schiffrin et al., 1991). The lower molecular mass receptor existed as a monomer or a dimer. cANF displaced binding to both high and low mole 125,000 and 65,000 Da (Schiffrin et al., 1991). The lower molecular mass receptor existed as a monomer or a dimer. cANF displaced binding to both high and low molecular mass receptors, suggesting that both receptors repre dimer. cANF displaced binding to both high and low
molecular mass receptors, suggesting that both receptors
represent R_2 receptors. In contrast, rat platelets con-
tained only a 66,000-Da receptor (Anand-Srivastava et
 dimer. cANF displaced binding to both high and low
molecular mass receptors, suggesting that both receptors
represent R_2 receptors. In contrast, rat platelets con-
tained only a 66,000-Da receptor (Anand-Srivastava et
 molecular mass receptors, suggesting that both receptors
represent R_2 receptors. In contrast, rat platelets con-
tained only a 66,000-Da receptor (Anand-Srivastava et
al., 1991). These data indicate that ANF binds avid represent R_2 receptors. In contrast, rat platelets contained only a 66,000-Da receptor (Anand-Srivastava et al., 1991). These data indicate that ANF binds avidly to platelet R_2 receptors. The R_2 receptor may be p tained only a 66,000-Da receptor (Anand-Srivastava et al., 1991). These data indicate that ANF binds avidly to platelet R_2 receptors. The R_2 receptor may be present in varying forms as a monomer or dimer of the 66,0 al., 1991). The
platelet R₂ rec
varying forms
receptor or as
binds cANF. varying forms as a monomer or dimer of the 66,000-Da
receptor or as a nonreducible $130,000$ -Da form that also
binds cANF.
C. Atrial Natriuretic Factor R₁ Receptors

nervous system ANF-binding sites with the exception of sites by Scatchard analysis (Ballerman et al., 1985; Schif-
the choroid plexus and arachnoid mater (Brown and frin et al., 1985). After ANF was recognized as a GC As discussed above, initial studies of ANF receptor binds cANF.
C. Atrial Natriuretic Factor R_1 Receptors
As discussed above, initial studies of ANF receptor
binding indicated a homogeneous population of binding
sites by Scatchard analysis (Ballerman et al., 1985; Schif C. Atrial Natriuretic Factor R_1 Receptors
As discussed above, initial studies of ANF recept
binding indicated a homogeneous population of bindi
sites by Scatchard analysis (Ballerman et al., 1985; Schi
frin et al., 198 Frin et al., 1985). After ANF was recognized as a GC
stimulant, comparisons of ANF receptor
frin et al., 1985). After ANF was recognized as a GC
stimulant, comparisons of ANF binding and cGMP pro-As discussed above, initial studies of ANF receptor
binding indicated a homogeneous population of binding
sites by Scatchard analysis (Ballerman et al., 1985; Schif-
frin et al., 1985). After ANF was recognized as a GC
sti binding indicated a homogeneous population of binding
sites by Scatchard analysis (Ballerman et al., 1985; Schif-
frin et al., 1985). After ANF was recognized as a GC
stimulant, comparisons of ANF binding and cGMP pro-
duc sites by Scatchard analysis (Ballerman et al., 1985; Schiffrin et al., 1985). After ANF was recognized as a GC
stimulant, comparisons of ANF binding and cGMP pro-
duction were performed (Hamet et al., 1984; Waldman
et al., frin et al., 1985). After ANF was recognized as a GC
stimulant, comparisons of ANF binding and cGMP pro-
duction were performed (Hamet et al., 1984; Waldman
et al., 1984; Winquist et al., 1984). Truncated analogs of
ANF fa stimulant, comparisons of ANF binding and cGMP production were performed (Hamet et al., 1984; Waldman
et al., 1984; Winquist et al., 1984). Truncated analogs of
ANF failed to stimulate GC but bound to ANF receptors
with th duction were performed (Hamet et al., 1984; Waldman
et al., 1984; Winquist et al., 1984). Truncated analogs of
ANF failed to stimulate GC but bound to ANF receptors
with the same affinity as native ANF (Scarbourough et
al. ANF failed to stimulate GC but bound to ANF receptors
with the same affinity as native ANF (Scarbourough et
al., 1986; Leitman et al., 1988; Leitman and Murad,
1986). Specifically, ANF(103-123) bound to ANF recep-
tors but ANF failed to stimulate GC but bound to ANF receptors
with the same affinity as native ANF (Scarbourough et
al., 1986; Leitman et al., 1988; Leitman and Murad,
1986). Specifically, ANF(103-123) bound to ANF recep-
tors but with the same affinity as native ANF (Scarbourough et al., 1986; Leitman et al., 1988; Leitman and Murad, 1986). Specifically, ANF(103–123) bound to ANF receptors but was a poor stimulator of GC (Leitman et al., 1986), lea al., 1986; Leitman et al., 1988; Leitman and Murad.
1986). Specifically, ANF(103–123) bound to ANF receptors but was a poor stimulator of GC (Leitman et al., 1986), leading to the interpretation that diverse ANF receptors 1986). Specifically, ANF(103-123) bound to ANF re
tors but was a poor stimulator of GC (Leitman et
1986), leading to the interpretation that diverse l
receptors exist in most tissues. The ANF receptor
pled to GC was pro tors but was a poor stimulator of GC (Leitman et al.
1986), leading to the interpretation that diverse ANI
receptors exist in most tissues. The ANF receptor cou
pled to GC was proposed to be present in low concentra
tions 1986), leading to the interpretation that diverse ANF receptors exist in most tissues. The ANF receptor coupled to GC was proposed to be present in low concentrations and to have a low affinity for $ANF(103-123)$. Converse receptors exist in most tissues. The ANF receptor
pled to GC was proposed to be present in low conce
tions and to have a low affinity for ANF(103–123).
versely, the most abundant receptor bound ANF
123) with high affinity ed to GC was proposed to be present in low concentra-
nns and to have a low affinity for ANF(103–123). Con-
rsely, the most abundant receptor bound ANF(103–
3) with high affinity but did not couple to GC.
Schenk et al. (19

versely, the most abundant receptor bound ANF(103-123) with high affinity but did not couple to GC.
Schenk et al. (1985) identified two binding sites for
ANF in bovine aortic smooth muscle with molecular
masses of 180,000 versely, the most abundant receptor bound ANF(103-123) with high affinity but did not couple to GC.
Schenk et al. (1985) identified two binding sites for
ANF in bovine aortic smooth muscle with molecular
masses of 180,000 123) with high affinity but did not couple to GC.
Schenk et al. (1985) identified two binding sites for
ANF in bovine aortic smooth muscle with molecular
masses of 180,000 and 66,000 Da. Leitman et al. (1986)
demonstrated Schenk et al. (1985) identified two binding sites for
ANF in bovine aortic smooth muscle with molecular
masses of 180,000 and 66,000 Da. Leitman et al. (1986)
demonstrated that truncated ANF analogs selectively
bound to th ANF in bovine aortic smooth muscle with molecular masses of 180,000 and 66,000 Da. Leitman et al. (1986) demonstrated that truncated ANF analogs selectively bound to the 66,000-Da site, indicating that the GC-coupled recep masses of 180,000 and 66,000 Da. Leitman et al. (1986)
demonstrated that truncated ANF analogs selectively
bound to the 66,000-Da site, indicating that the GC-
coupled receptor was of higher molecular mass. However,
the hi demonstrated that truncated ANF analogs selective
bound to the 66,000-Da site, indicating that the G
coupled receptor was of higher molecular mass. Howev
the higher molecular mass ANF receptor was identifi
as a 130,000-Da bound to the 66,000-Da site, indicating that the GC coupled receptor was of higher molecular mass. Howeve the higher molecular mass ANF receptor was identified as a 130,000-Da receptor in their study and most subsequent st coupled receptor was of higher molecular mass. However, the higher molecular mass ANF receptor was identified as a 130,000-Da receptor in their study and most subsequent studies. Furthermore, ANF binding and GC activity co the higher molecular mass ANF receptor was identified
as a 130,000-Da receptor in their study and most subse-
quent studies. Furthermore, ANF binding and GC activ-
ity copurified during the course of GC purification, sug-
 as a 130,000-Da receptor in their study and most subsequent studies. Furthermore, ANF binding and GC activity copurified during the course of GC purification, suggesting that ANF bound to a protein containing GC enzyme act quent studies. Furthermore, ANF binding and GC activity copurified during the course of GC purification, suggesting that ANF bound to a protein containing GC enzyme activity (Kuno et al., 1986). Ultimately, Chinkers et al. ity copurified during the course of GC purification, suggesting that ANF bound to a protein containing Genzyme activity (Kuno et al., 1986). Ultimately, Chinken et al. (1989) transfected COS-7 cells with brain GC cDN. and gesting that ANF bound to a protein containing GC
enzyme activity (Kuno et al., 1986). Ultimately, Chinkers
et al. (1989) transfected COS-7 cells with brain GC cDNA
and demonstrated increased GC activity and ANF bind-
ing enzyme activity (Kuno et al., 1986). Ultimately, Chink
et al. (1989) transfected COS-7 cells with brain GC cDl
and demonstrated increased GC activity and ANF bi
ing following transfection. The cDNA encoded a prot
with a pr et al. (1989) transfected COS-7 cells with brain GC cDN
and demonstrated increased GC activity and ANF bin
ing following transfection. The cDNA encoded a prote
with a predicted molecular mass of 115,852 Da, consin
ent with and demonstrated increased GC activity and ANF bind-
ing following transfection. The cDNA encoded a protein
with a predicted molecular mass of 115,852 Da, consist-
ent with the electrophoretic results predicting a molec-
u ing following transfection. The cDNA encoded a protein
with a predicted molecular mass of 115,852 Da, consist-
ent with the electrophoretic results predicting a molec-
ular mass of 120,000 to 180,000 Da. The data of Chinke

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ANAND-SRIVASTAVA AND TRACHTE

dence indicating that ANF binds to a receptor containing 66-kDa transmemb

a GC moiety. This combination of an ANF receptor- Fuller et al., 1988; I ANAND-SRIV
dence indicating that ANF binds to a receptor contain
a GC moiety. This combination of an ANF recept
binding protein and GC has subsequently been de ANAND-SRIVAS
dence indicating that ANF binds to a receptor containin
a GC moiety. This combination of an ANF recepto
binding protein and GC has subsequently been desi
nated GC-A or the ANF A receptor. The binding of AN dence indicating that ANF binds to a receptor containing 66-
a GC moiety. This combination of an ANF receptor-
binding protein and GC has subsequently been desig-
nated GC-A or the ANF A receptor. The binding of ANF cula
t a GC moiety. This combination of an ANF receptor-
binding protein and GC has subsequently been designated GC-A or the ANF A receptor. The binding of ANF
to this receptor normally is half-maximal at concentra-
tions of 100 a GC moiety. This combination of an ANF receptor-
binding protein and GC has subsequently been designated GC-A or the ANF A receptor. The binding of ANF combined to this receptor normally is half-maximal at concentra-
tion binding protein and GC has subsequently been designated GC-A or the ANF A receptor. The binding of ANF to this receptor normally is half-maximal at concentrations of 100 to 1000 pM, whereas half-maximal activation of GC us nated GC-A or the ANF A receptor. The binding of AN
to this receptor normally is half-maximal at concentr
tions of 100 to 1000 pM, whereas half-maximal activatio
of GC usually requires concentrations of 1 to 10 nM AN
Thus, to this receptor normally is half-maximal at concentra-
tions of 100 to 1000 pM, whereas half-maximal activation
of GC usually requires concentrations of 1 to 10 nM ANF.
Thus, the binding does not correlate with cGMP gener tions of 100 to 1000 pM, whereas half-maximal activation elof GC usually requires concentrations of 1 to 10 nM ANF. ey.
Thus, the binding does not correlate with cGMP gener-
ation, although they are presumably mediated by of GC usually requires concentrations of 1 to 10 nM ANF.
Thus, the binding does not correlate with cGMP gener-
ation, although they are presumably mediated by the
same molecule. This discrepancy was justified initially
by Thus, the binding does not correlate with cGMP gener-
ation, although they are presumably mediated by the et al
same molecule. This discrepancy was justified initially al.,
by the presence of other ANF receptors that coul ation, although they are presumably mediated by the et same molecule. This discrepancy was justified initially all by the presence of other ANF receptors that could alter dividing; however, even tissues containing only th same molecule. This discrepancy was justified initially
by the presence of other ANF receptors that could alter
binding; however, even tissues containing only the R_1
receptor demonstrated the same discrepancy between
b by the presence of other ANF receptors that could alter do
binding; however, even tissues containing only the R₁ the
receptor demonstrated the same discrepancy between co
binding affinity and activation of GC (Fethiere e binding; however, even tissues containing only the R_1
receptor demonstrated the same discrepancy between
binding affinity and activation of GC (Fethiere et al.,
1989). The explanation for the differing potencies of
ANF receptor demonstrated the same discrepancy bet
binding affinity and activation of GC (Fethiere e
1989). The explanation for the differing potenci
ANF on these two events, which presumably are
diated by the same molecule, m binding affinity and activation of GC (Fethiere et al., 1989). The explanation for the differing potencies of ANF on these two events, which presumably are mediated by the same molecule, may involve dephosphorylation of th 1989). The explanation for
ANF on these two events, v
diated by the same molecule,
ation of the GC, resulting in a
(Potter and Garbers, 1992).
The gene encoding rat GC NF on these two events, which presumably are me-
ated by the same molecule, may involve dephosphoryl-
ion of the GC, resulting in a desensitization to stimuli
otter and Garbers, 1992).
The gene encoding rat GC-A contains 1 diated by the same molecule, may involve dephosphoryl-
ation of the GC, resulting in a desensitization to stimuli
that
(Potter and Garbers, 1992).
The gene encoding rat GC-A contains 17.5 kilobases
heno
(Yamaguchi et al.,

ation of the GC, resulting in a desensitization to stimuli
(Potter and Garbers, 1992).
The gene encoding rat GC-A contains 17.5 kilobases
(Yamaguchi et al., 1990) consisting of 22 exons and 21
introns. The first six exons (Potter and Garbers, 1992). See Free encoding rat GC-A contains 17.5 kilobases he (Yamaguchi et al., 1990) consisting of 22 exons and 21 Handrons. The first six exons encode the extracellular on region of GC-A, accounting The gene encoding rat GC-A contains 17.5 kilobases
(Yamaguchi et al., 1990) consisting of 22 exons and 21
introns. The first six exons encode the extracellular
region of GC-A, accounting for ANF binding. This region
contai introns. The first six exons encode the extracellular
region of GC-A, accounting for ANF binding. This region
contains considerable homology with the extracellular
regions of other ANF receptors. The membrane-span-
ning do introns. The first six exons encode the extracellular
region of GC-A, accounting for ANF binding. This region
contains considerable homology with the extracellular
regions of other ANF receptors. The membrane-span-
ning do region of GC-A, accounting for ANF binding. This region Accountains considerable homology with the extracellular leading regions of other ANF receptors. The membrane-spanning domain is encoded by exons 8 to 15, with the G contains considerable homology w
regions of other ANF receptors. T
ning domain is encoded by exon 7.
domain is encoded by exons 8 to 15,
encoded by exons 16 to 22.
Another ANF receptor coupling gions of other ANF receptors. The membrane-span-
ng domain is encoded by exon 7. A protein kinase-like
main is encoded by exons 8 to 15, with the GC domain
coded by exons 16 to 22.
Another ANF receptor coupling to GC subse

ming domain is encoded by exons 7. A protein kinase-like
domain is encoded by exons 8 to 15, with the GC domain
encoded by exons 16 to 22.
Another ANF receptor coupling to GC subsequently
and rat brain
(Chang et al., 1989 domain is encoded by exons 8 to 15, with the GC domain
encoded by exons 16 to 22.
Another ANF receptor coupling to GC subsequently
was identified in human placental tissue and rat brain
(Chang et al., 1989; Schulz et al., encoded by exons 16 to 22.

Another ANF receptor coupling to GC subsequently

was identified in human placental tissue and rat brain

(Chang et al., 1989; Schulz et al., 1990). This receptor

bound ANF but had a higher af Another ANF receptor coupling to GC subsequently
was identified in human placental tissue and rat brain
(Chang et al., 1989; Schulz et al., 1990). This receptor
bound ANF but had a higher affinity for BNP, although
the bi was identified in human placental tissue and rat brain sil

(Chang et al., 1989; Schulz et al., 1990). This receptor po

bound ANF but had a higher affinity for BNP, although sp

the binding affinity for either natriureti (Chang et al., 1989; Schulz et al., 1990). This receptor ported
bound ANF but had a higher affinity for BNP, although
the binding affinity for either natriuretic peptide was
activity
slight (Schulz et al., 1990). This rec bound ANF but had a higher affinity for BNP, although
the binding affinity for either natriuretic peptide was
slight (Schulz et al., 1990). This receptor was termed the
inhib
ANF B receptor or GC-B, as opposed to the ANF A the binding affinity for either natriuretic peptide was
slight (Schulz et al., 1990). This receptor was termed the
ANF B receptor or GC-B, as opposed to the ANF A
receptor described in the previous sections. The GC-B
was slight (Schulz et al., 1990). This receptor was termed the ANF B receptor or GC-B, as opposed to the ANF A receptor described in the previous sections. The GC-B was cloned and had 62% overall homology with GC-A and 74 to 7 Schulz et al., 1990). This receptor was termed the

ANF B receptor or GC-B, as opposed to the ANF A

was cloned and had 62% overall homology with GC-A

was cloned and had 62% overall homology with GC-A

and 74 to 78% intr receptor described in the previous sections. The GC-B
was cloned and had 62% overall homology with GC-A
and 74 to 78% intracellular homology (Chang et al., 1989;
Schulz et al., 1990). The predicted molecular mass was
114,9 was cloned and had 62% overall homology with GC
and 74 to 78% intracellular homology (Chang et al., 198
Schulz et al., 1990). The predicted molecular mass w
114,952 Da, similar to the GC-A receptor. The po
affinity of the and 74 to 78% intracellular homology (Chang et al., 19
Schulz et al., 1990). The predicted molecular mass v
114,952 Da, similar to the GC-A receptor. The po
affinity of the GC-B for either ANF or BNP was ince
sistent with Schulz et al., 1990). The predicted molecular mass was
114,952 Da, similar to the GC-A receptor. The poor
affinity of the GC-B for either ANF or BNP was incon-
sistent with a functional role for this receptor in mediat-
in 114,952 Da, similar to the GC-A receptor. The poor
affinity of the GC-B for either ANF or BNP was incon-
sistent with a functional role for this receptor in mediat-
ing natriuretic effects of either peptide (Schulz et al. affinity of the GC-B for either ANF or BNP was inconsistent with a functional role for this receptor in mediating natriuretic effects of either peptide (Schulz et al., 1990). More recently, another ANF-like peptide, CNP (E sistent with a functional role for this receptor in mediating natriuretic effects of either peptide (Schulz et al., 1990). More recently, another ANF-like peptide, CNP (Eguchi et al., 1992), stimulated GC activity of the G ing natriuretic effects of either peptide (Schulz et 1990). More recently, another ANF-like peptide, C (Eguchi et al., 1992), stimulated GC activity of the (B receptor more potently than either ANF or Bl suggesting that CN 1990). More recently, another ANF-like peptide, CNP
(Eguchi et al., 1992), stimulated GC activity of the GC-
B receptor more potently than either ANF or BNP,
suggesting that CNP is its natural ligand. The distribu-
tion of (Eguchi et al., 1992), stimulated GC activity of the GC-
B receptor more potently than either ANF or BNP, in
suggesting that CNP is its natural ligand. The distribu-
dion of GC-A and GC-B differed depending on the tissue. B receptor more potently than either ANF or BNP, $\frac{104}{6}$
suggesting that CNP is its natural ligand. The distribu-
tion of GC-A and GC-B differed depending on the tissue.
The GC-A preponderated in renal tissue, whereas suggesting that CNP is its natural ligand. The distribution of GC-A and GC-B differed depending on the tissue.
The GC-A preponderated in renal tissue, whereas the GC-B was the most abundant form in human fetal brain and po tion of GC-A and GC-B differed depending on the tissue.
The GC-A preponderated in renal tissue, whereas the
GC-B was the most abundant form in human fetal brain
and porcine atrium (Chang et al., 1989). The significance
of and porcine atrium (Chang et al., 1989). The significance

Receptors

this GC-B remains to be determined.
Atrial Natriuretic Factor R_2 Receptors/cANF
ceptors
ANF R_2 receptors, also designated ANF clearance re-
ptors or cANF receptors, are homodimers of a 64- to D. Atrial Natriuretic Factor R₂ Receptors/cANF al.,
Receptors man
ANF R₂ receptors, also designated ANF clearance re- of g
ceptors or cANF receptors, are homodimers of a 64- to loric

N AND TRACHTE
66-kDa transmembrane protein (Schenk et al., 1985;
Fuller et al., 1988; Leitman et al., 1988) and are distrib-A AND TRACHTE
66-kDa transmembrane protein (Schenk et al., 19
Fuller et al., 1988; Leitman et al., 1988) and are distr
uted in several tissues and cells including platelets, v A AND TRACHTE
66-kDa transmembrane protein (Schenk et al., 1985;
Fuller et al., 1988; Leitman et al., 1988) and are distrib-
uted in several tissues and cells including platelets, vas-
cular smooth muscle cells, glomeruli, 66-kDa transmembrane protein (Schenk et al., 1985; Fuller et al., 1988; Leitman et al., 1988) and are distributed in several tissues and cells including platelets, vascular smooth muscle cells, glomeruli, collecting ducts, 66-kDa transmembrane protein (Schenk et al., 1985; Fuller et al., 1988; Leitman et al., 1988) and are distributed in several tissues and cells including platelets, vascular smooth muscle cells, glomeruli, collecting ducts, Fuller et al., 1988; Leitman et al., 1988) and are distributed in several tissues and cells including platelets, vascular smooth muscle cells, glomeruli, collecting ducts, pituitary glands, adrenal glands, zona glomerulosa uted in several tissues and cells including platelets, vas-
cular smooth muscle cells, glomeruli, collecting ducts,
pituitary glands, adrenal glands, zona glomerulosa, cer-
ebral cortex, brain striatum, the ciliary process cular smooth muscle cells, glomeruli, collecting ducts
pituitary glands, adrenal glands, zona glomerulosa, cer
ebral cortex, brain striatum, the ciliary process of the
eye, Purkinje fibers of the cardiac conduction system
 pituitary glands, adrenal glands, zona glomerulosa, cerebral cortex, brain striatum, the ciliary process of the eye, Purkinje fibers of the cardiac conduction system, Leydig tumor cells, and other tissues (Anand-Srivastava ebral cortex, brain striatum, the ciliary process of the eye, Purkinje fibers of the cardiac conduction system, Leydig tumor cells, and other tissues (Anand-Srivastava et al., 1991; Bianchi et al., 1986, 1989, 1985; De Lea eye, Purkinje fibers of the cardiac conduction system,
Leydig tumor cells, and other tissues (Anand-Srivastava
et al., 1991; Bianchi et al., 1986, 1989, 1985; De Lean et
al., 1984a; Schenk et al., 1985; Ohashi et al., 1988 Leydig tumor cells, and other tissues (Anand-Srivastava
et al., 1991; Bianchi et al., 1986, 1989, 1985; De Lean et
al., 1984a; Schenk et al., 1985; Ohashi et al., 1988). The
density of these receptors in most tissues is h et al., 1991; Bianchi et al., 1986, 1989, 1985; De Lean et
al., 1984a; Schenk et al., 1985; Ohashi et al., 1988). The
density of these receptors in most tissues is higher than
that of ANF R₁ receptors. For example, in en density of these receptors in most tissues is higher than
that of ANF R_1 receptors. For example, in endothelial
cells, the ANF R_2 receptors make up about 94% of the
total ANF receptor population (Leitman et al., 198 maity of these receptors in most tissues is higher than
at of ANF R_1 receptors. For example, in endothelial
lls, the ANF R_2 receptors make up about 94% of the
tal ANF receptor population (Leitman et al., 1986).
Maac

that of ANF R_1 receptors. For example, in endothelial
cells, the ANF R_2 receptors make up about 94% of the
total ANF receptor population (Leitman et al., 1986).
Maack and his colleagues (1987) demonstrated that
ANF cells, the ANF R_2 receptors make up about 94% of the total ANF receptor population (Leitman et al., 1986).
Maack and his colleagues (1987) demonstrated that ANF R_2 receptors are non-GC-coupled receptors and are biol total ANF receptor population (Leitman et al., 1986).

Maack and his colleagues (1987) demonstrated that

ANF R_2 receptors are non-GC-coupled receptors and are

biologically silent regarding renal actions. They propose Maack and his colleagues (1987) demonstrated that ANF R_2 receptors are non-GC-coupled receptors and are biologically silent regarding renal actions. They proposed that the primary function of these receptors was the ANF R_2 receptors are non-GC-coupled receptors and arbiologically silent regarding renal actions. They propose
that the primary function of these receptors was the
sequestration and metabolic clearance of ANF and
hence, biologically silent regarding renal actions. They proposed
that the primary function of these receptors was the
sequestration and metabolic clearance of ANF and,
hence, called these receptors clearance or C-receptors.
Howe that the primary function of these receptors was the sequestration and metabolic clearance of ANF and, hence, called these receptors clearance or C-receptors.
However, using human thyroid cultured cells possessing only ANF sequestration and metabolic clearance of ANF and,
hence, called these receptors clearance or C-receptors.
However, using human thyroid cultured cells possessing
only ANF R₂ receptors, Tseng et al. (1990) showed that
ANF hence, called these receptors clearance or C-receptors.
However, using human thyroid cultured cells possessing
only ANF R_2 receptors, Tseng et al. (1990) showed that
ANF inhibited cAMP production and thyroglobulin re-
 However, using human thyroid cultured cells possessing
only ANF R_2 receptors, Tseng et al. (1990) showed that
ANF inhibited cAMP production and thyroglobulin re-
lease; furthermore, the inhibition of thyroglobulin rele only ANF R_2 receptors, Tseng et al. (1990) showed that
ANF inhibited cAMP production and thyroglobulin re-
lease; furthermore, the inhibition of thyroglobulin release
paralleled declines in cAMP concentrations, suggest ANF inhibited cAMP production and thyroglobulin re-
lease; furthermore, the inhibition of thyroglobulin release
paralleled declines in cAMP concentrations, suggesting
that ANF acts via a cAMP pathway in thyroid cells.
The lease; furthermore, the inhibition of thyroglobulin release
paralleled declines in cAMP concentrations, suggesting
that ANF acts via a cAMP pathway in thyroid cells.
These studies indicated that ANF R_2 receptors couple paralleled declines in cAMP concentrations, suggesting
that ANF acts via a cAMP pathway in thyroid cells.
These studies indicated that ANF R_2 receptors coupled
to adenylyl cyclase/cAMP signal transduction pathways
and that ANF acts via a cAMP pathway in thyroid cells.
These studies indicated that ANF R₂ receptors coupled
to adenylyl cyclase/cAMP signal transduction pathways
and refuted the hypothesis that they were biologically
silent to adenylyl cyclase/cAMP signal transduction pathways
and refuted the hypothesis that they were biologically
silent. Furthermore, Anand-Srivastava et al. (1991) re-
ported that rat platelets, devoid of particulate GC, re-
 to adenylyl cyclase/cAMP signal transduction pathways
and refuted the hypothesis that they were biologically
silent. Furthermore, Anand-Srivastava et al. (1991) re-
ported that rat platelets, devoid of particulate GC, re-
 and refuted the hypothesis that they were biologically
silent. Furthermore, Anand-Srivastava et al. (1991) re-
ported that rat platelets, devoid of particulate GC, re-
spond to ANF with an inhibition of adenylyl cyclase
ac silent. Furthermore, Anand-Srivastava et al. (1991) re-
ported that rat platelets, devoid of particulate GC, re-
spond to ANF with an inhibition of adenylyl cyclase
activity as well as a reduction in cAMP levels. The
inhib ported that rat platelets, devoid of particulate GC, respond to ANF with an inhibition of adenylyl cyclasedivity as well as a reduction in cAMP levels. The inhibition was dependent on the presence of guanir nucleotides and spond to ANF with an inhibition of adenylyl cyclase
activity as well as a reduction in cAMP levels. The
inhibition was dependent on the presence of guanine
nucleotides and was blocked by PT or amiloride treat-
ments, sugg activity as well as a reduction in cAMP levels. The
inhibition was dependent on the presence of guanine
nucleotides and was blocked by PT or amiloride treat-
ments, suggesting that ANF R_2 receptors couple to the
adenyl inhibition was dependent on the presence of guanine
nucleotides and was blocked by PT or amiloride treat-
ments, suggesting that ANF R_2 receptors couple to the
adenylyl cyclase/cAMP system. These results were con-
firm nucleotides and was blocked by PT or amiloride trea
ments, suggesting that ANF R_2 receptors couple to th
adenylyl cyclase/cAMP system. These results were con
firmed in NIH-3T3 cells possessing pure populations $\frac{1}{2}$ firmed in NIH-3T3 cells possessing pure populations of ANF R_2 receptors. ANF inhibited adenylyl cyclase activity in these cells in a concentration-dependent manner with an apparent K_i of about 100 pM (Anand-Srivast firmed in NIH-3T3 cells possessing pure populations of ANF R_2 receptors. ANF inhibited adenylyl cyclase activity in these cells in a concentration-dependent manner with an apparent K_i of about 100 pM (Anand-Srivastav ANF R_2 receptors. ANF inhibited adenylyl cyclase activ in these cells in a concentration-dependent man with an apparent K_i of about 100 pM (Anand-Srivast et al., unpublished observations). In addition, ANF duced cAMP ity in these cells in a concentration-dependent man
with an apparent K_i of about 100 pM (Anand-Srivast
et al., unpublished observations). In addition, ANF
duced cAMP levels in HeLa cells expressing predo
nantly ANF R_2 with an apparent K_i of about 100 pM (Anand-Srivastava
et al., unpublished observations). In addition, ANF re-
duced cAMP levels in HeLa cells expressing predomi-
nantly ANF R₂ receptors (Koyama et al., 1992), supportet al., unpublished observations). In addition, ANF
duced cAMP levels in HeLa cells expressing predo
nantly ANF R₂ receptors (Koyama et al., 1992), supp
ing the contention that ANF R₂ receptors couple to
adenylyl cycla ced cAMP levels in HeLa cells expressing predomi-
ntly ANF R₂ receptors (Koyama et al., 1992), support-
g the contention that ANF R₂ receptors couple to the
enylyl cyclase/cAMP signal transduction system.
Further confi nantly ANF R_2 receptors (Koyama et al., 1992), supporting the contention that ANF R_2 receptors couple to the adenylyl cyclase/cAMP signal transduction system.
Further confirmation regarding the coupling of ANF R_2

ing the contention that ANF R_2 receptors couple to the
adenylyl cyclase/cAMP signal transduction system.
Further confirmation regarding the coupling of ANF
 R_2 /cANF receptors to the adenylyl cyclase/cAMP sys-
tem was adenylyl cyclase/cAMP signal transduction system.
Further confirmation regarding the coupling of ANF
R₂/cANF receptors to the adenylyl cyclase/cAMP sys-
tem was provided by the use of the ring-deleted analog
of ANF, cANF Further confirmation regarding the coupling of ANF $R_2/cANF$ receptors to the adenylyl cyclase/ $cAMP$ system was provided by the use of the ring-deleted analog of ANF, cANF and other linear truncated analogs, which specifica $R_2/cANF$ receptors to the adenylyl cyclase/cAMP system was provided by the use of the ring-deleted analog of ANF, cANF and other linear truncated analogs, which specifically interact with ANF R_2 receptors (Maack et al. tem was provided by the use of the ring-deleted a
of ANF, cANF and other linear truncated analogs, specifically interact with ANF R₂ receptors (Mas
al., 1987). These analogs inhibited adenylyl cyclas
tivity in several ti of ANF, cANF and other linear truncated analogs, which
specifically interact with ANF R₂ receptors (Maack et
al., 1987). These analogs inhibited adenylyl cyclase ac-
tivity in several tissues in a concentration-dependent specifically interact with ANF R_2 receptors (Maack et al., 1987). These analogs inhibited adenylyl cyclase activity in several tissues in a concentration-dependent manner; the inhibition was dependent on the presence o al., 1987). These analogs inhibited adenylyl cyclase activity in several tissues in a concentration-dependent manner; the inhibition was dependent on the presence of guanine nucleotides and was blocked by PT and amiloride

ANF RECEPTORS AND SIGNAL 1
cANF also inhibited the production of cAMP but not
cGMP, indicating that cANF/R₂ receptors are coupled ANF RECEPTORS AND SIGNAL TR
cANF also inhibited the production of cAMP but not be
cGMP, indicating that cANF/R₂ receptors are coupled cy
to the adenylyl cyclase/cAMP signal transduction sys-ANF also inhibited the production of cAMP but not cGMP, indicating that $cANF/R_2$ receptors are coupled to the adenylyl cyclase/ $cAMP$ signal transduction system. The inhibitory effect of $cANF$ was additive with the cANF also inhibited the production of cAMP but not be cGMP, indicating that cANF/ R_2 receptors are coupled cy to the adenylyl cyclase/cAMP signal transduction system. The inhibitory effect of cANF was additive with the CANF also inhibited the production of CAMP but not cGMP, indicating that CANF/R₂ receptors are coupled to the adenylyl cyclase/CAMP signal transduction system. The inhibitory effect of CANF was additive with the inhibit cGMP, indicating that cANF/R₂ receptors are co
to the adenylyl cyclase/cAMP signal transduction
tem. The inhibitory effect of cANF was additive wi
inhibition observed with ANF(99-126), indicating
cANF receptors are ANF to the adenylyl cyclase/cAMP signal transduction system. The inhibitory effect of cANF was additive with the inhibition observed with ANF(99-126), indicating that cANF receptors are ANF R_2 receptors (Anand-Srivastava e as well as luteinizing hormone-stimulated, production of progesterone secretion, suggesting that $ANF R₂$ receptors are not biologically silent but have a physiological role. cANF receptors are ANF R_2 receptors (Anand-Srivastava et al., 1990). In addition, cANF inhibited the basal, as well as luteinizing hormone-stimulated, production of progesterone secretion, suggesting that ANF R_2 rec va et al., 1990). In addition, cANF inhibited the basal, receptor well as luteinizing hormone-stimulated, production of 12 ogesterone secretion, suggesting that ANF R_2 receptors element to the R₂ receptor has been a

as well as luteinizing hormone-stimulated, production of
progesterone secretion, suggesting that ANF R_2 receptors
are not biologically silent but have a physiological role.
The physiological role of the R_2 receptor progesterone secretion, suggesting that ANF R_2 recept
are not biologically silent but have a physiological rol
The physiological role of the R_2 receptor has be
documented by various other studies. Levin and Fra
(199 are not biologically silent but have a physiological role. The physiological role of the R_2 receptor has been a p
documented by various other studies. Levin and Frank R_2
(1991) showed that ANF inhibits rat astroglia The physiological role of the R_2 receptor has be
documented by various other studies. Levin and Fra
(1991) showed that ANF inhibits rat astroglial prolif
ation through R_2 receptors. Johnson et al. (1991) a
reported documented by various other studies. Levin and Frank \sim (1991) showed that ANF inhibits rat astroglial prolifer-
ation through R_2 receptors. Johnson et al. (1991) also Tieported the R_2 receptor-mediated inhibition (1991) showed that ANF inhibits rat astroglial proliferation through R_2 receptors. Johnson et al. (1991) also reported the R_2 receptor-mediated inhibition of electrically induced purinergic and adrenergic contractil ation through R_2 receptors. Johnson et al. (1991) also
reported the R_2 receptor-mediated inhibition of electri-
cally induced purinergic and adrenergic contractile force
generation in rabbit isolated vasa deferentia reported the R_2 receptor-mediated inhibition of electrically induced purinergic and adrenergic contractile force
generation in rabbit isolated vasa deferentia. In addition,
ANF-induced inhibition of endothelial and vas cally induced purinergic and adrenergic contractile force
generation in rabbit isolated vasa deferentia. In addition,
ANF-induced inhibition of endothelial and vascular
smooth muscle cell proliferation was also reported to generation in rabbit isolated vasa deferentia. In addition,
ANF-induced inhibition of endothelial and vascular
smooth muscle cell proliferation was also reported to be
mediated through ANF R_2 receptors (Cahill and Hass smooth muscle cell proliferation was also reported to be mediated through ANF R_2 receptors (Cahill and Hassid, 1991; Itoh et al., 1988). The recent studies by Drewett et al. (1992), demonstrating the inhibition of aden smooth muscle cell proliferation was also reported to be
mediated through ANF R_2 receptors (Cahill and Hassid,
1991; Itoh et al., 1988). The recent studies by Drewett et
al. (1992), demonstrating the inhibition of aden mediated through ANF R₂ receptors (Cahill and Hassid, 1991; Itoh et al., 1988). The recent studies by Drewett et al. (1992), demonstrating the inhibition of adenylyl cyclase and neurotransmission by cANF in nerve growth 1991; Itoh et al., 1988). The recent studies by Drewett et
al. (1992), demonstrating the inhibition of adenylyl cy-
clase and neurotransmission by cANF in nerve growth
factor-treated pheochromocytoma cells, further suppor al. (1992), demonstrating the inhibition of adenylyl cy-
clase and neurotransmission by cANF in nerve growth
factor-treated pheochromocytoma cells, further supports
the physiological role and coupling of these receptors to clase and neurotransmission by cANF in nerve growth
factor-treated pheochromocytoma cells, further supports
the physiological role and coupling of these receptors to
the adenylyl cyclase/cAMP signal transduction system.
V factor-treated pheochromocytoma cells, further supports
the physiological role and coupling of these receptors to
the adenylyl cyclase/cAMP signal transduction system.
Very recently, Hu et al. (1992) showed that cANF and
 the physiological role and coupling of these receptors to
the adenylyl cyclase/cAMP signal transduction system.
Very recently, Hu et al. (1992) showed that cANF and
nanopiperazine ANF(11-15)NH₂, agents selective for the the adenylyl cyclase/cAMP signal transduction system.

Very recently, Hu et al. (1992) showed that cANF and

nanopiperazine ANF(11-15)NH₂, agents selective for the

ANF R₂ receptor, inhibited the in vivo translation o Very recently, Hu et al. (1992) showed that CANF
nanopiperazine ANF $(11-15)NH_2$, agents selective for
ANF R_2 receptor, inhibited the in vivo translation of
endothelin message and the endothelin secretion f
cultured b nanopiperazine ANF(11-15)NH₂, agents selective for the
ANF R₂ receptor, inhibited the in vivo translation of the
endothelin message and the endothelin secretion from
cultured bovine aortic endothelial cells. The cANF-ANF R_2 receptor, inhibited the in vivo translation of the
endothelin message and the endothelin secretion from
cultured bovine aortic endothelial cells. The cANF-me-
diated decrease in secretion of endothelin was rever endothelin message and the endothelin secretion from
cultured bovine aortic endothelial cells. The cANF-me
diated decrease in secretion of endothelin was reversed
by 8-bromo cAMP or amiloride, an agent preventing the
inhib endothelin message and the endothelin secretion from GC regions (Saheki et al., 1991; Yamaguchi et al., 1990).

cultured bovine aortic endothelial cells. The cANF-me-

diated decrease in secretion of endothelin was revers diated decrease in secretion of endothelin was reversed
by 8-bromo cAMP or amiloride, an agent preventing the
inhibition of adenylyl cyclase by ANF (Anand-Srivastava
et al., 1990, 1991). These data strongly support the
hy by 8-bromo cAMP or amiloride, an agent preventing the
inhibition of adenylyl cyclase by ANF (Anand-Srivastava
et al., 1990, 1991). These data strongly support the
hypothesis that R_2 receptors elicit physiological re-
s inhibition of adenylyl cycletering all, 1990, 1991). The hypothesis that R_2 recessions through their is transduction mechanisms.
Interestingly, Hirata ether is al., 1990, 1991). These data strongly support the segmenthesis that R_2 receptors elicit physiological re-
onses through their interaction with cAMP signal hurars
ansduction mechanisms. of 1
Interestingly, Hirata et al.

hypothesis that R_2 receptors elicit physiological is
sponses through their interaction with cAMP sign
transduction mechanisms.
Interestingly, Hirata et al., (1989a) showed that AP
and ANF(103-123) stimulate phosphatidy sponses through their interaction with cAMP signal
transduction mechanisms.
Interestingly, Hirata et al., (1989a) showed that ANF
and ANF(103-123) stimulate phosphatidylinositol turn-
over in the presence of guanine nucle transduction mechanisms.

Interestingly, Hirata et al., (1989a) showed that ANF

and ANF(103-123) stimulate phosphatidylinositol turn-

over in the presence of guanine nucleotides in cultured

bovine aortic smooth muscle Interestingly, Hirata et al., (1989a) showed that ANF 1993
and ANF(103-123) stimulate phosphatidylinositol turn-
over in the presence of guanine nucleotides in cultured
bovine aortic smooth muscle cells. ANF(103-123) was
 and ANF(103-123) stimulate phosphatidylinositol turn-
over in the presence of guanine nucleotides in cultured
bovine aortic smooth muscle cells. ANF(103-123) was
10-fold more potent than ANF, suggesting that ANF R_2
rec over in the presence of guanine nucleotides in cultured
bovine aortic smooth muscle cells. ANF(103-123) was
10-fold more potent than ANF, suggesting that ANF R_2
receptors couple to phosphatidylinositol turnover are
thr bovine aortic smooth muscle cells. $ANF(103-123)$ was more 10-fold more potent than ANF, suggesting that ANF R₂ with receptors couple to phosphatidylinositol turnover amid through guanine nucleotide regulatory proteins. 10-fold more potent than ANF, suggesting that ANF receptors couple to phosphatidylinositol turnove
through guanine nucleotide regulatory proteins. Take
together, it is possible that ANF R_2 receptors couple t
two differ receptors couple to phosphatidylinositol turnover at
through guanine nucleotide regulatory proteins. Taken f
together, it is possible that ANF R_2 receptors couple to
two different intracellular messengers, cAMP and pho through guanine nucleotide regulatory proteins. Taken
together, it is possible that ANF R_2 receptors couple to
two different intracellular messengers, cAMP and phos-
phatidylinositol turnover, or there exists a crosstogether, it is possible that ANF R_2 receptors couple to
two different intracellular messengers, cAMP and phos-
phatidylinositol turnover, or there exists a cross-talk rep
between these two second messengers. ANF could two different intracellular messengers, cAMP and phosing phatidylinositol turnover, or there exists a cross-talk repletween these two second messengers. ANF could inhibit 70 adenylyl cyclase/cAMP through its interaction w phatidylinositol turnover, or there exists a cross-
between these two second messengers. ANF could inh
adenylyl cyclase/cAMP through its interaction v
ANF R₂ receptors, and the decreased cAMP may be
stimulus for increase between these two second messengers. ANF could inhibit adenylyl cyclase/cAMP through its interaction with $ANF R_2$ receptors, and the decreased cAMP may be the stimulus for increased turnover of phosphatidylinositol by ANF adenylyl cyclase/cAMP through its interaction with enc
ANF R_2 receptors, and the decreased cAMP may be the T
stimulus for increased turnover of phosphatidylinositol cycl
by ANF in cultured bovine aortic cells. In other ANF R_2 receptors, and the decreased cAMP may be the
stimulus for increased turnover of phosphatidylinositol
by ANF in cultured bovine aortic cells. In other words,
the stimulation of phosphatidylinositol turnover by AN

be a secondary event mediated through the adenylyl cyclase/cAMP system coupled to ANF R_2 receptors. TRANSDUCTION MECHANISMS
be a secondary event mediated through the ader
cyclase/cAMP system coupled to ANF R_2 receptors.
The R_2 receptor was characterized initially by Sch

inhibition observed with ANF(99-126), indicating that was solubilized with octaethyleneglycol dodecyl ether and
cANF receptors are ANF R_2 receptors (Anand-Srivas-
tava et al., 1990). In addition, cANF inhibited the bas ANSDUCTION MECHANISMS 463

2 a secondary event mediated through the adenylyl

clase/cAMP system coupled to ANF R_2 receptors.

The R_2 receptor was characterized initially by Schenk

al. (1985) in bovine aortic smooth be a secondary event mediated through the adenylyl cyclase/ c AMP system coupled to ANF R_2 receptors.
The R_2 receptor was characterized initially by Schenk et al. (1985) in bovine aortic smooth muscle. The receptor be a secondary event mediated through the adenylyl
cyclase/cAMP system coupled to ANF R_2 receptors.
The R_2 receptor was characterized initially by Schenk
et al. (1985) in bovine aortic smooth muscle. The receptor
wa cyclase/cAMP system coupled to ANF R_2 receptors.
The R_2 receptor was characterized initially by Schenk
et al. (1985) in bovine aortic smooth muscle. The receptor
was solubilized with octaethyleneglycol dodecyl ether et al. (1985) in bovine aortic smooth muscle. The receptor et al. (1985) in bovine aortic smooth muscle. The receptor
was solubilized with octaethyleneglycol dodecyl ether and
purified by passing it over an ANF-agarose column. The
receptor migrated with a molecular weight equivale was solubilized with octaethyleneglycol dodecyl ether and
purified by passing it over an ANF-agarose column. The
receptor migrated with a molecular weight equivalent to
125,000 by sodium dodecyl sulfate-polyacrylamide gel
 purified by passing it over an ANF-agarose column. The
receptor migrated with a molecular weight equivalent to
125,000 by sodium dodecyl sulfate-polyacrylamide gel
electrophoresis. When reduced with dithiothreitol, the
rec receptor migrated with a molecular weight equivalent to 125,000 by sodium dodecyl sulfate-polyacrylamide gel
electrophoresis. When reduced with dithiothreitol, the
receptor had a electrophoretic mobility consistent with
a 125,000 by sodium dodecyl sulfate-polyacrylamide geelectrophoresis. When reduced with dithiothreitol, thereuptor had a electrophoretic mobility consistent with a protein of 60,500 Da. The cDNA for expression of the R_2 electrophoresis. When reduced with dithiothreitol, the receptor had a electrophoretic mobility consistent with a protein of 60,500 Da. The cDNA for expression of the R₂ receptor was isolated from bovine aortic smooth mus receptor had a electrophoretic mobility consistent with
a protein of 60,500 Da. The cDNA for expression of the
 R_2 receptor was isolated from bovine aortic smooth mus-
cle (Fuller et al., 1988) and expressed in *Xenopus* a protein of 60,500 Da. The cDNA for expression of the R_2 receptor was isolated from bovine aortic smooth mus-
cle (Fuller et al., 1988) and expressed in *Xenopus* oocytes.
The gene encoding this receptor varied in len R_2 receptor was isolated from bovine aortic smooth mus-
cle (Fuller et al., 1988) and expressed in *Xenopus* oocytes.
The gene encoding this receptor varied in length with
bovine forms being 8000 nucleotides in length, cle (Fuller et al., 1988) and expressed in *Xenopus* oocytes.
The gene encoding this receptor varied in length with
bovine forms being 8000 nucleotides in length, whereas
human forms were 5600 nucleotides long (Fuller et a The gene encoding this receptor varied in length with bovine forms being 8000 nucleotides in length, where human forms were 5600 nucleotides long (Fuller et a 1988). The protein encoded consisted of 537 amino acid containi bovine forms being 8000 nucleotides in length, whereas
human forms were 5600 nucleotides long (Fuller et al.,
1988). The protein encoded consisted of 537 amino acids
containing a large extracellular region, a single mem-
b human forms were 5600 nucleotides long (Fuller et al., 1988). The protein encoded consisted of 537 amino acids containing a large extracellular region, a single membrane-spanning domain, and a short cytoplasmic tail of 37 1988). The protein encoded consisted of 537 amino acids
containing a large extracellular region, a single mem-
brane-spanning domain, and a short cytoplasmic tail of
37 amino acids. A similar protein was encoded by human
p containing a large extracellular region, a single mem-
brane-spanning domain, and a short cytoplasmic tail of
37 amino acids. A similar protein was encoded by human
placenta, kidney, and fetal heart with the gene having a
 brane-spanning domain, and a short cytoplasmic tail of 37 amino acids. A similar protein was encoded by human placenta, kidney, and fetal heart with the gene having a nucleotide length of 5400 bases (Porter et al., 1990). 37 amino acids. A similar protein was encoded by human placenta, kidney, and fetal heart with the gene having a nucleotide length of 5400 bases (Porter et al., 1990). Saheki et al. (1991) found the gene in bovine tissues t placenta, kidney, and fetal heart with the gene having a nucleotide length of 5400 bases (Porter et al., 1990).
Saheki et al. (1991) found the gene in bovine tissues to consist of 8500 nucleotides with eight exons and seve nucleotide length of 5400 bases (Porter et al., 19
Saheki et al. (1991) found the gene in bovine tissue
consist of 8500 nucleotides with eight exons and s
massive introns. The extracellular region was code
exons 1 to 6. Ex Saheki et al. (1991) found the gene in bovine tissues
consist of 8500 nucleotides with eight exons and sev
massive introns. The extracellular region was coded
exons 1 to 6. Exons 7 and 8 encoded the membrar
spanning region consist of 8500 nucleotides with eight exons and seven
massive introns. The extracellular region was coded by
exons 1 to 6. Exons 7 and 8 encoded the membrane-
spanning region and the short cytoplasmic tail, respec-
tively massive introns. The extracellular region was coded by
exons 1 to 6. Exons 7 and 8 encoded the membrane-
spanning region and the short cytoplasmic tail, respec-
tively. This pattern is the same as that described for GC-
A, spanning region and the short cytoplasmic tail, respectively. This pattern is the same as that described for GC-
A, except that the gene for GC-A contains an additional
14 exons encoding the intracellular protein kinase an spanning region and the short cytoplasmic tail, respectively. This pattern is the same as that described for GC-
A, except that the gene for GC-A contains an additional
14 exons encoding the intracellular protein kinase an vely. This pattern is the same as that described for GC-
except that the gene for GC-A contains an additional
exons encoding the intracellular protein kinase and
C regions (Saheki et al., 1991; Yamaguchi et al., 1990).
Th

A, except that the gene for GC-A contains an additional
14 exons encoding the intracellular protein kinase and
GC regions (Saheki et al., 1991; Yamaguchi et al., 1990).
The significance of these differences in gene length 14 exons encoding the intracellular protein kinase and GC regions (Saheki et al., 1991; Yamaguchi et al., 1990).
The significance of these differences in gene length is not known, but the products of the human or bovine ge GC regions (Saheki et al., 1991; Yamaguchi et al., 1990).
The significance of these differences in gene length is
not known, but the products of the human or bovine
genes are nearly identical. They all encode a protein of
 The significance of these differences in gene length is
not known, but the products of the human or bovine
genes are nearly identical. They all encode a protein of
496 amino acids following removal of a 41-amino acid
segm not known, but the products of the human or bovine
genes are nearly identical. They all encode a protein of
496 amino acids following removal of a 41-amino acid
segment on the amino terminus. Two different cDNAs
encoding genes are nearly identical. They all encode a protein of 496 amino acids following removal of a 41-amino acid segment on the amino terminus. Two different cDNAs encoding the R_2 receptor were identified recently in the segment on the amino terminus. Two different cDNAs encoding the R_2 receptor were identified recently in the human umbilical vein. They differed only by the deletion of 123 nucleotides in one of the transcripts (Nunez e segment on the amino terminus. Two different cDNAs
encoding the R_2 receptor were identified recently in the
human umbilical vein. They differed only by the deletion
of 123 nucleotides in one of the transcripts (Nunez e encoding the R_2 receptor were identified recently in the human umbilical vein. They differed only by the deletion of 123 nucleotides in one of the transcripts (Nunez et al., 1991). This deletion did not alter the open human umbilical vein. They differed only by the delet
of 123 nucleotides in one of the transcripts (Nunez et
1991). This deletion did not alter the open reading fra
Interestingly, the second exon encoding the R_2 recep
 of 123 nucleotides in one of the transcripts (Nunez et al., 1991). This deletion did not alter the open reading frame.
Interestingly, the second exon encoding the R_2 receptor contained 123 nucleotides (Saheki et al., 1 1991). This deletion did not alter the open reading frame.
Interestingly, the second exon encoding the R_2 receptor
contained 123 nucleotides (Saheki et al., 1991). Further-
more, the first exon could combine with the t Interestingly, the second exon encoding the R_2 receptor contained 123 nucleotides (Saheki et al., 1991). Furthermore, the first exon could combine with the third exon without interrupting the reading frame or altering contained 123 nucleotides (Saheki et al., 1991). Furthermore, the first exon could combine with the third exon without interrupting the reading frame or altering the amino acid encoded by the third exon. Thus, these differ more, the first exon could combine with the third exon
without interrupting the reading frame or altering the
amino acid encoded by the third exon. Thus, these dif-
ferent transcripts would encode proteins differing by 41
 without interrupting the reading frame or altering the amino acid encoded by the third exon. Thus, these different transcripts would encode proteins differing by 41 amino acids, and the deletion would be predicted to occu amino acid encoded by the third exon. Thus, these dif-
ferent transcripts would encode proteins differing by 41
amino acids, and the deletion would be predicted to occur
in the extracellular binding region of the receptor ferent transcripts would encode proteins differing by 4 amino acids, and the deletion would be predicted to occur in the extracellular binding region of the receptor. On report found two vascular R_2 receptors of 60,000 amino acids, and the deletion would
in the extracellular binding region
report found two vascular R_2 rec
70,000 Da (Kato et al., 1991), con
ence of distinct ANF R_2 receptors.
The GTP dependence of ANF the extracellular binding region of the receptor. One
port found two vascular R_2 receptors of 60,000 and
,000 Da (Kato et al., 1991), consistent with the pres-
ce of distinct ANF R_2 receptors.
The GTP dependence of

report found two vascular R_2 receptors of 60,000 and 70,000 Da (Kato et al., 1991), consistent with the presence of distinct ANF R_2 receptors.
The GTP dependence of ANF effects on adenylyl cyclase and phospholipase 70,000 Da (Kato et al., 1991), consistent with the presence of distinct ANF R_2 receptors.
The GTP dependence of ANF effects on adenylyl cyclase and phospholipase C activities suggests the involvement of inhibitory G-pr ence of distinct ANF R_2 receptors.
The GTP dependence of ANF effects on ader
cyclase and phospholipase C activities suggests the
volvement of inhibitory G-proteins in the coupling of
receptors to adenylyl cyclase inhib The GTP dependence of ANF effects on adenylyl
cyclase and phospholipase C activities suggests the in-
volvement of inhibitory G-proteins in the coupling of R₂
receptors to adenylyl cyclase inhibition and phospholi-
pase Downloaded from pharmrev.aspetjournals.org at Thammasart University on December 8, 2012

464
ically have seven transmembrane-spanning domains, but
the R₂ receptor contains only one. Furthermore, the short ANAND-SRIVASTAV

ically have seven transmembrane-spanning domains, but

the R₂ receptor contains only one. Furthermore, the short

cytoplasmic segment has been postulated to preclude $\begin{array}{ll}\n & \text{ANAND-SRIVASTAVA}\n\end{array}$

ically have seven transmembrane-spanning domains, but

the R_2 receptor contains only one. Furthermore, the short

cytoplasmic segment has been postulated to preclude

signal transduction i ically have seven transmembrane-spanning domains, but
the R_2 receptor contains only one. Furthermore, the short
cytoplasmic segment has been postulated to preclude
signal transduction involving G-proteins. Some of thes ically have seven transmembrane-spanning domains, but
the R_2 receptor contains only one. Furthermore, the short
cytoplasmic segment has been postulated to preclude
signal transduction involving G-proteins. Some of thes the R_2 receptor contains only one. Furthermore, the cytoplasmic segment has been postulated to prosignal transduction involving G-proteins. Some of reservations have been refuted by recent finding other receptors conta cytoplasmic segment has been postulated to preclude
signal transduction involving G-proteins. Some of these
reservations have been refuted by recent findings that
other receptors containing only one transmembrane-
spanning et al., 1989; Church and Buick, 1988). The seservations have been refuted by recent findings the other receptors containing only one transmembrand spanning domain also couple to G-proteins (Nishimotet al., 1989; Church and reservations have been refuted by recent findings that other receptors containing only one transmembrane spanning domain also couple to G-proteins (Nishimotet al., 1989; Church and Buick, 1988). Furthermore Okamoto et al. other receptors containing only one transmembrased paraming domain also couple to G-proteins (Nishim et al., 1989; Church and Buick, 1988). Furthermo Okamoto et al. (1990) defined the structural requirement for the insulin spanning domain also couple to G-proteins (Nishimoto
et al., 1989; Church and Buick, 1988). Furthermore,
Okamoto et al. (1990) defined the structural requirement
for the insulin-like growth factor II mannose 6-phos-
phate et al., 1989; Church and Buick, 1988). Furthermore, Okamoto et al. (1990) defined the structural requirement for the insulin-like growth factor II mannose 6-phos-
phate receptor coupling to G-proteins as a 14-amino acid se Okamoto et al. (1990) defined the structural requirement and
for the insulin-like growth factor II mannose 6-phos-
phate receptor coupling to G-proteins as a 14-amino acid
segment enriched in basic amino acids. This segme for the insulin-like growth factor II mannose 6-phomore phate receptor coupling to G-proteins as a 14-amino accept
segment enriched in basic amino acids. This segme
increased GTP γ S binding to, GTPase activity of, an
GD phate receptor coupling to G-proteins as a 14-amino acide segment enriched in basic amino acids. This segment increased GTP γ S binding to, GTPase activity of, and GDP dissociation from, isolated G-proteins. The mech anis segment enriched in basic amino acids. This segment
increased GTP γ S binding to, GTPase activity of, and
GDP dissociation from, isolated G-proteins. The mech-
anism appeared to involve a sensitization to magnesium.
Inte increased GTP γ S binding to, GTPase activity of, and GDP dissociation from, isolated G-proteins. The mechanism appeared to involve a sensitization to magnesium.
Interestingly, the ANF R_2 receptor contained 14 basic a GDP dissociation from, isolated G-proteins. The mechanism appeared to involve a sensitization to magnesium.
Interestingly, the ANF R_2 receptor contained 14 basic amino acids in its 37-amino acid cytoplasmic domain.
The anism appeared to involve a sensitization to magnesium
Interestingly, the ANF R_2 receptor contained 14 basis
amino acids in its 37-amino acid cytoplasmic domain
The data of Okamoto et al. (1990) would predict that the
 amino acids in its 37-amino acid cytoplasmic domain.
The data of Okamoto et al. (1990) would predict that the R_2 receptor is capable of interacting with G-proteins, consistent with the functional studies mentioned abov R_2 receptor is capable of interacting with G-proteins,

consistent with the functional studies mentioned above.

E. Summary

The studies presented above indicate the existence of

at least three ANF receptors. Two R₁ receptors, GC-A

and GC-B, exist in many tissues but are l E. Summary

The studies presented above indicate the existence of

and GC-B, exist in many tissues but are lacking in the

platelet and NIH 3T3 fibroblast cells. The R₂ receptor is

cG. E. Summary

The studies presented above indicate the existence of

and GC-B, exist in many tissues but are lacking in the

platelet and NIH 3T3 fibroblast cells. The R₂ receptor is

present in almost all cells with the The studies presented above indicate the existence of
at least three ANF receptors. Two R_1 receptors, GC-A
and GC-B, exist in many tissues but are lacking in the
platelet and NIH 3T3 fibroblast cells. The R_2 recepto at least three ANF receptors. Two R_1 receptors, GC-A
and GC-B, exist in many tissues but are lacking in the
platelet and NIH 3T3 fibroblast cells. The R_2 receptor is
present in almost all cells with the possible exc and GC-B, exist in many tissues but are lacking in the platelet and NIH 3T3 fibroblast cells. The R_2 receptor is present in almost all cells with the possible exception of central nervous system neurons. All three rece platelet and NIH 3T3 fibroblast cells. The R_2 receptor
present in almost all cells with the possible exception
central nervous system neurons. All three receptors ha
been demonstrated to influence biological second me
 present in almost all cells with the possible exception of central nervous system neurons. All three receptors have
been demonstrated to influence biological second meaningers. The R_1 receptors elevate cGMP concentrati central nervous system neurons. All three receptors have
been demonstrated to influence biological second mes-
sengers. The R_1 receptors elevate cGMP concentrations,
and the R_2 receptor both inhibits adenylyl cyclas been demonstrated to influence biological second mes-
sengers. The R_1 receptors elevate CGMP concentrations,
and the R_2 receptor both inhibits adenylyl cyclase activ-
ity and augments phospholipase C activity. This sengers. The R_1 receptors elevate cGMP concentrations,
and the R_2 receptor both inhibits adenylyl cyclase activ-
ity and augments phospholipase C activity. This scenario
is shown in figure 1, where ANF, CNP, or BNP and the R_2 receptor both inhibits adenylyl cyclase activity and augments phospholipase C activity. This scenario is shown in figure 1, where ANF, CNP, or BNP can interact with R_1 receptors to generate cGMP. Converse ity and augments phospholipase C activity. This scenario
is shown in figure 1, where ANF, CNP, or BNP can
interact with R_1 receptors to generate cGMP. Con-
versely, ANF, cANF, CNP, or BNP interact with R_2
receptors is shown in figure 1, where ANF, CNP, or BNP
interact with R_1 receptors to generate cGMP. C
versely, ANF, cANF, CNP, or BNP interact with
receptors to either suppress cAMP concentrations
inhibiting adenylyl cyclase or interact with R_1 receptors to generate cGMP. Conversely, ANF, cANF, CNP, or BNP interact with R_2 more receptors to either suppress cAMP concentrations by continual including adenyiyi cyclase or elevate IP_3 and dia versely, ANF, cANF, CNP, or BNP interact with R_2
receptors to either suppress cAMP concentrations by
inhibiting adenylyl cyclase or elevate IP_3 and diacylglyc-
erol concentrations by activating phospholipase C. The
c inhibiting adenylyl cyclase or elevate IP_3 and diacylglycerol concentrations by activating phospholipase C. The cGMP produced by R_1 receptor activation can suppress both cAMP concentrations and phospholipase C activi inhibiting adenylyl cyclase or elevate IP_3 and diacylglerol concentrations by activating phospholipase C. T
cGMP produced by R_1 receptor activation can suppress both cAMP concentrations and phospholipase C activi
The erol concentrations by activating phospholipase C. The GMP produced by R_1 receptor activation can suppress both cAMP concentrations and phospholipase C activity. The GMP suppresses cAMP concentrations by activating pho CAMP produced by R_1 receptor activation can suppress
both cAMP concentrations and phospholipase C activity.
The cGMP suppresses cAMP concentrations by activation
ing phosphodiesterases to accelerate cAMP degradation.
B G-proteins. ing phosphodiesterases to accelerate cAMP degradation.
Both depicted actions of R_2 receptors are mediated by
G-proteins.
III. Signal Transduction Mechanisms
A. Overview *A. Overview*
A. Overview
Peptide hormon

due

III. Signal Transduction Mechanisms (c)

Overview

Peptide hormones and neurotransmitters interact with sig

ceptors on the cell membrane to transmit signals to the **III. Signal Transduction Mechanisms** (c) is

A. Overview ANI

Peptide hormones and neurotransmitters interact with sign

receptors on the cell membrane to transmit signals to they

effector systems such as adenylyl cycla receptors on the cell membrane to transmit signals to effector systems such as adenylyl cyclase, GC, and phos-
pholipase C systems, resulting in the generation of sec-A. Overview

Peptide hormones and neurotransmitters interact with

receptors on the cell membrane to transmit signals to

effector systems such as adenylyl cyclase, GC, and phos-

pholipase C systems, resulting in the gene Peptide hormones and neurotransmitters interact with signeceptors on the cell membrane to transmit signals to the effector systems such as adenylyl cyclase, GC, and phos-
pholipase C systems, resulting in the generation of receptors on the cell membrane to transmit signals to teffector systems such as adenylyl cyclase, GC, and phos-
pholipase C systems, resulting in the generation of second messengers such as cAMP, cGMP and IP₃, and t
diac pholipase C systems, resulting in the generation of second messengers such as cAMP, cGMP and IP₃, and diacylglycerol, respectively. The signal-transducing enzymes associated with ANF actions are GC, adenylyl cyclase, and ond messengers such as cAMP, cGMP and IP₃, and
diacylglycerol, respectively. The signal-transducing en-
zymes associated with ANF actions are GC, adenylyl
cyclase, and phospholipase C. ANF also influences po-
tassium, so

consistent with the functional studies mentioned above.
 $E. Summary$
 $E. Summary$

The studies presented above indicate the existence of
 $E. Summary$

The studies presented above indicate the existence of

activity. These actions suppre FIG. 1. ANF receptors and signal transduction pathways. ANF and related peptides, CNP and BNP, can interact with an R_1 receptor to FIG. 1. ANF receptors and signal transduction pathways. ANF and related peptides, CNP and BNP, can interact with an R₁ receptor to stimulate the production of cGMP. The other major type of receptor is FIG. 1. ANF receptors and signal transduction pathways. ANF and related peptides, CNP and BNP, can interact with an R₁ receptor to stimulate the production of cGMP. The other major type of receptor is the R₂ receptor. FIG. 1. ANF receptors and signal transduction pathways. ANF and related peptides, CNP and BNP, can interact with an R_1 receptor stimulate the production of cGMP. The other major type of receptor the R_2 receptor. ANF related peptides, CNP and BNP, can interact with an R₁ receptor to stimulate the production of cGMP. The other major type of receptor is the R₂ receptor. ANF, cANF, CNP, and BNP interact with this receptor, promoting c stimulate the production of cGMP. The other major type of receptor is
the R₂ receptor. ANF, cANF, CNP, and BNP interact with this recep-
tor, promoting coupling to GTP-binding (G) proteins to either inhibit
adenylyl cycl tor, promoting coupling to GTP-binding (G) proteins to either inhibit adenylyl cyclase (AC) activity or stimulate phospholipase C (PLC) activity. These actions suppress concentrations of cAMP and increase concentrations of adenylyl cyclase (AC) activity or stimulate phospholipase C (PLC) activity. These actions suppress concentrations of cAMP and increase concentrations of IP_3 and diacylglycerol (DAG). Interactions between the signal tran activity. These actions suppress concentrations of cAMP and increase concentrations of IP_3 and diacylglycerol (DAG). Interactions between the signal transduction systems for the two major natriuretic peptids systems can concentrations of IP₃ and diacylglycerol (DAG). Interactions between
the signal transduction systems for the two major natriuretic peptide
systems can occur because cGMP suppresses phospholipase C activity
to attenuate to attenuate the stimulation caused by the R_2 receptor. Furthermore, cGMP augments phosphodiesterase (PDE) activity to suppress cAMP concentrations, whereas R_2 receptor activation suppresses cAMP concentrations by i centrations by inhibition caused by the R₂ receptor. Furthermore,
cGMP augments phosphodiesterase (PDE) activity to suppress cAMP
concentrations, whereas R₂ receptor activation suppresses cAMP con-
centrations by inhib CGMP augments phosphodiesterase (PDE) activity to suppress cAMP concentrations, whereas R_2 receptor activation suppresses cAMP concentrations by inhibiting adenylyl cyclase activity. The second messengers thought to me concentrations, whereas R_2 receptor activation suppresses cAMP c centrations by inhibiting adenylyl cyclase activity. The second mess gers thought to mediate effects of natriuretic peptides are underli (i.e., cGMP, cAM **phate.** gers thought to mediate effects of natriuretic peptides are underlined
(i.e., cGMP, cAMP, diacylglycerol, and IP₃). Potentiating or inhibitory
effects are indicated by $(+)$ or $(-)$. PIP2, phosphatidylinositol bisphos-
p (i.e., cGMP, cAMP, diacylglycerol, and IP₃). Potentiating or inhibitory
effects are indicated by $(+)$ or $(-)$. PIP2, phosphatidylinositol bisphos-
phate.
ANF could act via the release of other autacoids such as
eicosano

connections are established. We shall concentrate on phate.
ANF could act via the release of other autacoids such as
eicosanoids or EDRF. These mechanisms will be
matched with ANF actions in the instances where such
connections are established. We shall concentrate on
ANF ef ANF could act via the release of other autacoids such as
eicosanoids or EDRF. These mechanisms will be
matched with ANF actions in the instances where such
connections are established. We shall concentrate on
ANF effects t eicosanoids or EDRF. These mechanisms will be
matched with ANF actions in the instances where such
connections are established. We shall concentrate on
ANF effects to alter GC or adenylyl cyclase activity
inasmuch as these matched with ANF actions in the instances where such
connections are established. We shall concentrate on
ANF effects to alter GC or adenylyl cyclase activity
inasmuch as these mechanisms are the best-clarified
signal tran nnections are established. We shall concentrate on
NF effects to alter GC or adenylyl cyclase activity
asmuch as these mechanisms are the best-clarified
mal transduction mechanisms associated with ANF.
For a signal transdu

ANF effects to alter GC or adenylyl cyclase activity
inasmuch as these mechanisms are the best-clarified
signal transduction mechanisms associated with ANF.
For a signal transduction system to be considered a
mediator of inasmuch as these mechanisms are the best-clarified
signal transduction mechanisms associated with ANF.
For a signal transduction system to be considered a
mediator of ANF effects, the following criteria must be
met: (a) signal transduction mechanisms associated with ANF.
For a signal transduction system to be considered a
mediator of ANF effects, the following criteria must be
met: (a) the signal transduction system must be affected
by mediator of ANF effects, the following criteria must be mediator of ANF effects, the following criteria must be met: (a) the signal transduction system must be affected by ANF concentrations causing biological responses, (b) the change in the signal transduction system must the change in the signal transduction system must produce the same qualitative biological effect as ANF, and (c) inhibition of the ANF effect on the signal transduction pathway should eliminate the biological effect of ANF by ANF concentrations causing biological responses, (b)
the change in the signal transduction system must pro-
duce the same qualitative biological effect as ANF, and
 (c) inhibition of the ANF effect on the signal trans the change in the signal transduction system must produce the same qualitative biological effect as ANF, and (c) inhibition of the ANF effect on the signal transduction pathway should eliminate the biological effect of ANF duce the same qualitative biological effect as ANF, and (c) inhibition of the ANF effect on the signal transduction pathway should eliminate the biological effect of ANF. These criteria do not definitively prove a role for (c) inhibition of the ANF effect on the signal transduction pathway should eliminate the biological effect of ANF. These criteria do not definitively prove a role for signal transduction systems in the actions of ANF, but tion pathway should eliminate the biological effect of ANF. These criteria do not definitively prove a role for signal transduction systems in the actions of ANF, but they clearly indicate a potential role for the suspect ANF. These criteria do not definitively prove a role for
signal transduction systems in the actions of ANF, but
they clearly indicate a potential role for the suspected
pathway in mediating ANF biological effects. The rec signal transduction systems in the actions of ANF, but
they clearly indicate a potential role for the suspected
pathway in mediating ANF biological effects. The recent
development of R_1 receptor antagonists has facilit they clearly indicate a potential role for the suspection pathway in mediating ANF biological effects. The recodevelopment of R_1 receptor antagonists has facilitate the tests for the involvement of R_1 receptors and pathway in mediating ANF biological effects. The recent
development of R_1 receptor antagonists has facilitated
the tests for the involvement of R_1 receptors and GC in
biological activities of ANF. Alternatively, the development of R_1 receptor antagonists has facilitated
the tests for the involvement of R_1 receptors and GC in
biological activities of ANF. Alternatively, the recogni-
tion of truncated ANF analogs as R_2 recepto the tests for the
biological activi
tion of truncate
has facilitated
ANF responses.

aspet

B. Guanylyl Cyclase/cyclic Guanosine Monophosphate ANF REC
B. Guanylyl Cyclase/cyclic Guanosin
Signal Transduction System
GC catalyzes the conversion of G

Signal Transduction System
GC catalyzes the conversion of GTP to cGMP, result-
ing in the phosphorylation of specific proteins through Signal Transduction System

GC catalyzes the conversion of GTP to cGMP, result-

ing in the phosphorylation of specific proteins through

the activation of cGMP dependent protein kinase. These

phosphorylated proteins medi B. Guanyiyi Cyclase/Cyclic Guanosine monophosphale
Signal Transduction System
GC catalyzes the conversion of GTP to cGMP, result-
ing in the phosphorylation of specific proteins through
the activation of cGMP dependent pr Signal Transauction System

GC catalyzes the conversion of GTP to cGMP, result-

ing in the phosphorylation of specific proteins through

the activation of cGMP dependent protein kinase. These

phosphorylated proteins medi GC catalyzes the conversion of GTP to cGMP, resulting in the phosphorylation of specific proteins through the activation of cGMP dependent protein kinase. These phosphorylated proteins mediate physiological responses to a ing in the phosphorylation of specific proteins through
the activation of cGMP dependent protein kinase. These
phosphorylated proteins mediate physiological responses
to activation of the enzyme. The GCs responding to ANF
 the activation of cGMP dependent protein kinase. These
phosphorylated proteins mediate physiological responses
to activation of the enzyme. The GCs responding to ANF
have molecular masses of 130,000 to 180,000 Da. Other
fo resact. we molecular masses of 130,000 to 180,000 Da. Other
rms of particulate GCs also respond to heat-stable
terotoxins or the sea urchin egg proteins, speract or
sact.
ANF stimulates particulate GC activity and elevates
iMP con

forms of particulate GCs also respond to heat-stable
enterotoxins or the sea urchin egg proteins, speract or
resact.
ANF stimulates particulate GC activity and elevates
cGMP concentrations in most tissues and cell lines.
c enterotoxins or the sea urchin egg proteins, speract or
resact.
CGMP soncentrations in most tissues and cell lines.
CGMP concentrations are increased in response to ANF \overline{B} (concentrations of 0.1 to 100 nM, with an resact.

ANF stimulates particulate GC activity and elevates

cGMP concentrations in most tissues and cell lines.

cGMP concentrations are increased in response to ANF B

concentrations of 0.1 to 100 nM, with an EC₅₀ in ANF stimulates particulate GC activity and elevates
cGMP concentrations in most tissues and cell lines.
cGMP concentrations are increased in response to ANF \overline{B} (concentrations of 0.1 to 100 nM, with an EC₅₀ in the CGMP concentrations in most tissues and cell lines.
CGMP concentrations are increased in response to ANF
concentrations of 0.1 to 100 nm, with an EC_{50} in the
range of 1 to 10 nm. The stimulatory action of ANF on
GC was CGMP concentrations are increased in response to ANF
concentrations of 0.1 to 100 nM, with an EC_{50} in the
range of 1 to 10 nM. The stimulatory action of ANF on
GC was observed initially in the kidney (Hamet et al.,
198 range of 1 to 10 nM. The stimulatory action of ANF on GC was observed initially in the kidney (Hamet et al., 1984; Waldman et al., 1984). Almost all other tissues were found to increase cGMP production in response to ANF, GC was observed initially in the kidney (Hamet et al., 1984; Waldman et al., 1984). Almost all other tissues $\frac{1084}{100}$ were found to increase cGMP production in response to ANF, including adrenal (Matsuoka et al., 19 1984; Waldman et al., 1984). Almost all other tissues
were found to increase cGMP production in response to
ANF, including adrenal (Matsuoka et al., 1985), vascular
tissues (Winquist et al., 1984), cardiac tissue (Cramb et ANF, including adrenal (Matsuoka et al., 1985), vascular
tissues (Winquist et al., 1984), cardiac tissue (Cramb et mechanisms involved in transduction of the signal from
al., 1987), lung (Ishii and Murad, 1989), endocrine tissues (Winquist et al., 1984), cardiac tissue (Cramb et mechanisms involved in transduction of the signal from
al., 1987), lung (Ishii and Murad, 1989), endocrine tissues
(Heisler et al., 1986), and neuronal tissues (Fi tissues (Winquist et al., 1984), cardiac tissue (Cramb et al., 1987), lung (Ishii and Murad, 1989), endocrine tissues the (Heisler et al., 1986), and neuronal tissues (Fiscus et al., 1987). Platelets do not contain ANF R al., 1987), lung (Ishii and Murad, 1989), endocrine tissues

(Heisler et al., 1986), and neuronal tissues (Fiscus et al.,

1987). Platelets do not contain ANF R₁ receptors; there-

fore, they do not respond to ANF with a (Heisler et a
1987). Plate
fore, they d
GC activity
al., 1991).
A few iso 87). Platelets do not contain ANF R_1 receptors; there-
re, they do not respond to ANF with an elevation of
C activity (Anand-Srivastava et al., 1991; Schiffrin et
, 1991).
A few isolated studies have failed to observe

fore, they do not respond to ANF with an elevation GC activity (Anand-Srivastava et al., 1991; Schiffrin al., 1991).
A few isolated studies have failed to observe GC accition in response to ANF, but these are usually asso GC activity (Anand-Srivastava et al., 1991; Schiffrin et
al., 1991).
A few isolated studies have failed to observe GC acti-
vation in response to ANF, but these are usually associ-
ated with cultured cells lacking an R₁ al., 1991).

A few isolated studies have failed to observe GC activation in response to ANF, but these are usually associated with cultured cells lacking an R_1 receptor. Inasmuch as the ANF stimulation of GC is an almo A few isolated studies have failed to observe GC activation in response to ANF, but these are usually associated with cultured cells lacking an R_1 receptor. Inasmuch as the ANF stimulation of GC is an almost universal vation in response to ANF, but these are usually associ-
ated with cultured cells lacking an R_1 receptor. Inasmuch
as the ANF stimulation of GC is an almost universal fact
finding and that this was the first second mes ated with cultured cells lacking an R_1 receptor. Inasmuch
as the ANF stimulation of GC is an almost universal
finding and that this was the first second messenger
widely recognized for ANF, all biological effects of AN as the ANF stimulation of GC is an almost universal
finding and that this was the first second messenger
widely recognized for ANF, all biological effects of ANF
have initially been ascribed to a signal transduction
mechan finding and that this was the first second messenger
widely recognized for ANF, all biological effects of ANF and
have initially been ascribed to a signal transduction
prechanism involving increased production of cGMP. ov widely recognized for ANF, all biological effects of ANF
have initially been ascribed to a signal transduction
mechanism involving increased production of cGMP.
This cGMP hypothesis of ANF actions can be tested
directly as have initially been ascribed to a signal transduction prote
mechanism involving increased production of cGMP. over
This cGMP hypothesis of ANF actions can be tested accel
directly as a result of recent advances in the prod mechanism involving increased production of cGMP. ^{or}
This cGMP hypothesis of ANF actions can be tested
directly as a result of recent advances in the production
of selective analogs or antagonists of ANF receptors. PT
al This cGMP hypothesis of ANF actions can be tested accel
directly as a result of recent advances in the production stimu
of selective analogs or antagonists of ANF receptors. PT Thes
also has served as a useful agent to ide directly as a result of recent advances in the production
of selective analogs or antagonists of ANF receptors. PT
also has served as a useful agent to identify effects of
ANF unrelated to cGMP generation, inasmuch as PT
b of selective analogs or antagonists of ANF receptors. PT The also has served as a useful agent to identify effects of do ANF unrelated to cGMP generation, inasmuch as PT Go blocks signal transduction pathways involving sel also has served as a useful agent to identify effects of don
ANF unrelated to cGMP generation, inasmuch as PT GC
blocks signal transduction pathways involving select G-
proteins while leaving the ANF effect on GC intact. T ANF unrelated to cGMP generation, inasmuch as PT
blocks signal transduction pathways involving select G-
proteins while leaving the ANF effect on GC intact. The
net conclusion from these experiments is that most ANF
effec blocks signal transduction pathways involving select
proteins while leaving the ANF effect on GC intact. T
net conclusion from these experiments is that most Al
effects cannot be attributed to an increased production
of cG proteins while leaving the ANF effect on GC intact. The historic net conclusion from these experiments is that most ANF of effects cannot be attributed to an increased production responsion of cGMP, although renal signal net conclusion from these experim
effects cannot be attributed to an
of cGMP, although renal signal
nisms for natriuretic actions of
differentiated from GC activation
The relationship between ANF nisms for natriuretic actions of ANF have not been

misms for natriuretic actions of ANF have not been that
differentiated from GC activation. G-1
The relationship between ANF receptor binding and por
GC activation warrants a discussion of the GC enzyme. enz
GCs are divided differentiated from GC activation.
The relationship between ANF receptor binding a
GC activation warrants a discussion of the GC enzyr
GCs are divided into two general categories, soluble a
particulate. The soluble GC is c The relationship between ANF receptor binding and po
GC activation warrants a discussion of the GC enzyme. en
GCs are divided into two general categories, soluble and Mi
particulate. The soluble GC is composed of two heter GC activation warrants a discussion of the GC enzyme GCs are divided into two general categories, soluble and particulate. The soluble GC is composed of two hetero-dimers with masses of approximately $70,000$ and $80,000$ particulate. The soluble GC is composed of two hetero-
dimers with masses of approximately 70,000 and 80,000 GC molecule. Such alterations of the protein kinase
Da, as reviewed by Goy (1991). The soluble GC is acti-
domain dimers with masses of approximately 70,000 and 80,000 Da, as reviewed by Goy (1991). The soluble GC is acti-

RANSDUCTION MECHANISMS
acetylcholine, after the vasodilators augment the prod
tion of an EDRF, probably nitric oxide (Murad, 198 TRANSDUCTION MECHANISMS
acetylcholine, after the vasodilators augment the production of an EDRF, probably nitric oxide (Murad, 1986).
The soluble GC is not a substrate for ANF and is unre-TRANSDUCTION MECHANISMS 46
acetylcholine, after the vasodilators augment the production of an EDRF, probably nitric oxide (Murad, 1986
The soluble GC is not a substrate for ANF and is unre-
lated to any known biological ac acetylcholine, after the vasodilators augment the tion of an EDRF, probably nitric oxide (Murr
The soluble GC is not a substrate for ANF and lated to any known biological action of ANF.
Particulate GCs are composed of a si etylcholine, after the vasodilators augment the production of an EDRF, probably nitric oxide (Murad, 1986).
he soluble GC is not a substrate for ANF and is unreced to any known biological action of ANF.
Particulate GCs are

to activation of the enzyme. The GCs responding to ANF Sharma et al., 1989). Five distinct forms of particulate
have molecular masses of 130,000 to 180,000 Da. Other GC have been identified. Two forms are present in echi-
 concentrations of 0.1 to 100 nM, with an EC_{50} in the Another particulate GC in the intestine was identified
range of 1 to 10 nM. The stimulatory action of ANF on as a receptor for heat-stable enterotoxins produced by
G tion of an EDRF, probably nitric oxide (Murad, 1986).
The soluble GC is not a substrate for ANF and is unre-
lated to any known biological action of ANF.
Particulate GCs are composed of a single protein with
masses of 130, The soluble GC is not a substrate for ANF and is unrelated to any known biological action of ANF.
Particulate GCs are composed of a single protein with
masses of 130,000 to 180,000 Da (Chinkers et al., 1989;
Sharma et al., lated to any known biological action of ANF.
Particulate GCs are composed of a single protein with
masses of 130,000 to 180,000 Da (Chinkers et al., 1989
Sharma et al., 1989). Five distinct forms of particulat
GC have been Particulate GCs are composed of a single protein with
masses of 130,000 to 180,000 Da (Chinkers et al., 1989;
Sharma et al., 1989). Five distinct forms of particulate
GC have been identified. Two forms are present in echimasses of 130,000 to 180,000 Da (Chinkers et al., 1989;
Sharma et al., 1989). Five distinct forms of particulate
GC have been identified. Two forms are present in echi-
noderm sperm and respond to specific echinoderm egg
p Sharma et al., 1989). Five distinct forms of particulate GC have been identified. Two forms are present in echinoderm sperm and respond to specific echinoderm egg proteins, resact and speract, to increase sperm cGMP concen noderm sperm and respond to specific echinoderm egg
proteins, resact and speract, to increase sperm cGMP
concentrations and motility (Hansbrough and Garbers,
1981; Suzuki et al., 1984). The R₁ receptor for ANF was
charac noderm sperm and respond to specific echinoderm egg
proteins, resact and speract, to increase sperm cGMP
concentrations and motility (Hansbrough and Garbers,
1981; Suzuki et al., 1984). The R₁ receptor for ANF was
charac proteins, resact and speract, to increase sperm cGMP concentrations and motility (Hansbrough and Garbers, 1981; Suzuki et al., 1984). The R_1 receptor for ANF was characterized as the two particulate GCs, GC-A and GC-B concentrations and motility (Hansbrough and Garbers, 1981; Suzuki et al., 1984). The R_1 receptor for ANF was characterized as the two particulate GCs, GC-A and GC-B (Chinkers and Garbers, 1991; Schulz et al., 1990). An 1981; Suzuki et al., 1984). The R₁ receptor for ANF was
characterized as the two particulate GCs, GC-A and GC-
B (Chinkers and Garbers, 1991; Schulz et al., 1990).
Another particulate GC in the intestine was identified
 characterized as the two particulate GCs, GC-A and GC-
B (Chinkers and Garbers, 1991; Schulz et al., 1990).
Another particulate GC in the intestine was identified
as a receptor for heat-stable enterotoxins produced by
bact B (Chinkers and Garbers, 1991; Schulz et al., 1990).
Another particulate GC in the intestine was identified
as a receptor for heat-stable enterotoxins produced by
bacteria (Schulz et al., 1990; Singh et al., 1991) and an
e Another particulate GC in the intestine was identified
as a receptor for heat-stable enterotoxins produced by
bacteria (Schulz et al., 1990; Singh et al., 1991) and an
endogenous protein, guanylin (Currie et al., 1992). Be as a receptor for heat-stable enterotoxins produced by
bacteria (Schulz et al., 1990; Singh et al., 1991) and an
endogenous protein, guanylin (Currie et al., 1992). Be-
cause ANF activates particulate GC, the rest of this
 bacteria (Schulz et al., 1990; Singh et al., 1991) and an endogenous protein, guanylin (Currie et al., 1992). Be-
cause ANF activates particulate GC, the rest of this discussion will concentrate on particulate GC and the endogenous protein, guanylin (Currie et al., 1992). Because ANF activates particulate GC, the rest of this discussion will concentrate on particulate GC and the mechanisms involved in transduction of the signal from the re use ANF activates particulate GC, the rest of this scussion will concentrate on particulate GC and the echanisms involved in transduction of the signal from e receptor portion of the molecule to the GC portion.
All of the

discussion will concentrate on particulate GC and
mechanisms involved in transduction of the signal f
the receptor portion of the molecule to the GC portic
All of the particulate GCs possess similar intracell
regions but v mechanisms involved in transduction of the signal from the receptor portion of the molecule to the GC portion All of the particulate GCs possess similar intracellul regions but varying extracellular domains, a characterist the receptor portion of the molecule to the GC portion.
All of the particulate GCs possess similar intracellular
regions but varying extracellular domains, a character-
istic expected of receptors responding to different e All of the particulate GCs possess similar intracellular regions but varying extracellular domains, a characteristic expected of receptors responding to different extracellular signals. They all are characterized by large regions but varying extracellular domains, a characteristic expected of receptors responding to different extra-
cellular signals. They all are characterized by large ex-
tracellular regions accounting for peptide binding, istic expected of receptors responding to different extra-
cellular signals. They all are characterized by large ex-
tracellular regions accounting for peptide binding, a sin-
gle transmembrane domain, and a large intracel cellular signals. They all are characterized by large ex-
tracellular regions accounting for peptide binding, a sin-
gle transmembrane domain, and a large intracellular
portion containing both a protein kinase-like domain
 tracellular regions accounting for peptide binding, a single transmembrane domain, and a large intracellular portion containing both a protein kinase-like domain and a GC domain (Chinkers and Garbers, 1991). Growth factor gle transmembrane domain, and a large intracellular
portion containing both a protein kinase-like domain
and a GC domain (Chinkers and Garbers, 1991). Growth
factor receptors resemble particulate GCs in that they
also poss portion containing both a protein kinase-like domain
and a GC domain (Chinkers and Garbers, 1991). Growth
factor receptors resemble particulate GCs in that they
also possess only one transmembrane-spanning region
and a pro and a GC domain (Chinkers and Garbers, 1991). Growth
factor receptors resemble particulate GCs in that they
also possess only one transmembrane-spanning region
and a protein kinase-like segment (Garbers, 1989). The
protein factor receptors resemble particulate GCs in that they
also possess only one transmembrane-spanning region
and a protein kinase-like segment (Garbers, 1989). The
protein kinase-like segment is necessary for ANF control
ov also possess only one transmembrane-spanning region
and a protein kinase-like segment (Garbers, 1989). The
protein kinase-like segment is necessary for ANF control
over GC activity. Deletion of this region resulted in
acc and a protein kinase-like segment (Garbers, 1989). The protein kinase-like segment is necessary for ANF control over GC activity. Deletion of this region resulted in accelerated cGMP formation but an inability of ANF to st protein kinase-like segment is necessary for ANF control
over GC activity. Deletion of this region resulted in
accelerated cGMP formation but an inability of ANF to
stimulate GC activity (Chinkers and Garbers, 1991).
These over GC activity. Deletion of this region resulted in accelerated cGMP formation but an inability of ANF to stimulate GC activity (Chinkers and Garbers, 1991). These data are consistent with the protein kinase-like domain accelerated cGMP formation but an inability of ANF to
stimulate GC activity (Chinkers and Garbers, 1991).
These data are consistent with the protein kinase-like
domain acting as a regulator to mediate an activation of
GC i stimulate GC activity (Chinkers and Garbers, 1991).
These data are consistent with the protein kinase-like
domain acting as a regulator to mediate an activation of
GC in response to ANF binding. In this scenario the
protei These data are consistent with the protein kinase-like
domain acting as a regulator to mediate an activation of
GC in response to ANF binding. In this scenario the
protein kinase-like domain would normally exert an in-
hib domain acting as a regulator to mediate an activation of GC in response to ANF binding. In this scenario the protein kinase-like domain would normally exert an inhibitory influence on GC activity. The inhibitory action of GC in response to ANF
protein kinase-like domain
hibitory influence on GC a
of the protein kinase reg
response to ANF binding.
The regulation of GC a otein kinase-like domain would normally exert an in-
bitory influence on GC activity. The inhibitory action
the protein kinase region presumably dissipates in
sponse to ANF binding.
The regulation of GC activity is quite of the protein kinase region presumably dissipates in

effects cannot be attributed to an increased production
of cGMP, although renal signal transduction mecha-
misms for natriuretic actions of ANF have not been
misms for natriuretic actions of ANF have not been
differentiate of the protein kinase region presumably dissipates in
response to ANF binding.
The regulation of GC activity is quite distinct from
that for adenylyl cyclases. There is no requirement fo
G-proteins and the catalytic subuni response to ANF binding.
The regulation of GC activity is quite distinct from
that for adenylyl cyclases. There is no requirement for
G-proteins and the catalytic subunit is a structural com-
ponent of the receptor molecul The regulation of GC activity is quite distinct from
that for adenylyl cyclases. There is no requirement for
G-proteins and the catalytic subunit is a structural com-
ponent of the receptor molecule in particulate GCs. The modifications of the protein kinase-like domain of the G-proteins and the catalytic subunit is a structural component of the receptor molecule in particulate GCs. The enzyme is activated by ATP (Goraczniak et al., 1992; Marala et al., 1992), and this activation is eliminated b ponent of the receptor molecule in particulate GCs. The
enzyme is activated by ATP (Goraczniak et al., 1992;
Marala et al., 1992), and this activation is eliminated by
modifications of the protein kinase-like domain of the enzyme is activated by ATP (Goraczniak et al., 1992;
Marala et al., 1992), and this activation is eliminated by
modifications of the protein kinase-like domain of the
GC molecule. Such alterations of the protein kinase
dom Marala et al., 1992), and this activation is eliminated by modifications of the protein kinase-like domain of the GC molecule. Such alterations of the protein kinase domain eliminate ATP binding and nearly eliminate the ac modifications of the protein kinase-like domain of the GC molecule. Such alterations of the protein kinase domain eliminate ATP binding and nearly eliminate the activation of the enzyme by ANF (Marala et al., 1982). Additi phorbol esters, which activate protein kinase C (Nambi

aspet

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et al., 1987; Jaiswal et al., 1988; Sekiya et al., 1991), ANF inhib

attenuate the activation of GC by ANF. This effect of cAMP conce ANAND-SRIVASTAVA
et al., 1987; Jaiswal et al., 1988; Sekiya et al., 1991),
attenuate the activation of GC by ANF. This effect of corprotein kinase C activators is eliminated by PT, suggest-ANAND-SRIVA
et al., 1987; Jaiswal et al., 1988; Sekiya et al., 199
attenuate the activation of GC by ANF. This effect
protein kinase C activators is eliminated by PT, sugge
ing a role for G-proteins in mediating the inhibi et al., 1987; Jaiswal et al., 1988; Sekiya et al., 1991),
attenuate the activation of GC by ANF. This effect of
protein kinase C activators is eliminated by PT, suggest-
ing a role for G-proteins in mediating the inhibitor et al., 1987; Jaiswal et al., 1988; Sekiya et al., 1991), A
attenuate the activation of GC by ANF. This effect of cAN
protein kinase C activators is eliminated by PT, suggest-
had no effect (Sekiya et al., 1991). PT alone attenuate the activation of GC by ANF. This effect of protein kinase C activators is eliminated by PT, suggesting a role for G-proteins in mediating the inhibitory effect (Sekiya et al., 1991). PT alone had no effect on GC protein kinase C activators is eliminated by PT, suggesting a role for G-proteins in mediating the inhibitory
effect (Sekiya et al., 1991). PT alone had no effect on
GC activity stimulated with ANF (Sekiya et al., 1991;
Dr ing a role for G-proteins in mediating the inhib
effect (Sekiya et al., 1991). PT alone had no effec
GC activity stimulated with ANF (Sekiya et al., 1
Drewett et al., 1990; Ljusegren et al., 1990). Ag
interacting with sulf GC activity stimulated with ANF (Sekiya et al., 1991; Drewett et al., 1990; Ljusegren et al., 1990). Agents interacting with sulfhydryl groups, such as N-ethylmal-
eimide, inhibit adenylyl cyclase activity (Ross and Gil-GC activity stimulated with ANF (Sekiya et al., 1991;
Drewett et al., 1990; Ljusegren et al., 1990). Agents cinteracting with sulfhydryl groups, such as N-ethylmal-
eimide, inhibit adenylyl cyclase activity (Ross and Gil-
 Drewett et al., 1990; Ljusegren et al., 1990). Agents
interacting with sulfhydryl groups, such as N-ethylmal-
eimide, inhibit adenylyl cyclase activity (Ross and Gil-
man, 1980) but have no effect on GC activity (Sharma
et interacting with sulfhydryl groups, such as N-ethylmal-
eimide, inhibit adenylyl cyclase activity (Ross and Gil-
man, 1980) but have no effect on GC activity (Sharma and
et al., 1989). These findings indicate that ANF acti eimide, inhibit adenylyl cyclase activity (Ross and Gilman, 1980) but have no effect on GC activity (Sharma and et al., 1989). These findings indicate that ANF activates inhibit GC activity via protein kinase C may involve et al., 1989). These findings indicate that ANF activates
GC independently of G-proteins, but agents acting to
inhibit GC activity via protein kinase C may involve a
G-protein to mediate their effects.
C. Adenylyl Cyclase/ *C. independently of G-proteins, but agents acting inhibit GC activity via protein kinase C may involve G-protein to mediate their effects.*
C. Adenylyl Cyclase/Cyclic Adenosine Monophosphate Signal Transduction System inhibit GC activity via protein kind
G-protein to mediate their effects.
C. Adenylyl Cyclase/Cyclic Adenosin
Signal Transduction System
The adenylyl cyclase/cAMP system

protein to mediate their effects.

Adenylyl Cyclase/Cyclic Adenosine Monophosphate

gnal Transduction System

The adenylyl cyclase/cAMP system is one of the best

aracterized signal transduction systems mediating C. Adenylyl Cyclase/Cyclic Adenosine Monophosphate

Signal Transduction System

The adenylyl cyclase/cAMP system is one of the best-

characterized signal transduction systems mediating t

physiological responses to a var examply the example of the hormones of the best-
Signal Transduction System
The adenylyl cyclase/cAMP system is one of the best-
characterized signal transduction systems mediating torrephysiological responses to a variety the adenylyl cyclase/cAMP system is one of the best-
characterized signal transduction systems mediating to
physiological responses to a variety of hormones and un
neurotransmitters. Adenylyl cyclase is composed of three
c The adenylyl cyclase/cAMP system is one of the best-
characterized signal transduction systems mediating tors
physiological responses to a variety of hormones and unab
neurotransmitters. Adenylyl cyclase is composed of th characterized signal transduction systems mediating to
physiological responses to a variety of hormones and un
neurotransmitters. Adenylyl cyclase is composed of three
components: receptor, catalytic subunit, and G_s or physiological responses to a variety of hormones and unable
neurotransmitters. Adenylyl cyclase is composed of three testis,
components: receptor, catalytic subunit, and G_s or G_i ney, su
proteins. The G-proteins act a neurotransmitters. Adenylyl cyclase is composed of three components: receptor, catalytic subunit, and G_s or G_i proteins. The G-proteins act as transducers and, in the presence of guanine nucleotides, transmit the sign components: receptor, catalytic subunit, and G_s or G_i proteins. The G-proteins act as transducers and, in the presence of guanine nucleotides, transmit the signal from the hormone-occupied receptor to the catalytic su proteins. The G-proteins act as transducers and, in the presence of guanine nucleotides, transmit the signal from the hormone-occupied receptor to the catalytic subunit. The hormonal stimulation and inhibition of adenylyl presence of guanine nucleotides, transmit the signal from the hormone-occupied receptor to the catalytic subunit. The hormonal stimulation and inhibition of adenylyl in cyclase are mediated through the G_{\bullet} and $G_{\rm i}$ the hormone-occupied receptor to the catalytic subunit.
The hormonal stimulation and inhibition of adenylyl
cyclase are mediated through the G_s and G_i proteins,
respectively (Gilman, 1984), resulting in increased or
d ne hormonal stimulation and inhibition of adenylyl in other tiss
clase are mediated through the G_e and G_i proteins, LLC-PK cel
spectively (Gilman, 1984), resulting in increased or al., 1989; Ts
creased formation of cA

cyclase are mediated through the G_s and G_i proteins, LL
respectively (Gilman, 1984), resulting in increased or
al.,
decreased formation of cAMP, respectively. 2
The G-proteins are heterotrimeric, consisting of α , respectively (Gilman, 1984), resulting in increased or al.,
decreased formation of cAMP, respectively. 2
The G-proteins are heterotrimeric, consisting of α , β , var
and γ subunits (Gilman, 1987). The α subunit decreased formation of cAMP, respectively. 2
The G-proteins are heterotrimeric, consisting of α , β , var
and γ subunits (Gilman, 1987). The α subunit binds and He
hydrolyses GTP and confers specificity in rec The G-proteins are heterotrimeric, consisting of α , β , va
and γ subunits (Gilman, 1987). The α subunit binds and H
hydrolyses GTP and confers specificity in receptor and (A
effector interactions (Stryer and Bo and γ subunits (Gilman, 1987). The α subunit binds and Hydrolyses GTP and confers specificity in receptor and (*A* effector interactions (Stryer and Bourne, 1986). Two effector interactions of the $G_{\alpha\alpha}$ protein, hydrolyses GTP and confers specificity in receptor and
effector interactions (Stryer and Bourne, 1986). Two
different forms of the G_{sc} protein, $G_{\text{sc-45}}$ and $G_{\text{sc-52}}$, have
been characterized with a third for effector interactions (Stryer and Bourne, 1986). Two
different forms of the $G_{s\alpha}$ protein, $G_{s\alpha-45}$ and $G_{s\alpha-52}$, have
been characterized with a third form, $G_{s\alpha-47}$, recently l
being identified in heart (Mura different forms of the G_{sc} protein, $G_{\text{sc-45}}$ and $G_{\text{sc-52}}$, have
been characterized with a third form, $G_{\text{sc-47}}$, recently
being identified in heart (Murakami and Yasuda, 1986).
These different forms of G been characterized with a third form, $G_{\text{sc-47}}$, recently
being identified in heart (Murakami and Yasuda, 1986).
These different forms of G_{sc} arise from several species
of mRNA, which appear to be products of alt being identified in heart (Murakami and Yasuda, 1986). These different forms of G_{ac} arise from several species to mRNA, which appear to be products of alternate splicing of a common precursor (Robishaw et al., 1986; These different forms of $G_{s\alpha}$ arise from several species tide of mRNA, which appear to be products of alternate adesplicing of a common precursor (Robishaw et al., 1986; AN Bray et al., 1986). On the other hand, three splicing of a common precursor (Robishaw et al., 1986; Bray et al., 1986). On the other hand, three distinct G_i , 1, 2, and 3, have been identified, characterized, and shown to be products of different genes (Jones and R splicing of a common precursor (Robishaw et al., 1986; Bray et al., 1986). On the other hand, three distinct G_i , 1, 2, and 3, have been identified, characterized, and shown to be products of different genes (Jones and R Bray et al., 1986). On the other hand, three distinct G_i , 19
1, 2, and 3, have been identified, characterized, and the
shown to be products of different genes (Jones and Reed, cre
1987; Itoh et al., 1988). The G-protein 1, 2, and 3, have been identified, characterized, a shown to be products of different genes (Jones and Ree 1987; Itoh et al., 1988). The G-proteins are also targe of bacterial toxins that are useful probes for defining tin shown to be products of different genes (Jones and Reed, 1987; Itoh et al., 1988). The G-proteins are also targets of bacterial toxins that are useful probes for defining the interaction of the regulatory proteins and othe 1987; Itoh et al., 1988). The G-proteins are also targe
of bacterial toxins that are useful probes for defining th
interaction of the regulatory proteins and other comp
nents of the adenylyl cyclase system. Bacterial toxi of bacterial toxins that are useful probes for defining the
interaction of the regulatory proteins and other compo-
nents of the adenylyl cyclase system. Bacterial toxins, pape
such as cholera toxin and PT, have been show interaction of the regulatory proteins and other components of the adenylyl cyclase system. Bacterial toxins, such as cholera toxin and PT, have been shown to ADP-
ribosylate the α subunits of G_e and G_i , as well as nents of the adenylyl cyclase system. Bacterial toxins, p
such as cholera toxin and PT, have been shown to ADP-
ribosylate the α subunits of G_e and G_i , as well as G_o , and
thereby modify the characteristics of the such as cholera toxin and PT, have been shown to ADP-
ribosylate the α subunits of G_{\bullet} and G_i , as well as G_o , and
thereby modify the characteristics of the proteins (Cassel
and Pfeuffer, 1978; Hewlett et al., 1 ribosylate the α subunits of G_a and G_i , as well as G_o , and thereby modify the characteristics of the proteins (Cassel and Pfeuffer, 1978; Hewlett et al., 1984; Ui, 1984; Katada and Ui, 1981, 1982; Hazeki and Ui, thereby modify the characteristics of the proteins (Cassel and Pfeuffer, 1978; Hewlett et al., 1984; Ui, 1984; Katada and Ui, 1981, 1982; Hazeki and Ui, 1981; Neer et al., m 1984). Cholera toxin irreversibly activates the and Pfeuffer, 1978; Hewlett et al., 1984; Ui, 1984; Katada ades
and Ui, 1981, 1982; Hazeki and Ui, 1981; Neer et al., may
1984). Cholera toxin irreversibly activates the G_a protein, enri
causing stimulation of adenylyl and Ui, 1981, 1982; Hazeki and Ui, 1981; Neer et al., 1984). Cholera toxin irreversibly activates the G_s protein, causing stimulation of adenylyl cyclase, whereas PT acts on G_i and G_o proteins. The PT attenuates G_i 1984). Cholera toxin irreversibly act
causing stimulation of adenylyl cyclon G_i and G_o proteins. The PT at
inhibit adenylyl cyclase in respons
activation (Hazeki and Ui, 1981).

AND TRACHTE
ANF inhibited adenylyl cyclase activity and lowered
MP concentrations in various target tissues where A AND TRACHTE
ANF inhibited adenylyl cyclase activity and lowered
cAMP concentrations in various target tissues where
ANF exerts physiological effects. We will describe the ANF inhibited adenylyl cyclase activity and lowered
cAMP concentrations in various target tissues where
ANF exerts physiological effects. We will describe the
ANF effects on this signal transduction system in detail ANF inhibited adenylyl cyclase activity and lowered
cAMP concentrations in various target tissues where
ANF exerts physiological effects. We will describe the
ANF effects on this signal transduction system in detail
in eac ANF inhibited adenylyl cyclase activity and lowered
cAMP concentrations in various target tissues where
ANF exerts physiological effects. We will describe the
ANF effects on this signal transduction system in detail
in eac cAMP concentrations in various target tissues where
ANF exerts physiological effects. We will describe the
ANF effects on this signal transduction system in detail
in each tissue separately. In addition, the inability of
s ANF exerts physiological effects. We will describe the
ANF effects on this signal transduction system in detail
in each tissue separately. In addition, the inability of
several investigators to observe the inhibition of ad ANF effects on this signal
in each tissue separately.
several investigators to obs
cyclase by ANF and the
inability will be discussed.
1. Vasculature. Soon aft several investigators to observe the inhibition of adenylyl
cyclase by ANF and the possible reasons for such an
inability will be discussed.
1. *Vasculature*. Soon after the discovery of ANF, An-
and-Srivastava et al. (198

cyclase by ANF and the possible reasons for such an inability will be discussed.

1. Vasculature. Soon after the discovery of ANF, An-

and-Srivastava et al. (1984) demonstrated that ANF

inhibits adenylyl cyclase activity and-Srivastava et al. (1984) demonstrated that ANF inability will be discussed.

1. Vasculature. Soon after the discovery of ANF, An-

and-Srivastava et al. (1984) demonstrated that ANF

inhibits adenylyl cyclase activity in various vascular tis-

sues including aorta, ren 1. Vasculature. Soon after the discovery of ANF, An-
and-Srivastava et al. (1984) demonstrated that ANF
inhibits adenylyl cyclase activity in various vascular tis-
sues including aorta, renal arteries, and mesenteric ar-
 and-Srivastava et al. (1984) demonstrated that ANF inhibits adenylyl cyclase activity in various vascular tissues including aorta, renal arteries, and mesenteric arteries. The maximal inhibition observed was 40 to 50% inhibits adenylyl cyclase activity in various vascular tis-
sues including aorta, renal arteries, and mesenteric ar-
teries. The maximal inhibition observed was 40 to 50%
with an apparent K_i of 0.1 to 1 nM. ANF also inh sues including aorta, renal arteries, and mesenteric arteries. The maximal inhibition observed was 40 to 50% with an apparent K_i of 0.1 to 1 nM. ANF also inhibited forskolin- and hormone-stimulated adenylyl cyclase acti teries. The maximal inhibition observed was 40 to 50% with an apparent K_i of 0.1 to 1 nM. ANF also inhibited forskolin- and hormone-stimulated adenylyl cyclase activity. The inhibitory effect of ANF was dependent on the with an apparent K_i of 0.1 to 1 nM. ANF also inhibit forskolin- and hormone-stimulated adenylyl cyclase a tivity. The inhibitory effect of ANF was dependent of the presence of guanine nucleotides, suggesting the involve forskolin- and hormone-stimulated adenylyl cyclase activity. The inhibitory effect of ANF was dependent on the presence of guanine nucleotides, suggesting the involvement of G-proteins in the coupling of ANF receptors to a tivity. The inhibitory effect of ANF was dependent on
the presence of guanine nucleotides, suggesting the in-
volvement of G-proteins in the coupling of ANF recep-
tors to adenylyl cyclase. On the other hand, ANF was
unabl the presence of guanine nucleotides, suggesting the in-
volvement of G-proteins in the coupling of ANF recep-
tors to adenylyl cyclase. On the other hand, ANF was
unable to inhibit adenylyl cyclase activity in spleen,
test volvement of G-proteins in the coupling of ANF receptors to adenylyl cyclase. On the other hand, ANF was unable to inhibit adenylyl cyclase activity in spleen, testis, adrenal medulla, and the proximal tubule of kidney, su tors to adenylyl cyclase. On the other hand, ANF was
unable to inhibit adenylyl cyclase activity in spleen,
testis, adrenal medulla, and the proximal tubule of kid-
ney, suggesting that the ANF receptors responsible for
e testis, adrenal medulla, and the proximal tubule of kidney, suggesting that the ANF receptors responsible for eliciting an adenylyl cyclase inhibition were absent in these tissues (Anand-Srivastava et al., 1984). The prestestis, adrenal medulla, and the proximal tubule of kid-
ney, suggesting that the ANF receptors responsible for
eliciting an adenylyl cyclase inhibition were absent in
these tissues (Anand-Srivastava et al., 1984). The pre ney, suggesting that the ANF receptors responsible for eliciting an adenylyl cyclase inhibition were absent in these tissues (Anand-Srivastava et al., 1984). The presence of only one ANF receptor subtype was also shown in eliciting an adenylyl cyclase inhibition were absent in
these tissues (Anand-Srivastava et al., 1984). The pres-
ence of only one ANF receptor subtype was also shown
in other tissues and cell lines such as 3T3 fibroblasts, these tissues (Anand-Srivasta-
ence of only one ANF recepto-
in other tissues and cell lines
LLC-PK cell line, and cultured-
al., 1989; Tseng et al., 1990).
2. Kidney. ANF inhibited ac-**2. All of South ANF** receptor subtype was also shown

2. Kidney. Then and cultured thyroid cells (Fethiere et

2. Kidney. ANF inhibited adenylyl cyclase activity in

2. Kidney. ANF inhibited adenylyl cyclase activity in

in other tissues and cell lines such as 3T3 fibroblasts,
LLC-PK cell line, and cultured thyroid cells (Fethiere et
al., 1989; Tseng et al., 1990).
2. Kidney. ANF inhibited adenylyl cyclase activity in
various renal structu LLC-PK cell line, and cultured thyroid cells (Fethiere et al., 1989; Tseng et al., 1990).
2. Kidney. ANF inhibited adenylyl cyclase activity in various renal structures, such as glomeruli, loops of Henle, and collecting du al., 1989; Tseng et al., 1990).

2. Kidney. ANF inhibited adenylyl cyclase activity in

various renal structures, such as glomeruli, loops of

Henle, and collecting ducts, but not in proximal tubules

(Anand-Srivastava et forskolin- and hormone-stimulated adenylyl cyclase activity. The inhibitory effect of ANF was dependent on volvement of G-proteins in the coupling of ANF reception where to adenylyl cyclase. On the other hand, ANF was una various renal structures, such as glomeruli, loops of Henle, and collecting ducts, but not in proximal tubules (Anand-Srivastava et al., 1986). The maximal inhibitory effects were 45% in glomeruli and collecting ducts Henle, and collecting ducts, but not in proximal tubules (Anand-Srivastava et al., 1986). The maximal inhibitory effects were 45% in glomeruli and collecting ducts with an apparent K_i of 100 to 1000 pM and 30% in loo (Anand-Srivastava et al., 1986). The maximal inhibite
effects were 45% in glomeruli and collecting ducts wi
an apparent K_i of 100 to 1000 pM and 30% in loops
Henle with an apparent K_i of 10 to 50 pM. The inhibite
e effects were 45% in glomeruli and collecting ducts with
an apparent K_i of 100 to 1000 pM and 30% in loops of
Henle with an apparent K_i of 10 to 50 pM. The inhibitory
effect was dependent on the presence of guanine nuc an apparent K_i of 100 to 1000 pM and 30% in loops of
Henle with an apparent K_i of 10 to 50 pM. The inhibitory
effect was dependent on the presence of guanine nucleo-
tides (Anand-Srivastava et al., 1986). The inhibiti Henle with an apparent K_i of 10 to 50 pm. The inhibitory
effect was dependent on the presence of guanine nucleo-
tides (Anand-Srivastava et al., 1986). The inhibition of
adenylyl cyclase by ANF(26–55), ANF(56–92), and
A effect was dependent on the presence of guanine nucleotides (Anand-Srivastava et al., 1986). The inhibition of adenylyl cyclase by ANF(26–55), ANF(56–92), and ANF(104–123) in kidney was also shown (Vesely et al., 1987). In tides (Anand-Srivastava et al., 1986). The inhibition c
adenylyl cyclase by ANF(26–55), ANF(56–92), an
ANF(104–123) in kidney was also shown (Vesely et al
1987). In addition, Umemura et al. (1989) demonstrate
that ANF inhi adenylyl cyclase by ANF(26–55), ANF(56–92), and
ANF(104–123) in kidney was also shown (Vesely et al.,
1987). In addition, Umemura et al. (1989) demonstrated
that ANF inhibited parathyroid hormone-stimulated in-
creases in ANF(104–123) in kidney was also shown (Vesely et al., 1987). In addition, Umemura et al. (1989) demonstrated that ANF inhibited parathyroid hormone-stimulated increases in cAMP production in human glomeruli in a concentrat 1987). In addition, Umemura et al. (1989) demonstrated
that ANF inhibited parathyroid hormone-stimulated in-
creases in cAMP production in human glomeruli in a
concentration-dependent manner, to a maximum of 50%.
ANF also that ANF inhibited parathyroid hormone-stimulated in-
creases in cAMP production in human glomeruli in a
concentration-dependent manner, to a maximum of 50%.
ANF also significantly reduced arginine vasopressin and
forskoli creases in cAMP production in human glomeruli in a
concentration-dependent manner, to a maximum of 50%.
ANF also significantly reduced arginine vasopressin and
forskolin-stimulated cAMP levels in cultured rat renal
papilla concentration-dependent manner, to a maximum of 50%.
ANF also significantly reduced arginine vasopressin and
forskolin-stimulated cAMP levels in cultured rat renal
papillary collecting tubule cells (Ishikawa et al., 1985). ANF also significantly reduced arginine vasopressin and
forskolin-stimulated cAMP levels in cultured rat renal
papillary collecting tubule cells (Ishikawa et al., 1985).
However, ANF failed to inhibit adenylyl cyclase acti forskolin-stimulated cAMP levels in cultured rat renal
papillary collecting tubule cells (Ishikawa et al., 1985).
However, ANF failed to inhibit adenylyl cyclase activity
in whole kidney membranes (Waldman et al., 1984; An papillary collecting tubule cells (Ishikawa et al., 1985).
However, ANF failed to inhibit adenylyl cyclase activity
in whole kidney membranes (Waldman et al., 1984; An-
and-Srivastava et al., 1986). A lack of ANF effect on However, ANF failed to inhibit adenylyl cyclase activity
in whole kidney membranes (Waldman et al., 1984; An-
and-Srivastava et al., 1986). A lack of ANF effect on
adenylyl cyclase activity in whole kidney membranes
may be in whole kidney membranes (Waldman et al., 1984; An-
and-Srivastava et al., 1986). A lack of ANF effect on
adenylyl cyclase activity in whole kidney membranes
may be due to the possibility that these membranes are
enriched and-Srivastava et al., 1986). A lack of ANF effect adenylyl cyclase activity in whole kidney membranes amay be due to the possibility that these membranes and enriched with proximal tubules not possessing ANF ceptors. Seve adenylyl cyclase activity in whole kidney membranes
may be due to the possibility that these membranes are
enriched with proximal tubules not possessing ANF re-
ceptors. Several other investigators have been unsuc-
cessful may be due to the possibility that these membranes are
enriched with proximal tubules not possessing ANF re-
ceptors. Several other investigators have been unsuc-
cessful in demonstrating ANF effects to either inhibit
aden enriched with proximal tubules not possessing ANF receptors. Several other investigators have been unsuccessful in demonstrating ANF effects to either inhibit adenylyl cyclase or reduce cAMP concentrations in different nep

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PHARMACOLOGICAL REVIEWS

ANF RECEPTORS AND SIGNAL T
et al., 1986; Naray-Fejes-Toth et al., 1988; Chabardes et
al., 1987). The inability to demonstrate the ANF-me-ANF RECEPTORS AND SIG
et al., 1986; Naray-Fejes-Toth et al., 1988; Chabarde
al., 1987). The inability to demonstrate the ANF--
diated inhibition of adenylyl cyclase may be due to ANF RECEPTORS AND SIGNAL TRA
et al., 1986; Naray-Fejes-Toth et al., 1988; Chabardes et in
al., 1987). The inability to demonstrate the ANF-me-
diated inhibition of adenylyl cyclase may be due to the ce
assay conditions as et al., 1986; Naray-Fejes-Toth et al., 1988; Chabardes et al., 1987). The inability to demonstrate the ANF-me-
diated inhibition of adenylyl cyclase may be due to the assay conditions as well as the isolation of membrane
p preparations.

diated inhibition of adenylyl cyclase may be due to the
assay conditions as well as the isolation of membrane
preparations.
3. Adrenal. The inhibitory effect of ANF on basal and
stimulated enzyme activity by ACTH, angioten assay conditions as well as the isolation of membrane
preparations.
3. Adrenal The inhibitory effect of ANF on basal and
stimulated enzyme activity by ACTH, angiotensin II,
and forskolin was shown in adrenal cortical membr preparations.

3. Adrenal. The inhibitory effect of ANF on basal and

stimulated enzyme activity by ACTH, angiotensin II,

and forskolin was shown in adrenal cortical membranes

(Anand-Srivastava et al., 1985b; Waldman et 3. Adrenal. The inhibitory effect of ANF on basal and of stimulated enzyme activity by ACTH, angiotensin II, and forskolin was shown in adrenal cortical membranes mo (Anand-Srivastava et al., 1985b; Waldman et al., 1985). stimulated enzyme activity by ACTH, angiotensin II,
and forskolin was shown in adrenal cortical membranes
(Anand-Srivastava et al., 1985b; Waldman et al., 1985).
The maximal inhibition observed was about 30% with
an ap and forskolin was shown in adrenal cortical membrane (Anand-Srivastava et al., 1985b; Waldman et al., 1985). The maximal inhibition observed was about 30% with an apparent K_i between 50 and 1000 pM. These result were co (Anand-Srivastava et al., 1985b; Waldman et al., 198
The maximal inhibition observed was about 30% w
an apparent K_i between 50 and 1000 pm. These resu
were confirmed by Barrett and Isales (1988), who de
onstrated that A The maximal inhibition observed was about 30% with
an apparent K_i between 50 and 1000 pM. These results
were confirmed by Barrett and Isales (1988), who dem-
onstrated that ANF inhibited steroidogenesis at physio-
logic an apparent K_i between 50 and 1000 pM. These results Sri
were confirmed by Barrett and Isales (1988), who dem-
onstrated that ANF inhibited steroidogenesis at physio-
logical concentrations. Furthermore, ANF-mediated in were confirmed by Barrett and Isales (1988), who dem-
onstrated that ANF inhibited steroidogenesis at physio-
logical concentrations. Furthermore, ANF-mediated in-
inhibition of ACTH-stimulated aldosterone secretion, and
c onstrated that ANF inhibited steroidogenesis at ph
logical concentrations. Furthermore, ANF-mediate
hibition of ACTH-stimulated aldosterone secretion,
cAMP levels has also been reported in adenoma t
from patients with Cush logical concentrations. Furthermore, ANF-mediated in-
hibition of ACTH-stimulated aldosterone secretion, and
cAMP levels has also been reported in adenoma tissue
from patients with Cushing's syndrome or aldosterone-
produc hibition of ACTH-stimulated aldosterone secretion, and eny
cAMP levels has also been reported in adenoma tissue tra
from patients with Cushing's syndrome or aldosterone-
producing tumors (Naruse et al., 1987). Heisler et a cAMP levels has also been reported in adenoma tissue trat
from patients with Cushing's syndrome or aldosterone-
producing tumors (Naruse et al., 1987). Heisler et al. bloc
(1989) also found inhibitory effects of ANF on cAM from patients with Cushing's syndrome or aldosterone-
producing tumors (Naruse et al., 1987). Heisler et al.
(1989) also found inhibitory effects of ANF on cAMP fit
formation and steroidogenesis in response to ACTH in a
Y producing tumors (Naruse et al., 1987). Heisler et al. (1989) also found inhibitory effects of ANF on cAMP formation and steroidogenesis in response to ACTH in Y-1 adrenocortical tumor cells. These authors suggested that a (1989) also found inhibitory effects of ANF on cAMP ing
formation and steroidogenesis in response to ACTH in
 X -1 adrenocortical tumor cells. These authors suggested wh
that antagonism of ACTH-stimulated steroid synthesi formation and steroidogenesis in response to ACTH in
Y-1 adrenocortical tumor cells. These authors suggested where
that antagonism of ACTH-stimulated steroid synthesis hib
in Y-1 cells is probably due to the attenuation of Y-1 adrenocortical tumor cells. These authors suggested
that antagonism of ACTH-stimulated steroid synthesis
in Y-1 cells is probably due to the attenuation of cAMP
formation. ANF decreased both cAMP formation and
aldoster Y-1 cells is probably due to the attenuation of cAMP
rmation. ANF decreased both cAMP formation and
dosterone production in the rat adrenal-dispersed cap-
lar tissue (Matsuoka et al., 1985).
4. *Heart*. The inhibitory effe

sular tissue (Matsuoka et al., 1985).
4. Heart. The inhibitory effect of ANF on adenylyl
cyclase occurred in heart sarcolemma (Anand-Srivastava formation. ANF decreased both cAMP formation and
aldosterone production in the rat adrenal-dispersed cap
sular tissue (Matsuoka et al., 1985).
4. Heart. The inhibitory effect of ANF on adenyly
cyclase occurred in heart sar aldosterone production in the rat adrenal-dispersed capsular tissue (Matsuoka et al., 1985).

4. Heart. The inhibitory effect of ANF on adenylyl

cyclase occurred in heart sarcolemma (Anand-Srivastava et at

et al., 1984) sular tissue (Matsuoka et al., 1985).

4. Heart. The inhibitory effect of ANF on adenylyl

cyclase occurred in heart sarcolemma (Anand-Srivastava et

et al., 1984) and cultured cardiocytes from atria and

ventricles (Anan 4. Heart. The inhibitory effect of ANF on adenylyl
cyclase occurred in heart sarcolemma (Anand-Srivastava et
et al., 1984) and cultured cardiocytes from atria and
wentricles (Anand-Srivastava and Cantin, 1986). The
inhibi cyclase occurred in heart sarcolemma (Anand-Srivastava
et al., 1984) and cultured cardiocytes from atria and
wentricles (Anand-Srivastava and Cantin, 1986). The
inhibitory action of ANF was greater in atrial than
wentricu et al., 1984) and cultured cardiocytes from atria and
ventricles (Anand-Srivastava and Cantin, 1986). The
inhibitory action of ANF was greater in atrial than
ventricular cells. The maximal inhibition observed in
ventricula ventricles (Anand-Srivastava and Cantin, 1986). The inhibitory action of ANF was greater in atrial the ventricular cells. The maximal inhibition observed ventricular cells was 35% with an apparent K_i of 0.1 number wh inhibitory action of ANF was greater in atrial than
ventricular cells. The maximal inhibition observed in
ventricular cells was 35% with an apparent K_i of 0.1 nM,
whereas a 60% inhibition was observed in atrial cardi-
o ventricular cells. The maximal inhibition observed in ventricular cells was 35% with an apparent K_i of 0.1 nM, whereas a 60% inhibition was observed in atrial cardicorytes with an apparent K_i between 0.5 and 1 nM. As ventricular cells was 35% with an apparent K_i of 0.1 nm,
whereas a 60% inhibition was observed in atrial cardi-
ocytes with an apparent K_i between 0.5 and 1 nm. As
observed in vascular smooth muscle, the inhibition of whereas a 60% inhibition was observed in atrial cardi-
ocytes with an apparent K_i between 0.5 and 1 nM. As
observed in vascular smooth muscle, the inhibition of
adenylyl cyclase in heart was dependent on the presence
of ocytes with an apparent K_i between 0.5 and 1 nM. As observed in vascular smooth muscle, the inhibition of adenylyl cyclase in heart was dependent on the presence of guanine nucleotides (Anand-Srivastava and Cantin, 1986 adenylyl cyclase in heart was dependent on the presence
of guanine nucleotides (Anand-Srivastava and Cantin,
1986). ANF also decreased cAMP levels in both atrial
and ventricular cells (Anand-Srivastava and Cantin, 1986). guanine nucleotides (Anand-Srivastava and Cantin, 86). ANF also decreased cAMP levels in both atrial
d ventricular cells (Anand-Srivastava and Cantin, 86).
A decreased formation of cAMP caused by ANF in
ltured rat myocardi

1986). ANF also decreased cAMP levels in both atrial
and ventricular cells (Anand-Srivastava and Cantin,
1986).
A decreased formation of cAMP caused by ANF in
cultured rat myocardial cells and its correlation with the
velo and ventricular cells (Anand-Srivastava and Cantin, 1986).

A decreased formation of cAMP caused by ANF in cultured rat myocardial cells and its correlation with the velocity of contraction and calcium influx was also repo 1986). A decreased formation of cAMP caused by ANF in cultured rat myocardial cells and its correlation with the velocity of contraction and calcium influx was also reported (McCall and Fried, 1990). These investigators fo cultured rat myocardial cells and its correlation with the velocity of contraction and calcium influx was also reported (McCall and Fried, 1990). These investigators found that PT abolished both the attenuation of cAMP pro found that PT abolished both the attenuation of cAMP production and the cardiac effects caused by ANF, indicating that ANF receptors coupled to the adenylyl cyvelocity of contraction and calcium influx was also reported (McCall and Fried, 1990). These investigators found that PT abolished both the attenuation of cAMP production and the cardiac effects caused by ANF, indicating t ported (McCall and Fried, 1990). These investigators
found that PT abolished both the attenuation of cAMP
production and the cardiac effects caused by ANF, indi-
cating that ANF receptors coupled to the adenylyl cy-
clase/ found that PT abolished both the attenuation of cAMP
production and the cardiac effects caused by ANF, indi-
cating that ANF receptors coupled to the adenylyl cy-
clase/cAMP signal transduction system are responsible
for t production and the cardiac effects caused by ANF, indicating that ANF receptors coupled to the adenylyl cy-
clase/cAMP signal transduction system are responsible
for these biological effects. ANF inhibited adenylyl cy-
cla cating that ANF receptors coupled to the adenylyl cy-
clase/cAMP signal transduction system are responsible
for these biological effects. ANF inhibited adenylyl cy-
clase and reduced cAMP concentrations in Purkinje
fibers clase/cAMP signal transduction system are responsible
for these biological effects. ANF inhibited adenylyl cy-
clase and reduced cAMP concentrations in Purkinje
fibers of rabbit false tendons (Anand-Srivastava et al., mi
 for these biological effects. ANF inhibited adenylyl cy-
clase and reduced cAMP concentrations in Purkinje
fibers of rabbit false tendons (Anand-Srivastava et al.,
1989), indicating the existence of ANF receptors coupled
t fibers of rabbit false tendons (Anand-Srivastava et al., 1989), indicating the existence of ANF receptors coupled
to the adenylyl cyclase/cAMP signal transduction system in the conduction system of the heart.
5. Lung. Resi

al., 1987). The inability to demonstrate the ANF-me-
diated inhibition of adenylyl cyclase may be due to the
ceptors are coupled to adenylyl cyclase in a negative
assay conditions as well as the isolation of membrane
manne INTRANSDUCTION MECHANISMS

inhibited adenylyl cyclase activity in rat lung membrane

in a GTP-dependent manner, suggesting that ANF re-TRANSDUCTION MECHANISMS 467
inhibited adenylyl cyclase activity in rat lung membrane
in a GTP-dependent manner, suggesting that ANF re-
ceptors are coupled to adenylyl cyclase in a negative TRANSDUCTION MECHANISMS 467
inhibited adenylyl cyclase activity in rat lung membrane
in a GTP-dependent manner, suggesting that ANF re-
ceptors are coupled to adenylyl cyclase in a negative
manner through G-proteins. Anand manner through G-proteins activity in rat lung membrane
in a GTP-dependent manner, suggesting that ANF re-
ceptors are coupled to adenylyl cyclase in a negative
manner through G-proteins. Anand-Srivastava (1989)
confirmed inhibited adenylyl cyclase activity in rat lung membrane
in a GTP-dependent manner, suggesting that ANF re-
ceptors are coupled to adenylyl cyclase in a negative
manner through G-proteins. Anand-Srivastava (1989)
confirmed in a GTP-dependent manner, suggesting that AN
ceptors are coupled to adenylyl cyclase in a ne
manner through G-proteins. Anand-Srivastava (
confirmed these studies and observed a 35% inhi
of adenylyl cyclase by ANF in rat ptors are coupled to adenylyl cyclase in a negative
anner through G-proteins. Anand-Srivastava (1989)
nfirmed these studies and observed a 35% inhibition
adenylyl cyclase by ANF in rat lung membranes.
6. *Endocrine tissues*

manner through G-proteins. Anand-Srivastava (19)
confirmed these studies and observed a 35% inhibi
of adenylyl cyclase by ANF in rat lung membranes.
6. Endocrine tissues. ANF inhibited basal and
mone-stimulated adenylyl cy confirmed these studies and observed a 35% inhibition
of adenylyl cyclase by ANF in rat lung membranes.
6. Endocrine tissues. ANF inhibited basal and hor
mone-stimulated adenylyl cyclase activity at physiologi
cal concentr of adenylyl cyclase by ANF in rat lung membranes.
6. Endocrine tissues. ANF inhibited basal and h
mone-stimulated adenylyl cyclase activity at physiolo
cal concentrations in anterior and posterior pituitar
The inhibitory e 6. *Endocrine tissues*. ANF inhibited basal and hormone-stimulated adenylyl cyclase activity at physiological concentrations in anterior and posterior pituitaries. The inhibitory effects were GTP dependent (Anand-Srivastav mone-stimulated adenylyl cyclase activity at physiological concentrations in anterior and posterior pituitaries.
The inhibitory effects were GTP dependent (Anand-Srivastava et al., 1985a). However, Heisler et al. (1986) di cal concentrations in anterior and posterior pituitaries.
The inhibitory effects were GTP dependent (Anand-Srivastava et al., 1985a). However, Heisler et al. (1986)
did not find such an inhibition in homogenates or pri-
ma The inhibitory effects were GTP dependent (Anand-Srivastava et al., 1985a). However, Heisler et al. (1986) did not find such an inhibition in homogenates or primary cell cultures from rat anterior hypophysis. The inability Srivastava et al., 1985a). However, Heisler et al. (1986) did not find such an inhibition in homogenates or primary cell cultures from rat anterior hypophysis. The inability to observe the ANF-mediated inhibition of adeny did not find such an inhibition in homogenates or pri-
mary cell cultures from rat anterior hypophysis. The
inability to observe the ANF-mediated inhibition of ad-
enylyl cyclase could have been due to the high concen-
tr mary cell cultures from rat anterior hypophysis. The
inability to observe the ANF-mediated inhibition of ad-
enylyl cyclase could have been due to the high concen-
trations of GTP (300 μ M) used in their enzyme activity inability to observe the ANF-mediated inhibition of ad-
enylyl cyclase could have been due to the high concen-
trations of GTP (300 μ M) used in their enzyme activity
determinations; this GTP concentration completely
bl enylyl cyclase could have been due to the high concentrations of GTP $(300 \ \mu\text{M})$ used in their enzyme activity determinations; this GTP concentration completely blocks the inhibitory effect of the hormone, as shown in trations of GTP (300 μ **M**) used in their enzyme activity determinations; this GTP concentration completely blocks the inhibitory effect of the hormone, as shown in figure 2. The inhibitory effect of ANF on adenylyl cyc determinations; this GTP concentration completely blocks the inhibitory effect of the hormone, as shown in figure 2. The inhibitory effect of ANF on adenylyl cyclase activity is observed at lower concentrations of GTP, wh hibition. qure 2. The inhibitory effect of ANF on adenylyl cyclase
tivity is observed at lower concentrations of GTP,
nereas 300μ M GTP obliterates the ANF-mediated in-
bition.
Obana et al. (1985) also demonstrated that ANF sup-
 activity is observed at lower concentrations of GTP,
whereas 300μ M GTP obliterates the ANF-mediated in-
hibition.
Obana et al. (1985) also demonstrated that ANF sup-
pressed both cAMP levels and vasopressin release in

whereas 300 μ M GTP obliterates the ANF-mediated in-
hibition.
Obana et al. (1985) also demonstrated that ANF sup-
pressed both cAMP levels and vasopressin release in
superfused posterior pituitary glands. The inhibitio hibition.

Obana et al. (1985) also demonstrated that ANF sup-

pressed both cAMP levels and vasopressin release in

superfused posterior pituitary glands. The inhibition of

both adenylyl cyclase activity and cAMP generat Obana et al. (1985) also demonstrated that ANF sup-
pressed both cAMP levels and vasopressin release in
superfused posterior pituitary glands. The inhibition of
both adenylyl cyclase activity and cAMP generation by
ANF was pressed both cAMP levels and vasopressin release in
superfused posterior pituitary glands. The inhibition of
both adenylyl cyclase activity and cAMP generation by
ANF was reported in other endocrine systems. Pandey
et al. superfused posterior pituitary glands. The inhibit
both adenylyl cyclase activity and cAMP generati
ANF was reported in other endocrine systems. Pet al. (1985) showed that ANF decreased cAMP lev
murine Leydig tumor cells i both adenylyl cyclase activity and cAMP generation by
ANF was reported in other endocrine systems. Pandey
et al. (1985) showed that ANF decreased cAMP levels in
murine Leydig tumor cells in a concentration-dependent
manner ANF was reported in other endocrine systems. Pandey
et al. (1985) showed that ANF decreased cAMP levels in
murine Leydig tumor cells in a concentration-dependent
manner, which is associated with the inhibition of go-
nadot et al. (1985) showed that ANF decreased cAMP levels in murine Leydig tumor cells in a concentration-dependen
manner, which is associated with the inhibition of go
nadotropin-stimulated progesterone secretion. These re
sult

5. Lung. Resink et al. (1988) demonstrated that ANF values are means \pm 3 and 5.7 ± 7.1 pmol cAMP/(mg protein \cdot 10 min)⁻¹, respectively.

5. Lung. Resink et al. (1988) demonstrated that ANF values are means \pm 510 30 50 100 200 300
GTP γ S(M)
FIG. 2. Dependence on guanine nucleotides of adenylyl cyclase in
anterior pituitary homogenates. Adenylyl cyclase activity was deter-
mined at various concentrations of GTP γ S in the ab anterior pituitary homogenates. Adenylyl cyclase activity was deter-
mined at various concentrations of GTP γ S in the absence and presence
of 0.01 μ M ANF. The results are presented as percentages of inhibition
of ade mined at various concentrations of GTP γ S in the absence and presence of 0.01 μ M ANF. The results are presented as percentages of inhibition of adenylyl cyclase by ANF at various concentrations of GTP γ S. The basal \pm 3 and 55.7 \pm 7.1 pmol cAMP/(mg protein \cdot 10 min)⁻¹, respectively.

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 ANAND-SRIVASTAVA AND TRACHT
 ANAND cyclase activity, cAMP accumulation, and pro- cells expressing
 ANAND accumulation, and pro- cells expressing AMAND-SRIVAST
et al. (1991) who showed that ANF and CANF inhibited
adenylyl cyclase activity, cAMP accumulation, and pro-
gesterone secretion in murine Leydig tumor cells. How-ANAND-SRIVAS
et al. (1991) who showed that ANF and cANF inhibite
adenylyl cyclase activity, cAMP accumulation, and pro
gesterone secretion in murine Leydig tumor cells. How-
ever, Mukhopadhyay et al. (1986) were unable to et al. (1991) who showed that ANF and cANF inhibite
adenylyl cyclase activity, cAMP accumulation, and pro
gesterone secretion in murine Leydig tumor cells. How
ever, Mukhopadhyay et al. (1986) were unable to dem
onstrate s adenylyl cyclase activity, cAMP accumulation, and pro-
gesterone secretion in murine Leydig tumor cells. How-
 10 . Characterization of atrial natriuretic factor R_2 re-
ever, Mukhopadhyay et al. (1986) were unable to d ever, Mukhopadhyay et al. (1986) were unable to demever, Mukhopadhyay et al. (1986) were unable to dem-
onstrate such an inhibitory effect of ANF on basal or the
human chorionic gonadotropin-stimulated cAMP levels in
in these cells, where ANF stimulated testosterone pro-
 onstrate such an inhibitory effect of ANF on basal or human chorionic gonadotropin-stimulated cAMP levels in these cells, where ANF stimulated testosterone production in response to submaximal concentrations of human chori human chorionic gonadotropin-stimulated cAMP levels meant in these cells, where ANF stimulated testosterone pro-
duction in response to submaximal concentrations of Sri-
human chorionic gonadotropin (Bex and Corbin, 1985). in these cells, where ANF stimulated testosterone production in response to submaximal concentrations
human chorionic gonadotropin (Bex and Corbin, 1984
In addition, Budnik et al. (1987) also failed to show a
effect of ANF duction in response to submaximal concentrations of
human chorionic gonadotropin (Bex and Corbin, 1985).
In addition, Budnik et al. (1987) also failed to show any
effect of ANF on basal or gonadotropin-stimulated
cAMP leve fold. Fect of ANF on basal or gonadotropin-stimulated IMP levels and progesterone secretion in rat luteal is, whereas cGMP levels were stimulated about 12-
Id.
The ANF-mediated inhibition of cAMP production is been documented in

 $\begin{array}{ll}\n\text{cAMP levels and progenterone secretion in rat luted} \\
\text{cells, whereas cGMP levels were stimulated about 12-}\n\text{fold.} \\
\text{The ANF-mediated inhibition of cAMP production} \\
\text{has been documented in cultured human thyroid cells} \\
\text{that possess only ANF R}_2 \text{ receptor subtypes (Tseng et in-}\n\end{array}$ cells, whereas $CGMP$ levels were stimulated about 12-
fold.
The ANF-mediated inhibition of cAMP production
has been documented in cultured human thyroid cells
that possess only ANF R₂ receptor subtypes (Tseng et
al., 19 fold.
The ANF-mediated inhibition of cAMP production
has been documented in cultured human thyroid cells
that possess only ANF R_2 receptor subtypes (Tseng et
al., 1990). The inhibitory effect of ANF or prostaglandin
 E The ANF-mediated inhibition of CAMP product
has been documented in cultured human thyroid co
that possess only ANF R_2 receptor subtypes (Tseng
al., 1990). The inhibitory effect of ANF or prostaglane
 E_2 on parathyroi has been documented in cultured human thyroid cells
that possess only ANF R_2 receptor subtypes (Tseng et
al., 1990). The inhibitory effect of ANF or prostaglandin
 E_2 on parathyroid hormone-stimulated cAMP produc-
ti that posses:
al., 1990). T
E₂ on para
tion was als
al., 1989).
7. Neuro 1990). The inhibitory effect of ANF or prostaglandin
on parathyroid hormone-stimulated cAMP produc-
n was also noted in fetal rat bone cultures (Vargas et
1989).
7. *Neuronal tissue*. ANF and cANF also inhibited
enylyl cy

 E_2 on parathyroid hormone-stimulated cAMP production was also noted in fetal rat bone cultures (Vargas et al., 1989).

2. Neuronal tissue. ANF and cANF also inhibited and al., apparent K_i between 50 and 100 pM; the m tion was also noted in fetal rat bone cultures (Vargas e al., 1989).
 7. Neuronal tissue. ANF and cANF also inhibited adenylyl cyclase activity in rat brain striatum with an apparent K_i between 50 and 100 pM; the maxi al., 1989).

7. Neuronal tissue. ANF and cANF also inhibited

adenylyl cyclase activity in rat brain striatum with an

apparent K_i between 50 and 100 pM; the maximal inhi-

bitions were 60 to 65% (Anand-Srivastava et al 7. Neuronal tissue. ANF and CANF also inhibited adenylyl cyclase activity in rat brain striatum with an apparent K_i between 50 and 100 pM; the maximal inhibitions were 60 to 65% (Anand-Srivastava et al., 1990) However, adenylyl cyclase activity in rat brain striatum with an apparent K_i between 50 and 100 pM; the maximal inhitions were 60 to 65% (Anand-Srivastava et al., 1990).
However, Geiger et al. (1988) did not observe any inhition attenuates activity in fact biand structure which are that (1985c) showed that ninhibin, a sperm factor
apparent K_i between 50 and 100 pM; the maximal inhi-
bitions were 60 to 65% (Anand-Srivastava et al., 1990).
Howeve bitions were 60 to 65% (Anand-Srivastava et al., 1990).
However, Geiger et al. (1988) did not observe any inhi-
bition of adenylyl cyclase by ANF in different brain
areas, which may be due to the tissue differences and
di However, Geiger et al. (1988) did not observe any inhition of adenylyl cyclase by ANF in different brain addersa, which may be due to the tissue differences and tor different assay conditions used in their adenylyl cyclas bition of adenylyl cyclase by ANF in different braceas, which may be due to the tissue differences a different assay conditions used in their adenylyl cycle determinations. For example, 8μ M mercaptoethanol us in their areas, which may be due to the idifferent assay conditions used in determinations. For example, $8 \mu M$ in their enzyme assay could have tion of adenylyl cyclase by ANF.
8. Platelets. ANF and several true. fferent assay conditions used in their adenylyl cycla
terminations. For example, $8 \mu M$ mercaptoethanol use
their enzyme assay could have prevented the inhit
on of adenylyl cyclase by ANF.
8. Platelets. ANF and several tr

determinations. For example, 8μ M mercaptoethanol used
in their enzyme assay could have prevented the inhibi-
tion of adenylyl cyclase by ANF.
8. Platelets. ANF and several truncated analogs inhib-
trianglets devoid
its in their enzyme assay could have prevented the inhibition of adenylyl cyclase by ANF.

8. Platelets. ANF and several truncated analogs inhibition to the adenylyl cyclase activity in rat platelets devoid it of the ANF R₁ tion of adenylyl cyclase by ANF.

8. Platelets. ANF and several truncated analogs inh

ited the adenylyl cyclase activity in rat platelets dev

of the ANF R_1 receptor. The maximum inhibition

adenylyl cyclase activity 8. Platelets. ANF and several truncated analogs inhitited the adenylyl cyclase activity in rat platelets devoition of the ANF R_1 receptor. The maximum inhibition cadenylyl cyclase activity was 35 to 55% and was depende ited the adenylyl cyclase activity in rat platelets devoid
of the ANF R_1 receptor. The maximum inhibition of
adenylyl cyclase activity was 35 to 55% and was depend-
ent on the presence of guanine nucleotides. Furthermo or the ANF R_1 receptor. The maximum inhibition of the attenuation of ANF-mediated inhibition of adenylyl
adenylyl cyclase activity was 35 to 55% and was depend-
ent on the presence of guanine nucleotides. Furthermore,
 adenylyl cyclase activity was 35 to 55% and was depend
ent on the presence of guanine nucleotides. Furthermore
the inhibition was attenuated by PT or amiloride. AN:
reduced both cAMP concentrations and elevations is
adenyl ent on the presence of guanine nucleotides. Further
the inhibition was attenuated by PT or amiloride.
reduced both cAMP concentrations and elevatio
adenylyl cyclase activity caused by N-ethylcarbox
adenosine, isoproterenol the inhibition was attenu
reduced both cAMP con
adenylyl cyclase activity (adenosine, isoproterenol,
tava et al., 1991).
9. Other tissues. Bian duced both cAMP concentrations and elevations in
 9. other tissues. Bianchi et al. (1986) showed the
 9. Other tissues. Bianchi et al. (1986) showed the
 9. Other tissues. Bianchi et al. (1986) showed the
 9. Other

adenylyl cyclase activity caused by N-ethylcarboxamide
adenosine, isoproterenol, and forskolin (Anand-Srivas-
tava et al., 1991).
9. Other tissues. Bianchi et al. (1986) showed the
presence of ANF receptors in the ciliary tava et al., 1991).

9. *Other tissues*. Bianchi et al. (1986) showed the presence of ANF receptors in the ciliary process of the eye by autoradiography as well as by biochemical tech-

niques. ANF was found to inhibit ba tava et al., 1991).
9. Other tissues. Bianchi et al. (1986) showed
presence of ANF receptors in the ciliary process of
eye by autoradiography as well as by biochemical
niques. ANF was found to inhibit basal (GTP-depent) an 9. Other tissues. Bianchi et al. (1986) showed the S₁ presence of ANF receptors in the ciliary process of the w_i eye by autoradiography as well as by biochemical techniques. ANF was found to inhibit basal (GTP-depen presence of ANF receptors in the ciliary process of the eye by autoradiography as well as by biochemical techniques. ANF was found to inhibit basal (GTP-dependent) and hormone-stimulated adenylyl cyclase activity and to re eye by autoradiography as well as by biochemical tech-
niques. ANF was found to inhibit basal (GTP-depend-
ent) and hormone-stimulated adenylyl cyclase activity
and to reduce cAMP levels. In this tissue, however, in
Mittag niques. ANF was found to inhibit basal (GTP-dependent) and hormone-stimulated adenylyl cyclase activity and to reduce cAMP levels. In this tissue, however, Mittag et al. (1987) did not observe an inhibition of adenylyl cyc and to reduce cAMP levels. In this tissue, however, involvement of glycoprotein moiety in eliciting the inhib-
Mittag et al. (1987) did not observe an inhibition of itory response of ANF (Anand-Srivastava, 1992c). Phos-
ad Mittag et al. (1987) did not observe an inhibition of adenylyl cyclase activity by ANF because they did not include GTP in their assay system, which is a known absolute requirement for eliciting the inhibitory effects of A adenylyl cyclase activity by ANF because they did not pholipids were also shown to be involved in the expres-
include GTP in their assay system, which is a known sion of the inhibitory effect of ANF on adenylyl cyclase
abs 1986; Anand-Srivastava and Cantin, 1986). However, absolute requirement for eliciting the inhibitory effects

A AND TRACHTE
tion of cAMP levels by oxidized analogs of ANF in HeLa
cells expressing predominantly R_2 receptors. A AND TRACHTE
tion of cAMP levels by oxidized analogs of Alcells expressing predominantly R_2 receptors.
10. Characterization of atrial natriuretic fo

gesterone secretion in murine Leydig tumor cells. How-
ever, Mukhopadhyay et al. (1986) were unable to dem-
ceptor-mediated inhibition of adenylyl cyclase guanosine
onstrate such an inhibitory effect of ANF on basal or
tr human chorionic gonadotropin (Bex and Corbin, 1985). Resink et al., 1988). The optimal concentration of GTP
In addition, Budnik et al. (1987) also failed to show any or GTP γ S required to elicit the maximal inhibition d **10. CHARP I evels by oxidized analogs of ANF in HeLa**
 **10. Characterization of atrial natriuretic factor R₂ re-

10. Characterization of atrial natriuretic factor R₂ re-

ptor-mediated inhibition of adenylyl cyclase** *cells expressing predominantly* R_2 *receptors.*
10. Characterization of atrial natriuretic factor R_2 *receptor-mediated inhibition of adenylyl cyclase guanosine*
triphosphate dependency. As described earlier, t tion of cAMP levels by oxidized analogs of ANF in HeL
cells expressing predominantly R_2 receptors.
10. Characterization of atrial natriuretic factor R_2 receptor-mediated inhibition of adenylyl cyclase guanosin
triph cells expressing predominantly R_2 receptors.
10. Characterization of atrial natriuretic factor R_2 receptor-mediated inhibition of adenylyl cyclase guanosine
triphosphate dependency. As described earlier, the ANF-
me 10. Characterization of atrial natriuretic factor R_2
ceptor-mediated inhibition of adenylyl cyclase guanos
triphosphate dependency. As described earlier, the AN
mediated inhibition of adenylyl cyclase is absolutely
pen ceptor-mediated inhibition of adenylyl cyclase guanosine
triphosphate dependency. As described earlier, the ANF-
mediated inhibition of adenylyl cyclase is absolutely de-
pendent on the presence of guanine nucleotides (Ana triphosphate dependency. As described earlier, the ANF-
mediated inhibition of adenylyl cyclase is absolutely de-
pendent on the presence of guanine nucleotides (Anand-
Srivastava et al., 1987, 1989, 1991; Mittag et al., mediated inhibition of adenylyl cyclase is absolutely dependent on the presence of guanine nucleotides (Anand-Srivastava et al., 1987, 1989, 1991; Mittag et al., 1987; Resink et al., 1988). The optimal concentration of GTP pendent on the presence of guanine nucleotides (Anand Srivastava et al., 1987, 1989, 1991; Mittag et al., 1987
Resink et al., 1988). The optimal concentration of GTI
or GTP γ S required to elicit the maximal inhibition d Srivastava et al., 1987, 1989, 1991; Mittag et al., 1987; Resink et al., 1988). The optimal concentration of GTP or GTP γ S required to elicit the maximal inhibition depends on the tissue. For example, in pituitary, the or GTP γ S required to elicit the maximal inhibition depends on the tissue. For example, in pituitary, the maximal inhibition was observed between 3 and 5 μ M, whereas in other tissues, maximal inhibitory effects occur pends on the tissue. For example, in pituitary, the n
imal inhibition was observed between 3 and 5
whereas in other tissues, maximal inhibitory effects
curred at 10 μ M GTP γ S. Above this concentration,
inhibitory eff imal inhibition was observed between 3 and 5 μ M,
whereas in other tissues, maximal inhibitory effects oc-
curred at 10 μ M GTP γ S. Above this concentration, the
inhibitory effect is decreased, and at higher concent whereas in other tissues, maximal inhibitory effects oc-
curred at 10 μ M GTP γ S. Above this concentration, the
inhibitory effect is decreased, and at higher concentra-
tions, the effect is abolished (fig. 2). In addi curred at 10 μ M GTP γ S. Above this concentration
inhibitory effect is decreased, and at higher conce
tions, the effect is abolished (fig. 2). In addition,
inhibits adenylyl cyclase more effectively in the pre
of GTPinhibitory effect is
tions, the effect is
inhibits adenylyl cy
of GTP γ S than GT
tava et al., 1986).
As shown for ang hibits adenylyl cyclase more effectively in the presence GTP γ S than GTP or GMP-P(NH)P (Anand-Srivas-
va et al., 1986).
As shown for angiotensin II and other inhibitory hor-
one receptors, ANF receptors are also coupled

inhibits adenylyl cyclase more effectively in the presence of GTP γ S than GTP or GMP-P(NH)P (Anand-Srivat
tava et al., 1986).
As shown for angiotensin II and other inhibitory hor
mone receptors, ANF receptors are also co of GTP γ S than GTP or GMP-P(NH)P (Anand-Srivas-
tava et al., 1986).
As shown for angiotensin II and other inhibitory hor-
mone receptors, ANF receptors are also coupled to ad-
enylyl cyclase through a G_i protein (Anan tava et al., 1986).
As shown for angiotensin II and other inhibitory
mone receptors, ANF receptors are also coupled t
enylyl cyclase through a G_i protein (Anand-Srivast
al., 1985a,b,c, 1987; Resink et al., 1988). Anand-S As shown for angiotensin II and other inhibitory hor-
mone receptors, ANF receptors are also coupled to ad-
enylyl cyclase through a G_i protein (Anand-Srivastava et
al., 1985a,b,c, 1987; Resink et al., 1988). Anand-Sriv mone receptors, ANF receptors are also coupled to adenylyl cyclase through a G_i protein (Anand-Srivastava et al., 1985a,b,c, 1987; Resink et al., 1988). Anand-Srivastava et al. (1985c) showed that ninhibin, a sperm fact enylyl cyclase through a G₁ protein (Anand-Srivastava et al., 1985a,b,c, 1987; Resink et al., 1988). Anand-Srivastava et al. (1985c) showed that ninhibin, a sperm factor that attenuates adrenergic inhibition of platelet al., 1985a,b,c, 1987; Resink et al., 1988). Anand-Srivastava et al. (1985c) showed that ninhibin, a sperm factor that attenuates adrenergic inhibition of platelet adenylyl cyclase by blocking the G_i protein (Johnson et a tava et al. (1985c) showed that ninhibin, a sperm fact
that attenuates adrenergic inhibition of platelet aden
cyclase by blocking the G_i protein (Johnson et al., 19)
attenuated the inhibitory effects of GTP or ANF on
ad that attenuates adrenergic inhibition of platelet adenylyl
cyclase by blocking the G_i protein (Johnson et al., 1985),
attenuated the inhibitory effects of GTP or ANF on the
adenylyl cyclase activity. Subsequently, these cyclase by blocking the G_i protein (Johnson et al., 1985),
attenuated the inhibitory effects of GTP or ANF on the
adenylyl cyclase activity. Subsequently, these investiga-
tors found that PT also prevented the ANF effec attenuated the inhibitory effects of GTP or ANF on the
adenylyl cyclase activity. Subsequently, these investiga-
tors found that PT also prevented the ANF effects on
adenylyl cyclase activity (Anand-Srivastava et al., 1987 adenylyl cyclase activity. Subsequently, these investiga-
tors found that PT also prevented the ANF effects on
adenylyl cyclase activity (Anand-Srivastava et al., 1987,
1991). The blockade of ANF effects on adenylyl cyclas tors found that PT also prevented the ANF effects on
adenylyl cyclase activity (Anand-Srivastava et al., 1987,
1991). The blockade of ANF effects on adenylyl cyclase
by PT treatment was confirmed further by Resink et al.
(adenylyl cyclase activity (Anand-Srivastava et al., 1987, 1991). The blockade of ANF effects on adenylyl cyclase
by PT treatment was confirmed further by Resink et al. (1988) in rat lung membranes. Furthermore, amiloride
t 1991). The blockade of ANF effects on adenylyl cyclase
by PT treatment was confirmed further by Resink et al.
(1988) in rat lung membranes. Furthermore, amiloride
treatment, which interacts with G_i protein and inhibits
 by PT treatment was confirmed further by Resink et al. (1988) in rat lung membranes. Furthermore, amiloride treatment, which interacts with G_i protein and inhibits its functions (Anand-Srivastava, 1990), also resulted i (1988) in rat lung membranes. Furthermore, amiloride
treatment, which interacts with G_i protein and inhibits
its functions (Anand-Srivastava, 1990), also resulted in
the attenuation of ANF-mediated inhibition of adenyly treatment, which interacts with G_i protein and inhibits
its functions (Anand-Srivastava, 1990), also resulted in
the attenuation of ANF-mediated inhibition of adenylyl
cyclase. This finding supports the involvement of cyclase. e attenuation of ANF-mediated inhibition of adenylyl
clase. This finding supports the involvement of G_i
otein in the coupling of the ANF receptors to adenylyl
clase.
The inhibition of adenylyl cyclase by ANF is regulate cyclase. This finding supports the involvement of (protein in the coupling of the ANF receptors to adenyly cyclase.
The inhibition of adenylyl cyclase by ANF is regulate
by a variety of agents. Phorbol ester and calcium ph

protein in the coupling of the ANF receptors to adenylyl
cyclase.
The inhibition of adenylyl cyclase by ANF is regulated
by a variety of agents. Phorbol ester and calcium phos-
pholipid-dependent protein kinase (C-kinase) cyclase.
The inhibition of adenylyl cyclase by ANF is regula
by a variety of agents. Phorbol ester and calcium ph
pholipid-dependent protein kinase (C-kinase) attenua
the inhibitory effect of ANF on adenylyl cyclase (Anan
 The inhibition of adenylyl cyclase by ANF is regulated
by a variety of agents. Phorbol ester and calcium phos-
pholipid-dependent protein kinase (C-kinase) attenuated
the inhibitory effect of ANF on adenylyl cyclase (Anand by a variety of agents. Phorbol ester and calcium phos-
pholipid-dependent protein kinase (C-kinase) attenuated
the inhibitory effect of ANF on adenylyl cyclase (Anand-
Srivastava, 1992c). The ANF effect on adenylyl cyclas the inhibitory effect of ANF on adenylyl cyclase (Anand-Srivastava, 1992c). The ANF effect on adenylyl cyclase was also abolished by N-ethylmaleimide which uncouples receptors from the catalytic subunit of adenylyl cyclase the inhibitory effect of ANF on adenylyl cyclase (Anand-Srivastava, 1992c). The ANF effect on adenylyl cyclase
was also abolished by N-ethylmaleimide which uncouples
receptors from the catalytic subunit of adenylyl cyclase Srivastava, 1992c). The ANF effect on adenylyl cyclase
was also abolished by N-ethylmaleimide which uncouples
receptors from the catalytic subunit of adenylyl cyclase.
The ANF-mediated inhibition of adenyl cyclase was also was also abolished by N-ethylmaleimide which uncoupl
receptors from the catalytic subunit of adenylyl cyclas
The ANF-mediated inhibition of adenyl cyclase was al
attenuated by neurominidase treatment, indicating th
involve receptors from the catalytic subunit of adenylyl cyclas
The ANF-mediated inhibition of adenyl cyclase was ali
attenuated by neurominidase treatment, indicating th
involvement of glycoprotein moiety in eliciting the inhilit The ANF-mediated inhibition of adenyl cyclase was a
attenuated by neurominidase treatment, indicating t
involvement of glycoprotein moiety in eliciting the inh
itory response of ANF (Anand-Srivastava, 1992c). Ph
pholipids attenuated by neurominidase treatment, indicating the
involvement of glycoprotein moiety in eliciting the inhib-
itory response of ANF (Anand-Srivastava, 1992c). Phos-
pholipids were also shown to be involved in the expres (Anand-Srivastava, 1992c). by response of ANF (Anand-Srivastava, 1992c). Photolipids were also shown to be involved in the expression of the inhibitory effect of ANF on adenylyl cycla nand-Srivastava, 1992c).
ANF, as reported for other inhibitory ho pholipids were also shown to be involved in the expression of the inhibitory effect of ANF on adenylyl cyclase (Anand-Srivastava, 1992c).
(Anand-Srivastava, 1992c).
ANF, as reported for other inhibitory hormone receptors,

sion of the inhibitory effect of ANF on adenylyl cyclase
(Anand-Srivastava, 1992c).
ANF, as reported for other inhibitory hormone recep-
tors, inhibited adenylyl cyclase more effectively as so-
dium concentrations were inc

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ANF RECEPTORS AND SIGNA
and lithium suppressed inhibitory effects of ANF (An-
and-Srivastava et al., 1992c). Manganese also suppressed ANF RECEPTORS AND SIGNAL T.
and-Srivastava et al., 1992c). Manganese also suppressed
ANF effects on adenylyl cyclase. Manganese concentra-ANF RECEPTORS AND SICAL
and lithium suppressed inhibitory effects of ANF (and-Srivastava et al., 1992c). Manganese also suppre-
ANF effects on adenylyl cyclase. Manganese concentions of 1 mM and greater totally eliminated and lithium suppressed inhibitory effects of ANF (An-
and-Srivastava et al., 1992c). Manganese also suppressed C at
ANF effects on adenylyl cyclase. Manganese concentra-
tions of 1 mM and greater totally eliminated the AN and lithium suppressed inhibitory effects of ANF (A
and-Srivastava et al., 1992c). Manganese also suppress
ANF effects on adenylyl cyclase. Manganese concenti
tions of 1 mM and greater totally eliminated the Al
effects on ANF effects on adenylyl cyclase. Manganese concentrations of 1 mM and greater totally eliminated the ANF effects on adenylyl cyclase activity possibly by uncoupling ANF receptors from the catalytic subunit. These studies i NF effects on adenylyl cyclase. Manganese concentra-
ons of 1 mM and greater totally eliminated the ANF
fects on adenylyl cyclase activity possibly by uncou-
ing ANF receptors from the catalytic subunit.
These studies indi

tions of 1 mM and greater totally eliminated the ANF effects on adenylyl cyclase activity possibly by uncoupling ANF receptors from the catalytic subunit.
These studies indicate that ANF suppresses the adenylyl cyclase act effects on adenylyl cyclase activity possibly by uncou-
pling ANF receptors from the catalytic subunit. These studies indicate that ANF suppresses the ad-
enylyl cyclase activity in the majority of tissues studied. In
The pling ANF receptors from the catalytic subunit.

These studies indicate that ANF suppresses the ad-

enylyl cyclase activity in the majority of tissues studied.

The suppression of adenylyl cyclase activity in broken

cell These studies indicate that ANF suppresses the ad-
enylyl cyclase activity in the majority of tissues studied. In
The suppression of adenylyl cyclase activity in broken
incell preparations is critically dependent on the pr enylyl cyclase activity in the majority of tissues studied.
The suppression of adenylyl cyclase activity in broken
cell preparations is critically dependent on the presence
of GTP or GTP analogs, suggesting the mediation o The suppression of adenylyl cyclase activity in broken
cell preparations is critically dependent on the presence
of GTP or GTP analogs, suggesting the mediation of
effects by G-proteins. This possibility gains additional
s cell preparations is critically dependent on the presence the of GTP or GTP analogs, suggesting the mediation of nieffects by G-proteins. This possibility gains additional tisupport because PT prevents the ANF effect on ad of GTP or GTP analogs, suggesting the mediation of
effects by G-proteins. This possibility gains additional
support because PT prevents the ANF effect on adenylyl
cyclase. The receptor mediating the inhibitory effect of
A effects by G-proteins. This possibility gains additional support because PT prevents the ANF effect on adenylyl cyclase. The receptor mediating the inhibitory effect of ANF on adenylyl cyclase appears to be the R_2 rece support because PT prevents the ANF effect on adenylyl cyclase. The receptor mediating the inhibitory effect of ANF on adenylyl cyclase appears to be the R_2 receptor because the tissues lacking the R_2 receptor do no cyclase. The receptor mediating the inhibitory effect of ANF on adenylyl cyclase appears to be the R_2 receptor because the tissues lacking the R_2 receptor do not exhibit this response. The precise role of this pathw but results of a number of studies suggest this to be an important signal transduction pathway in cardiac, en-
docrine, and neuronal tissues, as well as in platelets. diating biological responses to ANF is not clearly defined, but results of a number of studies suggest this to be
important signal transduction pathway in cardiac,
docrine, and neuronal tissues, as well as in platelets.
D. Phospholipase C-mediated Signal Transduction
System

System

crine, and neuronal tissues, as well as in platelets.
 Phospholipase C-mediated Signal Transduction

stem

The metabolism of phosphatidylinositol bisphosphate

IP₃ and diacylglycerol has been recognized as a major D. Phospholipase C-mediated Signal Transduction
System
The metabolism of phosphatidylinositol bisphosphate
to IP_3 and diacylglycerol has been recognized as a major
signal transduction pathway for hormones mobilizing S ystem
The metabolism of phosphatidylinositol bisphosphate
to IP₃ and diacylglycerol has been recognized as a major
signal transduction pathway for hormones mobilizing
intracellular calcium. Resink et al. (1987) and H The metabolism of phosphatidylinositol bisphosphate
to IP₃ and diacylglycerol has been recognized as a major
signal transduction pathway for hormones mobilizing
intracellular calcium. Resink et al. (1987) and Hirata et
 The metabolism of phosphatidylinositol bisphosphate
to IP_3 and diacylglycerol has been recognized as a major
signal transduction pathway for hormones mobilizing a
intracellular calcium. Resink et al. (1987) and Hirata e to IP₃ and diacylglycerol has been recognized as a major posignal transduction pathway for hormones mobilizing al.
intracellular calcium. Resink et al. (1987) and Hirata et Da
al. (1989a) initially observed that ANF sti signal transduction pathway for hormones mobilizing al.
intracellular calcium. Resink et al. (1987) and Hirata et Da
al. (1989a) initially observed that ANF stimulated this tiv
process. Hirata et al. (1989a) also observed intracellular calcium. Resink et al. (1987) and Hirata et Day
al. (1989a) initially observed that ANF stimulated this tiva
process. Hirata et al. (1989a) also observed that the 1989
truncated ANF analog, ANF(103-123), pro al. (1989a) initially observed that ANF stimulated this tiva
process. Hirata et al. (1989a) also observed that the 198
truncated ANF analog, ANF(103-123), produced the port
same effect, thereby dissociating the action fro process. Hirata et al. $(1989a)$ also observed that the truncated ANF analog, ANF $(103-123)$, produced the same effect, thereby dissociating the action from the receptor. Therefore, phospholipase activation by Al appears truncated ANF analog, ANF(103-123), produced the p
same effect, thereby dissociating the action from the R_1 s
receptor. Therefore, phospholipase activation by ANF h
appears to be mediated by the R_2 receptor. The sig unknown. ceptor. Therefore, phospholipase activation by ANF hibitor
pears to be mediated by the R_2 receptor. The significant
mce of this action in mediating ANF effects is presently ing volume
known.
The stimulatory effect of A

appears to be mediated by the R_2 receptor. The significance of this action in mediating ANF effects is presently unknown.
The stimulatory effect of ANF on phospholipase C was observed in quiescent cells in the above st cance of this action in mediating ANF effects is present
unknown.
The stimulatory effect of ANF on phospholipase
was observed in quiescent cells in the above studie
Conversely, hormone-stimulated phospholipase C activ
ity the stimulatory effect of ANF on phospholipase C in
was observed in quiescent cells in the above studies. A
Conversely, hormone-stimulated phospholipase C activ-
ity was inhibited by either ANF or other stimulants of for
G The stimulatory effect of ANF on phospholipase C
was observed in quiescent cells in the above studies.
Conversely, hormone-stimulated phospholipase C activ-
ity was inhibited by either ANF or other stimulants of
GC activit was observed in quiescent cells in the above studies.
Conversely, hormone-stimulated phospholipase C activity was inhibited by either ANF or other stimulants of GC activity (Rapoport, 1986). ANF attenuated the increased ph Conversely, hormone-stimulated phospholipase C activ-
in tity was inhibited by either ANF or other stimulants of for
GC activity (Rapoport, 1986). ANF attenuated the in-
creased phospholipase C activity caused by angioten ity was inhibited by either ANF or other stimulants of GC activity (Rapoport, 1986). ANF attenuated the increased phospholipase C activity caused by angiotensin II, suggesting that this mechanism could function in vasodila GC activity (Rapoport, 1986). ANF attenuated the in-
creased phospholipase C activity caused by angiotensin
II, suggesting that this mechanism could function in
 $F. F$
vasodilator activities of ANF. Currently, ANF is thoug creased phospholipase C activity caused by angiotensin
II, suggesting that this mechanism could function in $F \cdot \alpha$
vasodilator activities of ANF. Currently, ANF is thought
to activate phospholipase C via the R_2 recept II, suggesting that this mechanism could fund
vasodilator activities of ANF. Currently, ANF is
to activate phospholipase C via the R_2 receptor
inhibit phospholipase C activity via an increase in
production as a result sodilator activities of ANF. Currently, ANF is thought
activate phospholipase C via the R_2 receptor and to
bibit phospholipase C activity via an increase in cGMP al
oduction as a result of R_1 receptor interactions.

to activate phospholipase C via the R_2 receptor and to inhibit phospholipase C activity via an increase in cGMP production as a result of R_1 receptor interactions.
A stimulation of phospholipase C activity by ANF ha inhibit phospholipase C activity via an increase in cG
production as a result of R_1 receptor interactions.
A stimulation of phospholipase C activity by ANF
been observed only in vascular tissue (Resink et al., 1
Hirata production as a result of R_1 receptor interactions.
A stimulation of phospholipase C activity by ANF has
been observed only in vascular tissue (Resink et al., 1988;
Hirata et al., 1989a). An inhibitory effect on phosph A stimulation of phospholipase C activity by ANF
been observed only in vascular tissue (Resink et al., 1
Hirata et al., 1989a). An inhibitory effect on phospl
pase C activity occurred in the kidney (Barnett et
1990) and va been observed only in vascular tissue (Resink et al., 1989). Hirata et al., 1989a). An inhibitory effect on phospholpase C activity occurred in the kidney (Barnett et al. 1990) and vascular tissue (Rapoport, 1986; Meyer-Le Hirata et al., 1989a). An inhibitory effect on phosphologase C activity occurred in the kidney (Barnett et a 1990) and vascular tissue (Rapoport, 1986; Meyer-Lenert et al., 1988). An absence of ANF effects on phologase C 1990) and vascular tissue (Rapoport, 1986; Meyer-Leh-
nert et al., 1988). An absence of ANF effects on phos-
pholipase C activity was reported in the adrenal (Good-
friends as production has not yet been investigated and
f

RANSDUCTION MECHANISMS
ultimate significance of ANF actions on phospholipase TRANSDUCTION MECHANISMS
ultimate significance of ANF action
C activity remains to be established. *E. Altered Ion Conductances*
E. Altered Ion Conductances
ANF was initially observed

timate significance of ANF actions on phospholipa
activity remains to be established.
Altered Ion Conductances
ANF was initially observed to enhance sodium excre-
on by the kidney (de Bold et al., 1981); therefore, i C activity remains to be established.

E. Altered Ion Conductances

ANF was initially observed to enhance sodium excre-

tion by the kidney (de Bold et al., 1981); therefore, its

ability to inhibit sodium conductance in r E. Altered Ion Conductances
ANF was initially observed to enhance sodium excre-
tion by the kidney (de Bold et al., 1981); therefore, its
ability to inhibit sodium conductance in renal tubules is
not surprising. Sodium con E. Allevel for conductances
ANF was initially observed to enhance sodium excre-
tion by the kidney (de Bold et al., 1981); therefore, its
ability to inhibit sodium conductance in renal tubules is
not surprising. Sodium con ANF was initially observed to enhance sodium excretion by the kidney (de Bold et al., 1981); therefore, its ability to inhibit sodium conductance in renal tubules is not surprising. Sodium conductance is altered by ANF in tion by the kidney (de Bold et al., 1981); therefore, its ability to inhibit sodium conductance in renal tubules is not surprising. Sodium conductance is altered by ANF in a variety of preparations other than kidney, such ability to inhibit sodium conductance in renal tubules is
not surprising. Sodium conductance is altered by ANF
in a variety of preparations other than kidney, such as
the vasculature, lung, neurons, and fibroblasts. The si not surprising. Sodium conductance is altered by ANF
in a variety of preparations other than kidney, such as
the vasculature, lung, neurons, and fibroblasts. The sig-
nificance of ANF effects on sodium currents in nonrenal in a variety of preparations other than kidney, such as the vasculature, lung, neurons, and fibroblasts. The significance of ANF effects on sodium currents in nonrenal tissues is unestablished, but indirect evidence sugges the vascul

nificance

tissues is

an integra

to ANF.

A numl ficance of ANF effects on sodium currents in nonrenal
sues is unestablished, but indirect evidence suggests
integral role for sodium in select biological responses
ANF.
A number of ANF actions could be mediated by an
hibit

because the tissues lacking the R_2 receptor do not exhibit inhibition of calcium conductance. ANF inhibits trans-
this response. The precise role of this pathway in me-
diating biological responses to ANF is not clearl tissues is unestablished, but indirect evidence sugges
an integral role for sodium in select biological respons
to ANF.
A number of ANF actions could be mediated by a
inhibition of calcium conductance. ANF inhibits tran
me an integral role for sodium in select biological responses
to ANF.
A number of ANF actions could be mediated by an
inhibition of calcium conductance. ANF inhibits trans-
membrane movements of calcium in the heart (Gisbert
 to ANF.
A number of ANF actions could be mediated by an
inhibition of calcium conductance. ANF inhibits trans-
membrane movements of calcium in the heart (Gisbert
and Fischmeister, 1988), stimulates the uptake of cal-
cium inhibition of calcium conductance. ANF inhibits transand Fischmeister, 1988), stimulates the uptake of calmembrane movements of calcium in the heart (Gisbert
and Fischmeister, 1988), stimulates the uptake of cal-
cium from intracellular stores in the vasculature (Corn-
well and Lincoln, 1988), and has variable effects on
calci and Fischmeister, 1988), stimulates the uptake of calcium from intracellular stores in the vasculature (Cornwell and Lincoln, 1988), and has variable effects on calcium channels in adrenal tissues (Barrett et al., 1991). T cium from intracellular stores in the vasculature (Cornwell and Lincoln, 1988), and has variable effects on calcium channels in adrenal tissues (Barrett et al., 1991). The central role of calcium in controlling a number of biological functions emphasizes the potential importance of this mechanism in mediating ANF effects. Icium channels in adrenal tissues (Barrett et al., 1991).

he central role of calcium in controlling a number of

blogical functions emphasizes the potential importance

this mechanism in mediating ANF effects.

ANF effect

The central role of calcium in controlling a number of
biological functions emphasizes the potential importance
of this mechanism in mediating ANF effects.
ANF effects on a variety of systems are inhibited by
potassium dep biological functions emphasizes the potential importance
of this mechanism in mediating ANF effects.
ANF effects on a variety of systems are inhibited by
potassium depletion (Matsuoka, et al., 1987; Rapoport et
al., 1985) of this mechanism in mediating ANF effects.

ANF effects on a variety of systems are inhibited by

potassium depletion (Matsuoka, et al., 1987; Rapoport et

al., 1985) or potassium channel inhibitors (Antoni and

Dayanithi ANF effects on a variety of systems are inhibited by
potassium depletion (Matsuoka, et al., 1987; Rapoport et
al., 1985) or potassium channel inhibitors (Antoni and
Dayanithi, 1990). Neuronal potassium channels are ac-
tiv potassium depletion (Matsuoka, et al., 1987; Rapopor
al., 1985) or potassium channel inhibitors (Antoni a
Dayanithi, 1990). Neuronal potassium channels are
tivated (Reiser et al., 1987) or inhibited (Pant and Smi
1989) by al., 1985) or potassium channel inhibitors (Antoni and Dayanithi, 1990). Neuronal potassium channels are activated (Reiser et al., 1987) or inhibited (Pant and Smith, 1989) by ANF. Additionally, sodium-potassium cotranspor Dayanithi, 1990). Neuronal potassium channels are activated (Reiser et al., 1987) or inhibited (Pant and Smith, 1989) by ANF. Additionally, sodium-potassium cotransport with chloride was stimulated by ANF in vascular smoot tivated (Reiser et al., 1987) or inhibited (Pant and Smith,
1989) by ANF. Additionally, sodium-potassium cotrans-
port with chloride was stimulated by ANF in vascular
smooth muscle (O'Donnell and Owen, 1986a). Most in-
hib 1989) by ANF. Additionally, sodium-potassium cotra
port with chloride was stimulated by ANF in vasco
smooth muscle (O'Donnell and Owen, 1986a). Most
hibitors of adenylyl cyclase activate both potassi
channels and sodium/hy port with chloride was stimulated by ANF in vascular smooth muscle (O'Donnell and Owen, 1986a). Most inhibitors of adenylyl cyclase activate both potassium channels and sodium/hydrogen antiports while suppressing voltage-s smooth muscle (O'Donnell and Owen, 1986a). Most in-
hibitors of adenylyl cyclase activate both potassium
channels and sodium/hydrogen antiports while suppress-
ing voltage-sensitive calcium channels (Limbird, 1988);
thus, hibitors of adenylyl cyclase activate both potassium
channels and sodium/hydrogen antiports while suppress-
ing voltage-sensitive calcium channels (Limbird, 1988);
thus, all of these effects on ionic transport could be
inv channels and sodium/hydrogen antiports while suppress-
ing voltage-sensitive calcium channels (Limbird, 1988);
thus, all of these effects on ionic transport could be
involved in the various signal-transducing pathways for
 ing voltage-sensitive calcium channels (Limbird, 1988);
thus, all of these effects on ionic transport could be
involved in the various signal-transducing pathways for
ANF. The efficacy of potassium depletion or channel
inh thus, all of these effects on ionic transport could be
involved in the various signal-transducing pathways for
ANF. The efficacy of potassium depletion or channel
inhibition to suppress ANF effects suggests a central role
 involved in the various signa
ANF. The efficacy of potas
inhibition to suppress ANF effor potassium in mediating
smooth muscle and neurons. *F. Production to suppress ANF eff*
for potassium in mediating
smooth muscle and neurons.
F. Production of Eicosanoids
ANF has been reported to re

r potassium in mediating ANF effects in vascular
nooth muscle and neurons.
Production of Eicosanoids
ANF has been reported to release arachidonic acid and
ostaglandins from vascular smooth muscle (Resink et smooth muscle and neurons.

F. Production of Eicosanoids

ANF has been reported to release arachidonic acid and

prostaglandins from vascular smooth muscle (Resink et

al., 1987). However, experiments with cyclooxygenase F. Production of Eicosanoids
ANF has been reported to release arachidonic acid and
prostaglandins from vascular smooth muscle (Resink et
al., 1987). However, experiments with cyclooxygenase
inhibitors have failed to identi F. 1 Follocitor by Excolations

ANF has been reported to release arachidonic acid a

prostaglandins from vascular smooth muscle (Resink

al., 1987). However, experiments with cyclooxygen

inhibitors have failed to identify ANF has been reported to release arachidonic acid and
prostaglandins from vascular smooth muscle (Resink et
al., 1987). However, experiments with cyclooxygenase
inhibitors have failed to identify any ANF effect depend-
ent prostaglandins from vascular smooth muscle (Resink et al., 1987). However, experiments with cyclooxygenase inhibitors have failed to identify any ANF effect dependent on prostaglandin or thromboxane production. Thus, altho al., 1987). However, experiments with cyclooxygenase
inhibitors have failed to identify any ANF effect depend-
ent on prostaglandin or thromboxane production. Thus,
although ANF can activate eicosanoid synthesis, this
acti inhibitors have failed to identify any ANF effect depent on prostaglandin or thromboxane production. The although ANF can activate eicosanoid synthesis, thaction appears to be a phenomenon not required recognized ANF effec ent on prostaglandin or thromboxane production. The although ANF can activate eicosanoid synthesis, action appears to be a phenomenon not required recognized ANF effects on any organ system. Areadonic acid is also converte although ANF can activate eicosanoid synthesis, the action appears to be a phenomenon not required if recognized ANF effects on any organ system. Aracle donic acid is also converted to leukotriene and epoxyge ase products. action appears to be a phenomenon not required for
recognized ANF effects on any organ system. Arachi-
donic acid is also converted to leukotriene and epoxygen-
ase products. The effect of ANF on leukotriene or epoxy-
gena donic acid is also converted to leukotriene and epoxygen-

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G. Production of Endothelium-derived Relaxing Factor

The seminal work of Furchgott and Zawadski (1980) are depicted in figure 3. They include activation of GC,
led to the recognition of the vascular endothelium as the phospholipase C, sodium-potassium-chloride exchange,
sour 470 ANAND-SRIVASTAVA ANAND-SRIVASTAVA

d. Production of Endothelium-derived Relaxing Factor est

ded to the recognition of the vascular endothelium as the

source of a substance mediating the vasodilation pro-G. Production of Endothelium-derived Relaxing Factor
The seminal work of Furchgott and Zawadski (1980)
led to the recognition of the vascular endothelium as the
source of a substance mediating the vasodilation pro-
duced b duced by *Endothelium-derived Relaxing Factor*
The seminal work of Furchgott and Zawadski (1980)
led to the recognition of the vascular endothelium as the
source of a substance mediating the vasodilation pro-
duced by acet The seminal work of Furchgott and Zawadski (1980)
led to the recognition of the vascular endothelium as the
source of a substance mediating the vasodilation pro-
duced by acetylcholine, ATP, bradykinin, and other au-
taco led to the recognition of the vascular endothelium as the source of a substance mediating the vasodilation produced by acetylcholine, ATP, bradykinin, and other autacoids. The vasodilator produced by the endothelium appear source of a substance mediating the vasodilation pro-
duced by acetylcholine, ATP, bradykinin, and other au-
tacoids. The vasodilator produced by the endothelium
appears to be nitric oxide (Moncada et al., 1987; Palmer
et duced by acetylcholine, ATP, bradykinin, and other autacoids. The vasodilator produced by the endothelium appears to be nitric oxide (Moncada et al., 1987; Palmer et al., 1987, 1988). Nitric oxide activates soluble GC to a tacoids. The vasodilator produced by the endothelium appears to be nitric oxide (Moncada et al., 1987; Palmer $\int_{\text{act}}^{\text{fact}}$
et al., 1987, 1988). Nitric oxide activates soluble GC to discougnent cGMP concentrations whic Figure 1.1987, 1988). Nitric oxide activates soluble GC to
entrations which, then, presumably
cause vasodilation. Because the vasodilator effect of ANF
is independent of the endothelium and because the
cause the vasodilati augment cGMP concentrations which, then, presumably
cause vasodilation. Because the vasodilator effect of ANF (1984) demonstrated aortic vasodilation and GC activa-
is independent of the endothelium and because the
cGMP ge augment cGMP concentrations which, then, presumab
cause vasodilation. Because the vasodilator effect of AN
is independent of the endothelium and because the
cGMP generation in response to ANF is caused entire
by an activat cause vasodilation. Because the vasodilator effect of ANF
is independent of the endothelium and because the
cGMP generation in response to ANF is caused entirely
by an activation of particulate and not soluble GC (Win-
qu is independent of the endoth
cGMP generation in response t
by an activation of particulate a
quist et al., 1984), we conclude
independent of the endothelium. Iv. Biological Actions of particulate and not soluble GC (We

Iv. et al., 1984), we conclude that ANF effects

pendent of the endothelium.
 IV. Biological Actions of Atrial Natriuretic
 Factor

Factor independent of the endothelium.
 IV. Biological Actions of Atrial Natriuretic Factor
 A. Vascular Effects of Atrial Natriuretic Factor

Cardiovascular effects of ANF include hypote

IV. Biological Actions of Atrial Natriuretic
Factor
Vascular Effects of Atrial Natriuretic Factor
Cardiovascular effects of ANF include hypotension
id leakage from the vasculature, vasodilation, an Factor This Rector This Rector Cardiovascular effects of Atrial Natriuretic Factor of the Cardiovasculature, vasodilation, and of fluid leakage from the vasculature, vasodilation, and of inhibition of mitogenesis. The hypo A. Vascular Effects of Atrial Natriuretic Factor

Cardiovascular effects of ANF include hypotension,

fluid leakage from the vasculature, vasodilation, and

inhibition of mitogenesis. The hypotension caused by

ANF is ofte A. *Vascuar Effects of Atrial Natriuretic ractor*
Cardiovascular effects of ANF include hypotension,
fluid leakage from the vasculature, vasodilation, and
inhibition of mitogenesis. The hypotension caused by
ANF is often a fluid leakage from the vasculature, vasodilation, and
inhibition of mitogenesis. The hypotension caused by
ANF is often attributed to a decrease in cardiac output
rather than to a vasodilation. The vasodilator activity is inhibition of mitogenesis. The hypotension caused by d
ANF is often attributed to a decrease in cardiac output
rather than to a vasodilation. The vasodilator activity is
considered a physiological action but is not univer ANF is often attributed to a decrease in cardiac output
rather than to a vasodilation. The vasodilator activity is
considered a physiological action but is not universally
observed in vivo with ANF infusions, although bolu rather than to a vasodilation. The vasodilator activity is unconsidered a physiological action but is not universally a observed in vivo with ANF infusions, although bolus injections uniformly cause a decrease in total pe considered a physiological action but is not universally observed in vivo with ANF infusions, although bolus injections uniformly cause a decrease in total peripheral resistance (Winquist and Hintze, 1990). The increased v observed in vivo with ANF infusions, although bolus injections uniformly cause a decrease in total peripheral resistance (Winquist and Hintze, 1990). The increased vascular permeability observed in response to ANF adminis injections uniformly cause a decrease in total peripheral
resistance (Winquist and Hintze, 1990). The increased AN
vascular permeability observed in response to ANF ad-
ministration has not been studied to a great extent. resistance (Winquist and Hintze, 1990). The increased vascular permeability observed in response to ANF administration has not been studied to a great extent. It involves an increase in the capillary surface area for fluid vascular permeability observed in response to ANF ad-
ministration has not been studied to a great extent. It $G C$
involves an increase in the capillary surface area for fluid
exchange (Huxley and Meyer, 1990) and occurs involves an increase in the capillary surface area for fluid
exchange (Huxley and Meyer, 1990) and occurs in ne-
phrectomized animals (Almeida et al., 1986). This ANF
effect on vascular permeability affects water and elect involves an increase in the capillary surface area for fluid
exchange (Huxley and Meyer, 1990) and occurs in ne-
phrectomized animals (Almeida et al., 1986). This ANF
effect on vascular permeability affects water and elec exchange (Huxley and Meyer, 1990) and occurs in ne-
phrectomized animals (Almeida et al., 1986). This ANF
effect on vascular permeability affects water and electro-
lytes but does not involve an increased permeability to
a phrectomized animals (Almeida et al., 1986). This ANF
effect on vascular permeability affects water and electro-
lytes but does not involve an increased permeability to
albumin (Huxley and Meyer, 1990). The ANF effects on
 effect on vascular permeability affects water and electro-
lytes but does not involve an increased permeability to
albumin (Huxley and Meyer, 1990). The ANF effects on
vascular permeability were mimicked by activators of
G albumin (Huxley and Meyer, 1990). The ANF effects on vascular permeability were mimicked by activators of GC, suggesting that this action involves an interaction of ANF with R_1 receptors to elevate cGMP concentrations vascular permeability were mimicked by activators GC, suggesting that this action involves an interaction of ANF with R_1 receptors to elevate cGMP concentritions (Meyer and Huxley, 1992). This review will concentrate o GC, suggesting that this action involves an interaction of ANF with R_1 receptors to elevate cGMP concentrations (Meyer and Huxley, 1992). This review will concentrate on the vasodilator effect inasmuch as the mecanism sively. nns (Meyer and Huxley, 1992). This review will con-
ntrate on the vasodilator effect inasmuch as the mech-
ism of ANF vasodilation has been investigated exten-
rely.
The receptor accounting for vasodilator effects has not

centrate on the vasodilator effect inasmuch as the mechanism of ANF vasodilation has been investigated extensively.
The receptor accounting for vasodilator effects has not been identified. As the ensuing discussion will i anism of ANF vasodilation has been investigated extensively.

The receptor accounting for vasodilator effects has not

been identified. As the ensuing discussion will indicate,

ANF R_1 receptor antagonists do not preve sively.
The receptor accounting for vasodilator effects has not
been identified. As the ensuing discussion will indicate,
ANF R₁ receptor antagonists do not prevent, or only
slightly inhibit, the vasodilator activity of The receptor accounting for vasodilator effects has not
been identified. As the ensuing discussion will indicate,
ANF R_1 receptor antagonists do not prevent, or only
slightly inhibit, the vasodilator activity of ANF (I been identified. As the ensuing discussion will indicate,
ANF R_1 receptor antagonists do not prevent, or only
slightly inhibit, the vasodilator activity of ANF (Imura
et al., 1992), and ANF vasodilator responses remain ANF R_1 receptor antagonists do not prevent, or only slightly inhibit, the vasodilator activity of ANF (Imura et al., 1992), and ANF vasodilator responses remain intact in the presence of the R_2 receptor agonist, cAN slightly inhibit, the vasodilator activity of ANF (Imuster al., 1992), and ANF vasodilator responses remaintact in the presence of the R_2 receptor agonist, cANE (Elmquist and Trachte, 1992). The signaling pathwebr of p et al., 1992), and ANF vasodilator responses remain
intact in the presence of the R_2 receptor agonist, cANF on the
(Elmquist and Trachte, 1992). The signaling pathway
for ANF remains unknown, although a number of poten intact in the presence of the R_2 receptor agonist, cANF C (P)
(Elmquist and Trachte, 1992). The signaling pathway ride
for ANF remains unknown, although a number of poten-
tial mediators of the relaxant effect are (Elmquist and Trachte, 1992). The signaling pathway $\frac{1}{10}$ for ANF remains unknown, although a number of potential mediators of the relaxant effect are influenced by a ANF. Interestingly, the antimitogenic effect of A for ANF remains unknown, although a number of poten-
tial mediators of the relaxant effect are influenced by
ANF. Interestingly, the antimitogenic effect of ANF
mediated by the ANF R_2 receptor because
cANF prevents the tial mediators of the relaxant effect are influenced by act ANF. Interestingly, the antimitogenic effect of ANF $_{\text{wa}}^{\text{pr}}$ mappears to be mediated by the ANF R_2 receptor because was cANF prevents the antimitogenic

A AND TRACHTE
established intracellular effects of ANF in vascular tissue
are depicted in figure 3. They include activation of GC, A AND TRACHTE
established intracellular effects of ANF in vascular tissue
are depicted in figure 3. They include activation of GC,
phospholipase C, sodium-potassium-chloride exchange, A AND TRACHTE
established intracellular effects of ANF in vascular tissue
are depicted in figure 3. They include activation of GC,
phospholipase C, sodium-potassium-chloride exchange,
and sodium-hydrogen antiport, and an i established intracellular effects of ANF in vascular tissue
are depicted in figure 3. They include activation of GC,
phospholipase C, sodium-potassium-chloride exchange,
and sodium-hydrogen antiport, and an inhibition of a are depicted in figure 3. They include activation of GC,
phospholipase C, sodium-potassium-chloride exchange,
and sodium-hydrogen antiport, and an inhibition of ad-
envivi cyclase.

1. *Role ofguanylyl cyclase activation in atrial natriuretic factor vasodikition.* The vasodilator activity of ANF was and sodium-hydrogen antiport, and an inhibition of ad-
enylyl cyclase.
1. Role of guanylyl cyclase activation in atrial natriuretic
factor vasodilation. The vasodilator activity of ANF was
discovered initially as a renal v enylyl cyclase.

1. Role of guanylyl cyclase activation in atrial natriuretic

factor vasodilation. The vasodilator activity of ANF was

discovered initially as a renal vasodilating principal in

an atrial extract (Currie 1. Role of guanylyl cyclase activation in atrial natriure
factor vasodilation. The vasodilator activity of ANF w
discovered initially as a renal vasodilating principal
an atrial extract (Currie et al., 1983). Winquist et
(factor vasodilation. The vasodilator activity of ANF v
discovered initially as a renal vasodilating principal
an atrial extract (Currie et al., 1983). Winquist et
(1984) demonstrated aortic vasodilation and GC activion
in discovered initially as a renal vasodilating principal in
an atrial extract (Currie et al., 1983). Winquist et al.
(1984) demonstrated aortic vasodilation and GC activa-
tion in response to ANF. Additional studies demon-
s an atrial extract (Currie et al., 1983). Winquist et al. (1984) demonstrated aortic vasodilation and GC activation in response to ANF. Additional studies demonstrated a rough correlation between GC stimulation and vasodila (1984) demonstrated aortic vasodilation and GC activation in response to ANF. Additional studies demonstrated a rough correlation between GC stimulation and vasodilation (Fiscus et al., 1985; Rapoport et al., 1985). All st tion in response to ANF. Additional studies demonstrated a rough correlation between GC stimulation and vasodilation (Fiscus et al., 1985; Rapoport et al., 1985).
All studies of vascular smooth muscle reported an elevation strated a rough correlation between GC stimulation and
vasodilation (Fiscus et al., 1985; Rapoport et al., 1985).
All studies of vascular smooth muscle reported an ele-
vation of cGMP concentrations in response to ANF.
Add vasodilation (Fiscus et al., 1985; Rapoport et al., 1985).
All studies of vascular smooth muscle reported an elevation of cGMP concentrations in response to ANF.
Additionally, nitrovasodilators relaxed vascular smooth
musc All studies of vascular smooth muscle reported an elevation of cGMP concentrations in response to ANF.
Additionally, nitrovasodilators relaxed vascular smooth
muscle by an activation of soluble GC (Murad, 1988).
This corre vation of cGMP concentrations in response to ANF.
Additionally, nitrovasodilators relaxed vascular smooth
muscle by an activation of soluble GC (Murad, 1988).
This correlative evidence among ANF, cGMP, and vas-
odilation w Additionally, nitrovasodilators relaxed vascumuscle by an activation of soluble GC (Mu
This correlative evidence among ANF, cGMI
odilation was interpreted as favoring cGMP
ond messenger of dilator responses to ANF.
The evi uscle by an activation of soluble GC (Murad, 1988).
his correlative evidence among ANF, cGMP, and vas-
ilation was interpreted as favoring cGMP as the sec-
d messenger of dilator responses to ANF.
The evidence against cGMP

Cardiovascular effects of ANF include hypotension, The evidence against cGMP as the second messenger
fluid leakage from the vasculature, vasodilation, and of ANF vasodilator responses initially surfaced as a
inhibition of This correlative evidence among ANF, cGMP, and vas-
odilation was interpreted as favoring cGMP as the sec-
ond messenger of dilator responses to ANF.
The evidence against cGMP as the second messenger
of ANF vasodilator res odilation was interpreted as favoring cGMP as the second messenger of dilator responses to ANF.
The evidence against cGMP as the second messenger
of ANF vasodilator responses initially surfaced as a
dissociation of vasodil ond messenger of dilator responses to ANF.
The evidence against cGMP as the second messenge
of ANF vasodilator responses initially surfaced as
dissociation of vasodilatory and cGMP responses
ANF(103-125) relaxed rabbit aor The evidence against cGMP as the second messenger
of ANF vasodilator responses initially surfaced as a
dissociation of vasodilatory and cGMP responses.
ANF(103-125) relaxed rabbit aortic rings without stim-
ulating GC (Bud of ANF vasodilator responses initially surfaced as a dissociation of vasodilatory and cGMP responses.
ANF(103–125) relaxed rabbit aortic rings without stimulating GC (Budzik et al., 1987), whereas Willenbrock et al. (1989) dissociation of vasodilatory and cGMP responses.
ANF(103–125) relaxed rabbit aortic rings without stim-
ulating GC (Budzik et al., 1987), whereas Willenbrock et
al. (1989) observed an oxidized derivative, oxidized
Met¹¹⁰ ANF(103–125) relaxed rabbit aortic rings without stimulating GC (Budzik et al., 1987), whereas Willenbrock et al. (1989) observed an oxidized derivative, oxidized Met¹¹⁰ ANF, to relax rat aorta with only a minimal activ ulating GC (Budzik et al., 1987), whereas Willenbrock et
al. (1989) observed an oxidized derivative, oxidized
Met¹¹⁰ ANF, to relax rat aorta with only a minimal
activation of GC. Furthermore, ANF(105–121) and other
ANF a al. (1989) observed an oxidized derivative, oxidized

Met¹¹⁰ ANF, to relax rat aorta with only a minimal

activation of GC. Furthermore, ANF(105–121) and other

ANF analogs stimulated GC but were 1000-fold less

potent activation of GC. Furthermore, ANF(105-121) and other
ANF analogs stimulated GC but were 1000-fold less
potent in relaxing aortic rings (Budzik et al., 1987). A
GC inhibitor, LY83583, also prevented the GC response
to ANF ANF analogs stimulated GC but were 1000-fold less Similarly, a linear ANF analog with two cysteine residues

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FIG. 3. Vascular signal transduction pathways for ANF.

on the R₁ receptor to generate cGMP which can inhibit pho

C (PLC) activity. The cGMP also activates a sodium-potasside exchange or an uptake of FIG. 3. Vascular signal transduction pathways for ANF. ANF acts
on the R_1 receptor to generate cGMP which can inhibit phospholipase
C (PLC) activity. The cGMP also activates a sodium-potassium-chlo-
ride exchange or an probably interacts with the CMP which can inhibit phospholipase C (PLC) activity. The cGMP also activates a sodium-potassium-chloride exchange or an uptake of calcium in cellular organelles. ANF probably interacts with the C (PLC) activity. The cGMP also activates a sodium-potassium-chlo-
ride exchange or an uptake of calcium in cellular organelles. ANF
probably interacts with the R_2 receptor to inhibitory G-protein (G). The G-
protein m activity by a mechanism involving an inhibitory G-protein (G). The G-
protein may activate sodium-hydrogen exchange or phospholipase C.
The relaxation caused by ANF may occur independently of the path-
ways described. The

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ANF RECEPTORS AND SIGNAL TRANSDUCTION MECHANISMS 471

ANF RECEPTORS AND SIGNAL TRA
modified by various alkyl groups antagonized cGMP teir
accumulation, but not vasorelaxation, in response to inh ANF RECEPTORS AND SIGNAL TRANE modified by various alkyl groups antagonized cGMP tein
accumulation, but not vasorelaxation, in response to inhit
ANF (Kitajima et al., 1989). Finally, a R_1 receptor an- in r ANF RECEPTORS AND SIGNAL
modified by various alkyl groups antagonized $cGMP$
accumulation, but not vasorelaxation, in response to
ANF (Kitajima et al., 1989). Finally, a R_1 receptor an-
tagonist, A74186, inhibited the a modified by various alkyl groups antagonized cGMP accumulation, but not vasorelaxation, in response to ANF (Kitajima et al., 1989). Finally, a R₁ receptor antagonist, A74186, inhibited the activation of GC, but not the d modified by various alkyl groups antagonized cGMP to accumulation, but not vasorelaxation, in response to infused ANF (Kitajima et al., 1989). Finally, a R_1 receptor antagonist, A74186, inhibited the activation of GC, accumulation, but not vasorelaxation, in response to
ANF (Kitajima et al., 1989). Finally, a R_1 receptor an-
tagonist, A74186, inhibited the activation of GC, but not
the depressor response, to infused ANF (von Geldern ANF (Kitajima et al., 1989). Finally, a R_1 receptor antagonist, A74186, inhibited the activation of GC, but not dit the depressor response, to infused ANF (von Geldern et tri al., 1990). Another recently developed R_1 the depressor response, to infused ANF (von Geldern et trad., 1990). Another recently developed R_1 receptor antagentials, HS142-1, also failed to prevent the majority of the mayotensive response to infused ANF or BNP (al., 1990). Another recently developed R_1 receptor antag-
onist, HS142-1, also failed to prevent the majority of the
hypotensive response to infused ANF or BNP (Sano et
oral., 1992). These experiments were repeated in onist, HS142-1, also failed to prevent the majority of the hypotensive response to infused ANF or BNP (Sano et al., 1992). These experiments were repeated in isolated rabbit aortic rings with the same result, i.e., ANF re al., 1992). These experiments were repeated in isolated
rabbit aortic rings with the same result, i.e., ANF relaxed
the rings in the presence of R_1 receptor antagonists
(Elmquist and Trachte, 1992).
Most recently, HS-1 , 1992). These experiments were repeated in isolated
bbit aortic rings with the same result, i.e., ANF relaxed
e rings in the presence of R_1 receptor antagonists
lmquist and Trachte, 1992).
Most recently, HS-142-1 was

the rings in the presence of R_1 receptor antagonists
(Elmquist and Trachte, 1992).
Most recently, HS-142-1 was observed to slightly an-
tagonize ANF vasodilatory responses in rabbit aorta at
concentrations that essenti the rings in the presence of R_1 receptor antagonists reconcentrations (Elmquist and Trachte, 1992).
Most recently, HS-142-1 was observed to slightly antagonize ANF vasodilatory responses in rabbit aorta at reconcentrat (Elmquist and Trachte, 1992).

Most recently, HS-142-1 was observed to slightly an-

tagonize ANF vasodilatory responses in rabbit aorta at

reconcentrations that essentially abolished GC activation

encentrations that es Most recently, $HS-142-1$ was observed to slightly an-
tagonize ANF vasodilatory responses in rabbit aorta at rece
concentrations that essentially abolished GC activation entr
(Imura et al., 1992). HS-142-1 antagonized BNP tagonize ANF vasodilatory responses in rabbit aorta at reconcentrations that essentially abolished GC activation (Imura et al., 1992). HS-142-1 antagonized BNP dilatory tresponses far more potently than it affected respon concentrations that essentially abolished GC activation
(Imura et al., 1992). HS-142-1 antagonized BNP dilato
responses far more potently than it affected responses
ANF, although its effect on GC activation was essential
i (Imura et al., 1992). HS-142-1 antagonized BNP dilatory tifferenouses far more potently than it affected responses to an ANF, although its effect on GC activation was essentially and identical in the presence of either pe responses far more potently than it affected responses to ANF, although its effect on GC activation was essentially identical in the presence of either peptide. These experiments seriously question the hypothesis that ANF ANF, although its effect on GC activation was essentially
identical in the presence of either peptide. These exper-
iments seriously question the hypothesis that ANF acts
mas a vasodilator via an increase in GC activity. identical in the presence of either peptide. These exper-
intents seriously question the hypothesis that ANF acts
mudas a vasodilator via an increase in GC activity. Further
work with selective agonists or antagonists shou ANF. *2. Inhibitor via an increase in GC activity. Further*
2. Inhibitory effects of atrial natriuretic factor on vas-
2. Inhibitory effects of atrial natriuretic factor on vas-
lar adenylyl cyclase. ANF inhibited vascula

work with selective agonists or antagonists should clarify (C
the role of cGMP in mediating vascular responses to po
ANF.
2. Inhibitory effects of atrial natriuretic factor on vas-
are
cular adenylyl cyclase. ANF inhibited al.

2. Inhibitory effects of atrial natriuretic factor on vas-

cular adenylyl cyclase. ANF inhibited vascular smooth

muscle adenylyl cyclase activity (Anand-Srivastava et T

al., 1984; Resink et al., 1987), but the sign 2. Inhibitory effects of atrial natriuretic factor on vas-
cular adenylyl cyclase. ANF inhibited vascular smooth 1
muscle adenylyl cyclase activity (Anand-Srivastava et 7
al., 1984; Resink et al., 1987), but the significa cular adenylyl cyclase. ANF inhibited vascular smooth 1
muscle adenylyl cyclase activity (Anand-Srivastava et 7
al., 1984; Resink et al., 1987), but the significance of this is
action is unknown. Because, neither PT nor muscle adenylyl cyclase activity (Anand-Srivastava e al., 1984; Resink et al., 1987), but the significance of this action is unknown. Because, neither PT nor R_2 -bindin peptides affect dilatory responses to ANF (Ljusegr al., 1984; Resink et al., 1987), but the significance of this action is unknown. Because, neither PT nor R_2 -binding peptides affect dilatory responses to ANF (Ljusegren et al., 1990; Elmquist and Trachte, 1992), the AN action is unknown. Because, neither PT nor R_2 -binding ev
peptides affect dilatory responses to ANF (Ljusegren et ex
al., 1990; Elmquist and Trachte, 1992), the ANF vaso-
pedilator effect appears to be independent of bo peptides affect dilatory responses to ANF (Ljusegren et example). The ANF vaso-
al., 1990; Elmquist and Trachte, 1992), the ANF vaso-
dilator effect appears to be independent of both adenylyl p
cyclase inhibition and R₂ al., 1990; Elmquist and Trachte, 1992), the ANF vaso-
dilator effect appears to be independent of both adenylyl
cyclase inhibition and R_2 receptor interactions. The m
vasoconstriction elicited by ANF(103-125) in corona dilator effect appears to be independent of both adenyl cyclase inhibition and R_2 receptor interactions. The vasoconstriction elicited by $ANF(103-125)$ in corona arteries (Wangler et al., 1985) may be mediated through cyclase inhibition
vasoconstriction
arteries (Wangler
an inhibition of the
duction pathway.
3. Atrial natrius *3. Atrial natricus* effects on phospholipartic factor effects (Wangler et al., 1985) may be mediated through inverting inclusion of the adenylyl cyclase/cAMP signal trans-
 3. Atrial natriuretic factor effects on phospho

arteries (Wangler et al., 1985) may be mediated through in
an inhibition of the adenylyl cyclase/cAMP signal trans-
duction pathway.
3. Atrial natriuretic factor effects on phospholipase C in
the vasculature. The vasodilat duction pathway.
3. Atrial natriuretic factor effects on phospholipase C in
the vasculature. The vasodilator action of ANF was
suggestive of an inhibitory effect of ANF on phospholi-
pase C. Surprisingly, the initial repor duction pathway.

3. Atrial natriuretic factor effects on phospholipase C in

the vasculature. The vasodilator action of ANF was

suggestive of an inhibitory effect of ANF on phospholi-

pase C. Surprisingly, the initial r 3. Atrial natriuretic factor effects on phospholipase C in
the vasculature. The vasodilator action of ANF was
suggestive of an inhibitory effect of ANF on phospholi-
pase C. Surprisingly, the initial reports of ANF effect the vasculature. The vasodilator action of ANF was
suggestive of an inhibitory effect of ANF on phospholi-
pase C. Surprisingly, the initial reports of ANF effects
on phospholipase C indicated a stimulation. Resink et
al. suggestive of an inhibitory effect of ANF on phospholi-
pase C. Surprisingly, the initial reports of ANF effects to
on phospholipase C indicated a stimulation. Resink et
al. (1987) reported an enhanced rate of IP₃ accum pase C. Surprisingly, the initial reports of ANF effects tai
on phospholipase C indicated a stimulation. Resink et
al. (1987) reported an enhanced rate of IP_3 accumulation cul
in rabbit cultured aortic cells exposed to on phospholipase C indicated a stimulation. Resink et al. (1987) reported an enhanced rate of IP_3 accumulation in rabbit cultured aortic cells exposed to ANF. This observation was confirmed by Hirata et al. (1989a). Bot al. (1987) reported an enhanced rate of IP_3 accumulati
in rabbit cultured aortic cells exposed to ANF. Tl
observation was confirmed by Hirata et al. (1989a). Bo
of these studies measured modulatory effects on ba
unstimu in rabbit cultured aortic cells exposed to ANF. The observation was confirmed by Hirata et al. (1989a). Boof these studies measured modulatory effects on baunstimulated phospholipase C activity. Later experents examining p observation was confirmed by Hirata et al. (1989a). Both
of these studies measured modulatory effects on basal
unstimulated phospholipase C activity. Later experi-
ments examining phospholipase C activity after stimu-
lati of these studies measured modulatory effects on baunstimulated phospholipase C activity. Later experents examining phospholipase C activity after stimulation by contractile agonists uncovered an inhibited ANF effect on IP unstimulated phospholipase C activity. Later experi-
ments examining phospholipase C activity after stimu-
lation by contractile agonists uncovered an inhibitory (F
ANF effect on IP₃ generation (Rapoport, 1986; Meyer-
Le ments examining phospholipase C activity after stimulation by contractile agonists uncovered an inhibitory (ANF effect on IP₃ generation (Rapoport, 1986; Meyer-
Lehnert et al., 1988; Winquist and Hintze, 1990). The comb lation by contractile agonists uncovered an inhibitor
ANF effect on IP₃ generation (Rapoport, 1986; Meyer
Lehnert et al., 1988; Winquist and Hintze, 1990). Th
inhibition of phospholipase C activity was associate
with the ANF effect on IP₃ generation (Rapoport, 1986; Meyer-
Lehnert et al., 1988; Winquist and Hintze, 1990). The cGMP
inhibition of phospholipase C activity was associated ANF a
with the generation of cGMP, and cGMP analogs m Lehnert et al., 1988; Winquist and Hintze, 1990). The coinhibition of phospholipase C activity was associated A with the generation of cGMP, and cGMP analogs mim-
icked the ANF effect (Rapoport, 1986). Phospholipase C flu inhibition of phospholipase C activity was associated
with the generation of cGMP, and cGMP analogs mim-
icked the ANF effect (Rapoport, 1986). Phospholipase C
activation results in the generation of IP_3 and a protein
k

tagonist, A74186, inhibited the activation of GC, but not dibutyrate, were inhibited by ANF (Sauro and Fitzpatie depressor response, to infused ANF (von Geldern et trick, 1990). In contrast, Grammas et al. (1991) found no TRANSDUCTION MECHANISMS
tein kinase C activity caused by angiotensin II also was
inhibited by ANF (Tamm et al., 1990), and contractions TRANSDUCTION MECHANISMS
tein kinase C activity caused by angiotensin II also was
inhibited by ANF (Tamm et al., 1990), and contractions
in response to the protein kinase C stimulant, phorbol FRANSDUCTION MECHANISMS 471
tein kinase C activity caused by angiotensin II also was
inhibited by ANF (Tamm et al., 1990), and contractions
in response to the protein kinase C stimulant, phorbol
dibutyrate, were inhibited tein kinase C activity caused by angiotensin II also w
inhibited by ANF (Tamm et al., 1990), and contractic
in response to the protein kinase C stimulant, phore
dibutyrate, were inhibited by ANF (Sauro and Fitz
trick, 1990 tein kinase C activity caused by angiotensin II also was
inhibited by ANF (Tamm et al., 1990), and contractions
in response to the protein kinase C stimulant, phorbol
dibutyrate, were inhibited by ANF (Sauro and Fitzpa-
tr inhibited by ANF (Tamm et al., 1990), and contractions
in response to the protein kinase C stimulant, phorbol
dibutyrate, were inhibited by ANF (Sauro and Fitzpa-
trick, 1990). In contrast, Grammas et al. (1991) found no
e in response to the protein kinase C stimulant, phorbol
dibutyrate, were inhibited by ANF (Sauro and Fitzpa-
trick, 1990). In contrast, Grammas et al. (1991) found no
effect of ANF on phospholipase C activity in rat cerebra dibutyrate, were inhibited by ANF (Sauro and Fitzpatrick, 1990). In contrast, Grammas et al. (1991) found no effect of ANF on phospholipase C activity in rat cerebral microvessels. Thus, the significance of ANF influences trick, 1990). In contrast, Grammas et al. (1991) found no
effect of ANF on phospholipase C activity in rat cerebral
microvessels. Thus, the significance of ANF influences
on vascular phospholipase C activity remains unknow effect of ANF on phospholipase C activity in rat cerebral
microvessels. Thus, the significance of ANF influences
on vascular phospholipase C activity remains unknown,
and no clear evidence supports this pathway as a major
 muscle. At vascular phospholipase C activity remains unknown,

A no clear evidence supports this pathway as a major

grad transduction pathway for ANF in vascular smooth

4. Atrial natriuretic factor effects on ionic currents in

2. Inhibitory effects of atrial natriuretic factor on vas-

cular adenylyl cyclase. ANF inhibited vascular smooth 1989), presumably by a cGMP-dependent mechanism.

muscle adenylyl cyclase activity (Anand-Srivastava et The and no clear evidence supports this pathway as a major
 vascular smooth
 muscle.
 4. Atrial natriuretic factor effects on ionic currents in
 vascular smooth muscle. Winquist and Hintze (1990)

recently reviewed the signal transduction pathway for ANF in vascular smooth
muscle.
4. Atrial natriuretic factor effects on ionic currents in
vascular smooth muscle. Winquist and Hintze (1990)
recently reviewed the ability of ANF to stimulate 4. Atrial natriuretic factor effects on ionic currents in
vascular smooth muscle. Winquist and Hintze (1990) 4. Atrial natriuretic factor effects on ionic currents in vascular smooth muscle. Winquist and Hintze (1990) recently reviewed the ability of ANF to stimulate sodium entry into the cells and to decrease calcium concentrati vascular smooth muscle. Winquist and Hintze (1990)
recently reviewed the ability of ANF to stimulate sodium
entry into the cells and to decrease calcium concentra-
tions in vascular tissues. The critical ionic effects of A entry into the cells and to decrease calcium concentra-
tions in vascular tissues. The critical ionic effects of ANF
apparently involve a stimulation of the sodium-hydrogen
antiport mechanism exchanging extracellular sodiu tions in vascular tissues. The critical ionic effects of ANF
apparently involve a stimulation of the sodium-hydrogen
antiport mechanism exchanging extracellular sodium for
intracellular hydrogen inasmuch as rabbit aortas a tions in vascular tissues. The critical ionic effects of ANF
apparently involve a stimulation of the sodium-hydrogen
antiport mechanism exchanging extracellular sodium for
intracellular hydrogen inasmuch as rabbit aortas a apparently involve a stimulation of the sodium-hydrogen
antiport mechanism exchanging extracellular sodium for
intracellular hydrogen inasmuch as rabbit aortas accu-
mulated sodium in the presence of ANF by a mechanism
pre antiport mechanism exchanging extracellular sodium
intracellular hydrogen inasmuch as rabbit aortas ac
mulated sodium in the presence of ANF by a mechani
prevented by sodium-hydrogen antiport inhibit
(Gupta et al., 1989). intracellular hydrogen inasmuch as rabbit aortas accumulated sodium in the presence of ANF by a mechanism
prevented by sodium-hydrogen antiport inhibitors
(Gupta et al., 1989). Sodium-potassium-chloride cotrans-
port also mulated sodium in the presence of ANF by a mechanism
prevented by sodium-hydrogen antiport inhibitors
(Gupta et al., 1989). Sodium-potassium-chloride cotrans-
port also was stimulated by ANF in explants from rat
aorta (O'D prevented by sodium-hydrogen antiport inhibitors (Gupta et al., 1989). Sodium-potassium-chloride cotransport also was stimulated by ANF in explants from rat aorta (O'Donnell and Owen, 1986a,b; Owen et al., 1987) and in bov (Gupta et al., 1989). Sodium-potassium-chloride cotrans
port also was stimulated by ANF in explants from ra
aorta (O'Donnell and Owen, 1986a,b; Owen et al., 1987
and in bovine carotid endothelial cells (Fujita et al.
1989) aorta (O'Donnell and Owen, 1986a,b; Owen et al., 1987) aorta (O'Donnell and Owen, 1986a,b; Owen et al., 1987)
and in bovine carotid endothelial cells (Fujita et al.,
1989), presumably by a cGMP-dependent mechanism.
The activation was measured as intracellular⁸⁶Rb uptake
inhi and in bovine carotid endothelial cells (Fujita et al., 1989), presumably by a cGMP-dependent mechanism.
The activation was measured as intracellular ⁸⁶Rb uptake inhibited by bumetanide. No reports concerning the relevan The activation was measured as intracellular 86 Rb uptake
inhibited by bumetanide. No reports concerning the rel-
evance of this cotransport stimulation to vasodilation
exist as yet, and unfortunately, no studies have inhibited by bumetanide. No reports concerning the relevance of this cotransport stimulation to vasodilation exist as yet, and unfortunately, no studies have been performed to test whether bumetanide or other cotransport inhibitors alter vasodilatory effects of ANF. Inasmuch evance of this cotransport stimulation to vasodilation exist as yet, and unfortunately, no studies have been performed to test whether bumetanide or other cotransport inhibitors alter vasodilatory effects of ANF. Inasmuch exist as yet, and unfortunately, no studies have been
performed to test whether bumetanide or other cotrans-
port inhibitors alter vasodilatory effects of ANF. Inas-
much as the ANF vasodilator response was attenuated
in l performed to test whether bumetanide or other cotransport inhibitors alter vasodilatory effects of ANF. Inasmuch as the ANF vasodilator response was attenuated in low sodium buffer solutions, sodium appears to be involved port inhibitors alter vasodilatory effects of ANF. Inasmuch as the ANF vasodilator response was attenuated
in low sodium buffer solutions, sodium appears to be
involved in ANF vascular effects (Rapoport et al., 1985).
The much as the ANF vasodilator response was attenuated
in low sodium buffer solutions, sodium appears to be
involved in ANF vascular effects (Rapoport et al., 1985).
The signal transduction mechanisms leading to altered
sodiu in low sodium buffer solutions, sodium appears to be
involved in ANF vascular effects (Rapoport et al., 1985).
The signal transduction mechanisms leading to altered
sodium homeostasis have not been elucidated. For ex-
ampl involved in ANF vascular effects (Rapoport et al., 1985).
The signal transduction mechanisms leading to altered
sodium homeostasis have not been elucidated. For ex-
ample, the potential involvement of G-proteins in these
r The signal transduction mechanisms leading to altern
sodium homeostasis have not been elucidated. For e
ample, the potential involvement of G-proteins in the
responses has not been assessed with PT. The AN
receptor mediati tained. hyle, the potential involvement of G-proteins in these
sponses has not been assessed with PT. The ANF
ceptor mediating these effects also has not been ascer-
ined.
ANF suppressed calcium concentrations within vas-
lar smoo

responses has not been assessed with PT. The
receptor mediating these effects also has not been a
tained.
ANF suppressed calcium concentrations within
cular smooth muscle cells stimulated with a vasocon
tor by an undefined ANF suppressed calcium concentrations within vascular smooth muscle cells stimulated with a vasoconstrictor by an undefined mechanism (Hassid, 1986; Takuwa and Rasmussen, 1987; Cornwell and Lincoln, 1988; Taktained.
ANF suppressed calcium concentrations within vas
cular smooth muscle cells stimulated with a vasoconstric
tor by an undefined mechanism (Hassid, 1986; Takuw.
and Rasmussen, 1987; Cornwell and Lincoln, 1988; Tak
euc ANF suppressed calcium concentrations within vas-
cular smooth muscle cells stimulated with a vasoconstric-
tor by an undefined mechanism (Hassid, 1986; Takuwa
and Rasmussen, 1987; Cornwell and Lincoln, 1988; Tak-
euchi et cular smooth muscle cells stimulated with a vasoconstrictor by an undefined mechanism (Hassid, 1986; Takuwa
and Rasmussen, 1987; Cornwell and Lincoln, 1988; Tak-
euchi et al., 1989; Chiu et al., 1986; Taylor and Meisheri,
 tor by an undefined mechanism (Hassid, 1986; Takuwa
and Rasmussen, 1987; Cornwell and Lincoln, 1988; Tak-
euchi et al., 1989; Chiu et al., 1986; Taylor and Meisheri,
1986; Meyer-Lehnert et al., 1988). ANF also enhanced
cal and Rasmussen, 1987; Cornwell and Lincoln, 1988; Takeuchi et al., 1989; Chiu et al., 1986; Taylor and Meisheri, 1986; Meyer-Lehnert et al., 1988). ANF also enhanced calcium pump activity in rat aortic smooth muscle cells (euchi et al., 1989; Chiu et al., 1986; Taylor and Meisheri, 1986; Meyer-Lehnert et al., 1988). ANF also enhanced calcium pump activity in rat aortic smooth muscle cells (Furukawa et al., 1988). The increased calcium extrus 1986; Meyer-Lehnert et al., 1988). ANF also enhanced calcium pump activity in rat aortic smooth muscle cells (Furukawa et al., 1988). The increased calcium extrusion from aortic smooth muscle was mimicked by dibutyryl cGMP calcium pump activity in rat aortic smooth muscle cells
(Furukawa et al., 1988). The increased calcium extrusion
from aortic smooth muscle was mimicked by dibutyryl
cGMP and nitroprusside; therefore, it is conceivable that (Furukawa et al., 1988). The increased calcium extrusion
from aortic smooth muscle was mimicked by dibutyryl
cGMP and nitroprusside; therefore, it is conceivable that
ANF augments calcium pump activity via cGMP gener-
atio from aortic smooth muscle was mimicked by dibuty
cGMP and nitroprusside; therefore, it is conceivable t
ANF augments calcium pump activity via cGMP gen
ation. ANF also activates sodium-dependent calcium
flux from rat aorta cGMP and nitroprusside; therefore, it is conceivable that
ANF augments calcium pump activity via cGMP gener-
ation. ANF also activates sodium-dependent calcium ef-
flux from rat aorta (Furukawa et al., 1991). The augmen-
t ANF augments calcium pump activity via cGMP generation. ANF also activates sodium-dependent calcium efflux from rat aorta (Furukawa et al., 1991). The augmentation of this sodium-calcium exchange also would deplete vascul

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ANAND-SRIVASTAVA
1992 – The Manus ANAND-SRIVASTAVA
1994 – ANF effect on sodium-calcium exchange, again indicat-ANAND-SRIVA

ANAND-SRIVA

ANF effect on sodium-calcium exchange, again indic

ing the potential for cGMP as the mediator of A ANAND-SRIVASTAVA AI

reduce contractions. Dibutyryl cGMP mimicked the the

ANF effect on sodium-calcium exchange, again indicat-

ing the potential for cGMP as the mediator of ANF V

effects on calcium extrusion from vascu reduce contractions. Dibutyryl cGMP mimicked the
ANF effect on sodium-calcium exchange, again indicat
ing the potential for cGMP as the mediator of ANI
effects on calcium extrusion from vascular smooth mus
cle. These findi ANF effect on sodium-calcium exchange, again indicating the potential for cGMP as the mediator of ANF effects on calcium extrusion from vascular smooth muscle. These findings suggested that ANF influences calcium homeostas ANF effect on sodium-calcium exchange, again indicating the potential for cGMP as the mediator of ANF effects on calcium extrusion from vascular smooth muscle. These findings suggested that ANF influences calcium homeostas ing the potential for cGMP as the mediator of ANF veffects on calcium extrusion from vascular smooth mus-
cle. These findings suggested that ANF influences cal-
cium homeostasis to alter vascular tone, a hypothesis 198'
co effects on calcium extrusion from vascular smooth mus-
cle. These findings suggested that ANF influences cal-
cium homeostasis to alter vascular tone, a hypothesis 19
consistent with the accepted preeminence of calcium in cle. These findings suggested that ANF influences cal-
cium homeostasis to alter vascular tone, a hypothesis 19
consistent with the accepted preeminence of calcium in eff
mediating smooth muscle contractions. However, the compresses to alter vascular tone, a hypothesis 1:

consistent with the accepted preeminence of calcium in

mediating smooth muscle contractions. However, the

ANF vasodilatory effect was unaltered in medium devoid

of ca consistent with the accepted preeminence of calcium in endiating smooth muscle contractions. However, the all ANF vasodilatory effect was unaltered in medium devoid 13 of calcium, indicating that an inhibition of inwar mediating smooth muscle contractions. However, the al.
ANF vasodilatory effect was unaltered in medium devoid
of calcium, indicating that an inhibition of inwardly
directed calcium currents could not account for the entire ANF vasodilatory effect was unaltered in medium devoid
of calcium, indicating that an inhibition of inwardly
directed calcium currents could not account for the entire
wasodilation produced by ANF (Garcia et al., 1984). I of calcium, indicating that an inhibition of inwardly directed calcium currents could not account for the entire vasodilation produced by ANF (Garcia et al., 1984). It is probable that alterations in calcium homeostasis ar directed calcium currents could not account for the entire
vasodilation produced by ANF (Garcia et al., 1984). It is
probable that alterations in calcium homeostasis are
involved in ANF vasodilator effects, but the signal determined. obable that alterations in calcium homeostasis are volved in ANF vasodilator effects, but the signal trans-
ction pathways leading to these effects have not been
termined.
Potassium currents also are affected by ANF in nu-

merous systems. Rapoport et al. (1985) found ANF to the equire potassium for vasodilator activity, and numerous systems. Rapoport et al. (1985) found ANF to $\frac{1}{2}$ a variative require potassium for vasodilator activity duction pathways leading to these effects have not been
determined.
Potassium currents also are affected by ANF in numerous systems. Rapoport et al. (1985) found ANF to
require potassium for vasodilator activity, and numer determined.

Potassium currents also are affected by ANF in numerous systems. Rapoport et al. (1985) found ANF to a

require potassium for vasodilator activity, and numerous

studies have reported an inability of ANF to re Potassium currents also are affected by ANF in numerous systems. Rapoport et al. (1985) found ANF to appropriate require potassium for vasodilator activity, and numerous studies have reported an inability of ANF to revers merous systems. Rapoport et al. (1985) found ANF to require potassium for vasodilator activity, and numerous studies have reported an inability of ANF to reverse contractions produced by high potassium buffers (Garcia et a require potassium for vasodilator activity, and numerous
studies have reported an inability of ANF to reverse
contractions produced by high potassium buffers (Garcia
et al., 1984; Chiu et al., 1986). The data of O'Donnell
 studies have reported an inability of ANF to
contractions produced by high potassium buffer
et al., 1984; Chiu et al., 1986). The data of O
and Owen (1986a) also indicated that ANF in
potassium influx by stimulating sodium contractions produced by high potassium buffers (Garcia
et al., 1984; Chiu et al., 1986). The data of O'Donnell
and Owen (1986a) also indicated that ANF increases
potassium influx by stimulating sodium-potassium-chlo-
ride et al., 1984; Chiu et al., 1986). The data of O'Donne
and Owen (1986a) also indicated that ANF increase
potassium influx by stimulating sodium-potassium-chle
ride cotransport, and a GC inhibitor, LY83583, prevente
this eff and Owen (1986a) also indicated that ANF increases
potassium influx by stimulating sodium-potassium-chlo-
ride cotransport, and a GC inhibitor, LY83583, prevented
this effect (O'Donnell and Owen, 1986b). Furthermore,
memb potassium influx by stimulating sodium-potassium-chlo-
ride cotransport, and a GC inhibitor, LY83583, prevented
this effect (O'Donnell and Owen, 1986b). Furthermore,
membrane-permeable analogs of cGMP also stimulated
the s ride cotransport, and a GC inhibitor, LY83583, prevented
this effect (O'Donnell and Owen, 1986b). Furthermore,
membrane-permeable analogs of cGMP also stimulated
the sodium-potassium-chloride cotransport (O'Donnell
and Ow this effect (O'Donnell and Owen, 1986b). Furthermore,
membrane-permeable analogs of cGMP also stimulated
the sodium-potassium-chloride cotransport (O'Donnell
and Owen, 1986a; Fujita et al., 1989). These data are
consisten and Owen, 1986a; Fujita et al., 1989). These data are
and Owen, 1986a; Fujita et al., 1989). These data are
and Owen, 1986a; Fujita et al., 1989). These data are
consistent with the hypothesis that ANF interacts with
an the sodium-potassium-chloride cotransport (O'Doniand Owen, 1986a; Fujita et al., 1989). These data
consistent with the hypothesis that ANF interacts wan R₁ receptor to stimulate cGMP production result
in the activation o and Owen, 1986a; Fujita et al., 1989). These data are consistent with the hypothesis that ANF interacts with an R_1 receptor to stimulate CGMP production resulting in the activation of this transport mechanism. Calciuman R_1 receptor to stimulate cGMP production resulting
in the activation of this transport mechanism. Calcium-
activated potassium channels in rat aorta also were ac-
tivated by ANF and dibutyryl cGMP (Williams et al., an R_1 receptor to stimulate cGMP production resultin
in the activation of this transport mechanism. Calcium
activated potassium channels in rat aorta also were ac
tivated by ANF and dibutyryl cGMP (Williams et al
1988) in the activation of this transport mechanism. Calcium-
activated potassium channels in rat aorta also were ac-
tivated by ANF and dibutyryl cGMP (Williams et al.,
1988). This finding provides direct evidence for a stim-
u activated potassium channels in rat aorta also were activated by ANF and dibutyryl cGMP (Williams et al., 1988). This finding provides direct evidence for a stimulatory effect of ANF on potassium channels and suggests tha tivated by ANF and dibutyryl cGMP (Williams et al., $B. A$
1988). This finding provides direct evidence for a stim-
ulatory effect of ANF on potassium channels and sug-
gests that cGMP mediates the effect. However, the po-1988). This finding provides direct evidence for a stimulatory effect of ANF on potassium channels and suggests that cGMP mediates the effect. However, the potassium channel antagonist, tetraethylammonium (2 was mM), had gests that cGMP mediates the effect. However, the potassium channel antagonist, tetraethylammonium (2) gests that CGMP mediates the effect. However, the potassium channel antagonist, tetraethylammonium (2 mM), had no effect on vasodilator actions of ANF in isolated rabbit aorta (Elmquist and Trachte, 1992), suggesting that tassium channel antagonist, tetraethylammonium (2 mM), had no effect on vasodilator actions of ANF in isolated rabbit aorta (Elmquist and Trachte, 1992), suggesting that potassium channel activation is not a requirement fo isolated rabbit aorta (Elmquist and Trachte, 1992), suggesting that potassium channel activation is not a requirement for vasodilator activity of ANF. Therefore, although ANF influences potassium currents, the significance gesting that potassium channel activation is not a re-
quirement for vasodilator activity of ANF. Therefore,
although ANF influences potassium currents, the signif-
icance of ANF effects on potassium homeostasis in me-
dia quirement for vasodilator activity of ANF. Therefore, although ANF influences potassium currents, the significance of ANF effects on potassium homeostasis in mediating vasodilator responses is unestablished.
5. Atrial natriuretic factor effects on eicosanoid and endothelium-d

icance of ANF effects on potassium homeostasis in me-
diating vasodilator responses is unestablished. 198
5. Atrial natriuretic factor effects on eicosanoid and ma
endothelium-derived relaxing factor production in the vasdiating vasodilator responses is unestablished.
5. Atrial natriuretic factor effects on eicosanoid and
endothelium-derived relaxing factor production in the vas-
culature. ANF stimulated the release of arachidonic acid
fro 5. Atrial natriuretic factor effects on eicosanoid and malendothelium-derived relaxing factor production in the vas-
culature. ANF stimulated the release of arachidonic acid subjection quiescent rat aortic smooth muscle (R endothelium-derived relaxing factor production in the vas-
culature. ANF stimulated the release of arachidonic acid
from quiescent rat aortic smooth muscle (Resink et al.,
1988) but inhibited eicosanoid production in respo culature. ANF stimulated the release of arachidonic acid subject of a number of recent reviews. In general, kidneys
from quiescent rat aortic smooth muscle (Resink et al., respond to physiological concentrations of ANF, su from quiescent rat aortic smooth muscle (Resink et al., 1988) but inhibited eicosanoid production in response to phorbol esters (Tamm et al., 1990). The stimulatory effect of angiotensin II on eicosanoid production was sus 1988) but inhibited eicosanoid production in response to gephorbol esters (Tamm et al., 1990). The stimulatory in effect of angiotensin II on eicosanoid production was figured in the presence of ANF (Tamm et al., 1990). i phorbol esters (Tamm et al., 1990). The stimulatory effect of angiotensin II on eicosanoid production was sustained in the presence of ANF (Tamm et al., 1990). Cyclooxygenase inhibitors were ineffective in altering the vas

A AND TRACHTE
therefore, the possibility for eicosanoids to mediate ANF
vasodilator effects is remote. A AND TRACHTE
therefore, the possibility for exasodilator effects is remote.
Vasodilator responses to A

vasodilator effects is remote.
Vasodilator responses to ANF were independent of endothelium in rabbit aortic smooth muscle (Winquist et al., 1984) and cat coronary artery (Yanagisawa et al., therefore, the possibility for eicosanoids to mediate ANF vasodilator effects is remote.
Vasodilator responses to ANF were independent of endothelium in rabbit aortic smooth muscle (Winquist et al., 1984) and cat coronary therefore, the possibility for eicosanoids to mediate ANF
vasodilator effects is remote.
Vasodilator responses to ANF were independent of
endothelium in rabbit aortic smooth muscle (Winquist
et al., 1984) and cat coronary vasodilator effects is remote.

Vasodilator responses to ANF were independent of

endothelium in rabbit aortic smooth muscle (Winquist

et al., 1984) and cat coronary artery (Yanagisawa et al.,

1987). Methylene blue faile Vasodilator responses to ANF were independent of endothelium in rabbit aortic smooth muscle (Winquist et al., 1984) and cat coronary artery (Yanagisawa et al., 1987). Methylene blue failed to influence the relaxant effect endothelium in rabbit aortic smooth muscle (Winquist et al., 1984) and cat coronary artery (Yanagisawa et al., 1987). Methylene blue failed to influence the relaxant effect of ANF in rabbit aorta or renal arteries (Garcia et al., 1984) and cat coronary artery (Yanagisawa et al., 1987). Methylene blue failed to influence the relaxant effect of ANF in rabbit aorta or renal arteries (Garcia et al., 1984) or cat coronary arteries (Yanagisawa et 1987). Methylene blue failed to influence the relaxant effect of ANF in rabbit aorta or renal arteries (Garcia et al., 1984) or cat coronary arteries (Yanagisawa et al., 1987) but routinely inhibited dilator responses to E effect of ANF in rabbit aorta or renal arteries (Garcia et al., 1984) or cat coronary arteries (Yanagisawa et al., 1987) but routinely inhibited dilator responses to EDRF. These results indicated a direct relaxant effect o ANF. 87) but routinely inhibited dilator responses to EDRF.
hese results indicated a direct relaxant effect of ANF
d no role for endothelium in the vascular response to
NF.
6. Conclusion concerning vascular atrial natriuretic f

These results indicated a direct relaxant effect of ANF
and no role for endothelium in the vascular response to
ANF.
6. Conclusion concerning vascular atrial natriuretic fac-
tor transduction mechanisms. The most significa and no role for endothelium in the vascular response to
ANF.
6. Conclusion concerning vascular atrial natriuretic fac-
tor transduction mechanisms. The most significant novel
results regarding vasodilatory actions of ANF ANF.
6. Conclusion concerning vascular atrial natriuretic fac-
tor transduction mechanisms. The most significant novel
results regarding vasodilatory actions of ANF indicate
that R_1 receptors and cGMP are unrelated to, 6. Conclusion concerning vascular atrial natriuretic fac-
tor transduction mechanisms. The most significant novel
results regarding vasodilatory actions of ANF indicate
that R_1 receptors and cGMP are unrelated to, or o for transduction mechanisms. The most significant novel
results regarding vasodilatory actions of ANF indicate
that R_1 receptors and cGMP are unrelated to, or only
slightly involved in, relaxant effects. These data sug results regarding vasodilatory actions of ANF indicate
that R_1 receptors and cGMP are unrelated to, or only
slightly involved in, relaxant effects. These data suggest
a vasodilatory pathway of ANF independent of cGMP.
 that R₁ receptors and cGMP are unrelated to, or only slightly involved in, relaxant effects. These data suggest a vasodilatory pathway of ANF independent of cGMP. The receptor or signal transduction pathway mediating vas slightly involved in, relaxant effects. These data suggest
a vasodilatory pathway of ANF independent of cGMP.
The receptor or signal transduction pathway mediating
vascular effects of ANF have not been identified but
some a vasodilatory pathway of ANF independent of cGMP
The receptor or signal transduction pathway mediating
vascular effects of ANF have not been identified but
some potential pathways are depicted in figure 3. ANF
can enhance The receptor or signal transduction pathway medivascular effects of ANF have not been identifies some potential pathways are depicted in figure 3.
can enhance or suppress phospholipase C activity, vate sodium-hydrogen exch vascular effects of ANF have not been identified but
some potential pathways are depicted in figure 3. ANF
can enhance or suppress phospholipase C activity, acti-
vate sodium-hydrogen exchange, facilitate sodium-potas-
siu some potential pathways are depicted in figure 3. ANF
can enhance or suppress phospholipase C activity, acti-
vate sodium-hydrogen exchange, facilitate sodium-potas-
sium-chloride cotransport and calcium efflux by both
sod can enhance or suppress phospholipase C activity, activate sodium-hydrogen exchange, facilitate sodium-potas-
sium-chloride cotransport and calcium efflux by both
sodium-calcium exchange and calcium extrusion via a
calcium vate sodium-hydrogen exchange, facilitate sodium-potas-
sium-chloride cotransport and calcium efflux by both
sodium-calcium exchange and calcium extrusion via a
calcium pump, inhibit adenylyl cyclase activity, and pro-
mot sium-chloride cotransport and calcium efflux by both
sodium-calcium exchange and calcium extrusion via a
calcium pump, inhibit adenylyl cyclase activity, and pro-
mote the sequestration of intracellular calcium. The an-
ti sodium-calcium exchange and calcium extrusion via a
calcium pump, inhibit adenylyl cyclase activity, and pro-
mote the sequestration of intracellular calcium. The an-
timitogenic activity of ANF is mediated by the ANF R₂ calcium pump, inhibit adenylyl cyclase activity, and promote the sequestration of intracellular calcium. The antimitogenic activity of ANF is mediated by the ANF R₂ receptor by a mechanism independent of adenylyl cyclase mote the sequestration of intracellular calcium. The antimitogenic activity of ANF is mediated by the ANF R_2 receptor by a mechanism independent of adenylyl cyclase inhibition. The signal transduction pathway of this e receptor by a mechanism independent of adenylyl cyclase shown to mediate ANF effects on a tissue. *B. Atrial Natriuretic Factor Effects on the Kidney*
B. Atrial Natriuretic Factor Effects on the Kidney
*B. Atrial Natriuretic Factor Effects on the Kidney***
The chief function of ANF is perceived to be an action** For sites where the R_2 receptor has been definitively
shown to mediate ANF effects on a tissue.
B. Atrial Natriuretic Factor Effects on the Kidney
The chief function of ANF is perceived to be an action
on the kidney to

although ANF influences potassium currents, the signifermerulus (Nonoguchi et al., 1987), loop of Henle (Nono-

icance of ANF effects on potassium homeostasis in me-

diating vasodilator responses is unestablished.

5. Atr shown to mediate ANF effects on a tissue.

B. Atrial Natriuretic Factor Effects on the Kidney

The chief function of ANF is perceived to be an action

on the kidney to facilitate the excretion of sodium, water,

and potass B. Atrial Natriuretic Factor Effects on the Kidney
The chief function of ANF is perceived to be an action
on the kidney to facilitate the excretion of sodium, water,
and potassium (de Bold et al., 1981). This renal activit B. Atrial *Natriareux Factor Effects on the Kianey*
The chief function of ANF is perceived to be an action
on the kidney to facilitate the excretion of sodium, water,
and potassium (de Bold et al., 1981). This renal activi The chief function of ANF is perceived to be an action
on the kidney to facilitate the excretion of sodium, water,
and potassium (de Bold et al., 1981). This renal activity
was the first ANF action identified and is the ba on the kidney to facilitate the excretion of sodium, water, and potassium (de Bold et al., 1981). This renal activity was the first ANF action identified and is the basis for the autacoid's name. These effects often were a and potassium (de Bold et al., 1981). This renal activity
was the first ANF action identified and is the basis for
the autacoid's name. These effects often were associated
with an increase in glomerular filtration rate (Se was the first ANF action identified and is the basis for
the autacoid's name. These effects often were associated
with an increase in glomerular filtration rate (Seymour
et al., 1985). The renal sites of ANF action include the autacoid's name. These effects often were associat
with an increase in glomerular filtration rate (Seymet al., 1985). The renal sites of ANF action included t
inner medullary collecting duct (Light et al., 1989), g
mer with an increase in glomerular filtration rate (Seymour et al., 1985). The renal sites of ANF action included the inner medullary collecting duct (Light et al., 1989), glomerulus (Nonoguchi et al., 1987), loop of Henle (No et al., 1985). The renal sites of ANF action included tinner medullary collecting duct (Light et al., 1989), gluerulus (Nonoguchi et al., 1987), loop of Henle (Non guchi et al., 1987), and mesangial cell (Ballerman et a 19 inner medullary collecting duct (Light et al., 1989), glomerulus (Nonoguchi et al., 1987), loop of Henle (Nonoguchi et al., 1987), and mesangial cell (Ballerman et al., 1985), and some studies reported an inhibition of pro merulus (Nonoguchi et al., 1987), loop of Henle (Nonoguchi et al., 1987), and mesangial cell (Ballerman et al., 1985), and some studies reported an inhibition of proximal tubule reabsorption of sodium (Winaver et al., 1990 guchi et al., 1987), and mesangial cell (Ballerman et al., 1985), and some studies reported an inhibition of proximal tubule reabsorption of sodium (Winaver et al., 1990). The physiological relevance of these actions has b 1985), and some studies reported an inhibition of proximal tubule reabsorption of sodium (Winaver et al., 1990).
The physiological relevance of these actions has been the subject of a number of recent reviews. In general, mal tubule reabsorption of sodium (Winaver et al., 1990).
The physiological relevance of these actions has been the
subject of a number of recent reviews. In general, kidneys
respond to physiological concentrations of ANF, The physiological relevance of these actions has been the subject of a number of recent reviews. In general, kidneys respond to physiological concentrations of ANF, suggesting a potential physiological relevance. Establish subject of a number of recent reviews. In general, kidneys
respond to physiological concentrations of ANF, sug-
gesting a potential physiological relevance. Established
intracelluar actions of ANF in renal cells are shown respond to physiological concentrations of ANF, suggesting a potential physiological relevance. Established intracelluar actions of ANF in renal cells are shown in figure 4. They include activation of GC and reductions in gesting a potential physiological relevant
intracelluar actions of ANF in renal cell
figure 4. They include activation of GC
in adenylyl cyclase activity, phospholip
sodium influx, and calcium concentration
1. Role of rena tracelluar actions of ANF in renal cells are shown in
ure 4. They include activation of GC and reductions
adenylyl cyclase activity, phospholipase C activity,
dium influx, and calcium concentrations.
1. Role of renal guany

aspet

 $\begin{array}{c} \n\text{ATP} \ \n\end{array}$

FIG. 4. Renal signal transduction pathways for ANF. ANF can act

on either of two receptors, R₁ or R₂. The R₁ receptor generates cGMP

in response to ANF, and the cGMP can act to suppress FIG. 4. Renal signal transduction pathways for ANF. ANF can act on
on either of two receptors, R₁ or R₂. The R₁ receptor generates cGMP de
in response to ANF, and the cGMP can act to suppress phospholipase ily
C (PLC on either of two receptors, R₁ or R₄. The R₁ receptor generates cGN
in response to ANF, and the cGMP can act to suppress phospholip
C (PLC) activity or sodium channel opening. The cGMP also c
decrease intracellular c In response to ANF, and the CGMP can act to suppress phospholipase C (PLC) activity or sodium channel opening. The CGMP also can decrease intracellular calcium concentrations. ANF suppresses adenylyl cyclase (AC) activity In comparison of the receptor is probably the receptor involved. G, a decrease intracellular calcium concentrations. ANF suppresses adeny-
lyl cyclase (AC) activity, but the functional significance of this response
is unk decrease intracellular calcium concentrations. ANF suppresses adeny-
lyl cyclase (AC) activity, but the functional significance of this response
is unknown. The R₄ receptor is probably the receptor involved. G, a
putativ **(AC)** activity, but the functional significance of this responsibility cyclase (AC) activity, but the functional significance of this responsible is unknown. The R₄ receptor is probably the receptor involved. (putative phate. is unknown. The R_2 receptor is probably the receptor involved. G , a putative G -protein. Potentiating or inhibitory effects are indicated by $(+)$ or $(-)$. DAG, diacylglycerol; PIP2, phosphatidylinositol bisphos-
pha

putative G-protein. Potentiating or inhibitory effects are indicated by

(+) or (-). DAG, diacylglycerol; PIP2, phosphatidylinositol bisphos-

phate.

of ANF on GC was found initially in the kidney (Hamet st

et al., 1984; renal cGMP concentrations by ANF has been confirmed
by various investigators. The augmentation of development by ANF has been confirmed
by various investigators. The only debate regarding the a
of ANF on GC was found initially in the kidney (Hamet sti
et al., 1984; Waldman et al., 1984). The augmentation of diz
renal cGMP concentrations by ANF has been confirmed wh
by various investigators. The only debate rega of ANF on GC was found initially in the kidney (Hamet sties)
et al., 1984; Waldman et al., 1984). The augmentation of dizernal cGMP concentrations by ANF has been confirmed wh
by various investigators. The only debate rega et al., 1984; Waldman et al., 1984). The augmentation of diz
renal cGMP concentrations by ANF has been confirmed wh
by various investigators. The only debate regarding the or
stimulatory effect of ANF on renal GC involves reported cGMP concentrations by ANF has been confirmed
by various investigators. The only debate regarding the
stimulatory effect of ANF on renal GC involves the
proximal tubule. This segment of the kidney has been
reporte by various investigators. The only debate regarding the constitution of the stimulatory effect of ANF on renal GC involves the proximal tubule. This segment of the kidney has been reported to be devoid of an ANF effect on stimulatory effect of ANF on renal GC involves the conproximal tubule. This segment of the kidney has been whis
reported to be devoid of an ANF effect on GC (Hamet et ion
al., 1984; Tremblay et al., 1985). However, more se proximal tubule. This segment of the kidney has been
reported to be devoid of an ANF effect on GC (Hamet et
al., 1984; Tremblay et al., 1985). However, more sensitive
techniques used by Nonoguchi et al. (1987) revealed a
G reported to be devoid of an ANF effect on GC (Hamet et ideal, 1984; Tremblay et al., 1985). However, more sensitive of techniques used by Nonoguchi et al. (1987) revealed a pic Tresponse to ANF in the proximal tubule of r al., 1984; Tremblay et al., 1985). However, more sensitive techniques used by Nonoguchi et al. (1987) revealed a GC response to ANF in the proximal tubule of rabbits. These data overwhelmingly indicate the stimulation of r techniques used by Nonoguchi et al.
GC response to ANF in the proximal
These data overwhelmingly indicate t
renal GC by ANF, suggesting that cGM
the renal second messenger for ANF.
The increased production of cGMP C response to ANF in the proximal tubule of rabbits. A74
hese data overwhelmingly indicate the stimulation of and
nal GC by ANF, suggesting that cGMP could represent (vol
e renal second messenger for ANF.
The increased pr

These data overwhelmingly indicate the stimulation of
renal GC by ANF, suggesting that cGMP could represent
the renal second messenger for ANF.
The increased production of cGMP occurred at ANF
concentrations affecting ren renal GC by ANF, suggesting that cGMP could represent
the renal second messenger for ANF.
The increased production of cGMP occurred at ANF
concentrations affecting renal function and correlated
with ANF effects on the kidn the renal second messenger for ANF.

The increased production of cGMP occurred at ANF

concentrations affecting renal function and correlated

with ANF effects on the kidney (Richards, 1990). Fur-

thermore, membrane-perme The increased production of cGMP occurred at ANF
concentrations affecting renal function and correlated
with ANF effects on the kidney (Richards, 1990). Fur-
thermore, membrane-permeable analogs of cGMP, such
as dibutyryl concentrations affecting renal function and correlates with ANF effects on the kidney (Richards, 1990). Furthermore, membrane-permeable analogs of cGMP, such as dibutyryl cGMP, either had no effect (Hamet et al. 1984) or p with ANF effects on the kidney (Richards, 1990). Furthermore, membrane-permeable analogs of cGMP, such as dibutyryl cGMP, either had no effect (Hamet et al., 1984) or produced a diuresis reminiscent of ANF infusions in rat thermore, membrane-permeable analogs of cGMP, such
as dibutyryl cGMP, either had no effect (Hamet et al.,
1984) or produced a diuresis reminiscent of ANF infu-
sions in rat kidneys (Huang et al., 1986). Dibutyryl
cGMP also as dibutyryl cGMP, either had no effect (Hamet et al., 1984) or produced a diuresis reminiscent of ANF infusions in rat kidneys (Huang et al., 1986). Dibutyryl cGMP also prevented mesangial cell contractions in response to 1984) or produced a diuresis reminiscent of ANF infusions in rat kidneys (Huang et al., 1986). Dibutyryl cGMP also prevented mesangial cell contractions in response to angiotensin II, as does ANF (Appel et al., 1986). The sions in rat kidneys (Huang et al., 1986). Dibutyryl cGMP also prevented mesangial cell contractions in response to angiotensin II, as does ANF (Appel et al., p. 1986). The inhibitory effect of ANF on sodium transport in sponse to angiotensin II, as does ANF (Appel et al., 1986). The inhibitory effect of ANF on sodium transport in the inner medullary collecting duct and renal cell lines was mimicked by dibutyryl and 8-bromo cGMP (Cantiello sponse to angiotensin II, as does ANF (Appel et al., 1986). The inhibitory effect of ANF on sodium transport in the inner medullary collecting duct and renal cell lines was mimicked by dibutyryl and 8-bromo cGMP (Cantiello in the inner medullary collecting duct and renal cell lines
was mimicked by dibutyryl and 8-bromo cGMP (Can-
tiello and Ausiello, 1986; Mohrmann et al., 1987; Light
et al., 1989). Inhibitors of cGMP phosphodiesterase po-
t in the inner medullary collecting duct and renal cell lines
was mimicked by dibutyryl and 8-bromo cGMP (Can-
tiello and Ausiello, 1986; Mohrmann et al., 1987; Light
et al., 1989). Inhibitors of cGMP phosphodiesterase po-
t was mimicked by dibutyryl and 8-bromo cGMP (Can-
tiello and Ausiello, 1986; Mohrmann et al., 1987; Light ron se
et al., 1989). Inhibitors of cGMP phosphodiesterase pooles
tentiated ANF renal effects in rats (Wilkins et al tiello and Ausiello, 1986; Mohrmann et al., 1987; Light
et al., 1989). Inhibitors of cGMP phosphodiesterase po-
tentiated ANF renal effects in rats (Wilkins et al., 1990),
indicating that ANF could promote renal effects by et al., 1989). Inhibitors of cGMP phosphodiesterase po-
tentiated ANF renal effects in rats (Wilkins et al., 1990), al.,
indicating that ANF could promote renal effects by GC cyc
activation through ANF R₁ receptors. Add tentiated ANF renal effects in rats (Wilkins et al., 1990),
indicating that ANF could promote renal effects by GC
activation through ANF R_1 receptors. Additional support
for this hypothesis derives from the inability o indicating that ANF could promote renal effects by GC cycles activation through ANF R_1 receptors. Additional support et a for this hypothesis derives from the inability of cANF, a al. (specific R_2 receptor-binding p activation through ANF R_1 receptors. Additional support for this hypothesis derives from the inability of cANF, a alspecific R_2 receptor-binding peptide (Maack et al., 1987; ti Anand-Srivastava et al., 1990), to alt

FIG. 4. Renal signal transduction pathways for ANF. ANF can act
in response to ANF, and the GMP can act to suppress phospholipase
in response to ANF, and the GMP can act to suppress phospholipase
in the mediated by HS-142on either of two receptors, R_1 or R_2 . The R_1 receptor generates cGMP depressor action of acutely infused ANF is not necessarin response to ANF, and the cGMP can act to suppress phospholipase ily mediated by renal TRANSDUCTION MECHANISMS

ANF, indicating that ANF R_2 receptors do not mediate

renal actions. The most compelling evidence supporting FRANSDUCTION MECHANISMS 473
ANF, indicating that ANF R_2 receptors do not mediate
renal actions. The most compelling evidence supporting
a role for ANF R_1 receptors and GC in mediating renal TRANSDUCTION MECHANISMS 473
ANF, indicating that ANF R_2 receptors do not mediate
renal actions. The most compelling evidence supporting
a role for ANF R_1 receptors and GC in mediating renal
effects of ANF were obtai ANF, indicating that ANF R_2 receptors do not mediate
renal actions. The most compelling evidence supporting
a role for ANF R_1 receptors and GC in mediating renal
effects of ANF were obtained with selective ANF R_1 ANF, indicating that ANF R_2 receptors do not mediate
renal actions. The most compelling evidence supporting
a role for ANF R_1 receptors and GC in mediating renal
effects of ANF were obtained with selective ANF R_1 renal actions. The most compelling evidence supporting
a role for ANF R_1 receptors and GC in mediating renal
effects of ANF were obtained with selective ANF R_1
receptor antagonists. von Geldern et al. (1990) observe a role for ANF R_1 receptors and GC in mediating renal
effects of ANF were obtained with selective ANF R_1
receptor antagonists. von Geldern et al. (1990) observed
an ANF R_1 receptor antagonist, A74186, to eliminat receptor antagonists. von Geldern et al. (1990) observed
an ANF R_1 receptor antagonist, A74186, to eliminate the
renal effects of infused ANF, including the elevation in
urinary cGMP concentrations in rats. Similar o receptor antagonists. von Geldern et al. (1990) observed
an ANF R_1 receptor antagonist, A74186, to eliminate the
renal effects of infused ANF, including the elevation in
urinary cGMP concentrations in rats. Similar obs an ANF R_1 receptor antagonist, A74186, to eliminate the
renal effects of infused ANF, including the elevation in
urinary cGMP concentrations in rats. Similar observa-
tions were made by Sano et al. (1992) using a diffe renal effects of infused ANF, including the elevation in
urinary cGMP concentrations in rats. Similar observa-
tions were made by Sano et al. (1992) using a different
ANF R_1 receptor antagonist, HS-142-1. Therefore, urinary cGMP concentrations in rats. Similar observa-
tions were made by Sano et al. (1992) using a different
ANF R_1 receptor antagonist, HS-142-1. Therefore, ANF
effects in the kidney appear to be mediated by cGMP.
Th ANF R_1 receptor antagonist, HS-142-1. Therefore, ANF effects in the kidney appear to be mediated by cGMP. effects in the kidney appear to be mediated by cGN
This putative pathway is depicted in figure 4. The A
effect on blood pressure was unaltered by A74186 a
only slightly modified by HS-142-1, suggesting that
depressor actio This putative pathway is depicted
effect on blood pressure was una
only slightly modified by HS-142
depressor action of acutely infusee
ily mediated by renal mechanisms
Evidence opposing a mediating only slightly modified by HS-142-1, suggesting that the
depressor action of acutely infused ANF is not necessar-
ily mediated by renal mechanisms.
Evidence opposing a mediating role of cGMP in pro-

only slightly modified by HS-142-1, suggesting that the
depressor action of acutely infused ANF is not necessar-
ily mediated by renal mechanisms.
Evidence opposing a mediating role of cGMP in pro-
moting ANF renal effects depressor action of acutely infused ANF is not necessar-
ily mediated by renal mechanisms.
Evidence opposing a mediating role of cGMP in pro-
moting ANF renal effects exists but is relatively scarce
in comparison to the bu ily mediated by renal mechanisms.
Evidence opposing a mediating role of cGMP in pro-
moting ANF renal effects exists but is relatively scarce
in comparison to the bulk of evidence supporting cGMP
as the renal second messen Evidence opposing a mediating role of cGMP in pro-
moting ANF renal effects exists but is relatively scarce
in comparison to the bulk of evidence supporting cGMP
as the renal second messenger for ANF. Oxidation of the
meth in comparison to the bulk of evidence supporting cGMP
as the renal second messenger for ANF. Oxidation of the
methionine at position 110 of ANF (Met-O-ANF) yielded
a biologically active ANF peptide with minimal GC-
stimula in comparison to the bulk of evidence supporting cGMP
as the renal second messenger for ANF. Oxidation of the
methionine at position 110 of ANF (Met-O-ANF) yielded
a biologically active ANF peptide with minimal GC-
stimula as the renal second messenger for ANF. Oxidation of the methionine at position 110 of ANF (Met-O-ANF) yielde a biologically active ANF peptide with minimal GC stimulating activity (Willenbrock et al., 1989). The oxidized M methionine at position 110 of ANF (Met-O-ANF) yielded

a biologically active ANF peptide with minimal GC-

stimulating activity (Willenbrock et al., 1989). The oxi-

dized Met¹¹⁰-ANF produced diuresis and hypotension,
 a biologically active ANF peptide with minimal GC-
stimulating activity (Willenbrock et al., 1989). The oxi-
dized Met¹¹⁰-ANF produced diuresis and hypotension,
when injected into rats, but failed to alter urinary sodium stimulating activity (Willenbrock et al., 1989). The oxidized Met¹¹⁰-ANF produced diuresis and hypotension, when injected into rats, but failed to alter urinary sodium or cGMP excretion (Willenbrock et al., 1989). Thus, dized Met¹¹⁰-ANF produced diuresis and hypotensi
when injected into rats, but failed to alter urinary sodit
or cGMP excretion (Willenbrock et al., 1989). Thus, t
compound dissociated cGMP production and diure
while confi when injected into rats, but failed to alter urinary sodium
or cGMP excretion (Willenbrock et al., 1989). Thus, this
compound dissociated cGMP production and diuresis
while confirming the correlation between cGMP produc-
t or cGMP excretion (Willenbrock et al., 1989). Thus, this
compound dissociated cGMP production and diuresis
while confirming the correlation between cGMP produc-
tion and natriuresis. Other data supporting a dissociation
o compound dissociated cGMP production and diuresis
while confirming the correlation between cGMP production
and natriuresis. Other data supporting a dissociation
of cGMP from renal effects of ANF were obtained in the
prese while confirming the correlation between cGMP production and natriuresis. Other data supporting a dissociation of cGMP from renal effects of ANF were obtained in the presence of low doses of the R_1 receptor antagonist, tion and natriuresis. Other data supporting a dissociation
of cGMP from renal effects of ANF were obtained in the
presence of low doses of the R_1 receptor antagonist,
A74186, which prevented ANF effects on urine volume of cGMP from renal effects of ANF were obtained in the
presence of low doses of the R_1 receptor antagonist,
A74186, which prevented ANF effects on urine volume
and diuresis but not on urinary cGMP concentrations
(von G presence of low doses of the R_1 receptor antagonist,
A74186, which prevented ANF effects on urine volume
and diuresis but not on urinary cGMP concentrations
(von Geldern et al., 1990). Furthermore, ANF increased
urine A74186, which prevented ANF effects on urine volume
and diuresis but not on urinary cGMP concentrations
(von Geldern et al., 1990). Furthermore, ANF increased
urine volume and sodium excretion prior to a detectable
increas and diuresis but not
(von Geldern et al., i
urine volume and soo
increase in urinary c
et al., 1990).
The net conclusio on Geldern et al., 1990). Furthermore, ANF increased
ine volume and sodium excretion prior to a detectable
crease in urinary cGMP concentrations (von Geldern
al., 1990).
The net conclusion from these studies is that ANF
ob urine volume and sodium excretion prior to a detectal
increase in urinary cGMP concentrations (von Gelde
et al., 1990).
The net conclusion from these studies is that AP
probably produces natriuresis by stimulating the gene

increase in urinary cGMP concentrations (von Geldern
et al., 1990).
The net conclusion from these studies is that ANF
probably produces natriuresis by stimulating the gener-
ation of cGMP. The two studies dissociating cGMP et al., 1990).
The net conclusion from these studies is that ANF
probably produces natriuresis by stimulating the gener-
ation of cGMP. The two studies dissociating cGMP
production from some renal effects of ANF (Willenbro The net conclusion from these studies is that ANF
probably produces natriuresis by stimulating the gener-
ation of cGMP. The two studies dissociating cGMP
production from some renal effects of ANF (Willenbrock
et al., 1989 probably produces natriuresis by stimulating the genution of cGMP. The two studies dissociating cG production from some renal effects of ANF (Willenbird et al., 1989; von Geldern et al., 1990) emphasize potential for the i ation of cGMP. The two studies dissociatienduction from some renal effects of ANF (Wet al., 1989; von Geldern et al., 1990) emplement of other signal tion mechanisms in renal responses to ANF.
2. Inhibition of renal adenyi oduction from some renal effects of ANF (Willenbrock
al., 1989; von Geldern et al., 1990) emphasize the
tential for the involvement of other signal transduc-
on mechanisms in renal responses to ANF.
2. *Inhibition of renal* potential for the involvement of other signal transduction mechanisms in renal responses to ANF.
2. Inhibition of renal adenylyl cyclase. An inhibition of adenylyl cyclase by ANF was observed in various neph-

potential for the involvement of other signal transduction mechanisms in renal responses to ANF.
2. *Inhibition of renal adenylyl cyclase*. An inhibition of adenylyl cyclase by ANF was observed in various neph-
ron segment tion mechanisms in renal responses to ANF.
2. *Inhibition of renal adenylyl cyclase*. An inhibition of
adenylyl cyclase by ANF was observed in various neph-
ron segments such as glomeruli, collecting duct, and loop
of Henl 2. Inhibition of renal adenylyl cyclase. An inhibition of adenylyl cyclase by ANF was observed in various nephron segments such as glomeruli, collecting duct, and loop of Henle but not proximal tubules (Anand-Srivastava et adenylyl cyclase by ANF was observed in various nephron segments such as glomeruli, collecting duct, and loop
of Henle but not proximal tubules (Anand-Srivastava et
al., 1986). The inhibitory effect of ANF on adenylyl
cycl ron segments such as glomeruli, collecting duct, and loop
of Henle but not proximal tubules (Anand-Srivastava et
al., 1986). The inhibitory effect of ANF on adenylyl
cyclase was confirmed by other investigators (Ishikawa
e of Henle but not proximal tubules (Anand-Srivastav
al., 1986). The inhibitory effect of ANF on ader
cyclase was confirmed by other investigators (Ishik
et al., 1985; Obana et al., 1985). Recently, Umemu
al. (1989) reported al., 1986). The inhibitory effect of ANF on adenylyl cyclase was confirmed by other investigators (Ishikawa et al., 1985; Obana et al., 1985). Recently, Umemura et al. (1989) reported that ANF reduced cAMP concentrations i cyclase was confirmed by other investigators (Ishikawa
et al., 1985; Obana et al., 1985). Recently, Umemura et
al. (1989) reported that ANF reduced cAMP concentra-
tions in human glomeruli treated with parathyroid hor-
mon al. (1989) reported that ANF reduced cAMP concentrations in human glomeruli treated with parathyroid hormone. However, some investigators failed to observe an ANF effect on renal adenylyl cyclase activity (Waldman

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et al., 1984; Anand-Srivastava et al., 1986; other refer- tion, indicating

ences in Brenner et al., 1990). **Anandical property** ances within th 474
et al., 1984; Anand-Srivastava
ences in Brenner et al., 1990).
The adenylyl cyclase/cAMP

ANAND-SRIVA
al., 1984; Anand-Srivastava et al., 1986; other ref
ces in Brenner et al., 1990).
The adenylyl cyclase/cAMP system has been demon-
rated to affect glomerular filtration rate and tubu et al., 1984; Anand-Srivastava et al., 1986; other references in Brenner et al., 1990).
The adenylyl cyclase/cAMP system has been demon-
strated to affect glomerular filtration rate and tubular
function (Dousa et al., 1980 et al., 1984; Anand-Srivastava et al., 1986; other references in Brenner et al., 1990).
The adenylyl cyclase/cAMP system has been demonstrated to affect glomerular filtration rate and tubular function (Dousa et al., 1980; ences in Brenner et al., 1990). and
The adenylyl cyclase/cAMP system has been demon-
interated to affect glomerular filtration rate and tubular
function (Dousa et al., 1980; Morel et al., 1980). Dibutyryl
micAMP decreased The adenylyl cyclase/cAMP system has been demonstrated to affect glomerular filtration rate and tubular function (Dousa et al., 1980; Morel et al., 1980). Dibutyryl cAMP decreased the glomerular filtration rate of both sin strated to affect glomerular filtration rate and tubular
function (Dousa et al., 1980; Morel et al., 1980). Dibutyryl
cAMP decreased the glomerular filtration rate of both
single superficial nephrons and whole kidneys (Ish function (Dousa et al., 1980; Morel et al., 1980). Dibutyryl
cAMP decreased the glomerular filtration rate of both
single superficial nephrons and whole kidneys (Ishikawa
and Brenner, 1977). Similarly, inhibition of cAMP a cAMP decreased the glomerular filtration rate of bot
single superficial nephrons and whole kidneys (Ishikaw
and Brenner, 1977). Similarly, inhibition of cAMP a
cumulation induced by hormonal agonists, such as glu
cocortico single superficial nephrons and whole kidneys (Ishikavand Brenner, 1977). Similarly, inhibition of cAMP at cumulation induced by hormonal agonists, such as glacocorticoids (Aboud et al., 1979), enhanced single neptron glo and Brenner, 1977). Similarly, inhibition of cAMP accumulation induced by hormonal agonists, such as glucocorticoids (Aboud et al., 1979), enhanced single nephron glomerular filtration rate and whole kidney glomerular filt cumulation induced by hormonal agonists, such as glucacorricoids (Aboud et al., 1979), enhanced single neph-
ron glomerular filtration rate and whole kidney glomer-
the ular filtration rate (Baylis and Brenner, 1978). Thus cocorticoids (Aboud et al., 1979), enhanced single neph
ron glomerular filtration rate and whole kidney glomer
ular filtration rate (Baylis and Brenner, 1978). Thus, i
may be suggested that lowered intraglomerular cAMI
con ron glomerular filtration rate and whole kidney glomer-
ular filtration rate (Baylis and Brenner, 1978). Thus, it
may be suggested that lowered intraglomerular cAMP E
concentrations cause increased ultrafiltration. The pr ular filtration rate (Baylis and Brenner, 1978). Thus, it
may be suggested that lowered intraglomerular cAMP
concentrations cause increased ultrafiltration. The pres-
ence of ANF R₂ receptors, combined with the ability o may be suggested that lowered intraglomerular cAMP
concentrations cause increased ultrafiltration. The pres-
ence of ANF R_2 receptors, combined with the ability of
ANF to reduce adenylyl cyclase activity and cAMP con-
 concentrations cause increased ultrafiltration. The pre
ence of ANF R_2 receptors, combined with the ability
ANF to reduce adenylyl cyclase activity and cAMP co
centrations in different nephron segments, suggests th
the ence of ANF R_2 receptors, combined with the ability of pM,
ANF to reduce adenylyl cyclase activity and cAMP con-
centrations in different nephron segments, suggests that brou
the diuretic action of ANF may involve this ANF to reduce adenylyl cyclase activity and cAMP concentrations in different nephron segments, suggests that the diuretic action of ANF may involve this signal transduction pathway. This hypothesis was partially tested in the diuretic
duction pat
isolated rat
The cANF
al., 1987).
Evidence ction pathway. This hypothesis was partially tested in plated rat kidney using the R_2 -selective agent, cANF.
he cANF failed to produce a diuretic effect (Maack et , 1987).
Evidence favoring a functional role for this r

isolated rat kidney using the R_2 -selective agent, cANF. ANT
The cANF failed to produce a diuretic effect (Maack et bro)
al., 1987). inhicrophece favoring a functional role for this renal signal tuber
transduction mecha The cANF failed to produce a diuretic effect (Maack et al., 1987).

Evidence favoring a functional role for this renal signal

transduction mechanism included the finding that ANF

attenuated arginine vasopressin actions o al., 1987).
Evidence favoring a functional role for this renal signal
transduction mechanism included the finding that ANF
attenuated arginine vasopressin actions on cortical col-
lecting tubules by a mechanism inhibited b Evidence favoring a functional role for this renal signtransduction mechanism included the finding that Alattenuated arginine vasopressin actions on cortical clecting tubules by a mechanism inhibited by cAMP $_i$ alogs (Di transduction mechanism included the finding that ANF nitrattenuated arginine vasopressin actions on cortical col-
lecting tubules by a mechanism inhibited by cAMP an-
alogs (Dillingham and Anderson, 1986). These investi-
i attenuated arginine vasopressin actions on cortical col-
lecting tubules by a mechanism inhibited by cAMP an-
alogs (Dillingham and Anderson, 1986). These investi-
increases reasoned that the cAMP analogs were acting to
ma lecting tubules by a mechanism inhibited by cAMP analogs (Dillingham and Anderson, 1986). These investigators reasoned that the cAMP analogs were acting to maintain intracellular cAMP concentrations constant to eliminate t alogs (Dillingham and Anderson, 1986). These investigators reasoned that the cAMP analogs were acting to maintain intracellular cAMP concentrations constant to eliminate the effect of the ANF. The major argument against th gators reasoned that the cAMP analogs were acting to cl
maintain intracellular cAMP concentrations constant to
seliminate the effect of the ANF. The major argument magainst the hypothesis that ANF acts via a suppression a maintain intracellular cAMP concentrations constant to see
eliminate the effect of the ANF. The major argument magainst the hypothesis that ANF acts via a suppression and
of renal adenylyl cyclase activity involves the ab eliminate the effect of the ANF. The major argument magainst the hypothesis that ANF acts via a suppression and of renal adenylyl cyclase activity involves the ability of an R_1 receptor antagonist to prevent renal acti against the hypothesis that ANF acts via a suppression of renal adenylyl cyclase activity involves the ability of an R_1 receptor antagonist to prevent renal actions of ANF (von Geldern et al., 1990; Sano et al., 1992). of renal adenylyl cyclase activity involves the ability of an R_1 receptor antagonist to prevent renal actions of du
ANF (von Geldern et al., 1990; Sano et al., 1992). The AP
 R_1 receptor antagonist should dissociate an R_1 receptor antagonist to prevent renal actions of dual. ANF (von Geldern et al., 1990; Sano et al., 1992). The A R_1 receptor antagonist should dissociate the renal actions m of ANF from an inhibition of adenylyl ANF (von Geldern et al., 1990; Sano et al., 1992). The AI
R₁ receptor antagonist should dissociate the renal actions me
of ANF from an inhibition of adenylyl cyclase. It is hy
possible that a suppression of adenylyl cyc R_1 receptor antagonist should dissociate the renal action of ANF from an inhibition of adenylyl cyclase. I possible that a suppression of adenylyl cyclase action of ANF, but major natriuretic effect of ANF appears to b of ANF from an inhibition of a
possible that a suppression of ade
could be involved in the diuretic a
major natriuretic effect of ANF ap
ent of adenylyl cyclase modulation
3. Effects on renal phospholipase **3. Solution:** A suppression of adenylyl cyclase activity

and be involved in the diuretic action of ANF, but the

ajor natriuretic effect of ANF appears to be independ-

t of adenylyl cyclase modulation.

3. Effects on re major natriuretic effect of ANF appears to be independent of adenylyl cyclase modulation.
3. Effects on renal phospholipase C activity. Few reports exist concerning ANF influences on renal phospholipase

major natriuretic effect of ANF appears to be independ-

ent of adenylyl cyclase modulation. investing 3. Effects on renal phospholipase C activity. Few reports intrace

exist concerning ANF influences on renal phospholipa ent of adenylyl cyclase modulation.

3. Effects on renal phospholipase C activity. Few reports

exist concerning ANF influences on renal phospholipase

C activity. ANF had no effect on basal phospholipase C

activity but a 3. Effects on renal phospholipase C activity. Few repo
exist concerning ANF influences on renal phospholipase
C activity. ANF had no effect on basal phospholipase
activity but attenuated stimulatory effects of angioten
II exist concerning ANF influences on renal phospholipase w
C activity. ANF had no effect on basal phospholipase C A
activity but attenuated stimulatory effects of angiotensin le
II in mesangial cells (Barnett et al., 1990). activity but attenuated stimulatory effects of angiotensin II in mesangial cells (Barnett et al., 1990). The mechanism of this inhibitory effect probably involved elevated synthesis of cGMP, because nitroprusside, another activity but attenuated stimulatory effects of angiotensi
II in mesangial cells (Barnett et al., 1990). The mecha
nism of this inhibitory effect probably involved elevate
synthesis of cGMP, because nitroprusside, another s II in mesangial cells (Barnett et al., 1990). The mechanism of this inhibitory effect probably involved elevate synthesis of cGMP, because nitroprusside, another stimulator of GC, also reduced angiotensin effects on phos-
 nism of this inhibitory effect probably involved elevated
synthesis of cGMP, because nitroprusside, another stim-
ulator of GC, also reduced angiotensin effects on phos-
pholipid turnover. A stimulatory effect of ANF on ph synthesis of cGMP, because nitroprusside, another stim-
ulator of GC, also reduced angiotensin effects on phos-
pholipid turnover. A stimulatory effect of ANF on phos-
pholipase C activity was also found in the shark recta ulator of GC, also reduced angiotensin effects on phos-
pholipid turnover. A stimulatory effect of ANF on phos-
pholipase C activity was also found in the shark rectal
gland, with an increase in sodium and chloride secreti pholipid turnover. A stimulatory effect of ANF on phos-
pholipase C activity was also found in the shark rectal
gland, with an increase in sodium and chloride secretion
cheap and Valentich, 1991). The ultimate relationship pholipase C activity was also found gland, with an increase in sodium at (Ecay and Valentich, 1991). The undertween phospholipase C activity and kidney is not defined at this time.
4. Effects on renal ion currents. and, with an increase in sodium and chloride secretion cay and Valentich, 1991). The ultimate relationship tween phospholipase C activity and ANF effects in the dney is not defined at this time.
4. Effects on renal ion cur (Ecay and Valentich, 1991). The ultimate relationsh
between phospholipase C activity and ANF effects in the
kidney is not defined at this time.
4. Effects on renal ion currents. One of the most re
ognized actions of ANF is

N AND TRACHTE
tion, indicating that ANF probably alters ion condu
ances within the kidney. As mentioned earlier, A A AND TRACHTE
tion, indicating that ANF probably alters ion conduct-
ances within the kidney. As mentioned earlier, ANF
inhibited a cation channel in the renal medullary col-A AND TRACHTE
tion, indicating that ANF probably alters ion conduct-
ances within the kidney. As mentioned earlier, ANF
inhibited a cation channel in the renal medullary col-
lecting duct (Sonnenberg et al., 1986), and thi tion, indicating that ANF probably alters ion conduct-
ances within the kidney. As mentioned earlier, ANF
inhibited a cation channel in the renal medullary col-
lecting duct (Sonnenberg et al., 1986), and this effect was
m tion, indicating that ANF probably alters ion conductances within the kidney. As mentioned earlier, ANF inhibited a cation channel in the renal medullary collecting duct (Sonnenberg et al., 1986), and this effect was mimic ances within the kidney. As mentioned earlier, ANF
inhibited a cation channel in the renal medullary col-
lecting duct (Sonnenberg et al., 1986), and this effect was
mimicked by dibutyryl cGMP (Light et al., 1989). Fur-
th inhibited a cation channel in the renal medullary collecting duct (Sonnenberg et al., 1986), and this effect was
mimicked by dibutyryl cGMP (Light et al., 1989). Fur-
thermore, ANF stimulated GC activity. Therefore, ANF
co lecting duct (Sonnenberg et al., 1986), and this effect was
mimicked by dibutyryl cGMP (Light et al., 1989). Fur-
thermore, ANF stimulated GC activity. Therefore, ANF
could act to reduce sodium conductance in the inner
med cGMP. ermore, ANF stimulated GC activity. Therefore, ANF
uld act to reduce sodium conductance in the inner
edulla by a signal transduction pathway involving
RMP.
Similar results were obtained in a porcine renal epi-
elial cell l

centrations in different nephron segments, suggests that bromo cGMP reduced sodium conductance in this cell
the diuretic action of ANF may involve this signal trans-
discussion supporting the possibility that the ANF effec could act to reduce sodium conductance in the in
medulla by a signal transduction pathway involv
cGMP.
Similar results were obtained in a porcine renal e
thelial cell line (i.e., LLC-PK1). ANF reduced calcium
dependent sod medulla by a signal transduction pathway involving cGMP.

Similar results were obtained in a porcine renal epi-

the lial cell line (i.e., LLC-PK1). ANF reduced calcium-

dependent sodium conductance in this cell line wit CGMP.

Similar results were obtained in a porcine renal epithelial cell line (i.e., LLC-PK1). ANF reduced calcium

dependent sodium conductance in this cell line with a

EC₅₀ of 20 pM (Cantiello and Ausiello, 1986). The Similar results were obtained in a porcine renal epithelial cell line (i.e., LLC-PK1). ANF reduced calcium-
dependent sodium conductance in this cell line with an EC_{50} of 20 pM (Cantiello and Ausiello, 1986). The stimthe ial cell line (i.e., LLC-PK1). ANF reduced calcium-
dependent sodium conductance in this cell line with an
 EC_{50} of 20 pM (Cantiello and Ausiello, 1986). The stim-
ulatory effect of ANF on GC exhibited an EC_{50} of dependent sodium conductance in this cell line with an EC_{50} of 20 pM (Cantiello and Ausiello, 1986). The stimulatory effect of ANF on GC exhibited an EC_{50} of 100 pM, consistent with the possibility that cGMP could m EC_{50} of 20 pM (Cantiello and Ausiello, 1986). The stim-
ulatory effect of ANF on GC exhibited an EC_{50} of 100
pM, consistent with the possibility that cGMP could
mediate ANF effects on sodium conductance. Finally, 8ulatory effect of ANF on GC exhibited an EC_{50} of 100 pM, consistent with the possibility that cGMP could mediate ANF effects on sodium conductance. Finally, 8-bromo cGMP reduced sodium conductance in this cell line, ag pM, consistent with the possibility that cGMP could mediate ANF effects on sodium conductance. Finally, 8 bromo cGMP reduced sodium conductance in this celline, again supporting the possibility that the ANF effectional be mediate ANF effects on sodium conductance. Finally, 8-
bromo cGMP reduced sodium conductance in this cell
line, again supporting the possibility that the ANF effect
could be mediated by cGMP. Somewhat surprisingly,
ANF did bromo cGMP reduced sodium conductance in this cell
line, again supporting the possibility that the ANF effect
could be mediated by cGMP. Somewhat surprisingly,
ANF did not alter sodium-hydrogen antiport, nor did 8-
bromo c line, again supporting the possibility that the ANF effect
could be mediated by cGMP. Somewhat surprisingly,
ANF did not alter sodium-hydrogen antiport, nor did 8-
bromo cGMP in the LLC-PK1 cell line, although ANF
inhibite could be mediated by cGMP. Somewhat surprisingly,
ANF did not alter sodium-hydrogen antiport, nor did 8-
bromo cGMP in the LLC-PK1 cell line, although ANF
inhibited sodium-hydrogen antiport in rabbit proximal
tubules (Wina ANF did not alter sodium-hydrogen antiport, nor did 8-
bromo cGMP in the LLC-PK1 cell line, although ANF
inhibited sodium-hydrogen antiport in rabbit proximal
tubules (Winaver et al., 1990). Another stimulator of GC,
nitro bromo cGMP in the LLC-PK1 cell line, although ANF
inhibited sodium-hydrogen antiport in rabbit proximal
tubules (Winaver et al., 1990). Another stimulator of GC,
nitroprusside, also inhibited the sodium channel in the
LLCinhibited sodium-hydrogen antiport in rabbit proximal
tubules (Winaver et al., 1990). Another stimulator of GC,
nitroprusside, also inhibited the sodium channel in the
LLC-PK1 cells (Mohrmann et al., 1987). These results
a tubules (Winaver et al., 1990). Another stimulator of GC,
nitroprusside, also inhibited the sodium channel in the
LLC-PK1 cells (Mohrmann et al., 1987). These results
are consistent with the scenario that the ANF-mediated nitroprusside, also inhibited the sodium channel in the LLC-PK1 cells (Mohrmann et al., 1987). These results are consistent with the scenario that the ANF-mediated increases of cGMP concentrations influence sodium channels LLC-PK1 cells (Mohrmann et al., 1987). These resu
are consistent with the scenario that the ANF-mediat
increases of cGMP concentrations influence sodit
channels in an inhibitory manner. This pathway is p
sented in figure 4 are consistent with the scenario that the ANF-mediated
increases of cGMP concentrations influence sodium
channels in an inhibitory manner. This pathway is pre-
sented in figure 4. PT mimicked the ANF effects (Mohr-
mann et increases of cGMP concentrations influence sodiu
channels in an inhibitory manner. This pathway is pr
sented in figure 4. PT mimicked the ANF effects (Moh
mann et al., 1987), dissociating renal ANF effects fro
an inhibitio channels in an inhibitory manner. This pathway is presented in figure 4. PT mimicked the ANF effects (Mohrmann et al., 1987), dissociating renal ANF effects from an inhibition of adenylyl cyclase by a PT-sensitive mechanis sented in figure 4. PT mimicked the ANF effects (Mohrmann et al., 1987), dissociating renal ANF effects from
an inhibition of adenylyl cyclase by a PT-sensitive mechanism. These specific actions of ANF on sodium con-
duct mann et al., 1987), dissociating renal ANF effects from an inhibition of adenylyl cyclase by a PT-sensitive mediation. These specific actions of ANF on sodium conductance have not been examined in the presence ANF R_1 o an inhibition of adenylyl cyclase by a PT-sensitive mechanism. These specific actions of ANF on sodium conductance have not been examined in the presence of ANF R_1 or R_2 receptor-binding agents. These experiments wi anism. These specific actions of ANF or ductance have not been examined in th
ANF R_1 or R_2 receptor-binding agents.
ments will be crucial in determining the
hypothesized ANF transduction pathway.
Calcium was identif ANF R_1 or R_2 receptor-binding agents. These experiments will be crucial in determining the validity of the hypothesized ANF transduction pathway.
Calcium was identified as an essential component for ments will be crucial in determining the validity of the

ments will be crucial in determining the validity of the
hypothesized ANF transduction pathway.
Calcium was identified as an essential component for
ANF effects on rat isolated kidneys (Camargo et al.,
1984). The interacti hypothesized ANF transduction pathway.
Calcium was identified as an essential component for
ANF effects on rat isolated kidneys (Camargo et al.,
1984). The interaction of ANF with calcium fluxes was
investigated in mesangi Calcium was identified as an essential component for

ANF effects on rat isolated kidneys (Camargo et al.,

1984). The interaction of ANF with calcium fluxes was

investigated in mesangial cells, where ANF suppressed

int 1984). The interaction of ANF with calcium fluxes was investigated in mesangial cells, where ANF suppressed intracellular calcium concentrations from 110 to 60 nM with an EC₅₀ of 100 pM (Lermioglu et al., 1991). However, 1984). The interaction of ANF with calcium fluxes
investigated in mesangial cells, where ANF suppre-
intracellular calcium concentrations from 110 to 60
with an EC_{60} of 100 pM (Lermioglu et al., 1991). Howe
ANF (100 pM investigated in mesangial cells, where ANF suppre
intracellular calcium concentrations from 110 to 60
with an EC₆₀ of 100 pM (Lermioglu et al., 1991). Howe
ANF (100 pM) failed to stimulate GC activity. Never
less, the s intracellular calcium concentrations from 110 to 60 nm
with an EC₅₀ of 100 pM (Lermioglu et al., 1991). However,
ANF (100 pM) failed to stimulate GC activity. Neverthe-
less, the suppression of intracellular calcium con with an EC₅₀ of 100 pM (Lermioglu et al., 1991). However,
ANF (100 pM) failed to stimulate GC activity. Neverthe-
less, the suppression of intracellular calcium concentra-
tions by dibutyryl cGMP indicates the potential ANF (100 pM) failed to stimulate GC activity. Neverthe-
less, the suppression of intracellular calcium concentra-
tions by dibutyryl cGMP indicates the potential for
cGMP involvement in mediating ANF effects on calcium
ho less, the suppression of intracellular calcium concentrations by dibutyryl cGMP indicates the potential for cGMP involvement in mediating ANF effects on calcium homeostasis. The ANF effects on calcium homeostasis could be tions by dibutyryl cGMP indicates the potential for
cGMP involvement in mediating ANF effects on calcium
homeostasis. The ANF effects on calcium homeostasis
could be relevant to the effect on sodium channels inas-
much as cGMP involvement in mediating ANF effects on calcium
homeostasis. The ANF effects on calcium homeostasis
could be relevant to the effect on sodium channels inas-
much as the sodium channels suppressed by ANF were
calcium a homeostasis. The ANF effects on calcium homeostasis
could be relevant to the effect on sodium channels inas-
much as the sodium channels suppressed by ANF were
calcium activated. The influence of ANF on other ion
channels, much as the sodium channels suppressed by ANF were
calcium activated. The influence of ANF on other ion
channels, such as potassium, has not been assessed in
the kidney.
5. Role of renal eicosanoids and endothelium-derived Luch as the sodium channels suppressed by ANF were
 Insural example, such as potassium, has not been assessed in
 5. Role of renal eicosanoids and endothelium-derived
 False of renal eicosanoids and endothelium-deriv

relative activated. The influence of ANF on other ion channels, such as potassium, has not been assessed in the kidney.
the kidney.
5. Role of renal eicosanoids and endothelium-derived relaxing factor. The renal response t channels, such as potassium, has not been assessed in
the kidney.
5. Role of renal eicosanoids and endothelium-derived
relaxing factor. The renal response to ANF has not been
associated with the production of EDRF. The res the kidney.
5. Role of renal eicosanoids and endothelium-derived
relaxing factor. The renal response to ANF has not been
associated with the production of EDRF. The responsive
enzyme to ANF, the particulate GC, differs fro

ANF RECEPTORS AND SIGNAL T
enzyme responding to EDRF, the soluble GC (Moncada
et al., 1987; Palmer et al., 1987, 1988). This difference ANF RECEPTORS AND SIGNAL T
enzyme responding to EDRF, the soluble GC (Moncada
et al., 1987; Palmer et al., 1987, 1988). This difference
allows a distinction between endothelial and ANF influand a distinction between endothelial and ANF influences in the kidney. Only particulate GC was activated and and the kidney. Only particulate GC was activated enzyme responding to EDRF, the soluble GC (Moncada
et al., 1987; Palmer et al., 1987, 1988). This difference
allows a distinction between endothelial and ANF influ-
ences in the kidney. Only particulate GC was activated
by et al., 1987; Palmer et al., 1987, 1988). This difference
allows a distinction between endothelial and ANF influ-
ences in the kidney. Only particulate GC was activated
by ANF in the kidney (Waldman et al., 1984).
Renal ei allows a distinction between endothelial and ANF influences in the kidney. Only particulate GC was activated
by ANF in the kidney (Waldman et al., 1984).
Renal eicosanoid synthesis was stimulated by ANF
(Himmelstein et al. allows a distinction between endothelial and ANF influences in the kidney. Only particulate GC was activated
by ANF in the kidney (Waldman et al., 1984).
Renal eicosanoid synthesis was stimulated by ANF
(Himmelstein et al.

ences in the kidney. Only particulate GC was activated
by ANF in the kidney (Waldman et al., 1984).
Renal eicosanoid synthesis was stimulated by ANF
(Himmelstein et al., 1990), although the eicosanoid syn-
thesis was not r by ANF in the kidney (Waldman et al., 1984).
Renal eicosanoid synthesis was stimulated by ANF
(Himmelstein et al., 1990), although the eicosanoid syn-
thesis was not related to renal effects of ANF. The
stimulatory effect Renal eicosanoid synthesis was stimulated by ANF
(Himmelstein et al., 1990), although the eicosanoid syn-
thesis was not related to renal effects of ANF. The
stimulatory effect of angiotensin on eicosanoid synthesis
was su (Himmelstein et al., 1990), although the eicosanoid syn-
thesis was not related to renal effects of ANF. The
stimulatory effect of angiotensin on eicosanoid synthesis
was suppressed in isolated mesangial cells treated with thesis was not related to renal effects of ANF. The stimulatory effect of angiotensin on eicosanoid synthesis was suppressed in isolated mesangial cells treated with ANF (Barnett et al., 1990), indicating that ANF can supp stimulatory effect of angiotensin on eicosanoid synthes
was suppressed in isolated mesangial cells treated wit
ANF (Barnett et al., 1990), indicating that ANF ca
suppress eicosanoid synthesis as well as stimulate i
Three r was suppressed in isolated mesangial cells treated with ANF (Barnett et al., 1990), indicating that ANF car suppress eicosanoid synthesis as well as stimulate it Three reports dissociate renal effects of ANF from eicos ano ANF (Barnett et al., 1990), indicating that ANF can suppress eicosanoid synthesis as well as stimulate it.
Three reports dissociate renal effects of ANF from eicosanoid synthesis (Keeler, 1982; Garcia et al., 1984; Rod-
ri suppress eicosanoid synthesis as well as stimulate
Three reports dissociate renal effects of ANF from eico
anoid synthesis (Keeler, 1982; Garcia et al., 1984; Ro
riguez-Puyol et al., 1986). These studies demonstrat
that na Three reports dissociate renal effects of anoid synthesis (Keeler, 1982; Garcia e riguez-Puyol et al., 1986). These studies
that natriuretic effects of ANF are unreplaced that natriuretic effects of ANF are unreplaced or E oid synthesis (Keeler, 1982; Garcia et al., 1984; Rod-
guez-Puyol et al., 1986). These studies demonstrated
at natriuretic effects of ANF are unrelated to eicosa-
id or EDRF synthesis in the kidney.
6. *Conclusion regardin*

that natriuretic effects of ANF are unrelated to eicosanoid or EDRF synthesis in the kidney.
6. Conclusion regarding atrial natriuretic factor renal transduction mechanisms. The renal effects of ANF appear to be mediated p that natriuretic effects of ANF are unrelated to eicosa
noid or EDRF synthesis in the kidney.
6. Conclusion regarding atrial natriuretic factor rena
transduction mechanisms. The renal effects of ANF ap
pear to be mediated including the significant of EDRF synthesis in the kidney.

6. Conclusion regarding atrial natriuretic factor renal and intera

transduction mechanisms. The renal effects of ANF apcare of a

pear to be mediated primarily b transduction mechanisms. The renal effects of ANF appear to be mediated primarily by GC activation, as originally hypothesized. The cGMP could act via a number of pathways, including those enumerated in figure 4. A suppres pear to be mediated primarily by GC activation, as originally hypothesized. The cGMP could act via a number of pathways, including those enumerated in figure 4. A suppression of phospholipase C activity, sodium conductance inally hypothesized. The cGMP could act via a number of pathways, including those enumerated in figure 4. suppression of phospholipase C activity, sodium conductance, or intracellular calcium accumulation have a been propo of pathways, including those enumerated in figure 4.
suppression of phospholipase C activity, sodium conductance, or intracellular calcium accumulation have a
been proposed as important signal transduction pathways. ANF al suppression of phospholipase C activity, sodium con-
ductance, or intracellular calcium accumulation have all
been proposed as important signal transduction path-
ways. ANF also suppresses renal adenylyl cyclase activ-
it ANF. ways. ANF also suppresses renal adenylyl cyclase activity, an activity potentially relating to diuretic actions of ANF.
C. Effects of Atrial Natriuretic Factor on Aldosterone

Production

NF.
Effects of Atrial Natriuretic Factor on Aldosterone
oduction
Sodium excretion by the kidney is controlled by renal
ansport processes including one influenced by aldoste-C. Effects of Atrial Natriuretic Factor on Aldosterone
Production
Sodium excretion by the kidney is controlled by re
transport processes including one influenced by aldos
rone, a mineralocorticoid produced by the adrenal g C. Effects of Arrau Natriaretic Factor on Autosterone
Production
Sodium excretion by the kidney is controlled by renal
transport processes including one influenced by aldoste-
rone, a mineralocorticoid produced by the adre From excretion by the kidney is controlled by renal
transport processes including one influenced by aldoste-
rone, a mineralocorticoid produced by the adrenal glo-
merulosa. Aldosterone acts on the distal tubule of the
ki Sodium excretion by the kidney is controlled by renal
transport processes including one influenced by aldoste-
rone, a mineralocorticoid produced by the adrenal glo-
merulosa. Aldosterone acts on the distal tubule of the
k transport processes including one influenced by aldoste-
rone, a mineralocorticoid produced by the adrenal glo-
merulosa. Aldosterone acts on the distal tubule of the
kidney to enhance sodium exchange for potassium, re-
s rone, a mineralocorticoid produced by the adrenal glomerulosa. Aldosterone acts on the distal tubule of the kidney to enhance sodium exchange for potassium, resulting in excretion of potassium and the retention codium. The merulosa. Aldosterone acts on the distal tubule of the cGN kidney to enhance sodium exchange for potassium, resulting in excretion of potassium and the retention of bees sodium. These effects oppose ANF actions on renal f kidney to enhance sodium exchange for potassium, is
sulting in excretion of potassium and the retention
sodium. These effects oppose ANF actions on renal fun
tion. The renin-angiotensin system opposes most AN
effects and a sodium. These effects oppose ANF actions on renal function. The renin-angiotensin system opposes most ANF effects and also stimulates aldosterone secretion. Investigators were spurred by these potentially antagonistic acti sodium. These effects oppose ANF actions on renal function. The renin-angiotensin system opposes most ANF effects and also stimulates aldosterone secretion. Investigators were spurred by these potentially antagonistic acti effects and also stimulates aldosterone secretion. Investigators were spurred by these potentially antagonistic actions of ANF and aldosterone to explore ANF effects on aldosterone release. Aldosterone secretion was inhibi tigators were spurred by these potentially antagonistic AN
actions of ANF and aldosterone to explore ANF effects election aldosterone release. Aldosterone secretion was inhibited by physiological ANF concentrations in all actions of ANF and aldosterone to explore ANF effects
on aldosterone release. Aldosterone secretion was inhib-
ited by physiological ANF concentrations in all studies
testing this effect (Atarashi et al., 1984, 1985; De Le on aldosterone release. Aldosterone secretion was inhibited by physiological ANF concentrations in all studies
testing this effect (Atarashi et al., 1984, 1985; De Lean
et al., 1984b; Goodfriend et al., 1984; Kudo and Bair ited by physiological ANF concentrations in all studies resting this effect (Atarashi et al., 1984, 1985; De Lean set al., 1984b; Goodfriend et al., 1984; Kudo and Baird, is 1984; Ishii et al. 1985; Elliott and Goodfriend, testing this effect (Atarashi et al., 1984, 1985; De Lean
et al., 1984b; Goodfriend et al., 1984; Kudo and Baird, is c
1984; Ishii et al. 1985; Elliott and Goodfriend, 1986;
Chartier and Schiffrin, 1987; Higuchi et al., 1 et al., 1984b; Goodfriend et al., 1984; Kudo and Baird, 1984; Ishii et al. 1985; Elliott and Goodfriend, 1986; Chartier and Schiffrin, 1987; Higuchi et al., 1986; Naruse et al., 1987), suggesting that this ANF action could 1984; Ishii et al. 1985; Elliott and Goodfriend, 19
Chartier and Schiffrin, 1987; Higuchi et al., 1986; Narr
et al., 1987), suggesting that this ANF action could
physiologically significant and account for natriure
effects Chartier and Schiffrin, 1987; Higuchi et al., 1986; Naruse
et al., 1987), suggesting that this ANF action could be
physiologically significant and account for natriuretic
effects. Established ANF effects within adrenal glo et al., 1987), suggesting that this ANF action could be recept
physiologically significant and account for natriuretic adren-
effects. Established ANF effects within adrenal glomer-
al., 19
ulosa cells are shown in figure physiologically significant and account for natriuretic effects. Established ANF effects within adrenal glomer-
ulosa cells are shown in figure 5. They include an acti-
vation of GC, potassium channels, and L-type calcium
 effects. Established ANF effects within adulosa cells are shown in figure 5. They increasion of GC, potassium channels, and L-channels, whereas T-type calcium channels and adenylyl cyclase activity are depressed.
1. Guanyl

 $\begin{array}{c|c}\n & \overline{\text{ATP}} & \text{(-)} & \text{---} & \text{---} \\
\hline\n\end{array}$ FIG. 5. Adrenal signal transduction pathways for ANF. ANF ac
on at least two receptors in the adrenal. It augments cGMP production
but cGMP has not been identified as a s FIG. 5. Adrenal signal transduction pathways for ANF. ANF acts
on at least two receptors in the adrenal. It augments cGMP production,
but cGMP has not been identified as a second messenger for any
adrenal response (?). ANF FIG. 5. Adrenal signal transduction pathways for ANF. ANF acts
on at least two receptors in the adrenal. It augments CGMP production,
but cGMP has not been identified as a second messenger for any
adrenal response (?). ANF FIG. 5. Adrenal signal transduction pathways for ANF. ANF as on at least two receptors in the adrenal. It augments cGMP production but cGMP has not been identified as a second messenger for a adrenal response (?). ANF inh on at least two receptors in the adrenal. It augments cGMP productio
but cGMP has not been identified as a second messenger for an
adrenal response (?). ANF inhibits adenylyl cyclase (AC) activity v
an interaction with th adrenal response (?). ANF inhibits adenylyl cyclase (AC) activity via
an interaction with the R₂ receptor and a G-protein (G). The signifi-
cance of adenylyl cyclase suppression by ANF has not been determined,
but the R cance of adenylyl cyclase suppression by ANF has not been determined, but the R_2 receptor appears to mediate stimulatory ANF effects on L channels. ANF also inhibits calcium conductance through T channels. Potassium

FIG. 5. Aterian signal transfortion pathways for ANF. ANF acts are indicated by the signal natrice of λ ANF inhibits adenyly cycles (AO) activity via an interaction with the R_s receptor and a G-protein (G). The signi counting for most ionic influences of ANF are unknown. Potentiating
or inhibitory effects are indicated by $(+)$ or $(-)$.
atrial natriuretic factor. The ubiquitous finding that ANF
enhances cGMP production prompted the hyp or inhibitory enects are indicated by $(+)$ or $(-)$.

atrial natriuretic factor. The ubiquitous finding that ANF

enhances cGMP production prompted the hypothesis

involving cGMP as the second messenger of ANF in the

adre atrial natriuretic factor. The ubiquitous finding that ANF
enhances cGMP production prompted the hypothesis
involving cGMP as the second messenger of ANF in the
adrenal glomerulosa. Early experiments in the adrenal
confirm atrial natriuretic factor. The ubiquitous finding that ANF
enhances cGMP production prompted the hypothesis
involving cGMP as the second messenger of ANF in the
adrenal glomerulosa. Early experiments in the adrenal
confirm enhances cGMP production prompted the hypothesis
involving cGMP as the second messenger of ANF in the
adrenal glomerulosa. Early experiments in the adrenal
confirmed the activation of GC by ANF (Matsuoka et
al., 1985; Naru involving cGMP as the second messenger of ANF in th
adrenal glomerulosa. Early experiments in the adrena
confirmed the activation of GC by ANF (Matsuoka e
al., 1985; Naruse et al., 1987). This correlative evidenc
for cGMP confirmed the activation of GC by ANF (Matsuoka et al., 1985; Naruse et al., 1987). This correlative evidence for cGMP suppressing aldosterone secretion was challenged by the observation that aldosterone secretion was main for cGMP suppressing aldosterone secretion was chalal., 1985; Naruse et al., 1987). This correlative evidence
for cGMP suppressing aldosterone secretion was chal-
lenged by the observation that aldosterone secretion was
maintained in the presence of membrane-permeable
cGMP for cGMP suppressing aldosterone secretion was chal-
lenged by the observation that aldosterone secretion was
maintained in the presence of membrane-permeable
cGMP analogs such as 8-bromo cGMP or dibutyryl
cGMP (Elliott an lenged by the observation that aldosterone secretion was
maintained in the presence of membrane-permeable
cGMP analogs such as 8-bromo cGMP or dibutyryl
cGMP (Elliott and Goodfriend, 1986; Matsuoka et al.,
1987; Barrett an maintained in the presence of membrane-permeable
cGMP analogs such as 8-bromo cGMP or dibutyryl
cGMP (Elliott and Goodfriend, 1986; Matsuoka et al.,
1987; Barrett and Isales, 1988). The latter results have
been interpreted cGMP analogs such as 8-bromo cGMP or dibutyryl
cGMP (Elliott and Goodfriend, 1986; Matsuoka et al.,
1987; Barrett and Isales, 1988). The latter results have
been interpreted to reject the GC hypothesis of ANF
action in th cGMP (Elliott and Goodfriend, 1986; Matsuoka et al.,
1987; Barrett and Isales, 1988). The latter results have
been interpreted to reject the GC hypothesis of ANF
action in the adrenal glomerulosa. However, the critical
te 1987; Barrett and Isales, 1988). The latter results have
been interpreted to reject the GC hypothesis of ANF
action in the adrenal glomerulosa. However, the critical
test of this hypothesis with a recently available ANF been interpreted to reject the GC hypothesis of ANF
action in the adrenal glomerulosa. However, the critical
test of this hypothesis with a recently available ANF R_1
receptor antagonist indicated that HS-142-1 eliminat action in the adrenal glomerulosa. However, the critical
test of this hypothesis with a recently available ANF R_1
receptor antagonist indicated that HS-142-1 eliminated
ANF effects to both suppress aldosterone synthesi test of this hypothesis with a recently available ANF R_1
receptor antagonist indicated that HS-142-1 eliminated
ANF effects to both suppress aldosterone synthesis and
elevate cGMP production in bovine adrenal glomerulo receptor antagonist indicated that HS-142-1 eliminated
ANF effects to both suppress aldosterone synthesis and
elevate cGMP production in bovine adrenal glomerulosa
cells (Oda et al., 1992). These data suggest that R₁
rec ANF effects to both suppress aldosterone synthesis and elevate cGMP production in bovine adrenal glomerulosa cells (Oda et al., 1992). These data suggest that R_1 receptors mediate ANF effects to suppress aldosterone se elevate cGMP production in bovine adrenal glomerulosa
cells (Oda et al., 1992). These data suggest that R_1
receptors mediate ANF effects to suppress aldosterone
secretion, but the involvement of cGMP in the response
is Ils (Oda et al., 1992). These data suggest that R_1
ceptors mediate ANF effects to suppress aldosterone
cretion, but the involvement of cGMP in the response
questionable.
As indicated in earlier sections, radioligand-bi

alosa cells are shown in figure 5. They include an acti-
varior of GC, potassium channels, and L-type calcium
of alter cGMP responses to ANF (Horng et al., 1991).
channels, whereas T-type calcium channels conductance
canno secretion, but the involvement of cGMP in the response
is questionable.
As indicated in earlier sections, radioligand-binding
studies with ANF and cANF indicated that ANF R_1
receptors made up the majority of ANF recept adrenal glomerulosa (Mizuno et al., 1990; Heidemann et is questionable.

As indicated in earlier sections, radioligand-binding

studies with ANF and cANF indicated that ANF R_1

receptors made up the majority of ANF receptors in the

adrenal glomerulosa (Mizuno et al., 1990 As indicated in earlier sections, radioligand-binding
studies with ANF and cANF indicated that ANF R_1
receptors made up the majority of ANF receptors in the
adrenal glomerulosa (Mizuno et al., 1990; Heidemann et
al., 1 studies with ANF and cANF indicated that ANF R_1
receptors made up the majority of ANF receptors in the
adrenal glomerulosa (Mizuno et al., 1990; Heidemann et
al., 1991). A variety of pharmacological agents produced
inc receptors made up the majority of ANF receptors in the
adrenal glomerulosa (Mizuno et al., 1990; Heidemann et
al., 1991). A variety of pharmacological agents produced
increased binding of ANF to adrenal membranes but did
n adrenal glomerulosa (Mizuno et al., 1990; Heidemann al., 1991). A variety of pharmacological agents produce increased binding of ANF to adrenal membranes but dinot alter cGMP responses to ANF (Horng et al., 1991) These fin al., 1991). A variety of pharmacological agents produce
increased binding of ANF to adrenal membranes but di
not alter cGMP responses to ANF (Horng et al., 1991)
These findings led the authors to hypothesize the exist
ence increased binding of ANF to adrenal membranes but did
not alter cGMP responses to ANF (Horng et al., 1991).
These findings led the authors to hypothesize the exist-
ence of a GC-uncoupled receptor that suppressed aldo-
ste

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ANAND-SRIVASTAVA AND TRACHTE
R₂ receptor represents such an entity, but a linear ANF atives such as A
analog selective for the R₂ receptor failed to either mimic ylyl cyclase at 476
 R_2 receptor represents such an entity, but a linear ANF at
analog selective for the R_2 receptor failed to either mimic yi
or block the ANF effect on aldosterone secretion (Ses-ct ANAND-SRIVAST
 R_2 receptor represents such an entity, but a linear ANI

analog selective for the R_2 receptor failed to either mimi

or block the ANF effect on aldosterone secretion (Ses

sions et al., 1992). Similar R_2 receptor represents such an entity, but a linear ANF analog selective for the R_2 receptor failed to either mimic or block the ANF effect on aldosterone secretion (Sessions et al., 1992). Similarly, a truncated AN analog selective for the R_2 receptor failed to either mimic ylyl cyclase at concentrations that do not stimulate
or block the ANF effect on aldosterone secretion (Ses-cGMP production. Therefore, the R_2 receptor appe analog selective for the R₂ receptor failed to either mimic
or block the ANF effect on aldosterone secretion (Ses-
sions et al., 1992). Similarly, a truncated ANF derivative,
ANF(106-121), failed to alter aldosterone sy or block the ANF effect on aldosterone secretion (Ses-
sions et al., 1992). Similarly, a truncated ANF derivative, me
ANF(106-121), failed to alter aldosterone synthesis at cyc
concentrations selective for the R_2 recep sions et al., 1992). Similarly, a truncated ANF derivative, meta-
ANF(106-121), failed to alter aldosterone synthesis at cyconcentrations selective for the R_2 receptor (Isales et al., 1992) but altered both adenylyl cy ANF (106–121), failed to alter aldosterone synthesis aconcentrations selective for the R_2 receptor (Isales et a 1992) but altered both adenylyl cyclase activity are calcium influx. These data argue against a role for t concentrations selective for the R_2 receptor (Isales et al., 1992) but altered both adenylyl cyclase activity and calcium influx. These data argue against a role for the R_2 receptor mediating ANF effects on aldoster calcium influx. These data argue against a role for the R_2 receptor mediating ANF effects on aldosterone secretion and, by exclusion, support a role for R_1 receptors. The general conclusions from these studies are t R_2 receptor mediating ANF effects on aldosterone secretion and, by exclusion, support a role for R_1 receptors. et The general conclusions from these studies are that ANF 19 adrenal effects are probably mediated by tion and, by exclusion, support a role for R_1 receptors. et a
The general conclusions from these studies are that ANF 199
adrenal effects are probably mediated by R_1 receptors; ald
however, the involvement of cGMP i The general conclusions from these studies are that ANF adrenal effects are probably mediated by R_1 receptors;
however, the involvement of cGMP in this response has
been questioned by a number of studies. There is no
p adrenal effects are probably mediated by R_1 receptors; alcowever, the involvement of cGMP in this response has evolven questioned by a number of studies. There is no alto precedent for R_1 receptors to act independen however, the involvement of cGMP in this response has even questioned by a number of studies. There is no a precedent for R_1 receptors to act independently of cGMP; or therefore, the ultimate mediator of ANF effects in been questioned by a number of studies. There is
precedent for R_1 receptors to act independently of cGN
therefore, the ultimate mediator of ANF effects in
adrenal gland is unestablished but may be $cGMP$. Fut
experime precedent for R_1 receptors to act independently of cGl
therefore, the ultimate mediator of ANF effects in
adrenal gland is unestablished but may be cGMP. Fur
experiments using selective ANF R_1 or R_2 recep
binding therefore, the ultimate
adrenal gland is unestal
experiments using sele
binding agents should d
tion pathway involved.
2. Role of adenylyl cyc **Prenal gland is unestablished but may be CGMP. Future**
periments using selective ANF R_1 or R_2 receptor-
nding agents should define further the signal transduc-
2. Role of adenylyl cyclase inhibition in atrial n

experiments using selective ANF R_1 or R_2 receptor-
binding agents should define further the signal transduc-
tion pathway involved.
2. Role of adenylyl cyclase inhibition in atrial natriuretic
factor effects on ald binding agents should define further the signal transduction pathway involved.

2. Role of adenylyl cyclase inhibition in atrial natriuretic

factor effects on aldosterone secretion. ANF reduced ad-

enylyl cyclase activit tion pathway involved.

2. Role of adenylyl cyclase inhibition in atrial natriuretic

factor effects on aldosterone secretion. ANF reduced ad-

enylyl cyclase activity in the adrenal glomerulosa in all

studies examining t 2. Role of adenylyl cyclase inhibition in atrial natriuretic factor effects on aldosterone secretion. ANF reduced adenylyl cyclase activity in the adrenal glomerulosa in all studies examining this effect (Anand-Srivastava factor effects on aldosterone secretion. ANF reduced adenylyl cyclase activity in the adrenal glomerulosa in all studies examining this effect (Anand-Srivastava et al., 1985); Waldman et al. 1985; Matsuoka et al., 1985; Is studies examining this effect (Anand-Srivastava et al., anism of ANF action being the most investigated. Most 1985b; Waldman et al. 1985; Matsuoka et al., 1985; Ishii of the initial studies found no effect of ANF on ⁴⁵C studies examining this effect (Anand-Srivastava et al., anis
1985b; Waldman et al. 1985; Matsuoka et al., 1985; Ishii of t
et al., 1985; Naruse et al., 1987; Barrett and Isales, 1988; influ
Heisler et al., 1989; MacFarland 1985b; Waldman et al. 1985; Matsuoka et al., 1985; Ishii et al., 1985; Naruse et al., 1987; Barrett and Isales, 1988; Heisler et al., 1989; MacFarland et al., 1991; Isales et al., 1992). The suppression of adenylyl cyclas et al., 1985; Naruse et al., 1987; Barrett and Isales, 1988; influited Heisler et al., 1989; MacFarland et al., 1991; Isales et al., 19892). The suppression of adenylyl cyclase activity in (1980) bovine adrenals occurred Heisler et al., 1989; MacFarland et al., 1991; Isales et al., 1989). The suppression of adenylyl cyclase activity in (19
hovine adrenals occurred at concentrations of ANF ap-
proximating plasma levels. The EC₅₀ varied fr 1992). The suppression of adenylyl cyclase activity in bovine adrenals occurred at concentrations of ANF approximating plasma levels. The EC_{60} varied from 10 to 100 pM (Anand-Srivastava et al., 1985b; Barrett and Isale bovine adrenals occurred at concentrations of ANF approximating plasma levels. The EC₅₀ varied from 10 to 100 pM (Anand-Srivastava et al., 1985b; Barrett and Isales, 1988). ANF also inhibited the prostaglandin E₁, ACTH proximating plasma levels. The EC_{50} varied from 10 to A(100 pM (Anand-Srivastava et al., 1985b; Barrett and feclies, 1988). ANF also inhibited the prostaglandin E_1 , the ACTH, and forskolin stimulation of both adenyl 100 pM (Anand-Srivastava et al., 1985b; Barrett and fected by ANF (Apfeldorf et al., 1988; Isales et al., 1992); Isales, 1988). ANF also inhibited the prostaglandin E_1 , therefore, ANF was thought to act by mechanisms u ACTH, and forskolin stimulation of both adenylyl cy-ACTH, and forskolin stimulation of both adenylyl cy-
clase activity and steroidogenesis, suggesting that the
adenylyl cyclase/cAMP pathway may account for the
inhibitory effects of ANF on steroidogenesis. These find-
types clase activity and steroidogenesis, suggesting that the
adenylyl cyclase/cAMP pathway may account for the
inhibitory effects of ANF on steroidogenesis. These find-
ings suggested that ANF could act by reducing cAMP
concent ings suggested that ANF could act by reducing cAMP concentrations; however, PT dissociated the effect of ANF on adenylyl cyclase activity and aldosterone synthesis. PT did not alter ANF effects on aldosterone inhibitory effects of ANF on steroidogenesis. These findings suggested that ANF could act by reducing cAMP concentrations; however, PT dissociated the effect of ANF on adenylyl cyclase activity and aldosterone synthesis. P ings suggested that ANF could act by reducing cAMP
concentrations; however, PT dissociated the effect of
ANF on adenylyl cyclase activity and aldosterone syn-
thesis. PT did not alter ANF effects on aldosterone
synthesis b concentrations; however, PT dissociated the effect of the ANF on adenylyl cyclase activity and aldosterone synthesis. PT did not alter ANF effects on aldosterone synthesis but eliminated the suppression of adenylyl lovelas ANF on adenylyl cyclase activity and aldosterone syn-
thesis. PT did not alter ANF effects on aldosterone characteristic synthesis but eliminated the suppression of adenylyl lar-
cyclase activity (Barrett and Isales, 1988; thesis. PT did not alter ANF effects on aldosterone c
synthesis but eliminated the suppression of adenylyl la
cyclase activity (Barrett and Isales, 1988; MacFarland et c
al., 1991). Furthermore, truncated ANF derivatives s synthesis but eliminated the suppression of adenylyl larg
cyclase activity (Barrett and Isales, 1988; MacFarland et caus
al., 1991). Furthermore, truncated ANF derivatives such rett
as ANF(106–121) failed to suppress aldos cyclase activity (Barrett and Isales, 1988; MacFarland et cal., 1991). Furthermore, truncated ANF derivatives such reas ANF(106–121) failed to suppress aldosterone secretion cat concentrations producing maximal reductions al., 1991). Furthermore, truncated ANF derivatives such ret
as ANF(106–121) failed to suppress aldosterone secretion cal
at concentrations producing maximal reductions in br
cAMP concentrations (Isales et al., 1992). These as ANF(106–121) failed to suppress aldosterone secretion can at concentrations producing maximal reductions in br cAMP concentrations (Isales et al., 1992). These data mindicate that the ANF effect on aldosterone synthesis at concentrations producing maximal reductions in cAMP concentrations (Isales et al., 1992). These data indicate that the ANF effect on aldosterone synthesis is not mediated by an action on adenylyl cyclase. The recent st cAMP concentrations (Isales et al., 1992). These dividends indicate that the ANF effect on aldosterone synthesis not mediated by an action on adenylyl cyclase. There are recent study of MacFarland et al. (1991) suggested indicate that the ANF effect on aldosterone synthes
not mediated by an action on adenylyl cyclase.
recent study of MacFarland et al. (1991) suggested
ANF acts via the R_1 receptor to increase cGMP con
trations, resultin not mediated by an action on adenylyl cyclase. The independent study of MacFarland et al. (1991) suggested that concentrations, resulting in an activation of cAMP phosphodical esterase and a decrease in cAMP concentration recent study of MacFarland et al. (1991) suggested t
ANF acts via the R_1 receptor to increase cGMP conc
trations, resulting in an activation of cAMP phospho
esterase and a decrease in cAMP concentrations. T
mechanism ANF acts via the R_1 receptor to increase cGMP concentrations, resulting in an activation of cAMP phosphodiesterase and a decrease in cAMP concentrations. This the mechanism probably does not solely mediate the suppress trations, resulting in an activation of cAMP phosphodi-
esterase and a decrease in cAMP concentrations. This to
mechanism probably does not solely mediate the suppres-
hosion of adenylyl cyclase activity caused by ANF, bec esterase and a decrease in cAMP concentrations. The
mechanism probably does not solely mediate the suppre
sion of adenylyl cyclase activity caused by ANF, becau
ANF acts on adenylyl cyclase at concentrations failin
to alte

A AND TRACHTE
atives such as ANF(106–121) are full agonists on ader
ylyl cyclase at concentrations that do not stimulat A AND TRACHTE
atives such as $ANF(106-121)$ are full agonists on aden-
ylyl cyclase at concentrations that do not stimulate
cGMP production. Therefore, the R_2 receptor appears to A AND TRACHTE
atives such as $ANF(106-121)$ are full agonists on aden-
ylyl cyclase at concentrations that do not stimulate
cGMP production. Therefore, the R₂ receptor appears to
mediate the inhibitory effect of ANF on a atives such as $ANF(106-121)$ are full agonists on aden-
ylyl cyclase at concentrations that do not stimulate
cGMP production. Therefore, the R_2 receptor appears to
mediate the inhibitory effect of ANF on adrenal adenyl atives such as $ANF(106-121)$ are full agonists of the sylplom cyclase at concentrations that do not see CGMP production. Therefore, the R_2 receptor and mediate the inhibitory effect of ANF on adrenal cyclase activity b yl cyclase at concentrations that do not stimulate *3. Atrial production*. Therefore, the R_2 receptor appears to ediate the inhibitory effect of ANF on adrenal adenylyl clase activity but not on aldosterone release.
3. mediate the inhibitory effect of ANF on adrenal adenylyl cyclase activity but not on aldosterone release.
3. Atrial natriuretic factor effects on phospholipase C in

1992) but altered both adenylyl cyclase activity and *adrenal glomerulosa*. ANF failed to alter phospholipase calcium influx. These data argue against a role for the C activity in bovine adrenal glands whether they were mediate the inhibitory effect of ANF on adrenal adenylyl
cyclase activity but not on aldosterone release.
3. Atrial natriuretic factor effects on phospholipase C in
adrenal glomerulosa. ANF failed to alter phospholipase
C cyclase activity but not on aldosterone release.

3. Atrial natriuretic factor effects on phospholipase C in

adrenal glomerulosa. ANF failed to alter phospholipase

C activity in bovine adrenal glands whether they were

q 3. Atrial natriuretic factor effects on phospholipase C in adrenal glomerulosa. ANF failed to alter phospholipase C activity in bovine adrenal glands whether they were quiescent or stimulated with angiotensin II (Goodfrien adrenal glomerulosa. ANF failed to alter phospholipase
C activity in bovine adrenal glands whether they were
quiescent or stimulated with angiotensin II (Goodfriend
et al., 1984; Elliott and Goodfriend, 1986; Isales et al. C activity in bovine adrenal glands whether they were
quiescent or stimulated with angiotensin II (Goodfriend
et al., 1984; Elliott and Goodfriend, 1986; Isales et al.
1992). Angiotensin II is thought to generate increased quiescent or stimulated with angiotensin II (Goodfriend
et al., 1984; Elliott and Goodfriend, 1986; Isales et al.,
1992). Angiotensin II is thought to generate increased
aldosterone synthesis via a phospholipase C-dependen et al., 1984; Elliott and Goodfriend, 1986; Isales et al., 1992). Angiotensin II is thought to generate increased aldosterone synthesis via a phospholipase C-dependent event. Therefore, it was anticipated that ANF would al 1992). Angiotensin II is thought to generate increased
aldosterone synthesis via a phospholipase C-dependent
event. Therefore, it was anticipated that ANF would
alter phospholipase C activity, but the lack of its effect
o aldosterone synthesis via a phospholipase C-dependent
event. Therefore, it was anticipated that ANF would
alter phospholipase C activity, but the lack of its effect
on this enzyme system clearly excluded this mechanism
as event. Therefore, it was and
alter phospholipase C activit
on this enzyme system clearl
as a potential signal transd
for adrenal actions of ANF.
4. Atrial natriuretic factor ter phospholipase C activity, but the lack of its effect
a this enzyme system clearly excluded this mechanism
a potential signal transduction pathway accounting
r adrenal actions of ANF.
4. Atrial natriuretic factor effect

on this enzyme system clearly excluded this mechanism
as a potential signal transduction pathway accounting
for adrenal actions of ANF.
4. Atrial natriuretic factor effects on ion fluxes in the
adrenal glomerulosa. The eff as a potential signal transduction pathway accounting
for adrenal actions of ANF.
4. Atrial natriuretic factor effects on ion fluxes in the
adrenal glomerulosa. The effects of ANF on the ionic
conductance in the adrenal ha for adrenal actions of ANF.
4. Atrial natriuretic factor effects on ion fluxes in the
adrenal glomerulosa. The effects of ANF on the ionic
conductance in the adrenal have focused on calcium and
potassium and essentially ha 4. Atrial natriuretic factor effects on ion fluxes in the adrenal glomerulosa. The effects of ANF on the ionic conductance in the adrenal have focused on calcium and potassium and essentially have ignored sodium. The perce conductance in the adrenal have focused on calcium and
potassium and essentially have ignored sodium. The
perceived primacy of calcium in mediating angiotensin conductance in the adrenal have focused on calcium and
potassium and essentially have ignored sodium. The
perceived primacy of calcium in mediating angiotensin
effects in the adrenal has resulted in this potential mech-
an potassium and essentially have ignored sodium. The
perceived primacy of calcium in mediating angiotensin
effects in the adrenal has resulted in this potential mech-
anism of ANF action being the most investigated. Most
of effects in the adrenal has resulted in this potential mecheffects in the adrenal has resulted in this potential mechanism of ANF action being the most investigated. Most of the initial studies found no effect of ANF on ⁴⁵Ca influx (Goodfriend et al., 1984; Elliott and Goodfrien anism of ANF action being the most investigated. Most
of the initial studies found no effect of ANF on ⁴⁵Ca
influx (Goodfriend et al., 1984; Elliott and Goodfriend,
1986; Isales et al., 1992), although Chartier and Schif of the initial studies found no effect of ANF on ⁴⁶Ca
influx (Goodfriend et al., 1984; Elliott and Goodfriend,
1986; Isales et al., 1992), although Chartier and Schiffrin
(1987) observed ANF to inhibit ⁴⁶Ca influx in r influx (Goodfriend et al., 1984; Elliott and Goodfriend
1986; Isales et al., 1992), although Chartier and Schiffri
(1987) observed ANF to inhibit ⁴⁵Ca influx in respons
to high concentrations of potassium, angiotensin II 1986; Isales et al., 1992), although Chartier and Schiffrin (1987) observed ANF to inhibit ⁴⁵Ca influx in response to high concentrations of potassium, angiotensin II, or ACTH. Intracellular calcium concentrations were u to high concentrations of potassium, angiotensin II, or
ACTH. Intracellular calcium concentrations were unafto high concentrations of pot
ACTH. Intracellular calcium
fected by ANF (Apfeldorf et al
therefore, ANF was thought t
related to calcium metabolism
More recent studies reveal

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More recent studies revealed an inhibitory effect of fected by ANF (Apfeldorf et al., 1988; Isales et al., 1992);
therefore, ANF was thought to act by mechanisms un-
related to calcium metabolism.
More recent studies revealed an inhibitory effect of
ANF on T-type channels an therefore, ANF was thought to act by mechanisms un-
related to calcium metabolism.
More recent studies revealed an inhibitory effect of
ANF on T-type channels and a stimulatory effect on L-
type channels (McCarthy et al., related to calcium metabolism.

More recent studies revealed an inhibitory effect of

ANF on T-type channels and a stimulatory effect on L-

type channels (McCarthy et al., 1990; Barrett et al.,

1991). The inhibitory effe More recent studies revealed an inhibitory effect of ANF on T-type channels and a stimulatory effect on I type channels (McCarthy et al., 1990; Barrett et al. 1991). The inhibitory effect of ANF on aldosterone synthesis wa ANF on T-type channels and a stimulatory effect on L-
type channels (McCarthy et al., 1990; Barrett et al.,
1991). The inhibitory effect of ANF on aldosterone syn-
thesis was more potent when the membrane was depo-
larized type channels (McCarthy et al., 1990; Barrett et al., 1991). The inhibitory effect of ANF on aldosterone synthesis was more potent when the membrane was depolarized slightly, a potential activating primarily T-type channel 1991). The inhibitory effect of ANF on aldosterone synthesis was more potent when the membrane was depolarized slightly, a potential activating primarily T-type channels. Alternatively, ANF was less potent during large dep thesis was more potent when the membrane was depolarized slightly, a potential activating primarily T-typ channels. Alternatively, ANF was less potent durin large depolarizations of the membrane presumably because these co larized slightly, a potential activating primarily T-type channels. Alternatively, ANF was less potent during large depolarizations of the membrane presumably because these conditions activated L-type channels (Barrett et channels. Alternatively, ANF was less potent durined large depolarizations of the membrane presumably because these conditions activated L-type channels (Bannett et al., 1991). In fact, ANF increased intracellula calcium c large depolarizations of the membrane presumably be-
cause these conditions activated L-type channels (Bar-
rett et al., 1991). In fact, ANF increased intracellular
calcium concentrations in largely depolarized mem-
branes cause these conditions activated L-type channels (Barrett et al., 1991). In fact, ANF increased intracellular calcium concentrations in largely depolarized membranes, whereas it suppressed these concentrations in mildly de rett et al., 1991). In fact, ANF increased intracellular
calcium concentrations in largely depolarized mem-
branes, whereas it suppressed these concentrations in
mildly depolarized membranes (Barrett et al., 1991). The
tru calcium concentrations in largely depolarized mem-
branes, whereas it suppressed these concentrations in
mildly depolarized membranes (Barrett et al., 1991). The
truncated ANF derivative, ANF(106–121), augmented an
influx branes, whereas it suppressed these concentrations in
mildly depolarized membranes (Barrett et al., 1991). The
truncated ANF derivative, ANF(106–121), augmented an
influx of calcium probably via an activation of L-type
cha mildly depolarized membranes (Barrett et al., 1991). The
truncated ANF derivative, ANF(106–121), augmented an
influx of calcium probably via an activation of L-type
channels (Isales et al., 1992). This report suggests that truncated ANF derivative, ANF(106-121), augmented influx of calcium probably via an activation of L-ty channels (Isales et al., 1992). This report suggests the activation of L-type channels is mediated either the ANF R_2 influx of calcium probably via an activation of L-type
channels (Isales et al., 1992). This report suggests that
the activation of L-type channels is mediated either by
the ANF R_2 receptor or another non-GC-coupled rec channels (Isales et al., 1992). This report suggests that
the activation of L-type channels is mediated either by
the ANF R₂ receptor or another non-GC-coupled recep-
tor. These data indicate that ANF can alter calcium
h the activation of L-type channels is mediated either by
the ANF R₂ receptor or another non-GC-coupled recep-
tor. These data indicate that ANF can alter calcium
homeostasis, but two opposing mechanisms are involved.
Ulti the ANF R₂ receptor or another non-GC-coupled receptor. These data indicate that ANF can alter calcium homeostasis, but two opposing mechanisms are involved. Ultimately, no definitive evidence exists to identify alterati tor. These data indicate thomeostasis, but two oppos
Ultimately, no definitive e
terations in calcium fluxes a
in the adrenal glomerulosa.

ANF RECEPTORS AND SIGNAL
Potassium is another ion that can profoundly affect
dosterone synthesis and release. Elevations in potas-ANF RECEPTORS AND SIGN
Potassium is another ion that can profoundly affer
aldosterone synthesis and release. Elevations in pota-
sium concentrations in plasma represent one of the mo ANF RECEPTORS AND SIGNAL

Potassium is another ion that can profoundly affect

aldosterone synthesis and release. Elevations in potas-

sium concentrations in plasma represent one of the most

potent stimuli for aldosteron Potassium is another ion that can profoundly affect repaldosterone synthesis and release. Elevations in potas-
sium concentrations in plasma represent one of the most con
potent stimuli for aldosterone production. The ANF Potassium is another ion that can profoundly affect
aldosterone synthesis and release. Elevations in potas-
sium concentrations in plasma represent one of the most
potent stimuli for aldosterone production. The ANF
effect aldosterone synthesis and release. Elevations in potas-
sium concentrations in plasma represent one of the most
potent stimuli for aldosterone production. The ANF a
effect is to reverse this stimulatory effect of potassium sium concentrations in plasma represent one of the most corpotent stimuli for aldosterone production. The ANF al., effect is to reverse this stimulatory effect of potassium. vol
Matsuoka et al. (1987) examined aldosterone effect is to reverse this stimulatory effect of potassium.
Matsuoka et al. (1987) examined aldosterone release
from rat adrenals exposed to ANF in the presence and
absence of 5 mM potassium. ANF suppressed aldosterone
p effect is to reverse this stimulatory effect of potassiun Matsuoka et al. (1987) examined aldosterone relefrom rat adrenals exposed to ANF in the presence absence of 5 mM potassium. ANF suppressed aldoster production only Matsuoka et al. (1987) examined aldosterone release da
from rat adrenals exposed to ANF in the presence and the
absence of 5 mM potassium. ANF suppressed aldosterone bu
production only in the presence of potassium. Alterna from rat adrenals exposed to ANF in the presence a
absence of 5 mM potassium. ANF suppressed aldostero
production only in the presence of potassium. Alterr
tively, ANF augmented GC activity regardless of potassium concent absence of 5 mM potassium. ANF suppressed aldosterone
production only in the presence of potassium. Alterna-
tively, ANF augmented GC activity regardless of the
potassium concentration. These data suggest an involve-
ment production only in the presence of potassium. Alterna-
tively, ANF augmented GC activity regardless of the
potassium concentration. These data suggest an involve-
ment of potassium transport in mediating ANF effects
con
al tively, ANF augmented GC activity regardless of the potassium concentration. These data suggest an involvement of potassium transport in mediating ANF effects on aldosterone synthesis. This hypothesis has not been explored potassium concentration. These data suggest an involvement of potassium transport in mediating ANF effect
on aldosterone synthesis. This hypothesis has not beexplored further by using potassium channel inhibitor
or patch-c ment of potassium transport in mediating ANF effect
on aldosterone synthesis. This hypothesis has not beer
explored further by using potassium channel inhibitors
or patch-clamp techniques in the adrenal gland. How
ever, th on aldosterone synthesis. This hypothesis has not been
explored further by using potassium channel inhibitors fact
or patch-clamp techniques in the adrenal gland. How-
inc.
ever, the work by Matsuoka et al. (1987) obvious or patch-clamp techniques in the adrenal gland. However, the work by Matsuoka et al. (1987) obviously indicates that the ANF effect on potassium conductance is a potentially important site of ANF action in the adrenal gland. Free that the Work by Matsuoka et al. (1987) obviously indities that the ANF effect on potassium conductance is a stentially important site of ANF action in the adrenal and.
5. Atrial natriuretic factor effects on adrenal

cates that the ANF effect on potassium conductance is a chemically important site of ANF action in the adrenal digland.

5. Atrial natriuretic factor effects on adrenal eicosanoids to or endothelium-derived relaxing factor potentially important site of ANF action in the adres
gland.
5. Atrial natriuretic factor effects on adrenal eicosano
or endothelium-derived relaxing factor. The role of the
agents in adrenal actions of ANF have not been i gland.
5. Atrial natriuretic factor effects on adrenal eicosanoids
or endothelium-derived relaxing factor. The role of these
agents in adrenal actions of ANF have not been investi-
gated. Negative results with these agents 5. Atrial natriuretic factor effects on adrenal eicosanoids
or endothelium-derived relaxing factor. The role of these
agents in adrenal actions of ANF have not been investi-
gated. Negative results with these agents in ot or endothelium-derived relaxing factor. The role of these
agents in adrenal actions of ANF have not been investi-
gated. Negative results with these agents in other sys-
tems suggest that they are unlikely candidates as se experies in auterial actions of ATVF have not been investigated. Negative results with these agents in other systems suggest that they are unlikely candidates as second for messengers for ANF in the adrenal gland. (V
6. Co

tems suggest that they are unlikely candidates as second
messengers for ANF in the adrenal gland. (With 6. Conclusion on atrial natriuretic factor adrenal signal
transduction pathways. The mechanism of ANF action
in the a messengers for ANF in the adrenal gland.

6. Conclusion on atrial natriuretic factor adrenal signal

transduction pathways. The mechanism of ANF action

in the adrenal gland appears to be mediated by the ANF
 R_1 recept 6. Conclusion on atrial natriuretic factor adrenal signal
transduction pathways. The mechanism of ANF action
in the adrenal gland appears to be mediated by the ANF
 R_1 receptor. Because adrenal effects of ANF have been
 transduction pathways. The mechanism of ANF action
in the adrenal gland appears to be mediated by the AN
 R_1 receptor. Because adrenal effects of ANF have be
dissociated from cGMP actions, the exact mechanism
action is in the adrenal gland appears to be mediated by the ANF
 R_1 receptor. Because adrenal effects of ANF have been
dissociated from cGMP actions, the exact mechanism of
action is unresolved, potentially involving signal tran R_1 receptor. Because adrenal effects of ANF have been
dissociated from cGMP actions, the exact mechanism of
action is unresolved, potentially involving signal trans-
duction pathways distinct from cGMP but presumably
m dissociated from cGMP actions, the exact mechanism of action is unresolved, potentially involving signal trans-
duction pathways distinct from cGMP but presumably mediated by R_1 receptors. ANF effects on aldosterone re action is unresolved, potentially involving signal trans-
duction pathways distinct from cGMP but presumably
mediated by R_1 receptors. ANF effects on aldosterone
release have been dissociated from ANF R_2 receptor
st duction pathways distinct from cGMP but presumably
mediated by R_1 receptors. ANF effects on aldosterone
release have been dissociated from ANF R_2 receptor
stimulation and adenylyl cyclase inhibition; however,
aldost mediated by R_1 receptors. ANF effects on aldosterone
release have been dissociated from ANF R_2 receptor
stimulation and adenylyl cyclase inhibition; however, to the GC activation. Furthermore, PT prevented the
aldos release have been dissociated from ANF R_2 receptor
stimulation and adenylyl cyclase inhibition; however,
aldosterone secretion is normally stimulated by cAMP.
Therefore, the suppression of cAMP concentrations by
ANF po stimulation and adenylyl cyclase inhibition; however,
aldosterone secretion is normally stimulated by cAMP.
Therefore, the suppression of cAMP concentrations by
ANF potentially could suppress aldosterone secretion in
isola aldosterone secretion is normally stimulated by cAMP.
Therefore, the suppression of cAMP concentrations by
ANF potentially could suppress aldosterone secretion in
isolated cases. Other known adrenal effects of ANF in-
volv ANF potentially could suppress aldosterone secretion in
isolated cases. Other known adrenal effects of ANF in-
volve an activation of L-type calcium channels and an
inhibition of T-type calcium channels. Extracellular po-ANF potentially could suppress aldosterone secretion in
isolated cases. Other known adrenal effects of ANF in-
volve an activation of L-type calcium channels and an
inhibition of T-type calcium channels. Extracellular po-
 isolated cases. Other known adrenal effects of ANF involve an activation of L-type calcium channels and an inhibition of T-type calcium channels. Extracellular potassium was required for ANF effects in this tissue, suggest tassium was required for ANF effects in this tissue, suggesting an important role for potassium. The adrenal actions of ANF are depicted in figure 5. ggesting an important role for potassium. The adrenal
tions of ANF are depicted in figure 5.
Cardiac Effects of Atrial Natriuretic Factor
A predominant cardiovascular effect of infused ANF
a suppression of cardiac output (

D. Cardiac Effects ofAtrial Natriuretic Factor

actions of ANF are depicted in figure 5.

D. Cardiac Effects of Atrial Natriuretic Factor

A predominant cardiovascular effect of infused ANF

is a suppression of cardiac output (Brenner et al., 1990).

This effect could b D. Cardiac Effects of Atrial Natriuretic Factor
A predominant cardiovascular effect of infused ANF
is a suppression of cardiac output (Brenner et al., 1990).
This effect could be caused by either decreased venous
return a *D. Cartuac Effects of Atrial Natriaretic Factor*
A predominant cardiovascular effect of infused ANF
is a suppression of cardiac output (Brenner et al., 1990).
This effect could be caused by either decreased venous
return A predominant cardiovascular effect of infused ANF
is a suppression of cardiac output (Brenner et al., 1990).
This effect could be caused by either decreased venous
return as a result of fluid loss from the vasculature or is a suppression of cardiac output (Brenner et al., 1990).
This effect could be caused by either decreased venous
return as a result of fluid loss from the vasculature or by
decreased cardiac contractility. However, some This effect could be caused by either decreased venous
return as a result of fluid loss from the vasculature or by
decreased cardiac contractility. However, some studies
failed to show any inotropic effect of ANF on cardia return as a result of fluid loss from the vasculature or by decreased cardiac contractility. However, some studies failed to show any inotropic effect of ANF on cardiac contractility (Wangler et al., 1985; Burnett et al., decreased cardiac contractility. However, some studies
failed to show any inotropic effect of ANF on cardiac
contractility (Wangler et al., 1985; Burnett et al., 1987;
Yanagisawa et al., 1987; Bohm et al., 1988; Hutter, 19 contractility (Wangler et al., 1985; Burnett et al., 1987; cardiac contractility, potentially by an inhibitory effect on calcium

Yanagisawa et al., 1987; Bohm et al., 1988; Hutter, 1991),

whereas a slight, but statistica

reported (Meulmens et al., 1988; Vaxelaire et al., 1989; RANSDUCTION MECHANISMS 477

reported (Meulmens et al., 1988; Vaxelaire et al., 1989;

Rankin and Swift, 1990; McCall and Fried, 1990). Heart

contains both ANF R_1 and R_2 receptors (McCartney et TRANSDUCTION MECHANISMS 477
reported (Meulmens et al., 1988; Vaxelaire et al., 1989;
Rankin and Swift, 1990; McCall and Fried, 1990). Heart
contains both ANF R₁ and R₂ receptors (McCartney et
al., 1990), indicating th reported (Meulmens et al., 1988; Vaxelaire et al., 1989; Rankin and Swift, 1990; McCall and Fried, 1990). Heart contains both ANF R_1 and R_2 receptors (McCartney et al., 1990), indicating that either receptor could b reported (Meulmens et al., 1988; Vaxelaire et al., 1989;
Rankin and Swift, 1990; McCall and Fried, 1990). Heart
contains both ANF R_1 and R_2 receptors (McCartney et
al., 1990), indicating that either receptor could b Rankin and Swift, 1990; McCall and Fried, 1990). Heart
contains both ANF R_1 and R_2 receptors (McCartney et
al., 1990), indicating that either receptor could be in-
volved in cardiac responses to ANF. The most convin contains both ANF R_1 and R_2 receptors (McCartney et al., 1990), indicating that either receptor could be involved in cardiac responses to ANF. The most convincing data regarding a signal transduction pathway indicat al., 1990), indicating that either receptor could be involved in cardiac responses to ANF. The most convincing data regarding a signal transduction pathway indicate that ANF effects are mediated independently of cGMP, but volved in cardiac responses to ANF. The most convincing
data regarding a signal transduction pathway indicate
that ANF effects are mediated independently of cGMP,
but the exact signaling pathways have not been dis-
cerned. data regarding a signal transduction pathway indicate
that ANF effects are mediated independently of cGMP,
but the exact signaling pathways have not been dis-
cerned. The intracellular actions of ANF in cardiocytes
are pre that ANF effects are mediated independently of cGMP,
but the exact signaling pathways have not been dis-
cerned. The intracellular actions of ANF in cardiocytes
are presented in figure 6, including an activation of GC
and conductance. rned. The intracellular actions of ANF in cardiocytes
e presented in figure 6, including an activation of GC
id inhibitions of both adenylyl cyclase and calcium
nductance.
1. Role of guanylyl cyclase in mediating atrial na

are presented in figure 6, including an activation of GC
and inhibitions of both adenylyl cyclase and calcium
conductance.
1. Role of guanylyl cyclase in mediating atrial natriuretic
factor cardiac responses. As in almos and inhibitions of both adenylyl cyclase and calcium
conductance.
1. Role of guanylyl cyclase in mediating atrial natriuretic
factor cardiac responses. As in almost all tissues, ANF
increased the production of cGMP in rab conductance.

1. Role of guanylyl cyclase in mediating atrial natriuretic

factor cardiac responses. As in almost all tissues, ANF

increased the production of cGMP in rabbit ventricle

(Cramb et al., 1987), rat sarcolemma 1. Role of guanylyl cyclase in mediating atrial natriure factor cardiac responses. As in almost all tissues, A increased the production of cGMP in rabbit ventricles (Cramb et al., 1987), rat sarcolemma (Rugg et al., 198 $\$ factor cardiac responses. As in almost all tissues, ANF increased the production of cGMP in rabbit ventricle (Cramb et al., 1987), rat sarcolemma (Rugg et al., 1989), chick ventricles (Vaxelaire et al., 1989), and rat myoc (Cramb et al., 1987), rat sarcolemma (Rugg et al., 1989), chick ventricles (Vaxelaire et al., 1989), and rat myocardial cells (McCall and Fried, 1990). Meulemans et al. (1988) found dibutyryl cGMP and sodium nitroprusside (Cramb et al., 1987), rat sarcolemma (Rugg et al., 1989)
chick ventricles (Vaxelaire et al., 1989), and rat myocar
dial cells (McCall and Fried, 1990). Meulemans et al
(1988) found dibutyryl cGMP and sodium nitroprussid
to chick ventricles (Vaxelaire et al., 1989), and rat myocardial cells (McCall and Fried, 1990). Meulemans et al. (1988) found dibutyryl cGMP and sodium nitroprusside to suppress cardiac contractility similarly to ANF, indica dial cells (McCall and Fried, 1990). Meulemans et al.
(1988) found dibutyryl cGMP and sodium nitroprusside
to suppress cardiac contractility similarly to ANF, indi-
cating that cGMP could be a mediator of ANF cardiac
effec (1988) found dibutyryl cGMP and sodium nitroprusside
to suppress cardiac contractility similarly to ANF, indi-
cating that cGMP could be a mediator of ANF cardiac
effects. Arguments against the hypothesis that inotropic
e to suppress cardiac contractility similarly to ANF, indicating that cGMP could be a mediator of ANF cardiac effects. Arguments against the hypothesis that inotropic effects of ANF were mediated by cGMP include the followin cating that cGMP could be a mediator of ANF cardiac effects. Arguments against the hypothesis that inotropic effects of ANF were mediated by cGMP include the following: (*a*) ANF failed to stimulate GC in some studies (Wal effects. Arguments against the hypothesis that inotropic
effects of ANF were mediated by cGMP include the
following: (a) ANF failed to stimulate GC in some studies
(Waldman et al., 1984), (b) the cardiac R_1 receptor following: (a) ANF failed to stimulate GC in some studies (Waldman et al., 1984), (b) the cardiac R_1 receptor is a low-affinity receptor in rats (Rugg et al., 1989), and (c) ANF inhibited cardiac contractions and following: (a) ANF failed to stimulate GC in some studies (Waldman et al., 1984), (b) the cardiac R_1 receptor is a low-affinity receptor in rats (Rugg et al., 1989), and (c) ANF inhibited cardiac contractions and ca (Waldman et al., 1984), (b) the cardiac R_1 receptor is a low-affinity receptor in rats (Rugg et al., 1989), and (c) ANF inhibited cardiac contractions and calcium influx in cultured rat heart cells in the absence of low-affinity receptor in rats (Rugg et al., 1989), and (c)
ANF inhibited cardiac contractions and calcium influx
in cultured rat heart cells in the absence of a measurable
cGMP response (McCall and Fried, 1990). Rugg et ANF inhibited cardiac contractions and calcium influx
in cultured rat heart cells in the absence of a measurable
cGMP response (McCall and Fried, 1990). Rugg et al.
(1989) found two cardiac ANF-binding sites by Scatchard
 in cultured rat heart cells in the absence of a measurable cGMP response (McCall and Fried, 1990). Rugg et al. (1989) found two cardiac ANF-binding sites by Scatchard analysis, a high-affinity site with a K_d of 11 pM an cGMP response (McCall and Fried, 1990). Rugg et al.
(1989) found two cardiac ANF-binding sites by Scatchard
analysis, a high-affinity site with a K_d of 11 pM and a
low-affinity site with a K_d of 1200 pM. The activatio (1989) found two cardiac ANF-binding sites by Scatchard analysis, a high-affinity site with a K_d of 11 pM and a low-affinity site with a K_d of 1200 pM. The activation of GC by ANF correlated with the binding to the lo analysis, a high-affinity site with a K_d of 11 pM and a low-affinity site with a K_d of 1200 pM. The activation of GC by ANF correlated with the binding to the low-affinity site, suggesting a lack of physiological rele

FIG. 6. Cardiac signal transduction pathways for ANF. As with
previously described tissues, ANF acts on R_1 receptors to promote
cGMP formation and probably interacts with the R_2 receptor to inhibit
adenylyl cyclase FIG. 6. Cardiac signal transduction pathways for ANF. As with
previously described tissues, ANF acts on R₁ receptors to promote
cGMP formation and probably interacts with the R₂ receptor to inhibit
adenylyl cyclase (AC FIG. 6. Cardiac signal transduction pathways for ANF. As with
previously described tissues, ANF acts on R_1 receptors to promote
cGMP formation and probably interacts with the R_2 receptor to inhibit
adenylyl cyclase $cGMP$ formation and probably interacts with the R_2 receptor to inhibit adenylyl cyclase (AC) activity via a G-protein (G). The inhibitory pathway involving $cAMP$ apparently (?) mediates the suppression of cardiac contr adenylyl cyclase (AC) activity via a G-protein (G). The inhibitory
pathway involving cAMP apparently (?) mediates the suppression of
cardiac contractility, potentially by an inhibitory effect on calcium
influx. The influen pathway involving cAMP apparently (?) mediates the suppression of cardiac contractility, potentially by an inhibitory effect on calcium influx. The influence on calcium conductance could be mediated by a suppression of cAM inotropic effect of ANF. -, inhibitory effects.

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ANAND-SRIVASTA

inhibitory inotropic effect of ANF (McCall and Fried,

1990). Typically, PT exerts no effect on the activation ANAND-SRIVASTAVA

inhibitory inotropic effect of ANF (McCall and Fried,

1990). Typically, PT exerts no effect on the activation

of GC by ANF (Drewett et al., 1990); therefore, these ANAND-SRIVASTAVA

inhibitory inotropic effect of ANF (McCall and Fried, m

1990). Typically, PT exerts no effect on the activation A

of GC by ANF (Drewett et al., 1990); therefore, these

of data refute the hypothesis tha inhibitory inotropic effect of ANF (McCall and Fried, n
1990). Typically, PT exerts no effect on the activation A
of GC by ANF (Drewett et al., 1990); therefore, these o
data refute the hypothesis that ANF acts on cardiac inhibitory inotropic effect of ANF (McCall and Fri
1990). Typically, PT exerts no effect on the activat
of GC by ANF (Drewett et al., 1990); therefore, th
data refute the hypothesis that ANF acts on carc
tissue via the GC 1990). Typically, PT exerts no effect on the activation
of GC by ANF (Drewett et al., 1990); therefore, these
data refute the hypothesis that ANF acts on cardiac
tissue via the GC signal transduction pathway. Alterna-
tive of GC by ANF (Drewett et al., 1990); therefore, these of a data refute the hypothesis that ANF acts on cardiac chatissue via the GC signal transduction pathway. Alternatively, Le Grand et al. (1992) found that ANF suppres data refute the hypothesis that ANF acts on cardiac c
tissue via the GC signal transduction pathway. Alterna-
tively, Le Grand et al. (1992) found that ANF suppresses
calcium currents in human atria in the presence of GTP tively, Le Grand et al. (1992) found that ANF suppresses cells failed to respond to ANF in cells exposed to GTP γ S calcium currents in human atria in the presence of GTP instead of GTP (Le Grand et al., 1992). Because G tively, Le Grand et al. (1992) found that ANF suppresses
calcium currents in human atria in the presence of GTP
but not GTP γ S. They interpreted this finding to indicate
that cGMP formation from GTP is essential for the calcium currents in human atria in the prese
but not GTP γ S. They interpreted this finding
that cGMP formation from GTP is essen
inhibitory actions of ANF on calcium fluxe
mately results in negative inotropic effects.
2

*2. Role of adenylyl cyclase inhibition in cardiac re*that cGMP formation from GTP is essential for the inhibitory actions of ANF on calcium fluxes that ulti-
mately results in negative inotropic effects.
2. Role of adenylyl cyclase inhibition in cardiac re-
sponses to atrial inhibitory actions of ANF on calcium fluxes that ulti-
mately results in negative inotropic effects.
2. Role of adenylyl cyclase inhibition in cardiac re-
sponses to atrial natriuretic factor. The ANF influence
on cardiac mately results in negative inotropic effects.
2. Role of adenylyl cyclase inhibition in cardiac re-
sponses to atrial natriuretic factor. The ANF influence
on cardiac adenylyl cyclase activity has been variable,
depending 2. Role of adenylyl cyclase inhibition in cardiac re-
sponses to atrial natriuretic factor. The ANF influence lim
on cardiac adenylyl cyclase activity has been variable, prin
depending on the investigators performing the s sponses to atrial natriuretic factor. The ANF influence lon cardiac adenylyl cyclase activity has been variable, independing on the investigators performing the studies.
Investigators failed to observe an ANF effect on cAM on cardiac adenylyl cyclase activity has been variable, prepending on the investigators performing the studies. will investigators failed to observe an ANF effect on cAMP effect concentrations in rabbit ventricular myocyte depending on the investigators performing the studies. we investigators failed to observe an ANF effect on cAMP effect concentrations in rabbit ventricular myocytes (Cramb et mal., 1987) or chick ventricles (Vaxelaire et a Investigators failed to observe an ANF effect on cAMP concentrations in rabbit ventricular myocytes (Cramb et al., 1987) or chick ventricles (Vaxelaire et al., 1989). The term is primary evidence for the existence of this concentrations in rabbit ventricular myocytes (Cramhal., 1987) or chick ventricles (Vaxelaire et al., 1989). The primary evidence for the existence of this pathway versupplied by Anand-Srivastava et al. (1984, 1986, 19 and al., 1987) or chick ventricles (Vaxelaire et al., 1989). The treprimary evidence for the existence of this pathway was the supplied by Anand-Srivastava et al. (1984, 1986, 1990) et and McCall and Fried (1990). They found a primary evidence for the existence of this pathway was
supplied by Anand-Srivastava et al. (1984, 1986, 1990)
and McCall and Fried (1990). They found a time-de-
pendent decrease in cAMP concentrations following the
additio supplied by Anand-Srivastava et al. $(1984, 1986, 1990)$ et and McCall and Fried (1990) . They found a time-de-
pendent decrease in cAMP concentrations following the AN
addition of ANF to cardiac homogenates or cultured and McCall and Fried (1990). They found a time-de-
pendent decrease in cAMP concentrations following the
addition of ANF to cardiac homogenates or cultured cells. Ne
This decrease in cAMP concentrations correlated with
the pendent decrease in cAMP concentrations following the AN addition of ANF to cardiac homogenates or cultured cells. Ne This decrease in cAMP concentrations correlated with the observed decrease in velocity of contraction an addition of ANF to cardiac homogenates or cultured cells.
This decrease in cAMP concentrations correlated with
the observed decrease in velocity of contraction and
calcium influx in cultured rat cardiac cells (McCall and
F This decrease in cAMP concentrations correlated with
the observed decrease in velocity of contraction and
calcium influx in cultured rat cardiac cells (McCall and
Fried, 1990). Furthermore, PT prevented both the de-
crease the observed decrease in velocity of contraction and ANR calcium influx in cultured rat cardiac cells (McCall and most Fried, 1990). Furthermore, PT prevented both the de-
Fried, 1990). Furthermore, PT prevented both the d calcium influx in cultured rat cardiac cells (McCall and momorities). Furthermore, PT prevented both the de-
crease in cAMP concentrations and the negative ino-
tropic effects of ANF. ANF also has been observed to role
inh Fried, 1990). Furthermore, PT prevented both the decrease in cAMP concentrations and the negative ino-
tropic effects of ANF. ANF also has been observed to respectively calcium currents in frog ventricular cells by a the crease in cAMP concentrations and the negative ino-
tropic effects of ANF. ANF also has been observed to
inhibit calcium currents in frog ventricular cells by a
mechanism reversed by exogenous administration of
cAMP (Gisbe tropic effects of ANF. ANF also has been observed to right inhibit calcium currents in frog ventricular cells by a timechanism reversed by exogenous administration of cAMP (Gisbert and Fischmeister, 1988). Thus, current to inhibit calcium currents in frog ventricular cells by a the mechanism reversed by exogenous administration of cAMP (Gisbert and Fischmeister, 1988). Thus, current to evidence supports an inhibitory action of ANF on cardia mechanism reversed by exogenous administration of 6.
cAMP (Gisbert and Fischmeister, 1988). Thus, current *tran*
evidence supports an inhibitory action of ANF on cardiac latu
contractility involving a suppression of adeny cAMP (Gisbert and Fischmeister, 1988). Thus, currer
evidence supports an inhibitory action of ANF on cardia
contractility involving a suppression of adenylyl cyclas
activity. The receptor involved is suspected to be an F
A contractility involving a suppression of adenylyl cyclase
activity. The receptor involved is suspected to be an R_2
ANF receptor coupled in an inhibitory manner to aden-
ylyl cyclase.
3. Atrial natriuretic factor effect ntractility involving a suppression of adenylyl cyclase cGMP
tivity. The receptor involved is suspected to be an R₂ ies fine
NF receptor coupled in an inhibitory manner to aden-
lout mask place.
3. Atrial natriuretic fac

activity. The receptor involved is suspected to be an R₂ ies
 ANF receptor coupled in an inhibitory manner to aden-
 activity cyclase.
 3. Atrial natriuretic factor effects on phospholipase C diat
 activity in the ANF receptor coupled in an inhibitory manner to aden-

ylyl cyclase.

3. Atrial natriuretic factor effects on phospholipase C di

activity in the heart. Only one study has examined ANF

influences on cardiac phospholipase no Antinum Cyclase.

3. Atrial natriuretic factor effects on phospholipase C

activity in the heart. Only one study has examined ANF

influences on cardiac phospholipase C activity, finding

ino ANF effect in rabbit ventri 3. Atrial natriuretic factor effects on phospholipase
activity in the heart. Only one study has examined AN
influences on cardiac phospholipase C activity, find
no ANF effect in rabbit ventricular myocytes (Cramb
al., 1987 activity in the heart. Only one study has examined ANF
influences on cardiac phospholipase C activity, finding
no ANF effect in rabbit ventricular myocytes (Cramb et
al., 1987). Obviously, this potential ANF signal trans-
 influences on cardiac phospholipase C activity, finding in
no ANF effect in rabbit ventricular myocytes (Cramb et
al., 1987). Obviously, this potential ANF signal trans-
duction pathway should be investigated further, but no ANF effect in rabbit ventricular myocytes (Cramb e al., 1987). Obviously, this potential ANF signal trans duction pathway should be investigated further, but currently there is no evidence supporting a critical role for 4. 1987). Obviously, this potential ANF signal trans-

action pathway should be investigated further, but cur-

htly there is no evidence supporting a critical role for

1. Atrial natriuretic factor effects on ion fluxes i

duction pathway should be investigated further, but currently there is no evidence supporting a critical role for phospholipase C mediation of cardiac effects of ANF. Fernal *A. Atrial natriuretic factor effects on ion flu* rently there is no evidence supporting a critical role for

phospholipase C mediation of cardiac effects of ANF. Pot

4. Atrial natriuretic factor effects on ion fluxes in the

theart. The influence of ANF on calcium fluxe phospholipase C mediation of cardiac effects of ANF.
4. Atrial natriuretic factor effects on ion fluxes in the
heart. The influence of ANF on calcium fluxes in cardiac
tissue have been investigated in only three studies. A 4. Atrial natriuretic factor effects on ion fluxes in the et a
heart. The influence of ANF on calcium fluxes in cardiac fect
tissue have been investigated in only three studies. ANF act
inhibited calcium influx into rat a heart. The influence of ANF on calcium fluxes in cardiac fects have not been investigated extensively, but GC
tissue have been investigated in only three studies. ANF activation appears as the most likely causative factor tissue have been investigated in only three studies. ANF accumulated calcium influx into rat and human myocardial the cells (McCall and Fried, 1990; Le Grand et al., 1992) and recalcium currents into frog ventricles stimu inhibited calcium influx into rat and human myocardial
cells (McCall and Fried, 1990; Le Grand et al., 1992) and
calcium currents into frog ventricles stimulated by a β -
adrenergic agonist (Gisbert and Fischmeister, 19 cells (McCall and Fried, 1990; Le Grand et al., 1992) and
calcium currents into frog ventricles stimulated by a β -
adrenergic agonist (Gisbert and Fischmeister, 1988). As
mentioned above, this inhibition of calcium cur adrenergic agonist (Gisbert and Fischmeister, 1988). As
mentioned above, this inhibition of calcium currents
could have been mediated by alterations in cAMP con-
centrations. PT inhibited ANF effects in rat myocardial
cell mentioned above, this inhibition of calcium currents

A AND TRACHTE
ment of an inhibitory G-protein in cardiac actions of
ANF. This putative G-protein could act via an inhibition A AND TRACHTE
ment of an inhibitory G-protein in cardiac actions of
ANF. This putative G-protein could act via an inhibition
of adenylyl cyclase or via a direct action on calcium A AND TRACHTE
ment of an inhibitory G-protein in cardiac actions of
ANF. This putative G-protein could act via an inhibition
of adenylyl cyclase or via a direct action on calcium
channels. No data are available at this tim ment of an inhibitory G-protein in cardiac actions
ANF. This putative G-protein could act via an inhibit
of adenylyl cyclase or via a direct action on calci
channels. No data are available at this time to differ
tiate betw ment of an inhibitory G-protein in cardiac actions of ANF. This putative G-protein could act via an inhibition of adenylyl cyclase or via a direct action on calcium channels. No data are available at this time to differen ANF. This putative G-protein could act via an inhibition
of adenylyl cyclase or via a direct action on calcium
channels. No data are available at this time to differen-
tiate between the two potential pathways. Human atri of adenylyl cyclase or via a direct action on calcium
channels. No data are available at this time to differen-
tiate between the two potential pathways. Human atrial
cells failed to respond to ANF in cells exposed to GTP channels. No data are available at this time to differentiate between the two potential pathways. Human atrial
cells failed to respond to ANF in cells exposed to GTP γ S
instead of GTP (Le Grand et al., 1992). Because GT cells failed to respond to ANF in cells exposed to $GTP\gamma S$ cells failed to respond to ANF in cells exposed to GTP γ S
instead of GTP (Le Grand et al., 1992). Because GTP is
a precursor to cGMP, these investigators interpreted the
data to indicate that cGMP mediates effects of AN instead of GTP (Le Grand et al., 1992). Because a precursor to cGMP, these investigators interdata to indicate that cGMP mediates effects calcium fluxes. The effects of ANF on other have not been determined in cardiac tiss precursor to cGMP, these investigators interpreted
ta to indicate that cGMP mediates effects of ANF
lcium fluxes. The effects of ANF on other ionic flu
we not been determined in cardiac tissue.
5. Atrial natriuretic factor

data to indicate that cGMP mediates effects of ANF calcium fluxes. The effects of ANF on other ionic fluxe
have not been determined in cardiac tissue.
5. Atrial natriuretic factor effects on cardiac endoth
lium-derived rel calcium fluxes. The effects of ANF on other ionic fluxes
have not been determined in cardiac tissue.
5. Atrial natriuretic factor effects on cardiac endothe-
lium-derived relaxing factor or eicosanoid synthesis. Sur-
prisi have not been determined in cardiac tissue.
5. Atrial natriuretic factor effects on cardiac endothe-
lium-derived relaxing factor or eicosanoid synthesis. Sur-
prisingly, the only evidence for the involvement of ANF
with e 5. Atrial natriuretic factor effects on cardiac endothe-
lium-derived relaxing factor or eicosanoid synthesis. Sur-
prisingly, the only evidence for the involvement of ANF
with endothelium originated from a study of cardia dium-derived relaxing factor or eicosanoid synthesis. Sur-
prisingly, the only evidence for the involvement of ANF
with endothelium originated from a study of cardiac
effects of ANF. The inhibitory effect of ANF on papilla prisingly, the only evidence for the involvement of ANF
with endothelium originated from a study of cardiac
effects of ANF. The inhibitory effect of ANF on papillary
muscle from cat and rat was eliminated by short-term
tre effects of ANF. The inhibitory effect of ANF on papillary
muscle from cat and rat was eliminated by short-term
treatment with the detergent, Triton X-100, an effect
the authors ascribed to endothelial removal (Meulemans
et effects of ANF. The inhibitory effect of ANF on papillary
muscle from cat and rat was eliminated by short-term
treatment with the detergent, Triton X-100, an effect
the authors ascribed to endothelial removal (Meulemans
et muscle from cat and rat was eliminated by short-term
treatment with the detergent, Triton X-100, an effect
the authors ascribed to endothelial removal (Meulemans
et al., 1988). Inasmuch as the detergent could have caused
o treatment with the detergent, Triton X-100, an effect
the authors ascribed to endothelial removal (Meulemans
et al., 1988). Inasmuch as the detergent could have caused
other membrane damage, it is speculative to conclude a the authors ascribed to endothelial removal (Meulemans
et al., 1988). Inasmuch as the detergent could have caused
other membrane damage, it is speculative to conclude an
ANF dependence on endothelium in cardiac tissue.
Nev et al., 1988). Inasmuch as the detergent could have caused
other membrane damage, it is speculative to conclude an
ANF dependence on endothelium in cardiac tissue.
Nevertheless, the study emphasizes the need for more
thoro other membrane damage, it is speculative to conclude an ANF dependence on endothelium in cardiac tissue.
Nevertheless, the study emphasizes the need for more thorough investigations to determine the mechanism of ANF action ANF dependence on endothelium in cardiac tissue.
Nevertheless, the study emphasizes the need for more
thorough investigations to determine the mechanism of
ANF action in cardiac tissue. As elaborated earlier, the
most avid Nevertheless, the study emphasizes the need for more
thorough investigations to determine the mechanism of
ANF action in cardiac tissue. As elaborated earlier, the
most avid binding of ANF to cardiac tissue occurs in the
e thorough investigations to determine the mechanism of ANF action in cardiac tissue. As elaborated earlier, the most avid binding of ANF to cardiac tissue occurs in the endocardium, which is consistent with endothelium medi ANF action in cardiac tissue. As elaborated earlier, the most avid binding of ANF to cardiac tissue occurs in the endocardium, which is consistent with endothelium mediating cardiac effects. No studies have investigated th most avid b
endocardiu
diating care
role of eico
the heart.
6. Conclu endocardium, which is consistent with endothelium mediating cardiac effects. No studies have investigated the role of eicosanoid synthesis in mediating ANF effects on the heart.
6. Conclusions regarding atrial natriuretic

role of eicosanoid synthesis in mediating ANF effects on
the heart.
6. Conclusions regarding atrial natriuretic factor cardiac
transduction mechanisms. As in the adrenal and vascu-
lature, recent evidence questions the imp role of eicosanoid synthesis in mediating ANF effects on
the heart.
6. Conclusions regarding atrial natriuretic factor cardiac
transduction mechanisms. As in the adrenal and vascu-
lature, recent evidence questions the imp the heart.
6. Conclusions regarding atrial natriuretic factor cardia
transduction mechanisms. As in the adrenal and vascu
lature, recent evidence questions the importance of
GMP in mediating cardiac effects of ANF. Recent 6. Conclusions regarding atrial natriuretic factor cardiac
transduction mechanisms. As in the adrenal and vascu-
lature, recent evidence questions the importance of
cGMP in mediating cardiac effects of ANF. Recent stud-
ie transduction mechanisms. As in the adrenal and vasculature, recent evidence questions the importance of cGMP in mediating cardiac effects of ANF. Recent studies find a negative inotropic effect of ANF. The signal transduct lature, recent evidence questions the importance of cGMP in mediating cardiac effects of ANF. Recent studies find a negative inotropic effect of ANF. The signal transduction pathway involved has not been elucidated but may cGMP in mediating cardiac effects of ANF. Recent studies find a negative inotropic effect of ANF. The signatransduction pathway involved has not been elucidate but may involve a suppression of adenylyl cyclase mediated by ies find a negative inotropic effect of ANF. The signal
transduction pathway involved has not been elucidated
but may involve a suppression of adenylyl cyclase me-
diated by a G-protein, as depicted in figure 6. The nega-
 transduction pathway involved has not been elucidated
but may involve a suppression of adenylyl cyclase me-
diated by a G-protein, as depicted in figure 6. The nega-
tive inotropic effects are prevented by PT and may
invol but may involve a suppression of adenylyl cyclar diated by a G-protein, as depicted in figure 6. The tive inotropic effects are prevented by PT and involve an inhibition of calcium conductance, would inhibit both force and *E. Fulmonary Effects* are prevented by PT and may involve an inhibition of calcium conductance, which would inhibit both force and conduction velocity.
E. Pulmonary Effects of Atrial Natriuretic Factor

ANF produces bronchodilation (Ishii and Murad, 1989; would inhibit both force and conduction velocity.

E. Pulmonary Effects of Atrial Natriuretic Factor

ANF produces bronchodilation (Ishii and Murad, 1989;

Potvin and Varma, 1989) and ciliary paralysis (Tamaoki

et al., 19 E. Pulmonary Effects of Atrial Natriuretic Factor
ANF produces bronchodilation (Ishii and Murad, 1989;
Potvin and Varma, 1989) and ciliary paralysis (Tamaoki
et al., 1991). The mechanisms accounting for these ef-
fects hav E. Fulmonary Effects of Atrua Ivalrateur Factor
ANF produces bronchodilation (Ishii and Murad, 1989;
Potvin and Varma, 1989) and ciliary paralysis (Tamaoki
et al., 1991). The mechanisms accounting for these ef-
fects have ANF produces bronchodilation (Ishii and Murad, 1989;
Potvin and Varma, 1989) and ciliary paralysis (Tamaoki
et al., 1991). The mechanisms accounting for these ef-
fects have not been investigated extensively, but GC
activa Potvin and Varma, 1989) and ciliary paralysis (Tamaoki
et al., 1991). The mechanisms accounting for these ef-
fects have not been investigated extensively, but GC
activation appears as the most likely causative factor at
t et al., 1991). The mechanisms accounting for these effects have not been investigated extensively, but GC activation appears as the most likely causative factor at this point. Pulmonary adenylyl cyclase activity also is re fects have not been investigated extensively, but GC
activation appears as the most likely causative factor at
this point. Pulmonary adenylyl cyclase activity also is
reduced by ANF and may have a functional role in some
p this point. Pulmonary adenylyl cyclase activity also is this point. Pulmonary adenylyl cyclase activity also is
reduced by ANF and may have a functional role in some
pulmonary responses to ANF, but critical tests of this
hypothesis are lacking at present. Because of the limited reduced by ANF and may have a functional role in some
pulmonary responses to ANF, but critical tests of this
hypothesis are lacking at present. Because of the limited
amount of information available concerning pulmonary
ef pulmonary responses to ANF, but critical tests of this
hypothesis are lacking at present. Because of the limited
amount of information available concerning pulmonary
effects of ANF, only guanylyl and adenylyl cyclase will
 hypothesis are lacking at present. Because of the limited
amount of information available concerning pulmonary
effects of ANF, only guanylyl and adenylyl cyclase will
be discussed as potential pulmonary signal transduction

PHARMACOLOGICAL REVIEWS

aspet

ANF RECEPTORS AND SIGNAL TIT presented in figure 7. They are limited to an activation of GC and an inhibition of adenylyl cyclase.

ANF RECEPTORS AND SIGNAL

1. essented in figure 7. They are limited to an activation

GC and an inhibition of adenylyl cyclase.

1. Role of guanylyl cyclase in pulmonary effects of atrial

intriuretic factor. Bovine trache presented in figure 7. They are limited to an activation
of GC and an inhibition of adenylyl cyclase.
1. Role of guanylyl cyclase in pulmonary effects of atrial
natriuretic factor. Bovine tracheal muscle dilated in re-
spo presented in figure 7. They are limited to an activatiof GC and an inhibition of adenylyl cyclase.
1. Role of guanylyl cyclase in pulmonary effects of atractriuretic factor. Bovine tracheal muscle dilated in sponse to a va of GC and an inhibition of adenylyl cyclase.

1. Role of guanylyl cyclase in pulmonary effects of atrial

natriuretic factor. Bovine tracheal muscle dilated in re-

sponse to a variety of ANF congeners capable of stimu-

l 1. Role of guanylyl cyclase in pulmonary effects of atrial natriuretic factor. Bovine tracheal muscle dilated in response to a variety of ANF congeners capable of stimulating GC (Ishii and Murad, 1989). In contrast, ANF $($ natriuretic factor. Bovine tracheal muscle dilated in re-
sponse to a variety of ANF congeners capable of stimu-
lating GC (Ishii and Murad, 1989). In contrast, flue
ANF(103-123) neither stimulated GC nor relaxed tra-
chea sponse to a variety of ANF congeners capable of stimu-
lating GC (Ishii and Murad, 1989). In contrast, flue
ANF(103-123) neither stimulated GC nor relaxed tra-
cheal muscle. This information is consistent with an in p
act lating GC (Ishii and Murad, 1989). In contrast, 1
ANF(103-123) neither stimulated GC nor relaxed tra-
cheal muscle. This information is consistent with an
activation of R_1 receptors to stimulate GC activity to
produce ANF(103-123) neither stimulated GC nor relaxed tra-
cheal muscle. This information is consistent with an
activation of R_1 receptors to stimulate GC activity to
produce the tracheal relaxant, cGMP. Other evidence
favori cheal muscle. This information is consistent with an activation of R_1 receptors to stimulate GC activity to produce the tracheal relaxant, cGMP. Other evidence favoring this scheme includes the ability of dibutyryl cGM activation of R₁ receptors to stimulate GC activity to produce the tracheal relaxant, cGMP. Other evidence favoring this scheme includes the ability of dibutyryl cGMP to relax tracheal smooth muscle (Ishii and Murad, 198 produce the tracheal relaxant, cGMP. Other evidence F favoring this scheme includes the ability of dibutyryl cGMP to relax tracheal smooth muscle (Ishii and Murad, ir 1989). A similar conclusion has been advanced in rab favoring this scheme includes the ability of dibutyryl
cGMP to relax tracheal smooth muscle (Ishii and Murad,
1989). A similar conclusion has been advanced in rabbit
tracheal epithelium. ANF both decreased ciliary motility cGMP to relax tracheal smooth muscle (Ishii and M
1989). A similar conclusion has been advanced in r
tracheal epithelium. ANF both decreased ciliary mo
and elevated cGMP concentrations, and these activ
were augmented by a 1989). A similar conclusion has been advanced in rabbit
tracheal epithelium. ANF both decreased ciliary motility
and elevated cGMP concentrations, and these activities
were augmented by an inhibitor of cGMP phosphodies-
t tracheal epithelium. ANF both decreased ciliary motility
and elevated cGMP concentrations, and these activities
were augmented by an inhibitor of cGMP phosphodies-
terase, M & B 22948 (Tamaoki et al., 1991). Another
agent and elevated cGMP concentrations, and these activities
were augmented by an inhibitor of cGMP phosphodies-
terase, M & B 22948 (Tamaoki et al., 1991). Another
agent, ANF(Tyr106, 103-125), neither activated GC nor
inhibite were augmented by an inhibitor of cGMP phosphodies-
terase, M & B 22948 (Tamaoki et al., 1991). Another
agent, ANF (Tyr106, 103-125), neither activated GC nor
inhibited ciliary motility. Thus, most of the available
eviden terase, M & B 22948 (Tamaoki et al., 1991). Anoth
agent, ANF(Tyr106, 103-125), neither activated GC n
inhibited ciliary motility. Thus, most of the availat
evidence is consistent with ANF effects in the lung bei
mediated agent, ANF(Tyr106, 103-125), neither activated GC nor inhibited ciliary motility. Thus, most of the available evidence is consistent with ANF effects in the lung being mediated by cGMP. No studies have used ANF R_1 rece inhibited ciliary
evidence is consi
mediated by cGI
tor antagonists,
more rigorously.
2. Role of aden *2. Role of a consistent with ANF effects in the lung being* ediated by cGMP. No studies have used ANF R₁ receprediated by cGMP. No studies have used ANF R₁ receprediating atrial or *adenylyl cyclase inhibition in medi*

mediated by cGMP. No studies have used ANF R_1 receptor antagonists, PT, or cANF to test this hypothesis R_V
more rigorously.
2. Role of adenylyl cyclase inhibition in mediating atrial areas natriuretic factor effects tor antagonists, PT, or cANF to test this hypothesis more rigorously.

2. Role of adenylyl cyclase inhibition in mediating atrial

natriuretic factor effects in the lung. ANF reduced cAMP

concentrations in lungs from rat more rigorously.

2. Role of adenylyl cyclase inhibition in mediating atrial

natriuretic factor effects in the lung. ANF reduced cAMP

concentrations in lungs from rat (Anand-Srivastava et

al., 1988; Resink et al., 1988) 2. Role of adenylyl cyclase inhibition in mediating atrial natriuretic factor effects in the lung. ANF reduced CAMP concentrations in lungs from rat (Anand-Srivastava et al., 1988) but not from bovine trachea (Ishii and Mu natriuretic factor effects in the lung. ANF reduced cAM
concentrations in lungs from rat (Anand-Srivastava
al., 1988; Resink et al., 1988) or rabbit (Tkachuk et a
1989) but not from bovine trachea (Ishii and Mura
1989). Th concentrations in lungs from rat (Anand-Srivastava al., 1988; Resink et al., 1988) or rabbit (Tkachuk et al. 1989) but not from bovine trachea (Ishii and Mura 1989). The significance of this effect has not been asce tained al., 1988; Resink et al., 1988) or rabbit (Tkachuk et al., we
1989) but not from bovine trachea (Ishii and Murad, 1989). The significance of this effect has not been ascer-
tained but cAMP is considered to be a bronchodil 1989) but not from bovine trachea (Ishii and Murad, 1989). The significance of this effect has not been ascertained but cAMP is considered to be a bronchodilator; therefore, a suppression of adenylyl cyclase activity would 1989). The significance of this effect has not been ascertained but cAMP is considered to be a bronchodilator; therefore, a suppression of adenylyl cyclase activity would be an unlikely mediator of ANF relaxant effects. Wh tained but cAMP is considered to be a bronchodilator;
therefore, a suppression of adenylyl cyclase activity
would be an unlikely mediator of ANF relaxant effects.
Whether this ANF effect mediates other pulmonary re-
sponse unestabbished. build be an unlikely mediator of ANF relaxant effect
 ANF reffect mediates other pulmonary *r*

conses to ANF, such as suppressed ciliary motility,
 sestablished.
 *3. Conclusions regarding pulmonary transduction path-*Whether this ANF effect mediates other pulmonary responses to ANF, such as suppressed ciliary motility, is unestablished.
3. Conclusions regarding pulmonary transduction path-ways. ANF effects in the lung appear to be med

ATP⁽⁻⁾
FIG. 7. Pulmonary signal transduction pathways for ANF. ANF can
act on R₁ receptors to stimulate cGMP formation, and the cGMP
apparently (?) mediates the relaxant effect. ANF also inhibits adenylyl
cyclase (AC FIG. 7. Pulmonary signal transduction pathways for ANF. ANF can
act on R₁ receptors to stimulate cGMP formation, and the cGMP is
apparently (?) mediates the relaxant effect. ANF also inhibits adenylyl co
cyclase (AC), pr act on R_1 receptors to stimulate cGMP formation, and the apparently (?) mediates the relaxant effect. ANF also inhibits a cyclase (AC), presumably by an interaction with the R_2 recep coupling via a G-protein (G). Th

r
AMEN MECHANISMS (479)
The stimulation of GC; a suppression of adenylyl cyclase
also could be involved. The signal transduction pathways TRANSDUCTION MECHANISMS
a stimulation of GC; a suppression of adenylyl cyclase
also could be involved. The signal transduction pathways
for ANF in the lung have not been investigated thor-FRANSDUCTION MECHANISMS 47
a stimulation of GC; a suppression of adenylyl cyclas
also could be involved. The signal transduction pathway
for ANF in the lung have not been investigated thor
oughly, and these conclusions req a stimulation of GC; a suppression of adenylyl cycla
also could be involved. The signal transduction pathwa
for ANF in the lung have not been investigated the
oughly, and these conclusions require additional inve
tigations a stimulation of GC; a suppression of adenylyl cyclase
also could be involved. The signal transduction pathways
for ANF in the lung have not been investigated thor-
oughly, and these conclusions require additional inves-
t also could be involved. The signal transduction pathways
for ANF in the lung have not been investigated thor-
oughly, and these conclusions require additional inves-
tigations into receptor subtypes, PT sensitivity, and in for ANF in the lung have not been investigated thor-
oughly, and these conclusions require additional inves-
tigations into receptor subtypes, PT sensitivity, and in-
fluences on ionic fluxes and phospholipase activities. oughly, and these conclusions require additional
tigations into receptor subtypes, PT sensitivity, a
fluences on ionic fluxes and phospholipase activition
rudimentary pathways described thus far for ANF
in pulmonary tissue *Frequences on ionic fluxes and phospholipase activities. The rudimentary pathways described thus far for ANF effects in pulmonary tissues are presented in figure 7.
<i>F. Endocrine Effects of Atrial Natriuretic Factor* The

dimentary pathways described thus far for ANF effects
pulmonary tissues are presented in figure 7.
Endocrine Effects of Atrial Natriuretic Factor
The majority of ANF effects on the endocrine system
volves inhibition of hor in purmonary ussues are presented in ngure 7.

F. Endocrine Effects of Atrial Natriuretic Factor

The majority of ANF effects on the endocrine system

involves inhibition of hormone synthesis or release, as

was described F. Endocrine Effects of Atrial Natriuretic Factor
The majority of ANF effects on the endocrine system
involves inhibition of hormone synthesis or release, as
was described for aldosterone. Examples of endocrine
effects of F. Endocrine Effects of Atria Natriancic Factor
The majority of ANF effects on the endocrine system
involves inhibition of hormone synthesis or release,
was described for aldosterone. Examples of endocri-
effects of ANF i The majority of ANF effects on the endocrine system
involves inhibition of hormone synthesis or release, as
was described for aldosterone. Examples of endocrine
effects of ANF include lessened secretion of the follow-
ing: was described for aldosterone. Examples of endocrine effects of ANF include lessened secretion of the following: (a) ACTH, (b) antidiuretic hormone, (c) thyroid hormone or thyroglobulin, (d) progesterone, and (e) renin. In was described for aldosterone. Examples of endocreffects of ANF include lessened secretion of the following: (a) ACTH, (b) antidiuretic hormone, (c) thyre hormone or thyroglobulin, (d) progesterone, and renin. In cont effects of ANF include lessened secretion of the following: (a) ACTH, (b) antidiuretic hormone, (c) thyroid hormone or thyroglobulin, (d) progesterone, and (e) renin. In contrast, the release of testosterone and lute ing: (a) ACTH, (b) antidiuretic hormone, (c) thyroid hormone or thyroglobulin, (d) progesterone, and (e) renin. In contrast, the release of testosterone and luteinizing hormone was enhanced by ANF. The mechanisms acc hormone or thyroglobulin, (d) progesterone, and (e)
renin. In contrast, the release of testosterone and lutein-
izing hormone was enhanced by ANF. The mechanisms
accounting for these effects are uninvestigated in most
c renin. In contrast, the release of testosterone and lutein-
izing hormone was enhanced by ANF. The mechanisms
accounting for these effects are uninvestigated in most
cases. GC activation and adenylyl cyclase inhibition are izing hormone was enhanced by ANF. The mechanisms
accounting for these effects are uninvestigated in most
cases. GC activation and adenylyl cyclase inhibition are
two common ANF effects in most endocrine organs.
Evidence a accounting for these effects are uninvestigated in most cases. GC activation and adenylyl cyclase inhibition are
two common ANF effects in most endocrine organs
Evidence also exists for alterations in potassium current
med cases. GC activation and adenylyl cyclase inhibition are
two common ANF effects in most endocrine organs.
Evidence also exists for alterations in potassium currents
mediating inhibitory effects on ACTH release. In gen-
era two common ANF effects in most endocrine organs.
Evidence also exists for alterations in potassium currents
mediating inhibitory effects on ACTH release. In gen-
eral, there is a dearth of information concerning receptor
s Evidence also exists for alterations in potassium curren
mediating inhibitory effects on ACTH release. In ger
eral, there is a dearth of information concerning recept
subtypes functioning in endocrine organs, and PT ha
not mediating inhibitory effects on ACTH release. In general, there is a dearth of information concerning receptor subtypes functioning in endocrine organs, and PT has not been utilized to define potential transduction pathway eral, there is a dearth of information concerning receptor
subtypes functioning in endocrine organs, and PT has
not been utilized to define potential transduction path-
ways in any endocrine organ except the adrenal, as wa subtypes functioning in endocrine organs, and PT has
not been utilized to define potential transduction path-
ways in any endocrine organ except the adrenal, as was
described earlier. Thus, the information available is pri not been utilized to define potential transduction pathways in any endocrine organ except the adrenal, as was described earlier. Thus, the information available is primarily descriptive regarding the existence of an ANF ef ways in any endocrine organ except the adrenal, as was
described earlier. Thus, the information available is pri-
marily descriptive regarding the existence of an ANF
effect. We shall present evidence for ANF effects on GC described earlier. Thus, the information available is primarily descriptive regarding the existence of an ANF effects. We shall present evidence for ANF effects on GC, adenylyl cyclase, and ion channels, and their potentia of ANF within endocrine cells are presented in figure 8.

ATP
FIG. 8. Endocrine signal transduction pathways for ANF. ANF
activates R_1 receptors to accelerate cGMP formation. The cGMP
apparently mediates an enhanced release of testosterone from the
testis. ANF also presumab FIG. 8. Endocrine signal transduction pathways for ANF. ANF activates R_1 receptors to accelerate cGMP formation. The cGMP apparently mediates an enhanced release of testosterone from the testis. ANF also presumably int activates R₁ receptors to accelerate CGMP formation. The CGMP
apparently mediates an enhanced release of testosterone from the
testis. ANF also presumably interacts with R₂ receptors to inhibit
adenylyl cyclase (AC) ac couple to potassium channels via **and the G-protein**
(G). The decrease in cAMP concentrations appears to result in dimin-
ished release of various hormones. The adenylyl cyclase pathway may
couple to potassium channels via adenylyl cyclase (AC) activity by a mechanism involving a G-protein (G). The decrease in cAMP concentrations appears to result in diminished release of various hormones. The adenylyl cyclase pathway may couple to potassium (G). The decrease in cAMP concentrations appears to result in diminished release of various hormones. The adenylyl cyclase pathway may couple to potassium channels via the G-protein to inhibit hormone release also (?). Th ished release of various horm
couple to potassium channel
release also (?). The cGMP as
mediated by promiscuous ac
kinase. -, inhibitory effects.

PHARM
REV

PHARMACOLOGICAL REVIEWS

The major actions are to augment either GC or potassium A
channel activity or to suppress adenylyl cyclase activity. (1
1. Atrial natriuretic factor effects on guanylyl cyclase in
endocrine organs. GC activity in anterio The major actions are to augment either GC or potassium
channel activity or to suppress adenylyl cyclase activity.
1. Atrial natriuretic factor effects on guanylyl cyclase in
endocrine organs. GC activity in anterior pitui channel activity or to suppress adenylyl cyclase activity. (Pa

1. Atrial natriuretic factor effects on guanylyl cyclase in

endocrine organs. GC activity in anterior pituitaries was

action and Dutz-Bucher, 1989; Dayanith 1. Atrial natriuretic factor effects on guanylyl cyclase in conducrine organs. GC activity in anterior pituitaries was increased by ANF (Heisler et al., 1986; Abou-Samra et al., 1987; Koch and Lutz-Bucher, 1989; Dayanithi endocrine organs. GC activity in anterior pituitaries was
increased by ANF (Heisler et al., 1986; Abou-Samra et
al., 1987; Koch and Lutz-Bucher, 1989; Dayanithi and
Antoni, 1990), and many studies also observed a decrease
 increased by ANF (Heisler et al., 1986; Abou-Samra et al., 1987; Koch and Lutz-Bucher, 1989; Dayanithi and Antoni, 1990), and many studies also observed a decrease in ACTH release in response to ANF (Shibaski et al., 1986; al., 1987; Koch and Lutz-Bucher, 1989; Dayanithi and Antoni, 1990), and many studies also observed a decrea
in ACTH release in response to ANF (Shibaski et a
1986; King and Baertschi, 1989; Dayanithi and Anton
1990; Kovacs Antoni, 1990), and many studies also observed a decrease
in ACTH release in response to ANF (Shibaski et al.
1986; King and Baertschi, 1989; Dayanithi and Antoni
1990; Kovacs and Antoni, 1990). Dibutyryl cGMP inhib-
ited A in ACTH release in response to ANF (Shibaski et al., 1986; King and Baertschi, 1989; Dayanithi and Antoni, 1990; Kovacs and Antoni, 1990). Dibutyryl cGMP inhibited ACTH release, indicating that elevated cGMP concentrations 1986; King and Baertschi, 1989; Dayanithi and Antoni, could 1990; Kovacs and Antoni, 1990). Dibutyryl cGMP inhib-
ited ACTH release, indicating that elevated cGMP con-
centrations could potentially attenuate ACTH secretion 1990; Kovacs and Antoni, 1990). Dibutyryl cGMP inhibited ACTH release, indicating that elevated cGMP concentrations could potentially attenuate ACTH secretion.
Evidence against cGMP mediating ANF effects on ACTH release in ited ACTH release, indicating that elevated cGMP concentrations could potentially attenuate ACTH secretion. in
Evidence against cGMP mediating ANF effects on T
ACTH release included the observation that ANF(103-
121) stimu centrations could potentially attenuate ACTH secretion. in p
Evidence against cGMP mediating ANF effects on The
ACTH release included the observation that ANF(103-
121) stimulated GC but failed to affect ACTH release inhi
 Evidence against cGMP mediating ANF effects on
ACTH release included the observation that ANF(103-
121) stimulated GC but failed to affect ACTH release
(Dayanithi and Antoni, 1990). These data appear to
dissociate ANF effe ACTH release included the observation that ANF(103-121) stimulated GC but failed to affect ACTH release (Dayanithi and Antoni, 1990). These data appear to dissociate ANF effects on ACTH release from an activation of GC. An 121) stimulated GC but failed to affect ACTH release inhit
(Dayanithi and Antoni, 1990). These data appear to ical
dissociate ANF effects on ACTH release from an acti-
al.,
vation of GC. Another anterior pituitary hormone, (Dayanithi and Antoni, 1990). These data appear to dissociate ANF effects on ACTH release from an activation of GC. Another anterior pituitary hormone, luteinizing hormone, was released in greater amounts in the presence o dissociate ANF effects on ACTH release from an activation of GC. Another anterior pituitary hormone, lutionizing hormone, was released in greater amounts in phit the presence of ANF (Horvath et al., 1986; Steele, 1990), AN investigated. inizing hormone, was released in greater amounts in
e presence of ANF (Horvath et al., 1986; Steele, 1990),
it the potential involvement of cGMP has not been
vestigated.
The most recognized effect of ANF on the posterior
t

the presence of ANF (Horvath et al., 1986; Steele, 1990
but the potential involvement of cGMP has not bee
investigated.
The most recognized effect of ANF on the posteric
pituitary gland is decreased antidiuretic hormone se but the potential involvement of cGMP has not been
investigated.
The most recognized effect of ANF on the posteri
pituitary gland is decreased antidiuretic hormone secretion
(Samson, 1985). The addition of ANF to the post
 investigated.
The most recognized effect of ANF on the posterior
pituitary gland is decreased antidiuretic hormone secre-
tion (Samson, 1985). The addition of ANF to the poste-
rior pituitary gland elevated cGMP concentrat The most recognized effect of ANF on the posterior
pituitary gland is decreased antidiuretic hormone secre-
kion (Samson, 1985). The addition of ANF to the poste-
kior pituitary gland elevated cGMP concentrations (Ob-
rean pituitary gland is decreased antidiuretic hormone section (Samson, 1985). The addition of ANF to the position rituitary gland elevated cGMP concentrations (Cana et al., 1985); however, the significance of this actions to r tion (Samson, 1985). The addition of ANF to the pos
rior pituitary gland elevated cGMP concentrations ((
ana et al., 1985); however, the significance of this act
is unknown. The locus of ANF actions to reduce anti
uretic h rior pituitary gland elevated cGMP concentrations (Ob-
ana et al., 1985); however, the significance of this action
is unknown. The locus of ANF actions to reduce antidi-
uretic hormone release actually may reside in the ci ana et al., 1985); however, the significance of this action
is unknown. The locus of ANF actions to reduce antidi-
uretic hormone release actually may reside in the circum-
ventricular organs inasmuch as many investigator is unknown. The locus of ANF actions to reduce antidium-
uretic hormone release actually may reside in the circum-
for ventricular organs inasmuch as many investigators ob-
glaserved no ANF effect in isolated pituicytes (L uretic hormone release actually may reside in the circumventricular organs inasmuch as many investigators observed no ANF effect in isolated pituicytes (Luckman and Bicknell, 1991), although binding sites for ANF were pres ventricular organs inasmuch as many investigators ob-
served no ANF effect in isolated pituicytes (Luckman
and Bicknell, 1991), although binding sites for ANF were
present. These results indicate that cGMP production
was e served no ANF effect in isolated pituicytes (Luckman
and Bicknell, 1991), although binding sites for ANF were
present. These results indicate that cGMP production
was enhanced and antidiuretic hormone release was re-
duced and Bicknell, 1991), although binding sites for ANF were
present. These results indicate that cGMP production
was enhanced and antidiuretic hormone release was re-
duced, indicating the potential for a cause and effect
sce present. These results indicate that cGMP production occurs was enhanced and antidiuretic hormone release was recorduced, indicating the potential for a cause and effect thouse
scenario. However, the results do not provide was enhanced and ant
duced, indicating the
scenario. However, the
proof for a role of cG.
the posterior pituitary.
Thyroid tissue respo ceed, indicating the potential for a cause and effect the enario. However, the results do not provide conclusive soof for a role of cGMP in mediating ANF effects in the posterior pituitary.
Thyroid tissue responded to ANF scenario. However, the results do not provide conclusive
proof for a role of cGMP in mediating ANF effects in
the posterior pituitary.
Thyroid tissue responded to ANF with an inhibition
of thyroid hormone (Ahren, 1990) or

proof for a role of cGMP in mediating ANF effect
the posterior pituitary.
Thyroid tissue responded to ANF with an inhibit
of thyroid hormone (Ahren, 1990) or thyroglob
(Tseng et al., 1990) release. The inhibition of thyrog as Thyroid tissue responded to ANF with an inhibition
of thyroid hormone (Ahren, 1990) or thyroglobulin
(Tseng et al., 1990) release. The inhibition of thyroglob-
liulin release from cultured human thyroid cells occurred
c Thyroid tissue responded to ANF with an inhibition
of thyroid hormone (Ahren, 1990) or thyroglobulin
(Tseng et al., 1990) release. The inhibition of thyroglob-
ulin release from cultured human thyroid cells occurred
at AN of thyroid hormone (Ahren, 1990) or thyroglobulin se (Tseng et al., 1990) release. The inhibition of thyroglob-
ulin release from cultured human thyroid cells occurred contains averaged at ANF concentrations having no eff (Tseng et al., 1990) release. The inhibition of thyroglob-
ulin release from cultured human thyroid cells occurred
at ANF concentrations having no effect on cGMP con-
centrations. The EC_{50} for this inhibitory effect av ulin release from cultured human thyroid cells occurred con
at ANF concentrations having no effect on cGMP con-
centrations. The EC₆₀ for this inhibitory effect averaged 2
100 pM, suggesting a physiological relevance. T centrations. The EC_{50} for this inhibitory effect averaged 100 pM, suggesting a physiological relevance. These cells exclusively contained R_2 receptors, indicating that ANF acted independently of R_1 receptors. 100 pM, suggesting a physiological relevance. These cells exclusively contained R_2 receptors, indicating that ANF acted independently of R_1 receptors.
The stimulatory effect of ANF on testosterone production by test

exclusively contained R_2 receptors, indicating that ANF acted independently of R_1 receptors.
The stimulatory effect of ANF on testosterone production by testes was associated with a stimulation of GC, both effects o exclusively contained R_2 receptors, indicating that ANF cent
acted independently of R_1 receptors. crime
The stimulatory effect of ANF on testosterone produc-
tion by testes was associated with a stimulation of GC, e acted independently of R_1 receptors.
The stimulatory effect of ANF on testosterone production by testes was associated with a stimulation of GC, both effects occurring with an EC_{50} of approximately 6 nm (Pandey et a The stimulatory effect of ANF on testosterone produc-
tion by testes was associated with a stimulation of GC,
both effects occurring with an EC_{50} of approximately 6 1
nM (Pandey et al., 1986b). A recent report indicate tion by testes was associated with a stimulation of GC,
both effects occurring with an EC_{50} of approximately 6
nM (Pandey et al., 1986b). A recent report indicates that
ANF augments testosterone production by elevating both effects occurring with an EC₅₀ of approximately 6 nM (Pandey et al., 1986b). A recent report indicates that ANF augments testosterone production by elevating GMP concentrations to activate protein kinase A, res nM (Pandey et al., 1986b). A recent report indicates that (Pandey et al., 1986b). A recent report indicates that 1992 cGMP concentrations to activate protein kinase A, remesulting in increased testosterone secretion (Schum ANF augments testosterone production by elevating 19
cGMP concentrations to activate protein kinase A, resulting in increased testosterone secretion (Schumacher st
et al., 1992). Another ANF effect in the testis was a c;

180
 1. Atrial natriuretic factor effects on guanylyl cyclase activity. (Pandey et al., 1986b). Thus, the suppressed progester-
 1. Atrial natriuretic factor effects on guanylyl cyclase in one synthesis presumably oc A AND TRACHTE
ANF was more potent, occurring at an EC₅₀ of 100 pM
(Pandey et al., 1986b). Thus, the suppressed progester-(PAND TRACHTE

ANF was more potent, occurring at an EC_{50} of 100

(Pandey et al., 1986b). Thus, the suppressed proges

one synthesis presumably occurred independently of A AND TRACHTE
ANF was more potent, occurring at an EC_{60} of 100 pM
(Pandey et al., 1986b). Thus, the suppressed progester-
one synthesis presumably occurred independently of GC
activation. activation.

ANF decreased renin secretion to inhibit the genera-(Pandey et al., 1986b). Thus, the suppressed progester-
one synthesis presumably occurred independently of GC
activation.
ANF decreased renin secretion to inhibit the genera-
tion of sodium conserving hormones such as angi one synthesis presumably occurred independently of GC
activation.
ANF decreased renin secretion to inhibit the genera-
tion of sodium conserving hormones such as angiotensin
II and aldosterone (Maack et al., 1984; Burnett activation.

ANF decreased renin secretion to inhibit the genera-

tion of sodium conserving hormones such as angiotensin

II and aldosterone (Maack et al., 1984; Burnett et al.,

1984; Obana et al., 1985). Suppression of ANF decreased renin secretion to inhibit the genera-
tion of sodium conserving hormones such as angiotensin
II and aldosterone (Maack et al., 1984; Burnett et al.,
1984; Obana et al., 1985). Suppression of renin release
co tion of sodium conserving hormones such as angiotensin II and aldosterone (Maack et al., 1984; Burnett et al., 1984; Obana et al., 1985). Suppression of renin release could represent a primary antihypertensive mechanism of II and aldosterone (Maack et al., 1984; Burnett et al., 1984; Obana et al., 1985). Suppression of renin release could represent a primary antihypertensive mechanism of ANF inasmuch as ANF failed to lower blood pressure in 1984; Obana et al., 1985). Suppression of renin release could represent a primary antihypertensive mechanism of ANF inasmuch as ANF failed to lower blood pressure in the presence of constant angiotensin II concentrations i could represent a primary antihypertensive mechanis
of ANF inasmuch as ANF failed to lower blood pressu
in the presence of constant angiotensin II concentratio
in plasma (Mizelle et al., 1989; Granger et al., 1989
These re of ANF inasmuch as ANF failed to lower blood pressure
in the presence of constant angiotensin II concentrations
in plasma (Mizelle et al., 1989; Granger et al., 1989).
These results suggested that ANF must suppress angio-
 in the presence of constant angiotensin II concentration
in plasma (Mizelle et al., 1989; Granger et al., 198
These results suggested that ANF must suppress an
tensin II concentrations to lower arterial pressure. Thin
bibi in plasma (Mizelle et al., 1989; Granger et al., 1989).
These results suggested that ANF must suppress angio-
tensin II concentrations to lower arterial pressure. The
inhibitory effect on renin release occurred at physiolo These results suggested that ANF must suppress angio-
tensin II concentrations to lower arterial pressure. The
inhibitory effect on renin release occurred at physiolog-
ical ANF concentrations (Cuneo et al., 1987; Richards tensin II concentrations to lower arterial pressure. The
inhibitory effect on renin release occurred at physiolog-
ical ANF concentrations (Cuneo et al., 1987; Richards et
al., 1988; Brands and Freeman, 1988), also emphasi inhibitory effect on renin release occurred at physiolog-
ical ANF concentrations (Cuneo et al., 1987; Richards et
al., 1988; Brands and Freeman, 1988), also emphasizing
the potential relevance of suppressed renin release ical ANF concentrations (Cuneo et al., 1987; Richards et al., 1988; Brands and Freeman, 1988), also emphasizing
the potential relevance of suppressed renin release to
physiological effects of ANF. The receptors mediating
 al., 1988; Brands and Freeman, 1988), also emphasizing
the potential relevance of suppressed renin release to
physiological effects of ANF. The receptors mediating
ANF effects on renin secretion have not been identified.
 the potential relevance of
physiological effects of A
ANF effects on renin secretive investigations with
should clarify this issue.
Attempts to define sign ightly isological effects of ANF. The receptors mediating
NF effects on renin secretion have not been identified.
ture investigations with R_1 - and R_2 -selective ligands
ould clarify this issue.
Attempts to define sig

ANF effects on renin secretion have not been identified.
Future investigations with R_1 - and R_2 -selective ligands
should clarify this issue.
Attempts to define signal transduction pathways for
ANF in juxtaglomerular Future investigations with R_1 - and R_2 -selective ligands
should clarify this issue.
Attempts to define signal transduction pathways for
ANF in juxtaglomerular cells are in their infancy. Rat
kidney slices responded t should clarify this issue.
Attempts to define signal transduction pathways for
ANF in juxtaglomerular cells are in their infancy. Rat
kidney slices responded to ANF with both suppressed
renin secretion and augmented cGMP Attempts to define signal transduction pathways
ANF in juxtaglomerular cells are in their infancy. l
kidney slices responded to ANF with both suppres
renin secretion and augmented cGMP generation (Obs
et al., 1985; Ishii ANF in juxtaglomerular cells are in their infancy. Rat
kidney slices responded to ANF with both suppressed
renin secretion and augmented cGMP generation (Obana
et al., 1985; Ishii et al., 1985). The EC_{50} for the suppre kidney slices responded to ANF with both suppress
renin secretion and augmented cGMP generation (Obar
et al., 1985; Ishii et al., 1985). The EC_{50} for the suppre
sion of renin secretion was 58 nM. Another investigatio
f renin secretion and augmented cGMP generation (Obset al., 1985; Ishii et al., 1985). The EC_{50} for the supposion of renin secretion was 58 nM. Another investigat found ANF to reduce renin secretion in cultured juglomeru et al., 1985; Ishii et al., 1985). The EC_{50} for the suppression of renin secretion was 58 nM. Another investigation found ANF to reduce renin secretion in cultured juxtaglomerular cells with an EC_{50} of 10 pM, but th sion of renin secretion was 58 nM. Another investigation
found ANF to reduce renin secretion in cultured juxta-
glomerular cells with an EC_{50} of 10 pM, but the stimula-
tion of GC activity exhibited an EC_{50} of 100 n found ANF to reduce renin secretion in cultured juxta-
glomerular cells with an EC_{50} of 10 pM, but the stimula-
tion of GC activity exhibited an EC_{50} of 100 nM (Kurtz
et al., 1986). Thus, the suppression of renin re glomerular cells with an EC_{50} of 10 pM, but the stimulation of GC activity exhibited an EC_{50} of 100 nM (Kurtz et al., 1986). Thus, the suppression of renin release occurred at ANF concentrations that did not signifi tion of GC activity exhibited an EC_{50} of 100 nM (Kurtz
et al., 1986). Thus, the suppression of renin release
occurred at ANF concentrations that did not signifi-
cantly alter cGMP generation. Nevertheless, these au-
th et al., 1986). Thus, the suppression of renin release
occurred at ANF concentrations that did not signifi-
cantly alter cGMP generation. Nevertheless, these au-
thors concluded that ANF inhibited renin secretion via
a cGMP occurred at ANF concentrations that did not significantly alter cGMP generation. Nevertheless, these authors concluded that ANF inhibited renin secretion via a cGMP-dependent mechanism. Their rationale included the finding cantly alter cGMP generation. Nevertheless, these
thors concluded that ANF inhibited renin secretion
a cGMP-dependent mechanism. Their rationale inclu
the finding that a cGMP phosphodiesterase inhit
augmented the ANF effec thors concluded that ANF inhibited renin secretion via
a cGMP-dependent mechanism. Their rationale included
the finding that a cGMP phosphodiesterase inhibitor
augmented the ANF effect and that sodium nitroprus-
side, a st a cGMP-dependent mechanism. Their rationale included
the finding that a cGMP phosphodiesterase inhibitor
augmented the ANF effect and that sodium nitroprus-
side, a stimulant of soluble GC, also inhibited renin
secretion the finding that a cGMP phosphodiesterase inhibitor
augmented the ANF effect and that sodium nitroprus-
side, a stimulant of soluble GC, also inhibited renin
secretion (Kurtz et al., 1986). Further experiments uti-
lizing side, a stimulant of soluble GC, also inhibited renin secretion (Kurtz et al., 1986). Further experiments utilizing R_1 receptor antagonists are clearly necessary to confirm or refute this association between ANF effect on renin release and cGMP production.
2. Atrial natriuretic factor effects on adenylyl cyclase lizing R_1 receptor antagonists are clearly necessary to

lizing R_1 receptor antagonists are clearly necessary to
confirm or refute this association between ANF effects
on renin release and cGMP production.
2. Atrial natriuretic factor effects on adenylyl cyclase
activity in confirm or refute this association between ANF effec
on renin release and cGMP production.
2. Atrial natriuretic factor effects on adenylyl cycla
activity in endocrine tissues. ANF suppressed cAMP con
centrations in the ma on renin release and cGMP production.
2. Atrial natriuretic factor effects on adenylyl cyclase
activity in endocrine tissues. ANF suppressed cAMP con-
centrations in the majority of reports regarding endo-
crine tissues. A 2. Atrial natriuretic factor effects on adenylyl cyclass activity in endocrine tissues. ANF suppressed cAMP con centrations in the majority of reports regarding endocrine tissues. ANF and cANF reduced the adenylyl cy clase activity in endocrine tissues. ANF suppressed cAMP concentrations in the majority of reports regarding endocrine tissues. ANF and cANF reduced the adenylyl cy-
clase activity in the anterior pituitary (Anand-Srivastava
et centrations in the majority of reports regarding endo-
crine tissues. ANF and cANF reduced the adenylyl cy-
clase activity in the anterior pituitary (Anand-Srivastava
et al., 1985a, 1989), posterior pituitary (Obana et al. crine tissues. ANF and cANF reduced the adenylyl cy-
clase activity in the anterior pituitary (Anand-Srivastava
et al., 1985a, 1989), posterior pituitary (Obana et al.,
1985; Anand-Srivastava et al., 1985a), the Leydig cel clase activity in the anterior pituitary (Anand-Srivastiet al., 1985a, 1989), posterior pituitary (Obana et 1985; Anand-Srivastava et al., 1985a), the Leydig (Pandey et al., 1985, 1986b; Anand-Srivastava et 1990), thyroid et al., 1985a, 1989), posterior pituitary (Obana et al., 1985; Anand-Srivastava et al., 1985a), the Leydig cell (Pandey et al., 1985, 1986b; Anand-Srivastava et al., 1990), thyroid cells (Tseng et al., 1990), and juxtaglo-1985; Anand-Srivastava et al., 1985a), the Leydig cell (Pandey et al., 1985, 1986b; Anand-Srivastava et al., 1990), thyroid cells (Tseng et al., 1990), and juxtaglomerular cells (Obana et al., 1985). Alternatively, two stu (Pandey et al., 1985, 1986b; Anand-Srivastava et al., 1990), thyroid cells (Tseng et al., 1990), and juxtaglo-
merular cells (Obana et al., 1985). Alternatively, two
studies found no effect of ANF on pituitary adenylyl
cyc 1990), thyroid cells (Tseng et al., 1990), and juxtaglomerular cells (Obana et al., 1985). Alternatively, two
studies found no effect of ANF on pituitary adenylyl
cyclase activity (Heisler et al., 1986; Abou-Samra et al.,

ANF RECEPTORS AND SIGNAL TRANCES AND SIGNAL TRANCES in endocrine organs has not been determined in inhimost tissues. The EC₅₀ of ANF to suppress ACTH release have ANF RECEPTORS AND SIGNAL TR
clase in endocrine organs has not been determined in
most tissues. The EC₅₀ of ANF to suppress ACTH release
(King and Baertshci, 1989) and adenylyl cyclase activity ANF RECEPTORS AND SIGNAL TR
clase in endocrine organs has not been determined in
most tissues. The EC_{60} of ANF to suppress ACTH release
hat (King and Baertshci, 1989) and adenylyl cyclase activity
(Anand-Srivastava et clase in endocrine organs has not been determined in inhim ost tissues. The EC_{50} of ANF to suppress ACTH release have (King and Baertshci, 1989) and adenylyl cyclase activity on r (Anand-Srivastava et al., 1985a) in th clase in endocrine organs has not been determined in
most tissues. The EC₅₀ of ANF to suppress ACTH release
(King and Baertshci, 1989) and adenylyl cyclase activity
(Anand-Srivastava et al., 1985a) in the pituitary was 1 most tissues. The EC₅₀ of ANF to suppress ACTH release have no
(King and Baertshci, 1989) and adenylyl cyclase activity on reni
(Anand-Srivastava et al., 1985a) in the pituitary was 10 4. C
to 100 pM, indicating the pot (King and Baertshci, 1989) and adenylyl cyclase activity on 1
(Anand-Srivastava et al., 1985a) in the pituitary was 10 4
to 100 pM, indicating the potential for a cause and effect *tran*
relationship. ANF inhibited thyr (Anand-Srivastava et al., 1985a) in the pituitary was 10
to 100 pM, indicating the potential for a cause and effect the
relationship. ANF inhibited thyroglobulin release from scultured thyroid cells with the same potency to 100 pm, indicating the potential for a cause and effect relationship. ANF inhibited thyroglobulin release from cultured thyroid cells with the same potency (i.e., an EC_{50} of 100 pm) with which it inhibited adenylyl relationship. ANF inhibited thyroglobulin release fro
cultured thyroid cells with the same potency (i.e., $E C_{60}$ of 100 pM) with which it inhibited adenylyl cycla
activity (Tseng et al., 1990). Furthermore, dibutyr
cAMP cultured thyroid cells with the same potency (i.e., an precise of 100 pM) with which it inhibited adenylyl cyclase mactivity (Tseng et al., 1990). Furthermore, dibutyryl st cAMP prevented the inhibitory effect of ANF on t activity (Tseng et al., 1990). Furthermore, dibutyryl stimulates cGMP formation, and this second messenger cAMP prevented the inhibitory effect of ANF on thyro-
conceivably could mediate ANF effects. ANF also inhib-
globul activity (Tseng et al., 1990). Furthermore, dibutyryl scAMP prevented the inhibitory effect of ANF on thyro-
globulin release. Therefore, ANF could affect thyroid is
secretions by depressing adenylyl cyclase activity. The cAMP prevented the inhibitory effect of ANF on thyroglobulin release. Therefore, ANF could affect thyroid it secretions by depressing adenylyl cyclase activity. The c.
R₂ receptor apparently mediated this effect because globulin release. Therefore, ANF could affect thyroid secretions by depressing adenylyl cyclase activity. The R₂ receptor apparently mediated this effect because it was the only receptor identified in the thyroid cells u secretions by depressing adenylyl cyclase activity. The city receptor apparently mediated this effect because it b was the only receptor identified in the thyroid cells or utilized (Tseng et al., 1990). No information exi was the only receptor identified in the thyroid cells often in good agreement, suggesting that these effects utilized (Tseng et al., 1990). No information exists con-
are linked. The best evidence for this potential linka utilized (Tseng et al., 1990). No information exists concyclase activity and cAMP levels (Pandey et al., 1985, cerning the effect of selective receptor-binding agents or PT on ANF effects on thyroid function. Finally, the suppression of progesterone synthesis by ANF and cANF in Leydig cells correlated with their inhibition of ade PT on ANF effects on thyroid function. Finally, the are
suppression of progesterone synthesis by ANF and CANF the
in Leydig cells correlated with their inhibition of adenylyl tio
cyclase activity and CAMP levels (Pandey e suppression of progester
in Leydig cells correlated
cyclase activity and cAl
1986b; Anand-Srivastava
responses was 100 pM.
In the glomerulus, A Leydig cells correlated with their inhibition of adenylyl
clase activity and cAMP levels (Pandey et al., 1985, in
86b; Anand-Srivastava et al., 1990). The EC_{50} for both en
ponses was 100 pM.
In the glomerulus, ANF inhi

cyclase activity and cAMP levels (Pandey et al., 1985, 1986b; Anand-Srivastava et al., 1990). The EC_{50} for both responses was 100 pM.
In the glomerulus, ANF inhibited adenylyl cyclase activity with an EC_{50} of less t 1986b; Anand-Srivastava et al., 1990). The EC_{50} for both eff
responses was 100 pM.
In the glomerulus, ANF inhibited adenylyl cyclase Al
activity with an EC_{50} of less than 100 pM, indicating that
this effect also cou responses was 100 pm.
In the glomerulus, ANF inhibited adenylyl cyclase
activity with an EC_{60} of less than 100 pm, indicating that
this effect also could account for the reduction in renin
secretion (Obana et al., 1985 In the glomerulus, ANF inhibited adenylyl cyclase
activity with an EC_{50} of less than 100 pM, indicating that
this effect also could account for the reduction in renin
secretion (Obana et al., 1985). cAMP is a well-reco activity with an EC_{50} of less than 100 pM, indicating that this effect also could account for the reduction in renin secretion (Obana et al., 1985). cAMP is a well-recognized stimulant of renin secretion (Keeton and Ca this effect also could account for the reduction in resecretion (Obana et al., 1985). cAMP is a well-recognistimulant of renin secretion (Keeton and Campti 1980), indicating that a reduction in its intracelly concentration secretion (Obana et al., 1985). cAMP is a well-recognized stimulant of renin secretion (Keeton and Campbell, 1980), indicating that a reduction in its intracellular obsconcentration could reduce renin secretion. Unfortunat stimulant of renin secretion (Keeton and Campbe
1980), indicating that a reduction in its intracellul
concentration could reduce renin secretion. Unfort
nately, critical experiments utilizing PT have not be
performed to as 1980), indicating that a reduction in its intracellular ob
concentration could reduce renin secretion. Unfortu-
nately, critical experiments utilizing PT have not been
performed to assess the association between the reducconcentration could reduce renin secretion. Unfortu-
nately, critical experiments utilizing PT have not been
performed to assess the association between the reduc-
we value the inhibition in renincate
release. PT should el nately, critical experiments utilizing PT have not been
performed to assess the association between the reduc-
tion in cAMP concentrations and the reduction in renin
release. PT should eliminate the inhibition of renin
rel performed to assess the association between the reduction in cAMP concentrations and the reduction in renin release. PT should eliminate the inhibition of renin release caused by ANF, if the reduction in adenylyl cyclase tion in cAMP concentrations and the reduction in renin
release. PT should eliminate the inhibition of renin
release caused by ANF, if the reduction in adenylyl
cyclase activity is a causative factor in this response.
Simi release caused by ANF, if the reduction in cyclase activity is a causative factor in this r
Similarly, no results with the R_2 receptor ligance
are available to confirm or refute the involveme:
 R_2 receptor in the sup clase activity is a causative factor in this respon
milarly, no results with the R_2 receptor ligand, cAN
e available to confirm or refute the involvement of t
receptor in the suppression of renin release.
Collectively,

are available to confirm or refute the involvement R_2 receptor in the suppression of renin release.
Collectively, these endocrine studies indicate a
tial role for R_2 receptors in mediating an inhibitor
effect on ade *Freeptor in the suppression of renin release.* 1999
 3. Atrial natriuretic factor effects on ion conductance in
 3. Atrial natriuretic factor effects on ion conductance in
 3. Atrial natriuretic factor effects on ion

Collectively, these endocrine studies indicate a potential role for R_2 receptors in mediating an inhibitory ANF and Aceffect on adenylyl cyclase and hormone secretion. of AN
3. Atrial natriuretic factor effects on io tial role for R_2 receptors in mediating an inhibitory
effect on adenylyl cyclase and hormone secretion.
3. Atrial natriuretic factor effects on ion conducta
endocrine tissue. ANF suppressed ACTH release
isolated rat an effect on adenylyl cyclase and hormone secretion.
3. Atrial natriuretic factor effects on ion conductance is
endocrine tissue. ANF suppressed ACTH release from
isolated rat anterior pituitary cells in a concentration
depen 3. Atrial natriuretic factor effects on ion conductance in C
endocrine tissue. ANF suppressed ACTH release from a
isolated rat anterior pituitary cells in a concentration-
dependent manner that was sensitive to potassium c endocrine tissue. ANF suppressed ACTH release from all sisolated rat anterior pituitary cells in a concentration-
dependent manner that was sensitive to potassium chan-
nel inhibitors (Antoni and Dayanithi, 1990). Except f isolated rat anterior pituitary cells in a concentration-
dependent manner that was sensitive to potassium chan-
nel inhibitors (Antoni and Dayanithi, 1990). Except for
the results reported for aldosterone secretion above, dependent manner that was sensitive to potassium channel inhibitors (Antoni and Dayanithi, 1990). Except for the results reported for aldosterone secretion above, no other endocrine studies of the role of potassium channel nel inhibitors (Antoni and Dayanithi, 1990). Except for of the results reported for aldosterone secretion above, no effection of the role of potassium channel ett activation in ANF effects have been reported. The fre-sign the results reported for aldosterone secretion above, no
other endocrine studies of the role of potassium channel
activation in ANF effects have been reported. The fre-
quency of potassium channel involvement in other ANF
 other endocrine studies of the role of potassium channel
activation in ANF effects have been reported. The fre-
quency of potassium channel involvement in other ANF
effects is suggestive of this mechanism being of potenti tivation in ANF effects have been reported. The lency of potassium channel involvement in other A fects is suggestive of this mechanism being of poten portance in endocrine organs as well.
ANF failed to influence the infl

quency of potassium channel involvement in other AN
effects is suggestive of this mechanism being of potenti
importance in endocrine organs as well.
ANF failed to influence the influx of ⁴⁶Ca in juxtagle
merular cells (K effects is suggestive of this mechanism being of potent
importance in endocrine organs as well.
ANF failed to influence the influx of ⁴⁵Ca in juxtag
merular cells (Kurtz et al., 1986). Moreover, the int
cellular calcium importance in endocrine organs as well. and the ANF failed to influence the influx of ⁴⁵Ca in juxtaglo-
merular cells (Kurtz et al., 1986). Moreover, the intra-
cellular calcium concentrations were unchanged, indicat-
in

EXANSDUCTION MECHANISMS
inhibit renin secretion (Kurtz et al., 1986). Other ions
have not been investigated regarding the ANF influence FRANSDUCTION MECHANISMS

inhibit renin secretion (Kurtz et al., 1986). Other ions

have not been investigated regarding the ANF influence

on renin secretion. TRANSDUCTION ME
inhibit renin secre
have not been inve
on renin secretion.
4. Conclusion reg have not been investigated regarding the ANF influence
on renin secretion.
4. Conclusion regarding atrial natriuretic factor *signal*

inhibit renin secretion (Kurtz et al., 1986). Other ions have not been investigated regarding the ANF influence
on renin secretion.
4. Conclusion regarding atrial natriuretic factor signal
transduction mechanisms in endocr have not been investigated regarding the ANF influence
on renin secretion.
4. Conclusion regarding atrial natriuretic factor signal
transduction mechanisms in endocrine systems. The de-
scriptive nature of most experiments on renin secretion.
4. Conclusion regarding atrial natriuretic factor signal transduction mechanisms in endocrine systems. The scriptive nature of most experiments in endocrine tissue
precludes definitive conclusions regar 4. Conclusion regarding atrial natriuretic factor signal
transduction mechanisms in endocrine systems. The de-
scriptive nature of most experiments in endocrine tissues
precludes definitive conclusions regarding the involv transduction mechanisms in endocrine systems. The descriptive nature of most experiments in endocrine tissues
precludes definitive conclusions regarding the involve-
ment of ANF signal transduction mechanisms. ANF
stimulat scriptive nature of most experiments in endocrine tissu
precludes definitive conclusions regarding the involvement of ANF signal transduction mechanisms. AN
stimulates cGMP formation, and this second messeng
conceivably co precludes definitive conclusions regarding the involvement of ANF signal transduction mechanisms. AN
stimulates cGMP formation, and this second messenge
conceivably could mediate ANF effects. ANF also inhilits
adenylyl cyc ment of ANF signal transduction mechanisms. ANF
stimulates cGMP formation, and this second messenger
conceivably could mediate ANF effects. ANF also inhib-
its adenylyl cyclase activity fairly consistently in endo-
crine t stimulates cGMP formation, and this second messenger
conceivably could mediate ANF effects. ANF also inhib-
its adenylyl cyclase activity fairly consistently in endo-
crine tissue. The potency of ANF effects on inhibition conceivably could mediate ANF effects. ANF also inhibits adenylyl cyclase activity fairly consistently in endo-
crine tissue. The potency of ANF effects on inhibition of
both adenylyl cyclase activity and hormone release a its adenylyl cyclase activity fairly consistently in endo-
crine tissue. The potency of ANF effects on inhibition of
both adenylyl cyclase activity and hormone release are
often in good agreement, suggesting that these ef crine tissue. The potency of ANF effects on inhibition of both adenylyl cyclase activity and hormone release are often in good agreement, suggesting that these effects are linked. The best evidence for this potential link both adenylyl cyclase activity and hormone release are often in good agreement, suggesting that these effects are linked. The best evidence for this potential linkage exists in cultured thyroid cells where only R_2 rece often in good agreement, suggesting that these effection are linked. The best evidence for this potential linked exists in cultured thyroid cells where only R_2 receptare present, thus obviating a potential role for cGM exists in cultured thyroid cells where only R_2 receptors are present, thus obviating a potential role for cGMP in the response. Finally, potassium is crucial to the inhibition of ACTH release in anterior pituitary cell exists in cultured thyroid cells where only R_2 receptors are present, thus obviating a potential role for cGMP in the response. Finally, potassium is crucial to the inhibition of ACTH release in anterior pituitary cell are present, thus obviating a potential role for cGMP in
the response. Finally, potassium is crucial to the inhibi-
tion of ACTH release in anterior pituitary cells, suggest-
ing that ANF alters potassium currents to media the response. Finally, potassium is crucial to the inhibition of ACTH release in anterior pituitary cells, suggesting that ANF alters potassium currents to mediate its effects. Further work is urgently needed to critically tion of ACTH release in anterior pituitary cells, suggesting that ANF alters potassium currents to mediate its effects. Further work is urgently needed to critically test these hypothetical signal transduction mechanisms f ing that ANF alters
effects. Further work
these hypothetical si
ANF in endocrine t
shown in figure 8. these hypothetical signal transduction mechanisms for
ANF in endocrine tissues. The putative pathways are
shown in figure 8.
G. Atrial Natriuretic Factor Neuromodulatory Effects
The neuromodulatory effects of ANF initially

release. PT should eliminate the inhibition of renin duced catecholamine efflux from stimulated nerves
release caused by ANF, if the reduction in adenylyl (Nakamaru and Inagami, 1986) and adrenal glands
cyclase activity i are available to confirm or refute the involvement of the after central administration of ANF (Ermirio et al., R_2 receptor in the suppression of renin release. 1990), and (e) enhanced parasympathetic activity to Collec shown in figure 8.

G. Atrial Natriuretic Factor Neuromodulatory Effects

The neuromodulatory effects of ANF initially were

observed as a suppression of pressor responses to α shown in figure 8.

G. Atrial Natriuretic Factor Neuromodulatory Effects

The neuromodulatory effects of ANF initially were

observed as a suppression of pressor responses to α -

receptor agonists (Haass et al., 1985; G. Atrial Natriuretic Factor Neuromodulatory Effects
The neuromodulatory effects of ANF initially were
observed as a suppression of pressor responses to α -
receptor agonists (Haass et al., 1985; Zukowska-Grojec
et al., Eta al, 1986). The neuromodulatory effects of ANF initially were
observed as a suppression of pressor responses to α -
receptor agonists (Haass et al., 1985; Zukowska-Grojec
et al., 1986). Other neuronal effects of ANF The neuromodulatory effects of ANF initially were
observed as a suppression of pressor responses to α -
receptor agonists (Haass et al., 1985; Zukowska-Grojec
et al., 1986). Other neuronal effects of ANF subsequently
we observed as a suppression of pressor responses to α -
receptor agonists (Haass et al., 1985; Zukowska-Grojec
et al., 1986). Other neuronal effects of ANF subsequently
were discovered to include the following: (a) inhib et al., 1986). Other neuronal effects of ANF subsequently
were discovered to include the following: (a) inhibited
catecholamine synthesis (Debinski et al., 1987), (b) re-
duced catecholamine efflux from stimulated nerves
(were discovered to include the following: (*a*) inhibited catecholamine synthesis (Debinski et al., 1987), (*b*) reduced catecholamine efflux from stimulated nerves (Nakamaru and Inagami, 1986) and adrenal glands (Holtz et catecholamine synthesis (Debinski et al., 1987), *(b)* re-
duced catecholamine efflux from stimulated nerves
(Nakamaru and Inagami, 1986) and adrenal glands
(Holtz et al., 1987), *(c)* suppressed firing of hypothalamic
neu duced catecholamine efflux from stimulated nerves
(Nakamaru and Inagami, 1986) and adrenal glands
(Holtz et al., 1987), (c) suppressed firing of hypothalamic
neurons (Wong et al., 1986), (d) reduced blood pressure
after ce (Nakamaru and Inagami, 1986) and adrenal glands
(Holtz et al., 1987), (c) suppressed firing of hypothalamic
neurons (Wong et al., 1986), (d) reduced blood pressure
after central administration of ANF (Ermirio et al.,
1990) (Holtz et al., 1987), (c) suppressed firing of hypothalamic
neurons (Wong et al., 1986), (d) reduced blood pressure
after central administration of ANF (Ermirio et al.,
1990), and (e) enhanced parasympathetic activity neurons (Wong et al., 1986), (d) reduced blood pressure
after central administration of ANF (Ermirio et al.,
1990), and (e) enhanced parasympathetic activity to
suppress sympathetic influences on heart rate (Atchison
and A after central administration of ANF (Ermirio et al., 1990), and (e) enhanced parasympathetic activity to suppress sympathetic influences on heart rate (Atchison and Ackermann, 1990). The sympathoinhibitory effects of ANF h 1990), and (e) enhanced parasympathetic activity to
suppress sympathetic influences on heart rate (Atchison
and Ackermann, 1990). The sympathoinhibitory effects
of ANF have been confirmed in humans (Ebert and
Cowley, 1988; suppress sympathetic influences on heart rate (Atchison
and Ackermann, 1990). The sympathoinhibitory effects
of ANF have been confirmed in humans (Ebert and
Cowley, 1988; Floras, 1990; Kubo et al., 1990), but not
all studi and Ackermann, 1990). The sympathoinhibitory effects
of ANF have been confirmed in humans (Ebert and
Cowley, 1988; Floras, 1990; Kubo et al., 1990), but not
all studies support this concept (Roach et al., 1990). The
neurom of ANF have been confirmed in humans (Ebert and Cowley, 1988; Floras, 1990; Kubo et al., 1990), but not all studies support this concept (Roach et al., 1990). The neuromodulatory effect of ANF has been confirmed in numerou Cowley, 1988; Floras, 1990; Kubo et al., 1990), but not
all studies support this concept (Roach et al., 1990). The
neuromodulatory effect of ANF has been confirmed in
numerous in vitro studies, but the physiological releva all studies support this concept (Roach et al., 1990). The
neuromodulatory effect of ANF has been confirmed in
numerous in vitro studies, but the physiological relevance
of this effect has not been ascertained. The EC₅₀ neuromodulatory effect of ANF has been confirmed in
numerous in vitro studies, but the physiological relevance
of this effect has not been ascertained. The EC_{50} for the
effect in isolated adrenergic tissue is about 30 numerous in vitro studies, but the physiological relevance
of this effect has not been ascertained. The EC_{50} for the
effect in isolated adrenergic tissue is about 30 pM (Drew-
ett et al., 1990), indicating the potentia of this effect has not been ascertained. The EC₅₀ for the effect in isolated adrenergic tissue is about 30 pM (Drew-
ett et al., 1990), indicating the potential physiological
significance inasmuch as cerebrospinal concen fect in isolated adrenergic tissue is about 30 pM (Drew-
t et al., 1990), indicating the potential physiological
gnificance inasmuch as cerebrospinal concentrations of
NF average about 20 pM (Levin, 1988).
Another effect o

ett et al., 1990), indicating the potential physiological
significance inasmuch as cerebrospinal concentrations of
ANF average about 20 pM (Levin, 1988).
Another effect of ANF pertains to neuron-associated
cells in which A significance inasmuch as cerebrospinal concentrations of ANF average about 20 pm (Levin, 1988).
Another effect of ANF pertains to neuron-associate
cells in which ANF acts as an antimitogenic agent. AN
suppresses proliferat ANF average about 20 pm (Levin, 1988).

Another effect of ANF pertains to neuron-associated

cells in which ANF acts as an antimitogenic agent. ANF

suppresses proliferation of astroglial cells from rat dien-

cephalon (L Another effect of ANF pertains to neuron-associated
cells in which ANF acts as an antimitogenic agent. ANF
suppresses proliferation of astroglial cells from rat dien-
cephalon (Levin and Frank, 1991). This inhibitory effe suppresses proliferation of astroglial cells from rat dien-
cephalon (Levin and Frank, 1991). This inhibitory effect
on cell division is mimicked by the ANF R_2 -selective
ligand, cANF. Thus, as in vascular smooth muscle

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ANAND-SRIVASTAVA
timitogenic effects of ANF appear to be mediated by the Al
R₂ ANF receptor. The precise signal transduction path- 482

ANAND-SRIVAS

timitogenic effects of ANF appear to be mediated by th
 R_2 ANF receptor. The precise signal transduction path-

way involved has not been elucidated beyond the defin ANAND-SRIVA
timitogenic effects of ANF appear to be mediated by R_2 ANF receptor. The precise signal transduction pat
way involved has not been elucidated beyond the defin
tion of the receptor involved. The functional d timitogenic effects of ANF appear to be mediated by the R_2 ANF receptor. The precise signal transduction pathway involved has not been elucidated beyond the definition of the receptor involved. The functional data that timitogenic effects of ANF appear to be mediated by the ANI
 R_2 ANF receptor. The precise signal transduction path-

way involved has not been elucidated beyond the defini-

response to the receptor involved. The funct R_2 ANF receptor. The precise signal transduction pathway involved has not been elucidated beyond the definition of the receptor involved. The functional data that follow are consistent with a role for the R_2 recepto way involved has not been elucidated beyond the definition of the receptor involved. The functional data that follow are consistent with a role for the R_2 receptor in mediating neuromodulatory influences of ANF as well tion of the receptor involved. The functional data that
follow are consistent with a role for the R_2 receptor in
mediating neuromodulatory influences of ANF as well, l
although GC activation via the R_1 receptor also follow are consistent with a role for the R_2 receptor in et mediating neuromodulatory influences of ANF as well, liet although GC activation via the R_1 receptor also occurs. the major actions of ANF in neuronal tiss mediating neuromodulatory influences of ANF a
although GC activation via the R_1 receptor also α
The major actions of ANF in neuronal tissue, activity
of GC and potassium channel activity, and inhibit
adenylyl cyclas *n* Also occurs.
 ne major actions of ANF in neuronal tissue, activation
 GC and potassium channel activity, and inhibition of
 enylyl cyclase activity are shown in figure 9.
 1. Role of guanylyl cyclase activation

The major actions of ANF in neuronal tissue, activation
of GC and potassium channel activity, and inhibition of
adenylyl cyclase activity are shown in figure 9.
1. Role of guanylyl cyclase activation in neuronal re-
spon of GC and potassium channel activity, and inhibition of adenylyl cyclase activity are shown in figure 9.
1. Role of guanylyl cyclase activation in neuronal responses to atrial natriuretic factor. As with most tissues, neur adenylyl cyclase activity are shown in figure 9. action in Relative of guanylyl cyclase activation in neuronal responses to atrial natriuretic factor. As with most tissues, transuronal tissue responded to ANF with an eleva 1. Role of guanylyl cyclase activation in neuronal re-
sponses to atrial natriuretic factor. As with most tissues, tral ne
neuronal tissue responded to ANF with an elevated syn-
fact the
thesis of cGMP. This was demonstra sponses to atrial natriuretic factor. As with most tissues,
neuronal tissue responded to ANF with an elevated syn-
thesis of cGMP. This was demonstrated initially in the
PC12 cell, a representative adrenergic tissue deriv neuronal tissue responded to ANF with an elevated syn-
thesis of cGMP. This was demonstrated initially in the
PC12 cell, a representative adrenergic tissue derived from
a rat pheochromocytoma (Fiscus et al., 1987). The EC thesis of cGMP. This was demonstrated initially in the 1989; B:
PC12 cell, a representative adrenergic tissue derived from suggests
a rat pheochromocytoma (Fiscus et al., 1987). The EC₅₀ ANF efi
for ANF averaged about 1 PC12 cell, a representative adrenergic tissue derived from
a rat pheochromocytoma (Fiscus et al., 1987). The EC_{50}
for ANF averaged about 10 nm. The PC12 cells possessed
ANF receptors with the R_1 receptor accounting a rat pheochromocytoma (Fiscus et al., 1987). The E
for ANF averaged about 10 nM. The PC12 cells posses
ANF receptors with the R_1 receptor accounting for 7
of the total population (Rathinavelu and Isom, 19
Similarly, A for ANF averaged about 10 nm. The PC12 cells possessed
ANF receptors with the R_1 receptor accounting for 70%
of the total population (Rathinavelu and Isom, 1991).
Similarly, ANF augmented cGMP synthesis in astroglia-
r ANF receptors with the R_1 receptor accounting for 70% of the total population (Rathinavelu and Isom, 1991).
Similarly, ANF augmented cGMP synthesis in astroglia-
rich cultures from the mouse brain (Simonnet et al., 198 of the total population (Rathinavelu and Isom, 1991). astrainarly, ANF augmented cGMP synthesis in astroglia-
rich cultures from the mouse brain (Simonnet et al., the
1989) and in rat sympathetic ganglia (Torda et al., 19 Similarly, ANF augmented cGMP synth
rich cultures from the mouse brain (S
1989) and in rat sympathetic ganglia (Tc
These results indicated the presence c
receptors in tissues containing neurons.
Membrane-permeable analogs th cultures from the mouse brain (Simonnet et al., the 89) and in rat sympathetic ganglia (Torda et al., 1989). by J
nese results indicated the presence of functional R_1 cent
ceptors in tissues containing neurons. 2.
M 1989) and in rat sympathetic ganglia (Torda et al., 1989).
These results indicated the presence of functional R_1
receptors in tissues containing neurons.
Membrane-permeable analogs of GMP were found to
inhibit adrener

These results indicated the presence of functional R_1
receptors in tissues containing neurons.
Membrane-permeable analogs of GMP were found to
inhibit adrenergic neurotransmission, indicating the po-
tential for GMP receptors in tissues containing neurons.

Membrane-permeable analogs of cGMP were found to

inhibit adrenergic neurotransmission, indicating the po-

tential for cGMP to mediate ANF neuromodulatory ef-

fects (Drewett et Membrane-permeable analogs of cGMP were found to
inhibit adrenergic neurotransmission, indicating the po-
tential for cGMP to mediate ANF neuromodulatory ef-
fects (Drewett et al., 1989). Additional critical tests of
this inhibit adrenergic neurotransmission, indicating the potential for cGMP to mediate ANF neuromodulatory effects (Drewett et al., 1989). Additional critical tests of rthis hypothesis involved the effects of PT, R_2 -bindin tential for cGMP to mediate ANF neuromodulatory effects (Drewett et al., 1989). Additional critical tests of release this hypothesis involved the effects of PT, R_2 -binding peptides, and R_1 receptor antagonists. The fects (Drewett et al., 1989). Additional critical tests of respective this hypothesis involved the effects of PT, R_2 -binding et a peptides, and R_1 receptor antagonists. The inhibitory trateffect of ANF on adrenergic this hypothesis involved the effects of PT, R_2 -bindinepeptides, and R_1 receptor antagonists. The inhibitor effect of ANF on adrenergic neurotransmitter releasures was eliminated by PT, whereas the stimulatory effect peptides, and R_1 receptor antagonists. The inhibitory
effect of ANF on adrenergic neurotransmitter release
was eliminated by PT, whereas the stimulatory effect on
GC was maintained (Drewett et al., 1990). Furthermore,
 effect of ANF on adrenergic neurotransmitter release was eliminated by PT, whereas the stimulatory effect on GC was maintained (Drewett et al., 1990). Furthermore, and the R₂ receptor-selective agonist, cANF, reduced ev was eliminated by PT, whereas the stimulatory effect on GC was maintained (Drewett et al., 1990). Furthermore, the R_2 receptor-selective agonist, cANF, reduced evoked catecholamine release without affecting GC activity

FIG. 9. Neuronal signal transduction pathways for ANF. ANF activates R_1 receptors to increase cGMP production. The significance of fit this effect in peripheral neurons is undetermined. ANF interacts with R_2 recepto FIG. 9. Neuronal signal transduction pathways for ANF. ANF activates R_1 receptors to increase cGMP production. The significance of fithis effect in peripheral neurons is undetermined. ANF interacts with R_2 receptors tivates R_1 receptors to increase cGMP production. The significance of this effect in peripheral neurons is undetermined. ANF interacts with R_2 receptors to inhibit adenylyl cyclase (AC) by a pathway mediated by a Gthis effect in peripheral neurons is undetermined. ANF interacts with R_2 receptors to inhibit adenylyl cyclase (AC) by a pathway mediated by a G-protein (G). The reduction in cAMP appears to reduce the evoked secretion R₂ receptors to inhibit adenylyl cyclase (AC) by
by a G-protein (G). The reduction in cAMP a
evoked secretion of neurotransmitter. The G-pr
to potassium channels to increase the efflux of p
(?). -, inhibitory effects; +,

ANAND-SRIVASTAVA AND TRACHTE
mediated by the ANF effects on GC and neurotransmission, invalidating
msduction path- the hypothesis that cGMP mediates neuromodulatory responses to ANF. The neuromodulatory activity of A AND TRACHTE
ANF effects on GC and neurotransmission, invalidating
the hypothesis that cGMP mediates neuromodulatory
responses to ANF. The neuromodulatory activity of
cANF was confirmed in the rabbit vas deferens (Johnson ANF effects on GC and neurotransmission, invalidating
the hypothesis that cGMP mediates neuromodulatory
responses to ANF. The neuromodulatory activity of
cANF was confirmed in the rabbit vas deferens (Johnson
et al., 1991) ANF effects on GC and neurotransmission, invalidating
the hypothesis that cGMP mediates neuromodulatory
responses to ANF. The neuromodulatory activity of
cANF was confirmed in the rabbit vas deferens (Johnson
et al., 1991 the hypothesis that cGMP mediates neuromodulatory
responses to ANF. The neuromodulatory activity of
cANF was confirmed in the rabbit vas deferens (Johnson
et al., 1991), indicating that these conclusions are not
limited to responses to ANF. The neuromodulatory activity of cANF was confirmed in the rabbit vas deferens (Johnson et al., 1991), indicating that these conclusions are not limited to cultured PC12 cells. Finally, R_1 receptor ant cANF was confirmed in the rabbit vas deferens (Johnson et al., 1991), indicating that these conclusions are no limited to cultured PC12 cells. Finally, R_1 receptor an tagonists lacked an effect on ANF neuromodulatory i et al., 1991), indicating that these conclusions are not
limited to cultured PC12 cells. Finally, R_1 receptor an-
tagonists lacked an effect on ANF neuromodulatory in-
fluences in the rabbit vas deferens (Trachte, 1993 limited to cultured PC12 cell
tagonists lacked an effect on
fluences in the rabbit vas defe
ing to the rejection of the c
action in peripheral neurons.
The ANF signal transducti gonists lacked an effect on ANF neuromodulatory in-
nences in the rabbit vas deferens (Trachte, 1993), lead-
g to the rejection of the cGMP hypothesis of ANF
tion in peripheral neurons.
The ANF signal transduction mechanis

fluences in the rabbit vas deferens (Trachte, 1993), leading to the rejection of the cGMP hypothesis of ANF action in peripheral neurons.
The ANF signal transduction mechanism in the central nervous system has not been in ing to the rejection of the cGMP hypothesis of ANF action in peripheral neurons.
The ANF signal transduction mechanism in the central nervous system has not been investigated, but the fact that central receptors are of th action in peripheral neurons.

The ANF signal transduction mechanism in the central nervous system has not been investigated, but the

fact that central receptors are of the R_1 subtype (Quirion,

1989; Brown and Czarne The ANF signal transduction mechanism in the central nervous system has not been investigated, but the fact that central receptors are of the R_1 subtype (Quirion, 1989; Brown and Czarnecki, 1990; Konrad et al., 1991) s tral nervous system has not been investigated, but the fact that central receptors are of the R_1 subtype (Quirion, 1989; Brown and Czarnecki, 1990; Konrad et al., 1991) suggests that cGMP is the most probable mediator fact that central receptors are of the R_1 subtype (Quirion, 1989; Brown and Czarnecki, 1990; Konrad et al., 1991) suggests that cGMP is the most probable mediator of ANF effects. This hypothesis has not been tested thu 1989; Brown and Czarnecki, 1990; Konrad et al., 1991)
suggests that cGMP is the most probable mediator of
ANF effects. This hypothesis has not been tested thus
far with R_1 receptor antagonists or R_2 receptor-binding suggests that cGMP is the most probable mediator of ANF effects. This hypothesis has not been tested thus far with R_1 receptor antagonists or R_2 receptor-binding peptides. Interestingly, ANF depresses proliferation ANF effects. This hypothesis has not been tested thus
far with R_1 receptor antagonists or R_2 receptor-binding
peptides. Interestingly, ANF depresses proliferation of
astroglial cultures from rat diencephalon, and th far with R_1 receptor antagonists or R_2 receptor-binding
peptides. Interestingly, ANF depresses proliferation of
astroglial cultures from rat diencephalon, and this effect
is mimicked by cANF (Levin and Frank, 1991). peptides. Interestingly, ANF depresses proliferation of astroglial cultures from rat diencephalon, and this effect is mimicked by cANF (Levin and Frank, 1991). Thus, the antimitogenic effect of ANF appears to be mediated b astroglial cultures from i
is mimicked by cANF (
the antimitogenic effect
by R_2 receptors in tissue
central nervous system.
2. Role of adenylyl cyclo mimicked by cANF (Levin and Frank, 1991). Thus,
 2. Role of denylyl cyclase inhibition in atrial natriuretic
 2. Role of adenylyl cyclase inhibition in atrial natriuretic
 2. Role of adenylyl cyclase inhibition in a

the antimitogenic effect of ANF appears to be mediated
by R_2 receptors in tissues associated with neurons in the
central nervous system.
2. Role of adenylyl cyclase inhibition in atrial natriuretic
factor neuromodulato by R_2 receptors in tissues associated with neurons in t
central nervous system.
2. Role of adenylyl cyclase inhibition in atrial natriure
factor neuromodulatory effects. ANF inhibited adeny
cyclase activity with an $EC_{$ central nervous system.

2. Role of adenylyl cyclase inhibition in atrial natriuretic

factor neuromodulatory effects. ANF inhibited adenylyl

cyclase activity with an EC_{50} consistent with its inhibi-

tion of evoked c 2. Role of adenylyl cyclase inhibition in atrial natriuretic factor neuromodulatory effects. ANF inhibited adenylyl cyclase activity with an EC_{50} consistent with its inhibition of evoked catecholamine release (i.e., 21 cyclase activity with an EC_{50} consistent with its inhibition of evoked catecholamine release (i.e., 21 and 35 pM, respectively) in PC12 cells (Drewett et al., 1990). Whalin et al. (1991) also found ANF to decrease cAMP cyclase activity with an EC_{50} consistent with its inhibition of evoked catecholamine release (i.e., 21 and 35 pM, respectively) in PC12 cells (Drewett et al., 1990). Whalin et al. (1991) also found ANF to decrease cAMP tion of evoked catecholamine release (i.e., 21 and 35 pM, respectively) in PC12 cells (Drewett et al., 1990). Whalinet al. (1991) also found ANF to decrease cAMP concentrations but by a mechanism involving an activation o suggests that CMP is the most probable mediator of ANF offects. This hypothesis has not been tested thus far with R₁ receptor hatgonizats or R₂ receptor-binding peptides. Interestingly, ANF depresses proliferation of a et al. (1991) also found ANF to decrease cAMP co
trations but by a mechanism involving an activat
a cGMP-dependent phosphodiesterase at high ANI
centrations (1 μ M). PT blocked inhibitory effects of
and cANF on both ade trations but by a mechanism involving an activation of
a cGMP-dependent phosphodiesterase at high ANF con-
centrations $(1 \mu M)$. PT blocked inhibitory effects of ANF
and cANF on both adenylyl cyclase and neurotransmis-
si a cGMP-dependent phosphodiesterase at high ANF contrations $(1 \mu M)$. PT blocked inhibitory effects of Al and cANF on both adenylyl cyclase and neurotransm sion (Drewett et al., 1990), but not stimulatory efference of GC, centrations $(1 \mu M)$. PT blocked inhibitory effects of ANF
and cANF on both adenylyl cyclase and neurotransmis-
sion (Drewett et al., 1990), but not stimulatory effects
on GC, indicating that the suppression of cAMP conce and cANF on both adenylyl cyclase and neurotransmis
sion (Drewett et al., 1990), but not stimulatory effect
on GC, indicating that the suppression of cAMP concentrations was not dependent on cGMP generation. Fur
thermore, sion (Drewett et al., 1990), but not stimulatory effects
on GC, indicating that the suppression of cAMP concen-
trations was not dependent on cGMP generation. Fur-
thermore, membrane-permeable analogs of cAMP elim-
inated on GC, indicating that the suppression of cAMP concentrations was not dependent on cGMP generation. Furthermore, membrane-permeable analogs of cAMP eliminated inhibitory influences of ANF on evoked catecholamine release (D trations was not dependent on cGMP generation. Fur-
thermore, membrane-permeable analogs of cAMP elim-
inated inhibitory influences of ANF on evoked cat-
echolamine release (Drewett et al., 1992). These data are
consistent thermore, membrane-permeable analogs of cAMP elim-
inated inhibitory influences of ANF on evoked cat-
echolamine release (Drewett et al., 1992). These data are
consistent with the neuromodulatory pathway for ANF
involving inated inhibitory influences of ANF on evoked calculation
echolamine release (Drewett et al., 1992). These data a
consistent with the neuromodulatory pathway for AN
involving a suppression of cAMP generation mediate
by an holamine release (Drewett et al., 1992). These data are
nsistent with the neuromodulatory pathway for ANF
volving a suppression of cAMP generation mediated
an inhibitory G-protein coupled to the R_2 receptor.
This propo consistent with the neuromodulatory pathway for ANF
involving a suppression of cAMP generation mediated
by an inhibitory G-protein coupled to the R_2 receptor.
This proposed pathway for ANF actions in peripheral
neurons

involving a suppression of cAMP generation mediately an inhibitory G-protein coupled to the R_2 receptor
This proposed pathway for ANF actions in periphe
neurons is probably not valid for ANF actions in t
central nervou by an inhibitory G-protein coupled to the R_2 receptor.
This proposed pathway for ANF actions in peripheral
neurons is probably not valid for ANF actions in the
central nervous system. Numerous studies have identi-
fied This proposed pathway for ANF actions in peripheral
neurons is probably not valid for ANF actions in the
central nervous system. Numerous studies have identi-
fied central neuronal ANF receptors as R_1 receptors
(Quirio neurons is probably not valid for ANF actions in the central nervous system. Numerous studies have identi-
fied central neuronal ANF receptors as R_1 receptors (Quirion, 1989; Brown and Czarnecki, 1990; Konrad et al., 1 central nervous system. Numerous studies have identi-
fied central neuronal ANF receptors as R_1 receptors
(Quirion, 1989; Brown and Czarnecki, 1990; Konrad et
al., 1991). Thus, an absence of R_2 receptors in the cent fied central neuronal ANF receptors as R_1 receptors
(Quirion, 1989; Brown and Czarnecki, 1990; Konrad et
al., 1991). Thus, an absence of R_2 receptors in the central
nervous system would clearly preclude them as medi (Quirion, 1989; Brown and Czarnecki, 1990; Konrad et al., 1991). Thus, an absence of R_2 receptors in the central nervous system would clearly preclude them as mediators of ANF effects. The suppression of hypothalamic n al., 1991). Thus, an absence of R_2 receptors in the central
nervous system would clearly preclude them as mediators
of ANF effects. The suppression of hypothalamic nerve
firing caused by ANF is maintained in the presen nervous system would clearly preclude them as mediators
of ANF effects. The suppression of hypothalamic nerve
firing caused by ANF is maintained in the presence of
PT (Gridihar et al., 1992), providing evidence that a
supp of ANF effects. The suppress
firing caused by ANF is mai
PT (Gridihar et al., 1992),
suppression of adenylyl cycla
involved in this ANF effect.
3. Atrial natriuretic factor ing caused by ANF is maintained in the presence of Γ (Gridihar et al., 1992), providing evidence that a ppression of adenylyl cyclase activity probably is not volved in this ANF effect.
3. Atrial natriuretic factor effe PT (Gridihar et al., 1992), providing evidence that a suppression of adenylyl cyclase activity probably is not involved in this ANF effect.
3. Atrial natriuretic factor effects on neuronal ionic currents. The mechanisms by

REVIEW

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ANF RECEPTORS AND SIGNAL TRANT EXERPTORS AND SIGNAL TRANT EXERPTORS AND SIGNAL TRANT EXERPTIONS CONDITION TO COLOREL THE OUTSERVIES OF A SUMMARY SERVIES OF A SUMMARY SERVIES ON A SUMMARY SERVIES OF A SUMMARY SERVIES OF A S ANF RECEPTORS AND SIGNAL TRAM
transmitter release could include inhibitory effects on mol
nicotinic or calcium currents or a stimulatory effect on con-
outward potassium channels. All of these effects would AN. ANF RECEPTORS AND SIGNAL TRA
transmitter release could include inhibitory effects on
micotinic or calcium currents or a stimulatory effect on
coutward potassium channels. All of these effects would AN
tend to hyperpolarize transmitter release could include inhibitory effects on m
nicotinic or calcium currents or a stimulatory effect on co
outward potassium channels. All of these effects would A:
tend to hyperpolarize the neuron and presumabl transmitter release could include inhibitory effects on molestical
micotinic or calcium currents or a stimulatory effect on contoutward potassium channels. All of these effects would ANI
tend to hyperpolarize the neuron an micotinic or calcium currents or a stimulatory effect on outward potassium channels. All of these effects would tend to hyperpolarize the neuron and presumably make it less excitable. Bovine chromaffin cells responded to A outward potassium channels. All of these effects would formulated to hyperpolarize the neuron and presumably make it less excitable. Bovine chromaffin cells responded to the ANF with an inhibition of acetylcholine nicotini tend to hyperpolarize the neuron and presumably make F
it less excitable. Bovine chromaffin cells responded to
 \overline{ANF} with an inhibition of acetylcholine nicotinic cur-
rents (Borman et al., 1989). However, this inhibi it less excitable. Bovine chromaffin cells responded to ANF with an inhibition of acetylcholine nicotinic currents (Borman et al., 1989). However, this inhibitory effect of ANF only occurred at concentrations exceeding 1 ANF with an inhibition of acetylcholine nicotinic currents (Borman et al., 1989). However, this inhibitory seffect of ANF only occurred at concentrations exceeding 1 μ M, a concentration five orders of magnitude higher rents (Borman et al., 1989). However, this inhibitory
effect of ANF only occurred at concentrations exceeding
1 μ M, a concentration five orders of magnitude higher
than physiological ANF concentrations. Pressure pulses effect of ANF only occurred at concentrations exceeding receptive.
 $1 \mu M$, a concentration five orders of magnitude higher action

than physiological ANF concentrations. Pressure pulses ity, a

of ANF hyperpolarized rat 1 μ M, a concentration five orders of magnitude higher actional physiological ANF concentrations. Pressure pulses ity, of ANF hyperpolarized rat glioma cells in a manner 1. consistent with a stimulation of a rectifying than physiological ANF concentrations. Pressure pulses
of ANF hyperpolarized rat glioma cells in a manner
consistent with a stimulation of a rectifying potassium
channel (Reiser et al., 1987). Alternatively, ANF had no
net of ANF hyperpolarized rat glioma cells in a manner
consistent with a stimulation of a rectifying potassium
channel (Reiser et al., 1987). Alternatively, ANF had no
net effect on potassium transport in rat brain astrocytes
 consistent with a stimulation of a rectifying potassium
channel (Reiser et al., 1987). Alternatively, ANF had no
net effect on potassium transport in rat brain astrocytes
(Beaumont and Tan, 1990) or rat superior cervical g channel (Reiser et al., 1987). Alternatively, ANF had no
net effect on potassium transport in rat brain astrocytes spone
(Beaumont and Tan, 1990) or rat superior cervical gan-
glia (Pant and Smith, 1989). Bullfrog paravert net effect on potassium transport in rat brain astrocyt
(Beaumont and Tan, 1990) or rat superior cervical ga
glia (Pant and Smith, 1989). Bullfrog paravertebral ga
glia responded to ANF with an inhibition of potassiu
chann (Beaumont and Tan, 1990) or rat superior cervical gan-
glia (Pant and Smith, 1989). Bullfrog paravertebral gan-
glia responded to ANF with an inhibition of potassium spot-
channels, resulting in increased action potential glia (Pant and Smith, 1989). Bullfrog paravertebral ganglia responded to ANF with an inhibition of potassium channels, resulting in increased action potential formation (Pant and Smith, 1989). The influence of ANF on neuro glia responded to ANF with an inhibition of potassium
channels, resulting in increased action potential forma-
tion (Pant and Smith, 1989). The influence of ANF on
neuronal calcium channels has not been reported, but
the c channels, resulting in increased action potential formation (Pant and Smith, 1989). The influence of ANF on neuronal calcium channels has not been reported, but the central role of calcium in the control of exocytosis iden 1. (Pant and Smith, 1989). The influence of ANF on uronal calcium channels has not been reported, but e central role of calcium in the control of exocytosis entifies these as potential sites of ANF action.
4. Role of eicos

reuronal calcium channels has not been reported, but
the central role of calcium in the control of exocytosis
identifies these as potential sites of ANF action.
4. Role of eicosanoid production in atrial natriuretic
factor the central role of calcium in the control of exocytosis
identifies these as potential sites of ANF action.
4. Role of eicosanoid production in atrial natriuretic
factor neuromodulatory effects. Eicosanoids have not
been i identifies these as potential sites of ANF action.
4. Role of eicosanoid production in atrial natriure
factor neuromodulatory effects. Eicosanoids have n
been identified as mediators of ANF actions in any tiss
thus far. We 4. Role of eicosanoid production in atrial natriuretic factor neuromodulatory effects. Eicosanoids have not been identified as mediators of ANF actions in any tissue thus far. We failed to observe an ANF effect on prostagl factor neuromodulatory effects. Eicosanoids have not
been identified as mediators of ANF actions in any tissue of
thus far. We failed to observe an ANF effect on prosta-
glandin production in the rabbit vas deferens (Drewe been identified as mediators of ANF actions in any tissue thus far. We failed to observe an ANF effect on prosta-
glandin production in the rabbit vas deferens (Drewett et al., 1989), and the neuromodulatory effect of ANF thus far. We failed to observe an ANF effect on prosta-
glandin production in the rabbit vas deferens (Drewett
et al., 1989), and the neuromodulatory effect of ANF was
intact after indomethacin treatment in the rabbit vas
 et al., 1989), and the neuromodulatory effect of ANF was
intact after indomethacin treatment in the rabbit vas
deferens. These data indicated no role for prostaglandins
in mediating ANF effects in neuronal tissue. Other ei et al., 1989), and the neuromodulatory effect of ANF was
intact after indomethacin treatment in the rabbit vas
deferens. These data indicated no role for prostaglandins
in mediating ANF effects in neuronal tissue. Other ei intact after indomethacin treatment in the rabbit vas
deferens. These data indicated no role for prostaglandins $\frac{1}{10}$
in mediating ANF effects in neuronal tissue. Other eicosanoids, such as leukotrienes or epoxygenas far. mediating ANF effects in neuronal tissue. Other eisenoids, such as leukotrienes or epoxygenases, have
t been investigated as mediators of ANF actions thus
r.
5. Conclusions regarding atrial natriuretic factor sig-
ling pat

cosanoids, such as leukotrienes or epoxygenases, have

not been investigated as mediators of ANF actions thus

far.

5. Conclusions regarding atrial natriuretic factor sig-

naling pathways within neurons. A variety of stu not been investigated as mediators of ANF actions
far.
5. Conclusions regarding atrial natriuretic factor
naling pathways within neurons. A variety of studies
excluded cGMP as the mediator of ANF neuromo
tion in peripheral far.
5. Conclusions regarding atrial natriuretic factor
naling pathways within neurons. A variety of studies lexcluded cGMP as the mediator of ANF neuromod
tion in peripheral adrenergic neurons. The neuromod
latory pathway 5. Conclusions regarding atrial natriuretic factor signaling pathways within neurons. A variety of studies have excluded cGMP as the mediator of ANF neuromodulation in peripheral adrenergic neurons. The neuromodulatory pa rading pathways within neurons. A variety of studies have excluded cGMP as the mediator of ANF neuromodulation in peripheral adrenergic neurons. The neuromodulatory pathway appears to involve interactions with R_2 recep excluded cGMP as the mediator of ANF neuromodulation in peripheral adrenergic neurons. The neuromodulatory pathway appears to involve interactions with R_2 receptors leading to a suppression of both adenylyl cy-clase an tion in peripheral adrenergic neurons. The neuromodulatory pathway appears to involve interactions with R_2 receptors leading to a suppression of both adenylyl cyclase and neurotransmitter release with a G-protein media latory pathway appears to involve interactions with R_2
receptors leading to a suppression of both adenylyl cy-
clase and neurotransmitter release with a G-protein me-
diating the effect. Potassium channels also may be pathways are depicted in figure 9.
H. Atrial Natriuretic Factor Effects on Platelets diating the effect. Potassium channels also may be acti-

The platelet represents a relatively unique preparation pathways are depicted in figure 9.
H. Atrial Natriuretic Factor Effects on Platelets
The platelet represents a relatively unique preparation
for studying ANF mechanisms of action because it lacks
a particulate GC (Anand-Sr H. Atrial Natriuretic Factor Effects on Platelets
The platelet represents a relatively unique preparatic
for studying ANF mechanisms of action because it lack
a particulate GC (Anand-Srivastava et al., 1991; Schi
frin et a Fig. Atrial Natrialretic Factor Effects on Fiatelets
The platelet represents a relatively unique preparation
for studying ANF mechanisms of action because it lacks
a particulate GC (Anand-Srivastava et al., 1991; Schif-
f The platelet represents a relatively unique preparation
for studying ANF mechanisms of action because it lacks
a particulate GC (Anand-Srivastava et al., 1991; Schif-
frin et al., 1991). Thus, it is devoid of the R_1 re for studying ANF mechanisms of action because it lacks
a particulate GC (Anand-Srivastava et al., 1991; Schif-
frin et al., 1991). Thus, it is devoid of the R₁ receptor
(Anand-Srivastava et al., 1991), although Schiffrin a particulate GC (Anand-Srivastava et al., 1991; Schif-
frin et al., 1991). Thus, it is devoid of the R₁ receptor
(Anand-Srivastava et al., 1991), although Schiffrin et al.
(1991) found high molecular weight binding sit (Anand-Srivastava et al., 1991), although Schiffrin et al.

(1991) found high molecular weight binding sites (i.e.,

125,000) in human platelets. These sites were responsive

to cANF, a peptide selective for R_2 sites, (1991) found high molecular weight binding sites (i.e.,
125,000) in human platelets. These sites were responsive
to cANF, a peptide selective for R_2 sites, suggesting that
they represented R_2 receptors. However, som

molecular weight receptors in the presence of reducing
molecular weight receptors in the presence of reducing
conditions, suggesting that they differ from the typical TRANSDUCTION MECHANISMS 483
molecular weight receptors in the presence of reducing
conditions, suggesting that they differ from the typical
ANF R₂ receptor that has been cloned and sequenced. RANSDUCTION MECHANISMS

molecular weight receptors in the presence of reducing

conditions, suggesting that they differ from the typical

ANF R₂ receptor that has been cloned and sequenced.

Platelets responded to ANF wi molecular weight receptors in the presence of reductions, suggesting that they differ from the typid ANF R₂ receptor that has been cloned and sequence Platelets responded to ANF with an increased aggregation in response molecular weight receptors in the presence of reducing
conditions, suggesting that they differ from the typical
ANF R_2 receptor that has been cloned and sequenced.
Platelets responded to ANF with an increased aggrega-
 conditions, suggesting that they differ from the typical ANF R_2 receptor that has been cloned and sequenced.
Platelets responded to ANF with an increased aggregation in response to thrombin and epinephrine (Loeb and Ge ANF R_2 receptor that has been cloned and sequenced.
Platelets responded to ANF with an increased aggregation in response to thrombin and epinephrine (Loeb and Gear, 1988). The biological activity of ANF in the absence Platelets responded to ANF with an increased aggregation in response to thrombin and epinephrine (Loeb and Gear, 1988). The biological activity of ANF in the absence of R₁ receptors suggests that ANF acts via Receptors i tion in response to thrombin and epinephrine (Loeb an Gear, 1988). The biological activity of ANF in the alsence of R_1 receptors suggests that ANF acts via I receptors in platelets. The only established intraplateled a Gear, 1988). The biological
sence of R_1 receptors suggereceptors in platelets. The origan
action of ANF is a suppressity, as shown in figure 10.
1. Role of guanylyl cyclase nce of R₁ receptors suggests that ANF acts via R₂ ceptors in platelets. The only established intraplatelet tion of ANF is a suppression of adenylyl cyclase activ-
i, as shown in figure 10.
1. Role of guanylyl cyclas

receptors in platelets. The only established intraplatelet
action of ANF is a suppression of adenylyl cyclase activ-
ity, as shown in figure 10.
1. Role of guanylyl cyclase in atrial natriuretic factor
responses in platele action of ANF is a suppression of adenylyl cyclase activ-
ity, as shown in figure 10.
1. Role of guanylyl cyclase in atrial natriuretic factor
responses in platelets. Despite the reported absence of
the R_1 receptor in ity, as shown in figure 10.

1. Role of guanylyl cyclase in atrial natriuretic factor

responses in platelets. Despite the reported absence of

the R_1 receptor in human platelets, rat platelets re-

sponded to ANF (10, 1. Role of guanylyl cyclase in atrial natriuretic factor
responses in platelets. Despite the reported absence of
the R_1 receptor in human platelets, rat platelets re-
sponded to ANF (10,000 pM) with a 35% increase in
c responses in platelets. Despite the reported absence of the R_1 receptor in human platelets, rat platelets re-
sponded to ANF (10,000 pM) with a 35% increase in cGMP concentrations (Loeb and Gear, 1988). These
authors a the R_1 receptor in human platelets, rat platelets responded to ANF (10,000 pM) with a 35% increase in cGMP concentrations (Loeb and Gear, 1988). These authors also found ANF to enhance aggregatory responses to epinephr sponded to ANF (10,000 pM) with a 35% increase in cGMP concentrations (Loeb and Gear, 1988). These authors also found ANF to enhance aggregatory responses to epinephrine and thrombin. The maximal proaggregatory effect of A sponses to epinephrine and thrombin. The maximal sponses to epinephrine and thrombin. The maximal
proaggregatory effect of ANF occurred at a concentration
of 10 pM, a concentration usually devoid of effects on
GC activity. Nevertheless, these investigators concluded
that proaggregatory effect of ANF occurred at a concentration
of 10 pM, a concentration usually devoid of effects on
GC activity. Nevertheless, these investigators concluded
that ANF could be acting via generation of cGMP. Thi of 10 pM, a concentration usually devoid of ef GC activity. Nevertheless, these investigators contact that ANF could be acting via generation of cGM hypothesis has not been tested further with explaining R_1 or R_2 re *2. activity.* Nevertheless, these investigators concluded at ANF could be acting via generation of cGMP. This pothesis has not been tested further with experiments ing R₁ or R₂ receptor-binding agents or PT.
2. Role o

cGMP concentrations (Loeb and Gear, 1988). These and to concentrations also found ANF to enhance aggregatory re-
aponese to epinephrine and thrombin. The maximal proaggregatory effect of ANF occurred at a concentration
of that ANF could be acting via generation of cGMP. This hypothesis has not been tested further with experiments using R_1 or R_2 receptor-binding agents or PT.
2. *Role of adenylyl cyclase inhibition on platelet actions* hypothesis has not been tested further with experiments
using R_1 or R_2 receptor-binding agents or PT.
2. Role of adenylyl cyclase inhibition on platelet actions
of atrial natriuretic factor. ANF inhibited adenylyl c using R_1 or R_2 receptor-binding agents or PT.
2. Role of adenylyl cyclase inhibition on platelet act
of atrial natriuretic factor. ANF inhibited adenylyl
clase with an EC_{50} of 100 to 500 pM (Anand-Srivas
et al., 2. Role of adenylyl cyclase inhibition on platelet actions
of atrial natriuretic factor. ANF inhibited adenylyl cy-
clase with an EC₅₀ of 100 to 500 pM (Anand-Srivastava
et al., 1991), consistent with the ability of low clase with an EC_{50} of 100 to 500 pM (Anand-Srivastava
et al., 1991), consistent with the ability of low concentra-
tions of ANF to alter aggregatory responses to epineph-
rine and thrombin (Loeb and Gear, 1988). PT (5 et al., 1991), consistent with the ability of low concentra-
tions of ANF to alter aggregatory responses to epineph-
rine and thrombin (Loeb and Gear, 1988). PT (5 μ g/ml)
or amiloride (100 μ M) eliminated the inhibit tions of ANF to alter aggregatory responses to epineph-
rine and thrombin (Loeb and Gear, 1988). PT (5 μ g/ml)
or amiloride (100 μ M) eliminated the inhibition of ad-
enylyl cyclase (Anand-Srivastava et al., 1991). Th rine and thrombin (Loeb and Gear, 1988). PT (5 μ g/ml or amiloride (100 μ M) eliminated the inhibition of adenylyl cyclase (Anand-Srivastava et al., 1991). The effects on platelet aggregation were not assessed. Thes r or amiloride (100 μ M) eliminated the inhibition of adenylyl cyclase (Anand-Srivastava et al., 1991). The effects on platelet aggregation were not assessed. These results indicate that high-affinity R_2 receptors are enylyl cyclase (Anand-Srivastava et al., 1991). The effects on platelet aggregation were not assessed. These results indicate that high-affinity R_2 receptors are present on platelets, and their stimulation results in a fects on platelet aggregation were not assessed. These results indicate that high-affinity R_2 receptors are present on platelets, and their stimulation results in an inhibition of adenylyl cyclase. It appears that thes platelets. ent on platelets, and their stimulation results in an inhibition of adenylyl cyclase. It appears that these receptors are the functional ANF receptors present in platelets.
3. Conclusions regarding atrial natriuretic facto

FIG. 10. Platelet signal transduction pathways for ANF. ANF activates only R_2 receptors in the platelet, resulting in an inhibition of adenylyl cyclase (AC) activity. This suppression involves a G-protein FIG. 10. Platelet signal transduction pathways for ANF. ANF activates only R₂ receptors in the platelet, resulting in an inhibition of adenylyl cyclase (AC) activity. This suppression involves a G-protein (G) and apparen

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in platelets. ANF has a slight stimulatory effect on plat
let aggregation despite a complete absence of R_1 rece_l **484** ANAMD-SRIVAS
in platelets. ANF has a slight stimulatory effect on plate
let aggregation despite a complete absence of R_1 rece
tors. ANF inhibits adenylyl cyclase activity with an EC ANAND-SRIVASTAVA μ

in platelets. ANF has a slight stimulatory effect on plate-

let aggregation despite a complete absence of R_1 recep-

futors. ANF inhibits adenylyl cyclase activity with an EC₅₀ po

compatible in platelets. ANF has a slight stimulatory effect on plate
let aggregation despite a complete absence of R_1 recep
tors. ANF inhibits adenylyl cyclase activity with an EC_6
compatible with its modulation of platelet ag in platelets. ANF has a slight stimulatory effect on plate-
let aggregation despite a complete absence of R_1 recep-
tors. ANF inhibits adenylyl cyclase activity with an EC_{50}
compatible with its modulation of platele let aggregation despite a complete absence of R_1 receptors. ANF inhibits adenylyl cyclase activity with an EC_{50} p compatible with its modulation of platelet aggregation. d The presence of only R_2 receptors on pla tors. ANF inhibits adenylyl cyclase activity with an E
compatible with its modulation of platelet aggregat
The presence of only R_2 receptors on platelets sugg
that these are the receptors coupled to adenylyl cyc
in an compatible with its modulation of platelet aggregation.
The presence of only R_2 receptors on platelets suggests
that these are the receptors coupled to adenylyl cyclase
in an inhibitory manner. Whether other signal tra The presence of only R_2 receptors on platelets suggests A
that these are the receptors coupled to adenylyl cyclase g
in an inhibitory manner. Whether other signal transduc-
tion pathways are involved in ANF actions on that these are the receptors coupled to adenylyl cyclase
in an inhibitory manner. Whether other signal transduc-
tion pathways are involved in ANF actions on platelets
is presently undetermined. The hypothetical scheme for tion pathways are involved in ANF actions on platelets
is presently undetermined. The hypothetical scheme for
platelet transduction pathways is shown in figure 10.
V. Atrial Natriuretic Factor Receptor

Antagonists

V. Atrial Natriuretic Factor Receptor
Antagonists and the receptors is defining physiological actions of low
ANF and the receptors responsible for these actions is for
the dearth of specific ANF receptor antagonists. The c of the dearth of specific ANF receptor antagonists
A major hindrance in defining physiological actions of low
ANF and the receptors responsible for these actions is
the dearth of specific ANF receptor antagonists. The
deve A major hindrance in defining physiological actions of
ANF and the receptors responsible for these actions is
the dearth of specific ANF receptor antagonists. The
development of ANF receptor antagonists is underway,
but th A major hindrance in defining physiological actions of learth and the receptors responsible for these actions is for the dearth of specificity. The characteristic ANF receptor antagonists is underway, so but the available the dearth of specific ANF receptor antagonists. The development of ANF receptor antagonists is underway, but the available antagonists lack potency and specificity for ANF receptor subtypes. Initial studies used truncated development of ANF receptor antagonists is underway,
but the available antagonists lack potency and specificity
for ANF receptor subtypes. Initial studies used truncated
derivatives of ANF as selective inhibitors of R_2 but the available antagonists lack potency and specificity
for ANF receptor subtypes. Initial studies used truncated
derivatives of ANF as selective inhibitors of R_2 receptors.
These shortened forms of ANF were modifie for ANF receptor subtypes. Initial studies used truncated
derivatives of ANF as selective inhibitors of R_2 receptors.
These shortened forms of ANF were modified by peptide
substitution, resulting in selective binding t derivatives of ANF as selective inhibitors of R_2 receptors. fe
These shortened forms of ANF were modified by peptide
substitution, resulting in selective binding to R_2 receptors
(Maack et al., 1987; Olins et al., 19 These shortened forms of ANF were modified by peptide
substitution, resulting in selective binding to R_2 receptors
(Maack et al., 1987; Olins et al., 1988; Isales et al., 1992).
However, most of these selective binding substitution, resulting in selective binding to R_2 receptors (Maack et al., 1987; Olins et al., 1988; Isales et al., 1992). polynowever, most of these selective binding agents actually an possessed agonist activities ((Maack et al., 1987; Olins et al., 1988; Isales et al., 1992).
However, most of these selective binding agents actually
possessed agonist activities (Anand-Srivastava et al.,
1990; Drewett et al., 1990; Johnson et al., 199 However, most of these selective binding agents actually
possessed agonist activities (Anand-Srivastava et al.,
1990; Drewett et al., 1990; Johnson et al., 1991; Levin
and Frank, 1991; Hu et al., 1992; Isales et al., 1992) 1990; Drewett et al., 1990; Johnson et al., 1991; Levin and suppressed cGMP accumulation in response to ANF.
and Frank, 1991; Hu et al., 1992; Isales et al., 1992). This metabolite was produced by incubating ANF with
alth 1990; Drewett et al., 1990; Johnson et al., 1991; Levi
and Frank, 1991; Hu et al., 1992; Isales et al., 1992
although one vascular study found cANF to be an I
receptor antagonist (Cahill and Hassid, 1991). The bul
of thes and Frank, 1991; Hu et al., 1992; Isales et al., 1992), Talthough one vascular study found cANF to be an R_2 the receptor antagonist (Cahill and Hassid, 1991). The bulk to f these studies indicate that initial attempts although one vascular study found cANF to be an R_2 receptor antagonist (Cahill and Hassid, 1991). The bulk of these studies indicate that initial attempts at developing inhibitors of the R_2 receptor to prevent plasm receptor antagonist (Cahill and H of these studies indicate that in
oping inhibitors of the R_2 receptedness of natriuretic peptides
lective agonists for this receptor.
The identification of antagonis these studies indicate that initial attempts at devel-
ing inhibitors of the R_2 receptor to prevent plasma
barance of natriuretic peptides actually generated se-
tive agonists for this receptor.
The identification of a

oping inhibitors of the R_2 receptor to prevent plasma ot
clearance of natriuretic peptides actually generated se-
lective agonists for this receptor.
The identification of antagonists for the R_1 receptors (F
has occ clearance of natriuretic peptides actually generated se-
lective agonists for this receptor. $\qquad \qquad$ on
The identification of antagonists for the R_1 receptors (K
has occurred recently. Three major antagonists have
dee lective agonists for this receptor.
The identification of antagonists for the R_1 receptors
has occurred recently. Three major antagonists have
been identified, A74186, anantin, and HS-142-1. The
A74186 is a peptide der The identification of antagonists for the R_1 receptors (has occurred recently. Three major antagonists have obsen identified, A74186, anantin, and HS-142-1. The λ 74186 is a peptide derivative of ANF that suppresses been identified, A74186, anantin, and HS-142-1. The A74186 is a peptide derivative of ANF that suppresses cGMP production in response to ANF (von Geldern et al., 1990). The A74186 shifted concentration-response curves for been identified, A74186, anantin, and HS-142-1. The
A74186 is a peptide derivative of ANF that suppresses
cGMP production in response to ANF (von Geldern et
al., 1990). The A74186 shifted concentration-response
curves for A74186 is a peptide derivative of ANF that suppresses cGMP production in response to ANF (von Geldern et al., 1990). The A74186 shifted concentration-response curves for ANF 100-fold to the right at antagonist concentrati cGMP production in response to ANF (von Geldern
al., 1990). The A74186 shifted concentration-respon
curves for ANF 100-fold to the right at antagonist co
centrations of 10 μ M. Other antagonists have been of
veloped by al., 1990). The A74186 shifted concentration-response the curves for ANF 100-fold to the right at antagonist concentrations of 10 μ M. Other antagonists have been de-
veloped by this group, such as A68828, a linear subs centrations of 10 μ M. Other antagonists have been de-
veloped by this group, such as A68828, a linear substi-
tuted derivative of a truncated form of ANF (Holleman antagonists mentioned above. However, if ANF metab-
et centrations of 10 μ **M**. Other antagonists have been developed by this group, such as A68828, a linear substituted derivative of a truncated form of ANF (Holleman et al., 1991) that inhibits cGMP generation in response veloped by this group, such as A68828, a linear substituted derivative of a truncated form of ANF (Holleman et al., 1991) that inhibits cGMP generation in response to ANF with a half-maximal effect at 100 nM. Another simil tuted derivative of a truncated form of ANF (Holleman antive delay, 1991) that inhibits cGMP generation in response olitic ANF with a half-maximal effect at 100 nM. Another files similar agent, A71915 (1 μ M; von Gelder et al., 1991) that inhibits cGMP generation in respote ANF with a half-maximal effect at 100 nM. Anom similar agent, A71915 (1 μ M; von Geldern et al., 19 inhibited cGMP production in response to A(Trachte, 1993). Anant to ANF with a half-maximal effect at 100 nM. Another

similar agent, A71915 (1 μ M; von Geldern et al., 1990),

inhibited cGMP production in response to ANF

(Trachte, 1993). Anantin, a product of the microorga-

nism similar agent, A71915 (1 μ M; von Geldern et al., 1990), ical
inhibited cGMP production in response to ANF server
(Trachte, 1993). Anantin, a product of the microorga-
mism Streptomycetes coerulescens (Weber et al., 199 inhibited cGMP production in response to ANF ser
(Trachte, 1993). Anantin, a product of the microorga-
mism *Streptomycetes* coerulescens (Weber et al., 1991), ica
consists of a cyclic region of eight amino acids with a
te (Trachte, 1993). Anantin, a product of the microorga-
nism Streptomycetes coerulescens (Weber et al., 1991), icall
consists of a cyclic region of eight amino acids with a
nonapeptide tail (Wyss et al., 1991). Anantin has w nism *Streptomycetes coerulescens* (Weber et al., 1991), is
consists of a cyclic region of eight amino acids with a
nonapeptide tail (Wyss et al., 1991). Anantin has weak p
antagonistic activity, suppressing CGMP generati consists of a cyclic region of eight amino acids with a thomapeptide tail (Wyss et al., 1991). Anantin has weak antagonistic activity, suppressing cGMP generation in response to ANF at antagonist concentrations exceeding t nonapeptide tail (Wyss et al., 1991). Anantin has weak
antagonistic activity, suppressing cGMP generation in
response to ANF at antagonist concentrations exceeding
100 μ M (Weber et al., 1991). Anantin also suppressed
a antagonistic activity, suppressing cGMP generation in response to ANF at antagonist concentrations exceeding 100 μ M (Weber et al., 1991). Anantin also suppressed adenylyl cyclase activity, suggesting that it is an R_2

V. Atrial Natriuretic Factor Receptor

A major hindrance in defining physiological actions of low potency, limited availability, and lack of specificity

A major hindrance in defining physiological actions of low potency, the dearth of specific ANF receptor antagonists. The commercially, and none of them has been examined for development of ANF receptor antagonists is underway, selectivity between the GC-A and GC-B forms of the R_1 but t A AND TRACHTE
covered ANF antagonist is HS-142–1, a product of the
fungus *Aureobasidium* (Morishita et al., 1991a,b). It is a **A AND TRACHTE**
covered ANF antagonist is HS-142-1, a product of the
fungus *Aureobasidium* (Morishita et al., 1991a,b). It is a
polysaccharide consisting of β -1-6-linked glucose resi-A AND TRACHTE
covered ANF antagonist is HS-142-1, a product of the
fungus Aureobasidium (Morishita et al., 1991a,b). It is a
polysaccharide consisting of β -1-6-linked glucose resi-
dues esterified with capronic acid. H covered ANF antagonist is HS-142-1, a product of the
fungus Aureobasidium (Morishita et al., 1991a,b). It is a
polysaccharide consisting of β -1-6-linked glucose resi-
dues esterified with capronic acid. HS-142-1 reduce covered ANF antagonist is HS-142-1, a product of the
fungus Aureobasidium (Morishita et al., 1991a,b). It is a
polysaccharide consisting of β -1-6-linked glucose resi-
dues esterified with capronic acid. HS-142-1 reduce fungus Aureobasidium (Morishita et al., 1991a,b). It is a polysaccharide consisting of β -1-6-linked glucose residues esterified with capronic acid. HS-142-1 reduced ¹²⁵I
ANF binding by 50% at 10 μ M and suppressed polysaccharide consisting of β -1-6-linked glucose resi-
dues esterified with capronic acid. HS-142-1 reduced ¹²⁵I-
ANF binding by 50% at 10 μ M and suppressed cGMP
generation in response to ANF with a half-maximal
 ANF binding by 50% at 10 μ M and suppressed cGMP generation in response to ANF with a half-maximal effect at 1.8 μ g/ml (Ohyama et al., 1992), essentially eliminating cGMP production at 100 to 1000 μ g/ml (Toki et a ANF binding by 50% at 10 μ M and suppressed cGMP
generation in response to ANF with a half-maximal
effect at 1.8 μ g/ml (Ohyama et al., 1992), essentially
eliminating cGMP production at 100 to 1000 μ g/ml (Toki
et a generation in response to ANF with a half-maneffect at 1.8 μ g/ml (Ohyama et al., 1992), essen eliminating cGMP production at 100 to 1000 μ g/ml et al., 1992). This inhibitor is the most widely used antagonist, reduci effect at 1.8 μ g/ml (Ohyama et al., 1992), essentially eliminating cGMP production at 100 to 1000 μ g/ml (Toki et al., 1992). This inhibitor is the most widely used ANF antagonist, reducing or eliminating renal, anti eliminating cGMP production at 100 to 1000 μ g/ml (Toki et al., 1992). This inhibitor is the most widely used ANF antagonist, reducing or eliminating renal, anti-steroidogenic, and vasodilatory effects of ANF (Sano et a et al., 1992). This inhibitor is the most widely used ANF
antagonist, reducing or eliminating renal, anti-steroido-
genic, and vasodilatory effects of ANF (Sano et al., 1992;
Oda et al., 1992; Imura et al., 1992). These re antagonist, reducing or eliminating renal, anti-steroido-
genic, and vasodilatory effects of ANF (Sano et al., 1992;
Oda et al., 1992; Imura et al., 1992). These receptor
antagonists have a number of disadvantages includin genic, and vasodilatory effects of ANF (Sano et al., 1992;
Oda et al., 1992; Imura et al., 1992). These receptor
antagonists have a number of disadvantages including
low potency, limited availability, and lack of specifici Oda et al., 1992; Imura et al., 1992). These receptor
antagonists have a number of disadvantages including
low potency, limited availability, and lack of specificity
for individual receptors. None of these agents is avail antagonists have a number of disadvantages including
low potency, limited availability, and lack of specificity
for individual receptors. None of these agents is available
commercially, and none of them has been examined low potency, limited availability, and lack of specificity
for individual receptors. None of these agents is available
commercially, and none of them has been examined for
selectivity between the GC-A and GC-B forms of th for individual receptors. None of these agents is available commercially, and none of them has been examined for selectivity between the GC-A and GC-B forms of the R_1 receptor. Nevertheless, they currently provide the commercially, and none of them has been examined for
selectivity between the GC-A and GC-B forms of the R_1
receptor. Nevertheless, they currently provide the best
means to investigate the biological relevance of the di means to investigate the biological relevance of the different natriuretic peptide receptors and to evaluate the contribution of cGMP to natriuretic peptide actions.
Some metabolites of ANF also have been found to ceptor. Nevertheless, they currently provide the best
beans to investigate the biological relevance of the dif-
rent natriuretic peptide receptors and to evaluate the
ntribution of cGMP to natriuretic peptide actions.
Some

means to investigate the biological relevance of the different natriuretic peptide receptors and to evaluate the contribution of cGMP to natriuretic peptide actions.
Some metabolites of ANF also have been found to possess ferent natriuretic peptide receptors and to evaluate th
contribution of cGMP to natriuretic peptide actions.
Some metabolites of ANF also have been found t
possess antagonistic activity. Abell et al. (1989) observe
an ANF contribution of cGMP to natriuretic peptide actions.
Some metabolites of ANF also have been found to
possess antagonistic activity. Abell et al. (1989) observed
an ANF metabolite to be a partial agonist; it both stim-
ulat Some metabolites of ANF also have been found to
possess antagonistic activity. Abell et al. (1989) observed
an ANF metabolite to be a partial agonist; it both stim-
ulated cGMP accumulation in vascular smooth muscle
and su possess antagonistic activity. Abell et al. (1989) observed
an ANF metabolite to be a partial agonist; it both stim-
ulated cGMP accumulation in vascular smooth muscle
and suppressed cGMP accumulation in response to ANF.
T an ANF metabolite to be a partial agonist; it both stim-
ulated cGMP accumulation in vascular smooth muscle
and suppressed cGMP accumulation in response to ANF.
This metabolite was produced by incubating ANF with
thermolys ulated cGMP accumulation in vascular smooth muscle
and suppressed cGMP accumulation in response to ANF.
This metabolite was produced by incubating ANF with
thermolysin to cleave the cysteinyl-phenylalanyl bond of
the inter and suppressed cGMP accumulation in response to ANF.
This metabolite was produced by incubating ANF with
thermolysin to cleave the cysteinyl-phenylalanyl bond of
the internal 17-amino acid cyclic ring of ANF. It was not
ev This metabolite was produced by incubating ANF with
thermolysin to cleave the cysteinyl-phenylalanyl bond of
the internal 17-amino acid cyclic ring of ANF. It was not
evaluated for influences on any other ANF action. An-
o thermolysin to cleave the cysteinyl-phenylalanyl bond of
the internal 17-amino acid cyclic ring of ANF. It was not
evaluated for influences on any other ANF action. An-
other noncyclized derivative of ANF was created by
pl the internal 17-amino acid cyclic ring of ANF. It was not evaluated for influences on any other ANF action. Another noncyclized derivative of ANF was created by placing small groups, such as acetamidomethyl residues, on th evaluated for influences on any other ANF action. An-
other noncyclized derivative of ANF was created by
placing small groups, such as acetamidomethyl residues,
on the cysteine residues of ANF to prevent cyclization
(Kataj other noncyclized derivative of ANF was created b
placing small groups, such as acetamidomethyl residues
on the cysteine residues of ANF to prevent cyclizatio
(Katajima et al., 1989). The cysteine-substituted ANF
derivativ placing small groups, such as acetamidomethyl residues,
on the cysteine residues of ANF to prevent cyclization
(Katajima et al., 1989). The cysteine-substituted ANF
derivatives bound to ANF receptors, inhibited ANF stim-
u on the cysteine residues of ANF to prevent cyclization (Katajima et al., 1989). The cysteine-substituted ANF derivatives bound to ANF receptors, inhibited ANF stimulation of GC, but failed to modify vasodilator activity of (Katajima et al., 1989). The cysteine-substituted ANF
derivatives bound to ANF receptors, inhibited ANF stim-
ulation of GC, but failed to modify vasodilator activity
of ANF in vascular smooth muscle. These modified cys-
t derivatives bound to ANF receptors, inhibited ANF stim-
ulation of GC, but failed to modify vasodilator activity
of ANF in vascular smooth muscle. These modified cys-
teinyl forms of ANF did not stimulate GC, indicating
th ulation of GC, but failed to modify vasodilator activity
of ANF in vascular smooth muscle. These modified cys-
teinyl forms of ANF did not stimulate GC, indicating
that they were antagonists, totally devoid of agonist
acti teinyl forms of ANF did not stimulate GC, indicating
that they were antagonists, totally devoid of agonist teinyl forms of ANF did not stimulate GC, indicating
that they were antagonists, totally devoid of agonist
activity on R_1 receptors. The antagonistic activity of
these ANF metabolites is relatively weak, and these
comp that they were antagonists, totally devoid of agon
activity on R_1 receptors. The antagonistic activity
these ANF metabolites is relatively weak, and the
compounds provide no obvious advantages over the oth
antagonists activity on R_1 receptors. The antagonistic activity of these ANF metabolites is relatively weak, and these compounds provide no obvious advantages over the other antagonists mentioned above. However, if ANF metabolites these ANF metabolites is relatively weak, and the compounds provide no obvious advantages over the of antagonists mentioned above. However, if ANF metabolite physiologies function as ANF antagonists, then metabolite physio compounds provide no obvious advantages over the other
antagonists mentioned above. However, if ANF metab-
olites function as ANF antagonists, then metabolite pro-
files could be extremely important in defining physiolog-
 antagonists mentioned above. However, if ANF metab-
olites function as ANF antagonists, then metabolite pro-
files could be extremely important in defining physiolog-
ical activities of ANF. The metabolizing enzymes could
 olites function as ANF antagonists, then metabolite
files could be extremely important in defining physical
activities of ANF. The metabolizing enzymes of
serve a dual function of inactivating an agonist
generating an anta files could be extremely important in defining physiolog-
ical activities of ANF. The metabolizing enzymes could
serve a dual function of inactivating an agonist and
generating an antagonist simultaneously. Pharmacolog-
ic ical activities of ANF. The metabolizing enzymes could
serve a dual function of inactivating an agonist and
generating an antagonist simultaneously. Pharmacolog-
ically, these linear derivatives of ANF may serve as
templat serve a dual function
generating an antagonis
ically, these linear der
templates to be modific
potent ANF antagonists
The results with these merating an antagonist simultaneously. Pharmacolog-
ally, these linear derivatives of ANF may serve as
mplates to be modified for the development of more
tent ANF antagonists.
The results with these R_1 receptor antagon

ically, these linear derivatives of ANF may serve as
templates to be modified for the development of more
potent ANF antagonists.
The results with these R_1 receptor antagonists indicate
that renal effects of natriureti potent ANF antagonists.
The results with these R_1 receptor antagonists indicate
that renal effects of natriuretic peptides are mediated by
cGMP and the R_1 receptor (von Geldern et al., 1990;
Sano et al., 1992). Simi The results with these R_1 receptor antagonists indicate
that renal effects of natriuretic peptides are mediated by
cGMP and the R_1 receptor (von Geldern et al., 1990;
Sano et al., 1992). Similarly, adrenal effects o

et al., 1992) but not by R_2 -selective binding agents (Sessions et al., 1992). Aortic vasodilation was reversed by ANF RECEPTORS AND SIGNAL TRANET AL., 1992) but not by R_2 -selective binding agents (Ses-
sions et al., 1992). Aortic vasodilation was reversed by be p
HS-142–1 (Imura et al., 1992) but only at extremely high rece ANF RECEPTORS AND SIGNAL TRA
et al., 1992) but not by R_2 -selective binding agents (Sesistations et al., 1992). Aortic vasodilation was reversed by be
HS-142-1 (Imura et al., 1992) but only at extremely high reconcentra et al., 1992) but not by R₂-selective binding agents (Ses-
sions et al., 1992). Aortic vasodilation was reversed by be
HS-142-1 (Imura et al., 1992) but only at extremely high rec
concentrations, and the effect was very et al., 1992) but not by R_2 -selective binding agents (Sesisted as an agonization was reversed by be HS-142-1 (Imura et al., 1992) but only at extremely high reconcentrations, and the effect was very modest when paramet sions et al., 1992). Aortic vasodilation was reversed by HS-142-1 (Imura et al., 1992) but only at extremely high concentrations, and the effect was very modest when ANF was used as an agonist. The BNP curve was shifted m HS-142-1 (Imura et al., 1992) but only at extremely high rece
concentrations, and the effect was very modest when patl
ANF was used as an agonist. The BNP curve was shifted been
more effectively, suggesting a greater affi concentrations, and the effect was very modest when
ANF was used as an agonist. The BNP curve was shifted by
more effectively, suggesting a greater affinity of HS-142-
pl for GC-B than GC-A. These R_1 antagonists failed ANF was used as an agonist. The BNP curve was shifted bee
more effectively, suggesting a greater affinity of HS-142-
1 for GC-B than GC-A. These R_1 antagonists failed to trate
influence neuromodulatory and vasodilatory more effectively, suggesting a greater affinity of HS-14
1 for GC-B than GC-A. These R_1 antagonists failed
influence neuromodulatory and vasodilatory effects
ANF in rabbit isolated vas deferens (Trachte, 1993) a
rabbit 1 for GC-B than GC-A. These R_1 antagonists failed to influence neuromodulatory and vasodilatory effects of ANF in rabbit isolated vas deferens (Trachte, 1993) and rabbit isolated aorta, respectively (Trachte, 1993; Elm influence neuromodulatory and vasodilatory effects of ANF in rabbit isolated vas deferens (Trachte, 1993) and rabbit isolated aorta, respectively (Trachte, 1993; Elmquist and Trachte, 1992). Curiously, the hypotensive eff ANF in rabbit isolated vas deferens (Trachte, 1993) and rabbit isolated aorta, respectively (Trachte, 1993; Elmquist and Trachte, 1992). Curiously, the hypotensive effect nof ANF was resistant to R_1 receptor antagonism ist and Trachte, 1992). Curiously, the hypotensive effect normotensive animals and different models of experi-
of ANF was resistant to R_1 receptor antagonism in rats mental hypertension. Higher plasma ANF levels exist of ANF was resistant to R_1 receptor antagonism in rats
when either A74186 or HS-142-1 was used (von Geldern
et al., 1990; Sano et al., 1992), although both of these
agents blocked diuretic effects of ANF. Other ANF acwhen either A74186 or HS-142-1 was used (von Geldern various models of hypertension such as genetic hyperten-
et al., 1990; Sano et al., 1992), although both of these sion in SHRs (Gutkowska et al., 1986a; Imada et al.,
ag when either A74186 or HS-142–1 was used (von Gelder
et al., 1990; Sano et al., 1992), although both of thes
agents blocked diuretic effects of ANF. Other ANF ac
tions have not been investigated yet for an influence c
 R_1 et al., 1990; Sano et al., 1992), although both of these suggents blocked diuretic effects of ANF. Other ANF actions have not been investigated yet for an influence of R_1 receptor antagonists. The results of this limit agents blocked diuretic effects of ANF. Other ANF ac-
tions have not been investigated yet for an influence of $(Su$
 R_1 receptor antagonists. The results of this limited num-
ber of studies suggests that diuretic and ad tions have not been investigated yet for an influence of R_1 receptor antagonists. The results of this limited number of studies suggests that diuretic and adrenal effects are mediated by R_1 receptors. Vascular actio R_1 receptor antagonists. The results of this limited number of studies suggests that diuretic and adrenal effects are mediated by R_1 receptors. Vascular actions of ANI may be dependent on R_1 receptors, whereas hy ber of studies suggests that diuretic and adrenal effects
are mediated by R_1 receptors. Vascular actions of ANF
may be dependent on R_1 receptors, whereas hypotensive
and neuronal effects are, at least partially, ind are mediated by R_1 receptors. Vascular actions of ANF may be dependent on R_1 receptors, whereas hypotensive and neuronal effects are, at least partially, independent of these receptors. The future development of mor and neuronal effects are, at least partially, independent
of these receptors. The future development of more se-
lective and potent ANF receptor antagonists should im-
prove dramatically this analysis of receptor involveme these receptors. The future development of more se-
tive and potent ANF receptor antagonists should im-
ove dramatically this analysis of receptor involvement
ANF effects.
The major impetus for the development of ANF an-
g

in ANF effects.
The major impetus for the development of ANF antagonists is the desire to elevate plasma ANF concentralective and potent ANF receptor antagonists should
prove dramatically this analysis of receptor involven
in ANF effects.
The major impetus for the development of ANF
tagonists is the desire to elevate plasma ANF concentio prove dramatically this analysis of receptor involvem
in ANF effects.
The major impetus for the development of ANF
tagonists is the desire to elevate plasma ANF concent
tions by occupying R_2 receptors, resulting in the in ANF effects.
The major impetus for the development of ANF
tagonists is the desire to elevate plasma ANF concent
tions by occupying R_2 receptors, resulting in the suppi
sion of ANF clearance. Thus, most new ANF recep The major impetus for the development of ANF antagonists is the desire to elevate plasma ANF concentrations by occupying R_2 receptors, resulting in the suppression of ANF clearance. Thus, most new ANF receptor-
binding tagonists is the desire to elevate plasma ANF concentra-
tions by occupying R_2 receptors, resulting in the suppres-
sion of ANF clearance. Thus, most new ANF receptor-
binding compounds are designed to bind to R_2 re tions by occupying R_2 receptors, resulting in the suppres-
sion of ANF clearance. Thus, most new ANF receptor-
binding compounds are designed to bind to R_2 receptors, high
and no major attempts to develop R_1 anta sion of ANF clearance. Thus, most new ANF receptor-
binding compounds are designed to bind to R_2 receptors,
and no major attempts to develop R_1 antagonists are
occurring. The general strategy for clinical use of ANF binding compounds are designed to bind to R_2 receptors, higherd no major attempts to develop R_1 antagonists are occurring. The general strategy for clinical use of ANF an integents involves the use of R_2 -selectiv and no major attempts to develop R_1 antagonists accurring. The general strategy for clinical use of Alantagonists involves the use of R_2 -selective bindiagents in conditions of heart failure or hypertension accentuat occurring. The general strategy for clinical use of ANF antagonists involves the use of R_2 -selective binding for agents in conditions of heart failure or hypertension to gaccentuate renal and cardiovascular effects of antagonists involves the use of R_2 -selective binding
agents in conditions of heart failure or hypertension to
accentuate renal and cardiovascular effects of endoge-
nous ANF. These R_2 -binding agents often are combin agents in conditions of heart failure or hypertension to
accentuate renal and cardiovascular effects of endoge-
nous ANF. These R_2 -binding agents often are combined
with neutral endopeptidase inhibitors to elevate more accentuate renal and cardiovascular effects of endogenous ANF. These R_2 -binding agents often are combined creation with neutral endopeptidase inhibitors to elevate more for dramatically ANF plasma concentrations. No ob identified. dramatically ANF plasma concentrations. No obvious
clinical utility for the ANF R_1 antagonists has been
identified.
VI. Pathological Alterations in Transduction

Mechanisms

A. Introduction

Most studies investigating alterations in ANF signal transduction pathways in pathological states have concentrated on alterations in receptor populations. There-Mechanisms

Mechanisms

A. Introduction

Most studies investigating alterations in ANF signal

transduction pathways in pathological states have con-

centrated on alterations in receptor populations. There-A. Introduction
Most studies investigating alterations in ANF signal
transduction pathways in pathological states have contrated on alterations in receptor populations. The
fore, we shall emphasize only altered receptor po A. Introduction
Most studies investigating alterations in ANF sign
transduction pathways in pathological states have co
centrated on alterations in receptor populations. The
fore, we shall emphasize only altered receptor p Most studies investigating alterations in ANF signal
transduction pathways in pathological states have con-
centrated on alterations in receptor populations. There-
fore, we shall emphasize only altered receptor popula-
s transduction pathways in pathological states have concentrated on alterations in receptor populations. There-
fore, we shall emphasize only altered receptor popula-
Sitions associated with changes in GC or adenylyl cyclase centrated on alterations in receptor populations. Therefore, we shall emphasize only altered receptor populations associated with changes in GC or adenylyl cyclase responsiveness to ANF in a pathological state such as hype fore, we shall emphasize only altered receptor populations associated with changes in GC or adenylyl cyclase responsiveness to ANF in a pathological state such as hypertension and congestive heart failure. The potential me tions associated with changes in GC or adenylyl cyclase terponsiveness to ANF in a pathological state such as his hypertension and congestive heart failure. The potential in mechanisms accounting for ANF receptor alteratio responsiveness to ANF in a pathological state such as hand
hypertension and congestive heart failure. The potential in h
mechanisms accounting for ANF receptor alterations rece
could involve alterations in plasma concentra hypertension and congestive heart failure. The potential mechanisms accounting for ANF receptor alterations could involve alterations in plasma concentrations of ANF or other humoral agents acting to influence ANF receptor mechanisms accounting for ANF receptor alterations
could involve alterations in plasma concentrations
ANF or other humoral agents acting to influence Ale
receptor levels; therefore, the effects of sodium loadii
ANF, angiot

EXANSDUCTION MECHANISMS
istration, water deprivation, and sodium restriction will
be presented because they may impact on alterations of RANSDUCTION MECHANISMS 485
istration, water deprivation, and sodium restriction will
be presented because they may impact on alterations of
receptor number induced by various physiological or receptor MECHANISMS

FRANSDUCTION MECHANISMS

istration, water deprivation, and sodium restriction will

be presented because they may impact on alterations of

receptor number induced by various physiological or

patholog istration, water deprivation, and sodium restriction will
be presented because they may impact on alterations of
receptor number induced by various physiological or
pathological conditions. Most of the available data have
 istration, water deprivation, and sodium restriction will
be presented because they may impact on alterations of
receptor number induced by various physiological or
pathological conditions. Most of the available data have
 be presented because they may impact on alterations
receptor number induced by various physiological
pathological conditions. Most of the available data hi
been obtained in renal, adrenal, and vascular tissues a
platelets. pathological conditions. Most of the available data have
been obtained in renal, adrenal, and vascular tissues and
platelets. In general, conditions elevating ANF concen-
trations tend to decrease ANF receptors.
B. Hyperte been obtained in renal, adrenal, and vascular tissues and

atelets. In general, conditions elevating ANF concentrions tend to decrease ANF receptors.

Hypertension

The hypotensive effect of ANF is well established in

primotensive animals and different models of experitrations tend to decrease ANF receptors.

B. Hypertension

The hypotensive effect of ANF is well established

normotensive animals and different models of expe

mental hypertension. Higher plasma ANF levels exist B. Hypertension
The hypotensive effect of ANF is well established in
normotensive animals and different models of experi-
mental hypertension. Higher plasma ANF levels exist in
various models of hypertension such as geneti B. Hypertension
The hypotensive effect of ANF is well established
normotensive animals and different models of exp
mental hypertension. Higher plasma ANF levels exis
various models of hypertension such as genetic hyper
sio The hypotensive effect of ANF is well established in
normotensive animals and different models of experi-
mental hypertension. Higher plasma ANF levels exist in
various models of hypertension such as genetic hyperten-
sion normotensive animals and different models of experimental hypertension. Higher plasma ANF levels exist in various models of hypertension such as genetic hypertension in SHRs (Gutkowska et al., 1986a; Imada et al., 1985; Mo mental hypertension. Higher plasma ANF levels exist in various models of hypertension such as genetic hypertension in SHRs (Gutkowska et al., 1986a; Imada et al., 1985; Morii et al., 1986), DOCA salt hypertensive rats (Sug various models of hypertension such as genetic hypertension in SHRs (Gutkowska et al., 1986; Imada et al., 1985; Morii et al., 1986), DOCA salt hypertensive rats (Sugimoto et al., 1986; Schiffrin and St.-Louis, 1987), Dahl sion in SHRs (Gutkowska et al., 1986a; Imada et al., 1985; Morii et al., 1986), DOCA salt hypertensive rats (Sugimoto et al., 1986; Schiffrin and St.-Louis, 1987), Dahl salt-sensitive rats (Gutkowska et al., 1986b; Tanaka 1985; Morii et al., 1986), DOCA salt hypertensive rats (Sugimoto et al., 1986; Schiffrin and St.-Louis, 1987), Dahl salt-sensitive rats (Gutkowska et al., 1986b; Tanaka and Inagami, 1986), one-kidney, one-clip hypertensive (Sugimoto et al., 1986; Schiffrin and St.-Louis, 1987),
Dahl salt-sensitive rats (Gutkowska et al., 1986b; Tanaka
and Inagami, 1986), one-kidney, one-clip hypertensive
rats (Garcia et al., 1985), and two-kidney, one-clip h Dahl salt-sensitive rats (Gutkowska et al., 1986b; Tanaka
and Inagami, 1986), one-kidney, one-clip hypertensive
rats (Garcia et al., 1985), and two-kidney, one-clip hy-
pertensive rats (Garcia et al., 1986). Atrial ANF con 1985; Morii et al., 1986), DOCA salt hypertensive rats

(Suginoto et al., 1986; Schiffrin and St.-Louis, 1987),

(Suginoto et al., 1986; Schiffrin and St.-Louis, 1987),

Dahl salt-sensitive rats (Gutkowska et al., 1985b; T rats (Garcia et al., 1985), and two-kidney, one-clip hypertensive rats (Garcia et al., 1986). Atrial ANF contents
are lower in SHRs (Gutkowska et al., 1985; Garcia et al.,
1985; Imada et al., 1985; Morii et al., 1986) and pertensive rats (Garcia et al., 1986). Atrial ANF contents
are lower in SHRs (Gutkowska et al., 1985; Garcia et al.,
1985; Imada et al., 1985; Morii et al., 1986) and DOCA
salt hypertensive rats (Garcia et al., 1986) but n are lower in SHRs (Gutkowska et al., 1985; Garcia et al., 1985; Imada et al., 1985; Morii et al., 1986) and DOCA salt hypertensive rats (Garcia et al., 1986) but not in other forms of hypertension such as the two-kidney, o 1985; Imada et al., 1985; Morii et al., 1986) and DOCA
salt hypertensive rats (Garcia et al., 1986) but not in
other forms of hypertension such as the two-kidney, one-
clip model in which atrial ANF content is unaltered or salt hypertensive rats (Garcia et al., 1986) but not other forms of hypertension such as the two-kidney, on clip model in which atrial ANF content is unaltered elevated (Hirata et al., 1984; Garcia et al., 1985). On t othe other forms of hypertension such as the two-kidney, one-
clip model in which atrial ANF content is unaltered or
elevated (Hirata et al., 1984; Garcia et al., 1985). On the
other hand, atrial and plasma ANF levels are not s clip model in which atrial ANF content is unaltered or
elevated (Hirata et al., 1984; Garcia et al., 1985). On the
other hand, atrial and plasma ANF levels are not signif-
icantly different in stroke-prone SHRs from those elevated (Hirata et al.,

other hand, atrial and

icantly different in st

nonstroke-prone SHR

higher blood pressure.

1. Cardiovascular tis her hand, atrial and plasma ANF levels are not signif-

1. Cardiovascular tissues. Khalil et al., 1988) despite their

1. Cardiovascular tissues. Khalil et al. (1987) reported

1. Cardiovascular tissues. Khalil et al. (198

nonstroke-prone SHRs (Arai et al., 1988) despite their
higher blood pressure.
1. Cardiovascular tissues. Khalil et al. (1987) reported
an increased ANF receptor density and increased affinity
for ANF in cultured vascular s monstroke-prone SHRs (Arai et al., 1988) despite their
higher blood pressure.
1. Cardiovascular tissues. Khalil et al. (1987) reported
an increased ANF receptor density and increased affinity
for ANF in cultured vascular higher blood pressure.

1. Cardiovascular tissues. Khalil et al. (1987) reported

an increased ANF receptor density and increased affinity

for ANF in cultured vascular smooth muscle cells from

SHRs as compared to WKY rat 1. Cardiovascular tissues. Khalil et al. (1987) reported
an increased ANF receptor density and increased affinity
for ANF in cultured vascular smooth muscle cells from
SHRs as compared to WKY rats, whereas Resink et al.
(1 an increased ANF receptor density and increased affinity
for ANF in cultured vascular smooth muscle cells from
SHRs as compared to WKY rats, whereas Resink et al.
(1989) and Nakamura et al. (1988) confirmed the in-
creased for ANF in cultured vascular smooth muscle cells from
SHRs as compared to WKY rats, whereas Resink et al.
(1989) and Nakamura et al. (1988) confirmed the in-
creased receptor density but found a decreased affinity
for ANF SHRs as compared to WKY rats, whereas Resink et al. (1989) and Nakamura et al. (1988) confirmed the in creased receptor density but found a decreased affinity for ANF in SHRs. In contrast, ANF effects on cGMI concentration (1989) and Nakamura et al. (1988) confirmed the in-
creased receptor density but found a decreased affinity
for ANF in SHRs. In contrast, ANF effects on cGMP
concentrations were diminished in vascular smooth mus-
cle from creased receptor density but found a decreased affinity
for ANF in SHRs. In contrast, ANF effects on cGMP
concentrations were diminished in vascular smooth mus-
cle from SHRs (Nakamura et al., 1988; Sauro et al.,
1988). A concentrations were diminished in vascular smooth mus-
cle from SHRs (Nakamura et al., 1988; Sauro et al., 1988). A lower density of ANF-binding sites was found
in mesenteric vessels from SHRs (Cachofeiro et al., 1989) cle from SHRs (Nakamura et al., 1988; Sauro et al., 1988). A lower density of ANF-binding sites was found 1988). A lower density of ANF-binding sites was found
in mesenteric vessels from SHRs (Cachofeiro et al., 1989)
and one-kidney, one-clip hypertensive rats (Schiffrin,
1989) but not two-kidney, one-clip hypertensive rats
(in mesenteric vessels from SHRs (Cachofeiro et al., 1989)

and one-kidney, one-clip hypertensive rats (Schiffrin,

1989) but not two-kidney, one-clip hypertensive rats

(Schiffrin, 1989). Recently, Nuglozeh et al. (1990) 1989) but not two-kidney, one-clip hypertensive rats (Schiffrin, 1989). Recently, Nuglozeh et al. (1990) found
a reduced density of both R_1 and R_2 receptors in DOCA
salt hypertension. However, ANF suppressed adenylyl
cyclase more effectively in both aorta and hearts f a reduced density of both R_1 and R_2 receptors in DOCA salt hypertension. However, ANF suppressed adenylyl cyclase more effectively in both aorta and hearts from SHRs and DOCA salt hypertensive rats (Anand-Srivas-tav salt hypertension. However, ANF suppressed adenylyl cyclase more effectively in both aorta and hearts from SHRs and DOCA salt hypertensive rats (Anand-Srivastava, 1992b; Anand-Srivastava et al., 1993). The enhanced respons cyclase more effectively in both aorta and hearts from SHRs and DOCA salt hypertensive rats (Anand-Srivastava, 1992b; Anand-Srivastava et al., 1993). The enhanced responsiveness of ANF to inhibit adenylyl cyclase in hypert cyclase more effectively in both aorta and hearts from
SHRs and DOCA salt hypertensive rats (Anand-Srivas-
tava, 1992b; Anand-Srivastava et al., 1993). The en-
hanced responsiveness of ANF to inhibit adenylyl cyclase
in hy SHRs and DOCA salt hypertensive rats (Anand-Srivas-
tava, 1992b; Anand-Srivastava et al., 1993). The en-
hanced responsiveness of ANF to inhibit adenylyl cyclase
in hypertensive rats could not result from reductions in
rec tava, 1992b; Anand-Srivastava et al., 1993). The enhanced responsiveness of ANF to inhibit adenylyl cyclase
in hypertensive rats could not result from reductions in
receptor numbers but may be mediated by alterations in
po hanced responsiveness of ANF to inhibit adenylyl cyclase
in hypertensive rats could not result from reductions in
receptor numbers but may be mediated by alterations in
postreceptor events. The increase in receptor number in hypertensive rats could not result from reductions in receptor numbers but may be mediated by alterations in postreceptor events. The increase in receptor number in SHR vascular smooth muscle in the face of a decreased receptor numbers but may be mediated by alterations in postreceptor events. The increase in receptor number in SHR vascular smooth muscle in the face of a decreased cGMP response to ANF suggests a selective reduction of R

ANAND-SRIVASTAVA ANAS
ternatively, postreceptor events could be modified by $\frac{1}{2}$ in *k*
hypertension. hypertension.

ANAND-SRIVASTAVA

Pulmonary hypertension induced by a single injection

Pulmonary hypertension induced by a single injection

monocrotaline resulted in right ventricular hypertroternatively, postreceptor events could be modified
hypertension.
Pulmonary hypertension induced by a single inject
of monocrotaline resulted in right ventricular hyper
phy with elevated ventricular levels of ANF. Cardiac ternatively, postreceptor events could be modified by in . ons
hypertension. Consent to a single injection bot
of monocrotaline resulted in right ventricular hypertro-
phy with elevated ventricular levels of ANF. Cardiac a hypertension.

Pulmonary hypertension induced by a single injection

of monocrotaline resulted in right ventricular hypertro-

phy with elevated ventricular levels of ANF. Cardiac and

renal binding sites for ANF were decr Pulmonary hypertension induced by a single injection
of monocrotaline resulted in right ventricular hypertrephy with elevated ventricular levels of ANF. Cardiac an
renal binding sites for ANF were decreased significantly
b of monocrotaline resulted in right ventricular hyper
phy with elevated ventricular levels of ANF. Cardiac
renal binding sites for ANF were decreased significa
by the monocrotaline as judged by autoradiography (C
lenschlage renal binding sites for ANF were decreased significantly
by the monocrotaline as judged by autoradiography (Oeh-
lenschlager et al., 1989). Unfortunately, signal transduc-
tion pathways were not tested for alterations.
2.

by the monocrotaline as judged by autoradiography (Oeh-
lenschlager et al., 1989). Unfortunately, signal transduc-
tion pathways were not tested for alterations. soli
2. Kidney. Garcia et al. (1989) found a decrease with e lenschlager et al., 1989). Unfortunately, signal transduc-
tion pathways were not tested for alterations. so
2. Kidney. Garcia et al. (1989) found a decrease with
relative to WKY rats. A defect in ANF generation of si
cGMP tion pathways were not tested for alterations. so.
2. Kidney. Garcia et al. (1989) found a decrease with et
age in the density of glomerular ANF receptors in SHRs to
relative to WKY rats. A defect in ANF generation of sit
 2. Kidney. Garcia et al. (1989) found a decrease with age in the density of glomerular ANF receptors in SHRs relative to WKY rats. A defect in ANF generation of cGMP also was noted in SHRs at 16 weeks of age. The ANF effec age in the density of glomerular ANF receptors in SHRs tor,
relative to WKY rats. A defect in ANF generation of sites
cGMP also was noted in SHRs at 16 weeks of age. The but
ANF effect on renal adenylyl cyclase activity wa relative to WKY rats. A defect in ANF generation of cGMP also was noted in SHRs at 16 weeks of age. The ANF effect on renal adenylyl cyclase activity was not studied. Renal ANF receptor number was reduced in SHR kidneys in cGMP also was noted in SHRs at 16 weeks of age. The but
ANF effect on renal adenylyl cyclase activity was not (Naturalised. Renal ANF receptor number was reduced in in t
SHR kidneys in other studies also (Saito et al., 198 SHR kidneys in other studies also (Saito et al., 1986; SHR kidneys in other studies also (Saito et al., 1986;
Ogura et al., 1987). A reduction in blood pressure with
indapamide was associated with a further decrease in
both receptor number and affinity for ANF (Ogura et al.,
1 Ogura et al., 1987). A reduction in blood pressure with indapamide was associated with a further decrease in both receptor number and affinity for ANF (Ogura et al., 1986). The decline in both ANF receptors and GC responsi indapamide was associated with both receptor number and affinity
1986). The decline in both ANF
sponsiveness to ANF suggests a receptors present for ANF.
Glomerular ANF receptors incre th receptor number and affinity for ANF (Ogura 686). The decline in both ANF receptors and Gonsiveness to ANF suggests a reduction in the nu R_1 receptors present for ANF.
Glomerular ANF receptors increased in prehype r

1986). The decline in both ANF receptors and GC responsiveness to ANF suggests a reduction in the number of R_1 receptors present for ANF. bin
Glomerular ANF receptors increased in prehypertence
sive DOCA salt-treated r sponsiveness to ANF suggests a reduction in the numbulation of R₁ receptors present for ANF.

Glomerular ANF receptors increased in prehyperte

sive DOCA salt-treated rats but then decreased in thater hypertensive stage of R_1 receptors present for ANF.
Glomerular ANF receptors increased in prehypertensive DOCA salt-treated rats but then decreased in the
later hypertensive stage (Gauquelin et al., 1987b). Recep-
tor affinity for ANF wa Glomerular ANF receptors increased in prehyperten-
sive DOCA salt-treated rats but then decreased in the
later hypertensive stage (Gauquelin et al., 1987b). Recep-
AN
tor affinity for ANF was not altered. Nuglozeh et al. sive DOCA salt-treated rats but then decreased in the later hypertensive stage (Gauquelin et al., 1987b). Receptor affinity for ANF was not altered. Nuglozeh et al. (1990) recently found a decline in binding to both R_1 Later hypertensive stage (Gauquelin et al., 1987b). Recep-
tor affinity for ANF was not altered. Nuglozeh et al. hight
(1990) recently found a decline in binding to both R_1 and rate
 R_2 glomerular receptors from DOCA tor affinity for ANF was
(1990) recently found a dec
R₂ glomerular receptors fr
rats. Again, the signal transport were not explored further.
A marked up-regulation 990) recently found a decline in binding to both R_1 and glomerular receptors from DOCA salt hypertensive ts. Again, the signal transduction pathways for ANF receptor A marked up-regulation of glomerular ANF receptor

 R_2 glomerular receptors from DOCA salt hypertensive
rats. Again, the signal transduction pathways for ANF
were not explored further.
A marked up-regulation of glomerular ANF receptor
density occurred in two-kidney, one rats. Again, the signal transduction pathways for ANF B
were not explored further. gan.
A marked up-regulation of glomerular ANF receptor tion
density occurred in two-kidney, one-clip hypertensive 198
rats, whereas no chan were not explored further.

A marked up-regulation of glomerular ANF receptor

density occurred in two-kidney, one-clip hypertensive

rats, whereas no change or decreased glomerular ANF

receptor density was found in one-k A marked up-regulation of glomerular ANF receptor
density occurred in two-kidney, one-clip hypertensive
rats, whereas no change or decreased glomerular ANF
receptor density was found in one-kidney, one-clip hy-
pertensive density occurred in two-kidney, one-clip hypertensive
rats, whereas no change or decreased glomerular ANF
receptor density was found in one-kidney, one-clip hy-
pertensive rats (Gauquelin et al., 1987a; Garcia et al.,
1988 rats, whereas no change or decreased glomerular ANF do
receptor density was found in one-kidney, one-clip hy-
pertensive rats (Gauquelin et al., 1987a; Garcia et al., sh
1988) as compared to uninephrectomized controls. Fur receptor density was found in one-kidney, one-clip hypertensive rats (Gauquelin et al., 1987a; Garcia et al., 1988) as compared to uninephrectomized controls. Furthermore, glomerular ANF receptor density and affinity incre pertensive rats (Gauquelin et al., 1987a; Garcia et a
1988) as compared to uninephrectomized controls. Futhermore, glomerular ANF receptor density and affinincreased 2-fold 24 h after unclipping of one-kidney, or
clip hype 1988) as compared to uninephrectomized controls. Fur-
thermore, glomerular ANF receptor density and affinity b
increased 2-fold 24 h after unclipping of one-kidney, one-
clip hypertensive rats (Garcia et al., 1988). The un thermore, glomerular ANF receptor density and affinity
increased 2-fold 24 h after unclipping of one-kidney, one-
clip hypertensive rats (Garcia et al., 1988). The unclip-
ping was associated with a marked increase in plas increased 2-fold 24 h after unclipping of one-kidney, one-
clip hypertensive rats (Garcia et al., 1988). The unclip-
ping was associated with a marked increase in plasma
ANF concentrations. Interestingly, injected ANF de-
 clip hypertensive rats (Garcia et al., 1988). The unclip-
ping was associated with a marked increase in plasma al
ANF concentrations. Interestingly, injected ANF de-
sucreased blood pressure in both one- and two-kidney ele ping was associated with a marked increase in plasma and MNF concentrations. Interestingly, injected ANF decreased blood pressure in both one- and two-kidney eforms of renal hypertension but only elevated urinary cometable ANF concentrations. Interestingly, injected ANF de-
creased blood pressure in both one- and two-kidney elev
forms of renal hypertension but only elevated urinary com
cGMP concentrations in the two-kidney form (Garcia et 19 creased blood pressure in both one- and two-kidn
forms of renal hypertension but only elevated urina
cGMP concentrations in the two-kidney form (Garcia
al., 1985). These results suggest differential changes
receptor number forms of renal hypertension but only elevated urinary compare cGMP concentrations in the two-kidney form (Garcia et 1987). I
al., 1985). These results suggest differential changes in ited dis-
receptor number in the differ cGMP concentrations in the two-kidney form (Garcia et 198'
al., 1985). These results suggest differential changes in ited
receptor number in the different forms of renal hyper-
the tension and dissociates changes in blood al., 1985). These results suggest differential changes in ited
receptor number in the different forms of renal hyper-
tension and dissociates changes in blood pressure from Eva
changes in urinary cGMP concentrations in res receptor number in the different forms of renal hyper-
the tension and dissociates changes in blood pressure from Eva
changes in urinary cGMP concentrations in response to SANF. In addition, an increased binding capacity f tension and dissociates changes in blood pressure from
changes in urinary cGMP concentrations in response to
ANF. In addition, an increased binding capacity for ANF
in glomeruli from Dahl salt-sensitive rats occurs prior t changes in urinary cGMP concentrations in response to
ANF. In addition, an increased binding capacity for ANF bin glomeruli from Dahl salt-sensitive rats occurs prior to a
the increase in arterial blood pressure (Stewart e in glomeruli from Dahl salt-sensitive rats occurs prior to the increase in arterial blood pressure (Stewart et al., 1987); however, no change in the binding capacity for ANF was observed in 10-week-old animals with estab-l in glomeruli from I
the increase in art
1987); however, no
ANF was observed
lished hypertension
3. Adrenal. Adre e increase in arterial blood pressure (Stewart et al., 87); however, no change in the binding capacity for NF was observed in 10-week-old animals with estabhed hypertension.
3. Adrenal Adrenal diseases, such as aldosterono 1987); however, no change in the binding capacity for
ANF was observed in 10-week-old animals with estab-
lished hypertension.
3. Adrenal. Adrenal diseases, such as aldosteronoma
or Cushing adenoma, are associated with dra

I AND TRACHTE
in ANF receptor number. Shionoiri et al. (1989) dem-
onstrated the complete loss of adrenal ANF receptors is A AND TRACHTE
in ANF receptor number. Shionoiri et al. (1989) dem-
onstrated the complete loss of adrenal ANF receptors in
both of these conditions in patients. These patients were A AND TRACHTE
in ANF receptor number. Shionoiri et al. (1989) dem-
onstrated the complete loss of adrenal ANF receptors in
both of these conditions in patients. These patients were
unresponsive to ANF infusions regarding a in ANF receptor number. Shionoiri et al. (1989) demonstrated the complete loss of adrenal ANF receptors in both of these conditions in patients. These patients were unresponsive to ANF infusions regarding a suppression of in ANF receptor number. Shionoiri et al. (1989) demonstrated the complete loss of adrenal ANF receptors in both of these conditions in patients. These patients were unresponsive to ANF infusions regarding a suppression of onstrated the complete loss of adrenal ANI
both of these conditions in patients. These
unresponsive to ANF infusions regarding a
of basal or ACTH-stimulated aldosterone
sistent with the absence of ANF receptors.
4. Neural. th of these conditions in patients. These patients were
responsive to ANF infusions regarding a suppression
basal or ACTH-stimulated aldosterone release, con-
tent with the absence of ANF receptors.
4. *Neural*. Neural ANF

2. Kidney. Garcia et al. (1989) found a decrease in SHRs for enalarcial methods are in SHR and mucleus of the lenschlager et al., 1989). Unfortunately, signal transductions.

2. Kidney. Garcia et al. (1989) found a decre studied. Renal ANF receptor number was reduced in in the choroid plexus and subfornical organ of both young
SHR kidneys in other studies also (Saito et al., 1986; and old SHRs (McCarty and Plunkett, 1986a; Brown
Ogura et a unresponsive to ANF infusions regarding a suppression
of basal or ACTH-stimulated aldosterone release, con-
sistent with the absence of ANF receptors.
4. Neural. Neural ANF receptors were reduced in SHR
subfornical organ, of basal or ACTH-stimulated aldosterone release, consistent with the absence of ANF receptors.
4. Neural. Neural ANF receptors were reduced in SHR
subfornical organ, area postrema, and nucleus of the
solitary tract in both sistent with the absence of ANF receptors.
4. Neural. Neural ANF receptors were reduced in SF
subfornical organ, area postrema, and nucleus of t
solitary tract in both young and adult SHRs (Saavec
et al., 1989). An angiote 4. Neural. Neural ANF receptors were reduced in SHR
subfornical organ, area postrema, and nucleus of the
solitary tract in both young and adult SHRs (Saavedra
et al., 1989). An angiotensin-converting enzyme inhibi-
tor, en subfornical organ, area postrema, and nucleus of the solitary tract in both young and adult SHRs (Saavedra et al., 1989). An angiotensin-converting enzyme inhibitor, enalapril, decreased the number of ANF-binding sites in solitary tract in both young and adult SHRs (Saavedra
et al., 1989). An angiotensin-converting enzyme inhibi-
tor, enalapril, decreased the number of ANF-binding
sites in WKY rat subfornical organ and area postrema
but pro et al., 1989). An angiotensin-converting enzyme inhibitor, enalapril, decreased the number of ANF-binding
sites in WKY rat subfornical organ and area postrema
but produced the opposite effect in SHR area postrema
(Nazarali sites in WKY rat subfornical organ and area postrema
but produced the opposite effect in SHR area postrema sites in WKY rat subfornical organ and area postrema
but produced the opposite effect in SHR area postrema
(Nazarali et al., 1988). Receptors for ANF were reduced
in the choroid plexus and subfornical organ of both young
a but produced the opposite effect in SHR area postrema
(Nazarali et al., 1988). Receptors for ANF were reduced
in the choroid plexus and subfornical organ of both young
and old SHRs (McCarty and Plunkett, 1986a; Brown
and C in the choroid plexus and subfornical organ of both young and old SHRs (McCarty and Plunkett, 1986a; Brown
and Czarnecki, 1991). These data indicate the potential
for alterations of ANF receptors in the central nervous
system accounting for the blood pressure changes ob-
served i and old SHRs (N
and Czarnecki, 19
for alterations of
system accountin
served in SHRs.
Cerebral microv d Czarnecki, 1991). These data indicate the potential
r alterations of ANF receptors in the central nervous
stem accounting for the blood pressure changes ob-
rved in SHRs.
Cerebral microvessels from SHRs also possess fewe

for alterations of ANF receptors in the central nervous
system accounting for the blood pressure changes ob-
served in SHRs.
Cerebral microvessels from SHRs also possess fewer
binding sites for ANF (Okazaki et al., 1990) t system accounting for the blood pressure changes observed in SHRs.

Cerebral microvessels from SHRs also possess fewer

binding sites for ANF (Okazaki et al., 1990) than do

cerebral microvessels from WKY rats. The affinit served in SHRs.
Cerebral microvessels from SHRs also possess fewer
binding sites for ANF (Okazaki et al., 1990) than do
cerebral microvessels from WKY rats. The affinity for
ANF did not differ in the two strains. Curiously Cerebral microvessels from SHRs also possess fewer
binding sites for ANF (Okazaki et al., 1990) than do
cerebral microvessels from WKY rats. The affinity for
ANF did not differ in the two strains. Curiously, the
ANF recept binding sites for ANF (Okazaki et al., 1990) than do
cerebral microvessels from WKY rats. The affinity for
ANF did not differ in the two strains. Curiously, the
ANF receptors in the SHR choroid plexus possessed a
higher a cerebral microvessels from WKY rats. The affinity for ANF did not differ in the two strains. Curiously, the ANF receptors in the SHR choroid plexus possessed a higher affinity for ANF than did receptors from WKY rats. Thus ANF receptors in the SHR choroid plexus possessed a
higher affinity for ANF than did receptors from WKY
rats. Thus, receptors in vessels and neurons could be
regulated differentially.
Binding sites for ANF were reduced in

Binding sites for ANF were reduced in the stellate higher affinity for ANF than did receptors from WP
rats. Thus, receptors in vessels and neurons could
regulated differentially.
Binding sites for ANF were reduced in the stell.
ganglia of SHRs, but the stimulation of cGMP rats. Thus, receptors in vessels and neurons could be
regulated differentially.
Binding sites for ANF were reduced in the stellate
ganglia of SHRs, but the stimulation of cGMP produc-
tion was similar in SHRs and WKY rats regulated differentially.

Binding sites for ANF were reduced in the stellate

ganglia of SHRs, but the stimulation of cGMP produc-

tion was similar in SHRs and WKY rats (Gutkind et al.,

1987). These results suggest tha Binding sites for ANF were reduced in the stellate
ganglia of SHRs, but the stimulation of cGMP produc-
tion was similar in SHRs and WKY rats (Gutkind et al.,
1987). These results suggest that the R₂ receptor may be
down ganglia of SHRs, but the stimulation of cGMP production was similar in SHRs and WKY rats (Gutkind et al., 1987). These results suggest that the R₂ receptor may be down-regulated in the central nervous system of the SHR. tion was similar in SHRs and WKY rats (Gutkind et al., 1987). These results suggest that the R_2 receptor may be down-regulated in the central nervous system of the SHR. However, Anand-Srivastava (1992a) recently showed 1987). These results suggest that the R_2 receptor may be
down-regulated in the central nervous system of the
SHR. However, Anand-Srivastava (1992a) recently
showed a greater inhibition of adenylyl cyclase by ANF
in bra down-regulated in the central n
SHR. However, Anand-Srivast
showed a greater inhibition of ad
in brain striatum from SHRs as
brain striatum from WKY rats.
The regulation of ANF recept IR. However, Anand-Srivastava (1992a) recently
owed a greater inhibition of adenylyl cyclase by ANF
brain striatum from SHRs as compared to that in
ain striatum from WKY rats.
The regulation of ANF receptors in different b

showed a greater inhibition of adenylyl cyclase by ANF
in brain striatum from SHRs as compared to that in
brain striatum from WKY rats.
The regulation of ANF receptors in different brain
areas has been studied in various a in brain striatum from SHRs as compared to that in
brain striatum from WKY rats.
The regulation of ANF receptors in different brain
areas has been studied in various animal models of
altered body fluid balance. The ANF-bin brain striatum from WKY rats.
The regulation of ANF receptors in different brain
areas has been studied in various animal models of
altered body fluid balance. The ANF-binding sites in the
subfornical organ and choroid ple The regulation of ANF receptors in different brain
areas has been studied in various animal models of
altered body fluid balance. The ANF-binding sites in the
subfornical organ and choroid plexus were significantly
elevate areas has been studied in various animal models of altered body fluid balance. The ANF-binding sites in the subfornical organ and choroid plexus were significantly elevated in rats after 4 days of water deprivation as comp altered body fluid balance. The ANF-binding sites in the subformical organ and choroid plexus were significant
elevated in rats after 4 days of water deprivation compared to normally hydrated rats (Saavedra et a
1987). In subfornical organ and choroid plexus were significantly
elevated in rats after 4 days of water deprivation as
compared to normally hydrated rats (Saavedra et al.,
1987). In the Brattelboro rat, an animal model of inher-
it elevated in rats after 4 days of water deprivation as compared to normally hydrated rats (Saavedra et al., 1987). In the Brattelboro rat, an animal model of inherited diabetes insipidus, ANF-binding sites increased in the compared to normally hydrated rats (Saavedra et 1987). In the Brattelboro rat, an animal model of indited diabetes insipidus, ANF-binding sites increased the subfornical organ as compared to age-matched L Evans control rat 87). In the Brattelboro rat, an animal model of inher-
d diabetes insipidus, ANF-binding sites increased in
e subfornical organ as compared to age-matched Long
ans control rats (McCarty and Plunkett, 1986b).
Stewart et al.

ited diabetes insipidus, ANF-binding sites increased in
the subfornical organ as compared to age-matched Long
Evans control rats (McCarty and Plunkett, 1986b).
Stewart et al. (1987) studied ANF binding in different
brain a the subformical organ as compared to age-matched Long
Evans control rats (McCarty and Plunkett, 1986b).
Stewart et al. (1987) studied ANF binding in different
brain areas in 7-week-old Dahl salt-sensitive rats and
age-matc Evans control rats (McCarty and Plunkett, 1986b).
Stewart et al. (1987) studied ANF binding in differen
brain areas in 7-week-old Dahl salt-sensitive rats an
age-matched Dahl salt-resistant control normotensiv
rats. At thi Stewart et al. (1987) studied ANF binding in different
brain areas in 7-week-old Dahl salt-sensitive rats and
age-matched Dahl salt-resistant control normotensive
rats. At this age, the rats exhibited systolic blood pres-
 brain areas in 7-week-old Dahl salt-sensitive rats
age-matched Dahl salt-resistant control normoten
rats. At this age, the rats exhibited systolic blood p
sures slightly higher than age-matched normoten
control rats, where age-matched Dahl salt-resistant control normotensive
rats. At this age, the rats exhibited systolic blood pres-
sures slightly higher than age-matched normotensive
control rats, whereas no strain difference in ANF-bind-
in rats. At this a sures slightly
control rats, w
ing sites was a
area postrema.
5. Platelets. sures slightly higher than age-matched normotensive
control rats, whereas no strain difference in ANF-bind-
ing sites was observed in either the choroid plexus or
area postrema.
5. Platelets. Maximal ANF binding was unalte

PHARMACOLOGICAL REVIEWS

aspet

ANF RECEPTORS AND SIGNAL T
platelets from hypertensive patients (Duggan et al.,
1991), but SHR platelets possessed fewer ANF-binding ANF RECEPTORS AND SIGNAL
1991), but SHR platelets possessed fewer ANF-binding
1991), but SHR platelets possessed fewer ANF-binding
1991). Because platelets only con-ANF RECEPTORS AND SIGNA
platelets from hypertensive patients (Duggan et al.,
1991), but SHR platelets possessed fewer ANF-binding
sites (Schiffrin et al., 1991). Because platelets only con-
tain ANF R₂ receptors (Anand-S platelets from hypertensive patients (Duggan et al., 1991), but SHR platelets possessed fewer ANF-binding sites (Schiffrin et al., 1991). Because platelets only contain ANF R_2 receptors (Anand-Srivastava et al., 1991), platelets from hypertensive patients (Duggan et al., 1991), but SHR platelets possessed fewer ANF-binding sites (Schiffrin et al., 1991). Because platelets only contain ANF R_2 receptors (Anand-Srivastava et al., 1991), 1991), but SHR platelets possessed fewer ANF-binding
sites (Schiffrin et al., 1991). Because platelets only con-
tain ANF R_2 receptors (Anand-Srivastava et al., 1991),
the reduction probably represents a reduction in sites (Schiffrin et al., 1991). Because platelets only contain ANF R_2 receptors (Anand-Srivastava et al., 1991), the reduction probably represents a reduction in R_2 receptor number. Consistent with these suggestions the reduction probably represents a reduction in R_2 receptor number. Consistent with these suggestions, Anand-Srivastava (1993) reported a failure of ANF to inhibit adenylyl cyclase in SHR platelets. e reduction probably represents a reduction in R_2 re-
ptor number. Consistent with these suggestions, An-
regularly, fewer (1993) reported a failure of ANF to in-
in plit adenylyl cyclase in SHR platelets. failur
Simil

ceptor number. Consistent with these suggestions,
and-Srivastava (1993) reported a failure of ANF to
hibit adenylyl cyclase in SHR platelets.
Similarly, fewer ANF receptors occurred in S
spleen and thymus compared to tissu and-Srivastava (1993) reported a failure of ANF to in-
hibit adenylyl cyclase in SHR platelets.
Similarly, fewer ANF receptors occurred in SHR
spleen and thymus compared to tissues from normoten-
sive WKY controls (Khuriha hibit adenylyl cyclase in SHR platelets. Failum Similarly, fewer ANF receptors occurred in SHR the spleen and thymus compared to tissues from normoten-
sive WKY controls (Khurihara et al., 1987). However, tor the stimulati Similarly, fewer ANF receptors occurred in SHR
spleen and thymus compared to tissues from normoten-
sive WKY controls (Khurihara et al., 1987). However,
the stimulation of cGMP production caused by ANF in
isolated thymocyt spleen and thymus compared to tissues from normoten-
sive WKY controls (Khurihara et al., 1987). However,
the stimulation of cGMP production caused by ANF in
isolated thymocytes or spleen cells from SHRs was un-
altered (K sive WKY controls (Khurihara et al., 1987). However, tor
the stimulation of cGMP production caused by ANF in this
isolated thymocytes or spleen cells from SHRs was un-
altered (Khurihara et al., 1987). These data indicate the stimulation of cGM
isolated thymocytes or
altered (Khurihara et a
the ANF R₂, and not ti
reduced in hypertension
6. Summary. The ge blated thymocytes or spleen cells from SHRs was unit the details, 1987). These data indicate the ANF R₂, and not the GC-coupled receptors, may duced in hypertension.
6. *Summary*. The general pattern observed in hypersiv

the ANF R_2 , and not the GC-coupled receptors, may be reduced in hypertension.
6. Summary. The general pattern observed in hypertensive animals is a decrease in ANF binding to receptors in most organs. The GC response t tensive animals is a decrease in ANF binding to receptors reduced in hypertension. fait 6. Summary. The general pattern observed in hyper-
tensive animals is a decrease in ANF binding to receptors
in most organs. The GC response to ANF is also atten-
uated in the kidney and vascu uated in the kidney and vasculature but not in the thymus or spleen. This sequence of events is consistent with a reduction in R_1 receptors in kidney and the tensive animals is a decrease in ANF binding to receptors
in most organs. The GC response to ANF is also atten-
uated in the kidney and vasculature but not in the
lathymus or spleen. This sequence of events is consistent in most organs. The GC response to ANF is also atten-
uated in the kidney and vasculature but not in the lar
thymus or spleen. This sequence of events is consistent spon
with a reduction in R_1 receptors in kidney and t uated in the kidney and vasculature but not in the lathymus or spleen. This sequence of events is consistent sp
with a reduction in R_1 receptors in kidney and the or
vasculature and a selective reduction of R_2 recep thymus or spleen. This sequence of events is consistent spons
with a reduction in R_1 receptors in kidney and the or devasculature and a selective reduction of R_2 receptors in suppr
thymus and spleen. Platelet R_2 with a reduction in R_1 receptors in kidney and the vasculature and a selective reduction of R_2 receptors were reduced in also. Both R_1 and R_2 receptors were reduced in DOCA result hypertensive kidneys and vasc thymus and spleen. Platelet R_2 receptors were reduced in also. Both R_1 and R_2 receptors were reduced in DOCA resalt hypertensive kidneys and vasculature. Other models in of hypertension may affect ANF receptors d also. Both R_1 and R_2 receptors were reduced in DOCA rsalt hypertensive kidneys and vasculature. Other models in of hypertension may affect ANF receptors differentially, but this information is not available yet. The salt hypertensive kidneys and vasculature. Other mode
of hypertension may affect ANF receptors differentiall
but this information is not available yet. The ability
ANF to suppress adenylyl cyclase activity was enhance
in v of hypertension may affect ANF receptors differentially,
but this information is not available yet. The ability of
ANF to suppress adenylyl cyclase activity was enhanced
in vascular and cardiac hypertensive tissues but el but this information is not available yet. The ability ANF to suppress adenylyl cyclase activity was enhance in vascular and cardiac hypertensive tissues but elimeted in platelets. These data suggest either that vasculand ANF to suppress adenylyl cyclase activity was enhanced
in vascular and cardiac hypertensive tissues but elimi-
nated in platelets. These data suggest either that vascular
hand cardiac ANF R_2 receptors are up-regulated in vascular and cardiac
nated in platelets. These
and cardiac ANF R_2 receptension or that postrece
amplified in hypertension
 G Constative Hant Eail. **EXECUTE: ANTE R₂ receptors a**
 C. Congestive Heart Failure
 C. Congestive Heart Failure
 Congestive heart failure is a

amplified in hypertension. exp
al.,
C. Congestive Heart Failure
congestive heart failure is associated with excessive cree
sodium and water retention (Packer, 1988). Plasma ANF (Ro
concentrations are elevated in both anima C. Congestive Heart Failure
Concentrations are in associated with excessive
sodium and water retention (Packer, 1988). Plasma ANF
concentrations are elevated in both animals and humans
proportionally to the severity of the concentrations are elevated in both animals and humans 1988). If ANF caused a greater decline in ANF R_1 recepproportionally to the severity of the cardiac dysfunction tors than in R_2 receptors, then the GC response Congestive heart failure is associated with excessive
sodium and water retention (Packer, 1988). Plasma ANF (concentrations are elevated in both animals and humans
proportionally to the severity of the cardiac dysfunction
 sodium and water retention (Packer, 1988). Plasma ANF
concentrations are elevated in both animals and humans
proportionally to the severity of the cardiac dysfunction
(Franck et al., 1986; Tikkanen et al., 1985; Burnett et concentrations are elevated in both animals and humans
proportionally to the severity of the cardiac dysfunction
(Franck et al., 1986; Tikkanen et al., 1985; Burnett et
al., 1986; Rigger et al., 1988). However, ANF recepto proportionally to the severity of the cardiac dysfunction (Franck et al., 1986; Tikkanen et al., 1985; Burnett et al., 1986; Rigger et al., 1988). However, ANF receptor regulation and signal transduction mechanisms in hear (Franck et al., 1986; Tikkanen et al., 1985; Burnett et should
al., 1986; Rigger et al., 1988). However, ANF receptor number
regulation and signal transduction mechanisms in heart recept
failure have not been studied in de al., 1986; Rigger et al., 1988). However, ANF receptor nun regulation and signal transduction mechanisms in heart rece failure have not been studied in detail. Bianchi et al. decl (1989) used in vitro autoradiographic tech regulation and signal transduction mechanisms in hea
failure have not been studied in detail. Bianchi et ε
(1989) used in vitro autoradiographic techniques to sho
a reduction in ANF-binding sites in renal glomeruli in failure have not been studied in detail. Bianchi et al. dec
(1989) used in vitro autoradiographic techniques to show in
a reduction in ANF-binding sites in renal glomeruli in AN
mild and moderate, but not severe, heart fai (1989) used in vitro autoradiographic techniques to show
a reduction in ANF-binding sites in renal glomeruli in
mild and moderate, but not severe, heart failure. ANF-
binding sites in aorta were increased in moderate and
s mild and moderate, but not severe, heart failure. ANF-
binding sites in aorta were increased in moderate and
severe heart failure. Furthermore, Tsunoda et al. (1988)
reported decreased ANF binding in rat inner renal me-
du mild and moderate, but not severe, heart failure. ANF-
binding sites in aorta were increased in moderate and
severe heart failure. Furthermore, Tsunoda et al. (1988) add
reported decreased ANF binding in rat inner renal me binding sites in aorta were increased in moderate and
severe heart failure. Furthermore, Tsunoda et al. (1988) a
reported decreased ANF binding in rat inner renal me-
pdulla in proportion to the ventricular dysfunction in severe heart failure. Furthermore, Tsunoda et al. (1988) addition
reported decreased ANF binding in rat inner renal me-
dulla in proportion to the ventricular dysfunction in tions ((
heart failure. Abassi et al. (1991) reported decreased ANF binding in rat inner renal medulla in proportion to the ventricular dysfunction is
heart failure. Abassi et al. (1991) demonstrated increased
ANF effects on CGMP concentrations in glomeruli fron
rats dulla in proportion to the ventricular dysfunction in the
art failure. Abassi et al. (1991) demonstrated increased in
ANF effects on cGMP concentrations in glomeruli from (
rats with chronic aortocaval fistulas, an experim ANF effects on cGMP concentrations in glomeruli from (Gauquelin et al., 1988) by selectively increasing ANF rats with chronic aortocaval fistulas, an experimental R_2 receptors (Kollenda et al., 1990). Alternatively, so

RANSDUCTION MECHANISMS

ANF receptor-binding sites was observed in zona glo-

merulosa (Bianchi et al., 1989). A decrease in both ANF merubosa (Bianchi et al., 1989). A decrease in soma glomerulosa (Bianchi et al., 1989). A decrease in both ANF
Therulosa (Bianchi et al., 1989). A decrease in both ANF
Thereptor density and CGMP generation in glomeruli fro FRANSDUCTION MECHANISMS

ANF receptor-binding sites was observed in zona glo-

merulosa (Bianchi et al., 1989). A decrease in both ANF

receptor density and cGMP generation in glomeruli from

cardiomyopathic hamsters has b ANF receptor-binding sites was observed in zona glo-
merulosa (Bianchi et al., 1989). A decrease in both ANF
receptor density and cGMP generation in glomeruli from
cardiomyopathic hamsters has been reported (Levin et
al., ANF receptor-binding sites was observed in zona glue merulosa (Bianchi et al., 1989). A decrease in both AN receptor density and cGMP generation in glomeruli from cardiomyopathic hamsters has been reported (Levin al., 199 merulosa (Bianchi et al., 1989). A decrease in both ANF receptor density and cGMP generation in glomeruli from cardiomyopathic hamsters has been reported (Levin et al., 1990), indicating that ANF R_1 receptors are down-r receptor density and cGMP generation in glomeruli from
cardiomyopathic hamsters has been reported (Levin et
al., 1990), indicating that ANF R₁ receptors are down-
regulated in heart failure. A reduction of ANF receptors
 cardiomyopathic hamsters has been reported (Levin et al., 1990), indicating that ANF R_1 receptors are down-
regulated in heart failure. A reduction of ANF receptors
in platelets from patients with severe congestive hea al., 1990), indicating that ANF R_1 receptors are down-
regulated in heart failure. A reduction of ANF receptors
in platelets from patients with severe congestive heart
failure has also been shown (Schiffrin, 1988); how regulated in heart failure. A reduction of ANF recepto
in platelets from patients with severe congestive heartillure has also been shown (Schiffrin, 1988); however
the signal transduction mechanisms have not been e
plored in platelets from patients with severe congestive heart failure has also been shown (Schiffrin, 1988); however, the signal transduction mechanisms have not been explored. Because platelets possess only the R_2 ANF recep failure has also been shown (Schiffrin, 1988); however,
the signal transduction mechanisms have not been ex-
plored. Because platelets possess only the R_2 ANF recep-
tor (Anand-Srivastava et al., 1991), it is possible the signal transduction mechanisms have not been ex-
plored. Because platelets possess only the R_2 ANF recep-
tor (Anand-Srivastava et al., 1991), it is possible that
this receptor subtype is down-regulated in heart fa plored. Because platelets possess only the R_2 ANF receptor (Anand-Srivastava et al., 1991), it is possible that this receptor subtype is down-regulated in heart failure. Alternatively, Strom et al. (1988) failed to sho tor (Anand-Srivastava et al., 1991), it is possible that this receptor subtype is down-regulated in heart failure.
Alternatively, Strom et al. (1988) failed to show any difference in the number of ANF platelet receptors or this receptor subtype is down-regulated in heart failure.
Alternatively, Strom et al. (1988) failed to show any
difference in the number of ANF platelet receptors or
their affinity for ANF in patients with congestive heart centrations. fference in the number of ANF platelet receptors on
eir affinity for ANF in patients with congestive heart
ilure in spite of increased levels of plasma ANF con-
ntrations.
In summary, heart failure was associated with a ge

their affinity for ANF in patients with congestive heartilure in spite of increased levels of plasma ANF concentrations.
In summary, heart failure was associated with a geart down-regulation of ANF receptors, although vasc failure in spite of increased levels of plasma ANF concentrations.

In summary, heart failure was associated with a general down-regulation of ANF receptors, although vascular receptor numbers may be augmented. The GC resp centrations.
In summary, heart failure was associated with a general down-regulation of ANF receptors, although vascular receptor numbers may be augmented. The GC responsiveness to ANF was reported to be either increased o In summary, heart failure was associated with a general down-regulation of ANF receptors, although vascular receptor numbers may be augmented. The GC responsiveness to ANF was reported to be either increased or decreased i eral down-regulation of ANF receptors, although vascular receptor numbers may be augmented. The GC responsiveness to ANF was reported to be either increased or decreased in kidneys. Finally, the ability of ANF to suppress lar receptor numbers may be augmented. The GC responsiveness to ANF was reported to be either increased
or decreased in kidneys. Finally, the ability of ANF to
suppress adenylyl cyclase activity has not been explored
in c sponsiveness to ANF was reported to be either increased
or decreased in kidneys. Finally, the ability of ANF to
suppress adenylyl cyclase activity has not been explored
in congestive heart failure. The down-regulation of or decreased in kidneys. Finally, the abilit
suppress adenylyl cyclase activity has not b
in congestive heart failure. The down-regulareceptors appears to involve R_2 receptors,
involvement of R_1 receptors is undeter in congestive heart failure. The down-regulation of ANF receptors appears to involve R_2 receptors, whereas the involvement of R_1 receptors is undetermined.
D. Potential Mechanisms Accounting for Altered Atrial Natr

Natriuretic Factors appears to involve R₂ receptors is undetermi
*D. Potential Mechanisms Accounting for .
Natriuretic Factor Receptor Regulation*
The mechanisms controlling ANF rece

amplified in hypertension. The exposure of vascular smooth muscle to ANF (Hirata et al., 1991), and al., 1985b; Schiffrin et al., 1986b; Kato et al., 1991), and the reduction in receptor number is matched by a de-
Congesti volvement of R_1 receptors is undetermined.
 Potential Mechanisms Accounting for Altered Atrial
 atriuretic Factor Receptor Regulation

The mechanisms controlling ANF receptor expression

we not been defined, but e D. Potential Mechanisms Accounting for Altered Atrial
Natriuretic Factor Receptor Regulation
The mechanisms controlling ANF receptor expression
have not been defined, but endocrine factors such as
ANF, angiotensin II, estr D. Potential mechanisms Accounting for Attered Atrial
Natriuretic Factor Receptor Regulation
The mechanisms controlling ANF receptor expression
have not been defined, but endocrine factors such as
ANF, angiotensin II, estr The mechanisms controlling ANF receptor expression
have not been defined, but endocrine factors such as
ANF, angiotensin II, estrogen, and progesterone alter
ANF receptor binding. Receptors for ANF decline after
exposure o The mechanisms controlling ANF receptor expression
have not been defined, but endocrine factors such as
ANF, angiotensin II, estrogen, and progesterone alter
ANF receptor binding. Receptors for ANF decline after
exposure o have not been defined, but endocrine factors such as
ANF, angiotensin II, estrogen, and progesterone alter
ANF receptor binding. Receptors for ANF decline after
exposure of vascular smooth muscle to ANF (Hirata et
al., 198 ANF, angiotensin II, estrogen, and progesterone alter
ANF receptor binding. Receptors for ANF decline after
exposure of vascular smooth muscle to ANF (Hirata et
al., 1985b; Schiffrin et al., 1986b; Kato et al., 1991), and
 their affinity for ANF in patients with congestive heart
failure in spite of increased levels of plasma ANF con-
centrations.
In summary, heart failure was associated with a gen-
explanation of ANF receptors, atthough vas exposure of vascular smooth muscle to ANF (Hirata et al., 1985b; Schiffrin et al., 1986b; Kato et al., 1991), and the reduction in receptor number is matched by a decrease in the stimulation of cGMP production by ANF (Roub al., 1985b; Schiffrin et al., 1986b; Kato et al., 1991), an
the reduction in receptor number is matched by a d
crease in the stimulation of cGMP production by AN
(Roubert et al., 1987; Cahill et al., 1990; Chabrier et a
1 the reduction in receptor number is matched by a decrease in the stimulation of cGMP production by ANF (Roubert et al., 1987; Cahill et al., 1990; Chabrier et al., 1988). If ANF caused a greater decline in ANF R_1 recep crease in the stimulation of cGMP production by ANF (Roubert et al., 1987; Cahill et al., 1990; Chabrier et al., 1988). If ANF caused a greater decline in ANF R_1 receptors than in R_2 receptors, then the GC response (Roubert et al., 1987; Cahill et al., 1990; Chabrier et al., 1988). If ANF caused a greater decline in ANF R_1 receptors than in R_2 receptors, then the GC response to ANF should be attenuated to a greater extent than 1988). If ANF caused a greater decline in ANF R_1 receptors than in R_2 receptors, then the GC response to ANF should be attenuated to a greater extent than the receptor numbers. Alternatively, if ANF down-regulated A tors than in R_2 receptors, then the GC response to ANF
should be attenuated to a greater extent than the receptor
numbers. Alternatively, if ANF down-regulated ANF R_2
receptors to a greater extent than R_1 recepto should be attenuated to a greater extent than the receptor
numbers. Alternatively, if ANF down-regulated ANF R_2
receptors to a greater extent than R_1 receptors, then the
decline in receptor number should exceed the numbers. Alternatively, if ANF down-regulated ANF R_2
receptors to a greater extent than R_1 receptors, then the
decline in receptor number should exceed the decrease
in GC responsiveness. The proportional reduction i receptors to a greater extent than R_1 receptors, then
decline in receptor number should exceed the decre
in GC responsiveness. The proportional reduction
ANF receptor number and GC stimulation suggests
equivalent decli cline in receptor number should exceed the decrease
GC responsiveness. The proportional reduction in
NF receptor number and GC stimulation suggests an
uivalent decline in both ANF R_1 and R_2 receptors.
Water deprivat

in GC responsiveness. The proportional reduction in
ANF receptor number and GC stimulation suggests an
equivalent decline in both ANF R_1 and R_2 receptors.
Water deprivation or alterations in sodium intake are
additi ANF receptor number and GC stimulation suggest
equivalent decline in both ANF R_1 and R_2 receptors
Water deprivation or alterations in sodium intake
additional maneuvers to alter ANF concentration
plasma. Dehydration equivalent decline in both ANF R_1 and R_2 receptors.
Water deprivation or alterations in sodium intake are
additional maneuvers to alter ANF concentrations in
plasma. Dehydration reduced plasma ANF concentra-
tions (Water deprivation or alterations in sodium intake are
additional maneuvers to alter ANF concentrations in
plasma. Dehydration reduced plasma ANF concentra-
tions (Gauquelin et al., 1988; Kollenda et al., 1990) and
increase additional maneuvers to alter ANF concentrations in plasma. Dehydration reduced plasma ANF concentra-
tions (Gauquelin et al., 1988; Kollenda et al., 1990) and
increased the number of glomerular receptors for ANF
(Gauqueli plasma. Dehydration reduced plasma ANF concentra-
tions (Gauquelin et al., 1988; Kollenda et al., 1990) and
increased the number of glomerular receptors for ANF
(Gauquelin et al., 1988) by selectively increasing ANF
 R_2 increased the number of glomerular receptors for ANF (Gauquelin et al., 1988) by selectively increasing ANF

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al., 1990) by selectively reducing ANF R₁ receptors (Kol- tization of ANF r
al., 1990) by selectively reducing ANF R₁ receptors (Kol- tization of ANF r and the set of the selectively reducing ΔNFR receptors (Kol-
al., 1990) by selectively reducing ΔNFR receptors (Kol-
lenda et al., 1990). En ANAND-SRIVASTAVA

erman et al., 1985; Gauquelin et al., 1988; Kollenda et la

al., 1990) by selectively reducing $ANF R_1$ receptors (Kol-

lenda et al., 1990). Endothelial ANF receptors also were pa

suppressed by sodium erman et al., 1985; Gauquelin et al., 1988; Kollenda et la
al., 1990) by selectively reducing ANF R_1 receptors (Kollenda et al., 1990). Endothelial ANF receptors also were p
suppressed by sodium loading (Schiffrin, 198 erman et al., 1985; Gauquelin et al., 1988; Kollenda
al., 1990) by selectively reducing ANF R₁ receptors (K₁
lenda et al., 1990). Endothelial ANF receptors also we
suppressed by sodium loading (Schiffrin, 1988), but t al., 1990) by selectively reducing ANF R_1 receptors (Kollenda et al., 1990). Endothelial ANF receptors also were suppressed by sodium loading (Schiffrin, 1988), but this effect was mediated primarily by a decrease in lenda et al., 1990). Endothelial ANF receptors also were p
suppressed by sodium loading (Schiffrin, 1988), but this the
ffect was mediated primarily by a decrease in R_2 recep-
tors (Katafuchi et al., 1992). Sodium depr suppressed by sodium loading (Schiffrin, 1988), but this effect was mediated primarily by a decrease in R_2 receptors (Katafuchi et al., 1992). Sodium deprivation increased adrenal receptors for ANF primarily by elevati tors (Katafuchi et al., 1992). Sodium deprivation in-
creased adrenal receptors for ANF primarily by elevating
the number of ANF R_2 -binding sites (Sessions et al.,
1992). These data are consistent with a homologous
reg creased adrenal receptors for ANF primarily by elevating
the number of ANF R_2 -binding sites (Sessions et al.,
1992). These data are consistent with a homologous
regulation of ANF receptors leading to a down-regulation
 the number of ANF R_2 -binding sites (Sessions et al., 1992). These data are consistent with a homologous regulation of ANF receptors leading to a down-regulation as ANF concentrations increase in plasma. The mechanism o the number of ANF R_2 -binding sites (Sessions et al., 1992). These data are consistent with a homologous regulation of ANF receptors leading to a down-regulation as ANF concentrations increase in plasma. The mechanism o 1992). These data are consistent with a homologo regulation of ANF receptors leading to a down-regulation as ANF concentrations increase in plasma. The mech nism of the homologous regulation is unknown, b stable cGMP anal regulation of ANF receptors leading to a down-regulation on
as ANF concentrations increase in plasma. The mecha-
nism of the homologous regulation is unknown, but of
stable cGMP analogs selectively reduce ANF R_2 recepas ANF concentrations increase in plasma. The mech
nism of the homologous regulation is unknown, b
stable cGMP analogs selectively reduce ANF R_2 rect
tors in bovine endothelial cells (Kato et al., 1991), a
stable cAMP nism of the homologous regulation is unknown, but of stable cGMP analogs selectively reduce ANF R_2 recep-
tors in bovine endothelial cells (Kato et al., 1991), and gree
stable cAMP analogs increase ANF binding to neuro stable cGMP analogs selectively reduce ANF R_2 receptors in bovine endothelial cells (Kato et al., 1991), and gree stable cAMP analogs increase ANF binding to neuro-
blastoma receptors (Delporte et al., 1991). Because A tors in bovine endothelial cells (Kato et al., 1991), and
stable cAMP analogs increase ANF binding to neuro-
blastoma receptors (Delporte et al., 1991). Because ANF wil
both elevates cGMP concentrations and reduces cAMP ha stable cAMP analogs increase ANF bin
blastoma receptors (Delporte et al., 1991)
both elevates cGMP concentrations and
concentrations, either mechanism could
homologous regulation of ANF receptors.
In addition to the homolo astoma receptors (Delporte et al., 1991). Because ANF
th elevates cGMP concentrations and reduces cAMP
ncentrations, either mechanism could function in the
mologous regulation of ANF receptors.
In addition to the homologou

both elevates cGMP concentrations and reduces cAMP concentrations, either mechanism could function in the number of ANF receptors.

In addition to the homologous regulation of ANF receptors described above, ANF receptor n concentrations, either mechanism could function in the
homologous regulation of ANF receptors.
In addition to the homologous regulation of ANF re-
ceptors described above, ANF receptor number is also
influenced by humoral homologous regulation of ANF receptors.

In addition to the homologous regulation of ANF re-

ceptors described above, ANF receptor number is also

influenced by humoral factors that do not bind to the

ANF receptors. Ang ceptors described above, ANF receptor number is also influenced by humoral factors that do not bind to the ANF receptors. Angiotensin II has no acute effect on ANF binding in vascular tissue (Grammas et al., 1991) but decr influenced by humoral factors that do not bind to the ANF receptors. Angiotensin II has no acute effect compared ANF binding in vascular tissue (Grammas et al., 199
but decreases ANF binding after 24 h (Chabrier et a 1988; ANF receptors. Angiotensin II has no acute effect
ANF binding in vascular tissue (Grammas et al., 199
but decreases ANF binding after 24 h (Chabrier et
1988; Hirata et al., 1989b). The diminution of AN
binding sites greatl ANF binding in vascular tissue (Grammas et al., 1991)
but decreases ANF binding after 24 h (Chabrier et al., 1988; Hirata et al., 1989b). The diminution of ANF-
binding sites greatly exceeds the reduction in GC respon-
si but decreases ANF binding after 24 h (Chabrier et al., 1988; Hirata et al., 1989b). The diminution of ANF-
binding sites greatly exceeds the reduction in GC responsiveness to ANF (Hirata et al., 1989b). Chabrier et al.
(1 1988; Hirata et al., 1989b). The diminution of AN
binding sites greatly exceeds the reduction in GC respo
siveness to ANF (Hirata et al., 1989b). Chabrier et
(1988) actually observed an increased production
cGMP in respons binding sites greatly exceeds the reduction in GC responsiveness to ANF (Hirata et al., 1989b). Chabrier et (1988) actually observed an increased production cGMP in response to ANF concomitantly with a red tion in ANF rec siveness to ANF (Hirata et al., 1989b). Chabrier et al.

(1988) actually observed an increased production of tissue

cGMP in response to ANF concomitantly with a reduction

in ANF receptor numbers. This scenario is consis (1988) actually observed an increased production of cGMP in response to ANF concomitantly with a reduction in ANF receptor umbers. This scenario is consistent with a selective reduction in ANF R_2 receptors in response cGMP in response to ANF concomitantly with a reduction in ANF receptor numbers. This scenario is consistent with a selective reduction in ANF R_2 receptors in response to angiotensin II, whereas R_1 receptors were una tion in ANF receptor numbers. This scenario is consistent with a selective reduction in ANF R_2 receptors in response to angiotensin II, whereas R_1 receptors were unaffected or only slightly reduced in number. Gauque ent with a selective reduction in ANF R_2 receptors in response to angiotensin II, whereas R_1 receptors were unaffected or only slightly reduced in number. Gauquelin rol and the serving a selective reduction of ANF unaffected or only slightly reduced in number. Gauquelin
et al. (1991) confirmed this conclusion directly by ob-
serving a selective reduction of ANF R_2 receptors in the
vasculature of rats infused with angiotensin I aaffected or only slightly reduced in number. Gauquelin al. (1991) confirmed this conclusion directly by ob-
rving a selective reduction of ANF R_2 receptors in the sculature of rats infused with angiotensin II.
Uterine

et al. (1991) confirmed this conclusion directly by observing a selective reduction of ANF R₂ receptors in the vasculature of rats infused with angiotensin II.
Uterine ANF receptors were reduced by progesterone and incre and increased by estrogen (Potvin and Varma, 1991).
The up-regulation of ANF receptors in response to estro-
gen or pregnancy did not alter the distribution of R_1 and
 R_2 receptors, as judged by the displacement of A vasculature of rats infused with angiotensin II.

Uterine ANF receptors were reduced by progesterone

and increased by estrogen (Potvin and Varma, 1991).

The up-regulation of ANF receptors in response to estro-

gen or p Uterine ANF receptors were reduced by progesterone and increased by estrogen (Potvin and Varma, 1991).
The up-regulation of ANF receptors in response to estrogen or pregnancy did not alter the distribution of R_1 and R and increased by estrogen (Potvin and Varma, 1991).
The up-regulation of ANF receptors in response to estrogen or pregnancy did not alter the distribution of R_1 and R_2 receptors, as judged by the displacement of ANF The up-regulation of ANF receptors in response to estrate and the distribution of R_1 and R_2 receptors, as judged by the displacement of AN binding with the R_2 -selective ligand, cANF (Potvin and Varma, 1991). Conv gen or pregnancy did not alter the distribution of R_1 and R_2 receptors, as judged by the displacement of ANF binding with the R_2 -selective ligand, cANF (Potvin and Varma, 1991). Conversely, progesterone decreased R_2 receptors, as judged by the displacement of ANF
binding with the R_2 -selective ligand, cANF (Potvin and
Varma, 1991). Conversely, progesterone decreased ANF-
binding sites and eliminated binding to the R_1 recep binding with the R₂-selective ligand, cANF (Potvin and Varma, 1991). Conversely, progesterone decreased ANF-
binding sites and eliminated binding to the R₁ receptor
(Potvin and Varma, 1991). These results suggest that Varma, 1991). Conversely, progesterone decreased ANF-
binding sites and eliminated binding to the R₁ receptor
(Potvin and Varma, 1991). These results suggest that AC
estrogens up-regulate both the R₁ and the R₂ rece receptor. 'otvin and Varma, 1991). These results suggest the trogens up-regulate both the R_1 and the R_2 recept
t that progesterone selectively down-regulates the ceptor.
The results with ANF indicate that homologous desen-
iz estrogens up-regulate both the R_1 and the R_2 receptor
but that progesterone selectively down-regulates the R_1
receptor.
The results with ANF indicate that homologous desen-
sitization occurs, resulting in reduced

but that progesterone selectively down-regulates the R_1 receptor.
The results with ANF indicate that homologous desensitization occurs, resulting in reduced receptor numbers and an apparently equivalent reduction in bo receptor.
The results with ANF indicate that homologous desensitization occurs, resulting in reduced receptor numbers
and an apparently equivalent reduction in both general
types of ANF receptors. In contrast, the heterolo The results with ANF indicate that homologous desensitization occurs, resulting in reduced receptor numbers and an apparently equivalent reduction in both general types of ANF receptors. In contrast, the heterologous redu sitization occurs, resulting in reduced receptor numbers
and an apparently equivalent reduction in both general
types of ANF receptors. In contrast, the heterologous
reduction in ANF receptors caused by angiotensin II
inv and an apparently equivalent reduction in both gentypes of ANF receptors. In contrast, the heterolog reduction in ANF receptors caused by angiotensity involves an apparently selective reduction in ANF receptors, whereas pr

A AND TRACHTE
lates ANF R₁ receptors. Finally, the heterologous sens
tization of ANF responses by estrogen involved an a A AND TRACHTE
lates ANF R_1 receptors. Finally, the heterologous sensi-
tization of ANF responses by estrogen involved an ap-
parent up-regulation of both general types of ANF recep-A AND TRACHTE
lates ANF R_1 receptors. Finally, the heterologous sentization of ANF responses by estrogen involved an a
parent up-regulation of both general types of ANF rece
tors. The mechanisms accounting for alterati the mechanisms accounting the heterologous sensi-
tization of ANF responses by estrogen involved an ap-
parent up-regulation of both general types of ANF recep-
tors. The mechanisms accounting for alterations in
receptor lates ANF R_1 receptors. Finally, the heterologization of ANF responses by estrogen involparent up-regulation of both general types of tors. The mechanisms accounting for alt receptor regulation have not been elucidated VF responses by estrogen involution of both general types of
echanisms accounting for altion have not been elucidated
VII. General Conclusions
e data presented in this review Frace The mechanisms accounting for alterations
ceptor regulation have not been elucidated.
VII. General Conclusions
Much of the data presented in this review is sumniated in table 1. The EC_{50} is designated for ANF eff

ceptors described above, ANF receptor number is also enylyl cyclase activity is more sensitive than GC to ANF
influenced by humoral factors that do not bind to the in every tissue studied. This suggests that the high-
ANF receptor regulation have not been elucidated.

VII. General Conclusions

Much of the data presented in this review is summa-

rized in table 1. The EC_{50} is designated for ANF effects

on organ responses, GC activation, **VII. General Conclusions**
Much of the data presented in this review is summa-
rized in table 1. The EC_{50} is designated for ANF effects
on organ responses, GC activation, and adenylyl cyclase
inhibition. Many responses VII. General Conclusions

Much of the data presented in this review is summa-

rized in table 1. The EC_{50} is designated for ANF effects

on organ responses, GC activation, and adenylyl cyclase

inhibition. Many respons Much of the data presented in this review is summa-
rized in table 1. The EC_{50} is designated for ANF effects
on organ responses, GC activation, and adenylyl cyclase
inhibition. Many responses occur at ANF concentration rized in table 1. The EC_{50} is designated for ANF effects
on organ responses, GC activation, and adenylyl cyclase
inhibition. Many responses occur at ANF concentrations
of ≤ 100 pM, whereas GC activation normally re inhibition. Many responses occur at ANF concentrations of \leq 100 pM, whereas GC activation normally requires ANF concentrations of two to three orders of magnitude greater to achieve half-maximal activation. The cardioinhibition. Many responses occur at ANF concentrations
of ≤ 100 pM, whereas GC activation normally requires
ANF concentrations of two to three orders of magnitude
greater to achieve half-maximal activation. The cardio of <100 pM, whereas GC activation normally requires
ANF concentrations of two to three orders of magnitude
greater to achieve half-maximal activation. The cardio-
vascular and pulmonary effects of ANF correlate well
with G vascular and pulmonary effects of ANF correlate well
with GC activation, although the cardiovascular effects
have been dissociated from cGMP production by alter-
native techniques described earlier in the review. Most
othe native techniques described earlier in the review. Most vascular and pulmonary effects of ANF correlate with GC activation, although the cardiovascular efferency with GC activation, although the cardiovascular efferency consistant in the review. Mother tissue effects of ANF occ with GC activation, although the cardiovascular effects
have been dissociated from cGMP production by alter-
native techniques described earlier in the review. Most
other tissue effects of ANF occur with a potency consisthave been dissociated from cGMP production by alternative techniques described earlier in the review. Most other tissue effects of ANF occur with a potency consistent with adenylyl cyclase inhibition. Furthermore, adenylyl native techniques described earlier in the review. Most other tissue effects of ANF occur with a potency consistent with adenylyl cyclase inhibition. Furthermore, adenylyl cyclase activity is more sensitive than GC to AN:
 other tissue effects of ANF occur with a potency consistent with adenylyl cyclase inhibition. Furthermore, adenylyl cyclase activity is more sensitive than GC to ANF in every tissue studied. This suggests that the high-af ent with adenylyl cyclase inhibition. Furthermore, adenylyl cyclase activity is more sensitive than GC to ANF
in every tissue studied. This suggests that the high-
affinity ANF receptor is of the R_2 subtype which coupl enylyl cyclase activity is more sensitive than GC to ANF
in every tissue studied. This suggests that the high-
affinity ANF receptor is of the R_2 subtype which couples
to adenylyl cyclase. Tissues lacking a R_1 recep affinity ANF receptor is of the R_2 subtype which couples
to adenylyl cyclase. Tissues lacking a R_1 receptor exhibit
high-affinity binding of ANF, again suggesting that the
 R_2 receptor is a high-affinity-binding s finity ANF receptor is of the R_2 subtype which couples
adenylyl cyclase. Tissues lacking a R_1 receptor exhibit
gh-affinity binding of ANF, again suggesting that the
receptor is a high-affinity-binding site for ANF.

to adenylyl cyclase. Tissues lacking a R_1 receptor exhibit high-affinity binding of ANF, again suggesting that the R_2 receptor is a high-affinity-binding site for ANF.
Inasmuch as renal and vascular studies have sho high-affinity binding of ANF, again suggesting that the R_2 receptor is a high-affinity-binding site for ANF.
Inasmuch as renal and vascular studies have shown that the R_2 receptor is a low-affinity-binding site in t R_2 receptor is a high-affinity-binding site for ANF.
Inasmuch as renal and vascular studies have show
that the R_2 receptor is a low-affinity-binding site in the
tissues, the data presented in table 1 might be explai Inasmuch as renal and vascular studies have shown
that the R_2 receptor is a low-affinity-binding site in these
tissues, the data presented in table 1 might be explained
by the existence of multiple R_2 receptors. Alt that the R_2 receptor is a low-affinity-binding site in these
tissues, the data presented in table 1 might be explained
by the existence of multiple R_2 receptors. Alternatively,
the R_2 receptor may exhibit differe tissues, the data presented in table 1 might be explained
by the existence of multiple R_2 receptors. Alternatively,
the R_2 receptor may exhibit different binding affinities
in different tissues. Regardless of the ex by the existence of multiple R_2 receptors. Alternatively,
the R_2 receptor may exhibit different binding affinities
in different tissues. Regardless of the exact distribution
of ANF receptors, the data in table 1 sug the R_2 receptor may exhibit different binding affinities
in different tissues. Regardless of the exact distribution
of ANF receptors, the data in table 1 suggest a prominent
role of ANF receptors coupled to adenylyl cy ta in table 1 su
pupled to aden
ied. The differ
TABLE 1
mses at the level of

EXECUTE: Neurons
 Platelet
 **a half-maximal response (EC₅₀) in a measured variable such as a whole

a** half-maximal response (EC₅₀) in a measured variable such as a whole

organ response, GC, or adenylyl cyclase $\frac{30}{10}$ - $\frac{10,000}{10}$ - $\frac{21}{10}$

* The numbers represent reported concentrations of ANF producing

a half-maximal response (EC₅₀) in a measured variable such as a whole

organ response, GC, or adenylyl cycla **Platest**
 v The numbers represent reported concentrations of ANF producing

a half-maximal response (EC₅₀) in a measured variable such as a whole

organ response; CC, or adenylyl cyclase inhibition. References for the

ANF RECEPTORS AND SIGNAL
ANF in stimulating GC activity and tissue-specific re-
sponses further questions the relationship between ANF in stimulating GC activity and tissue-specific re-
sponses further questions the relationship between
cGMP generation and organ responses to ANF. ANF in stimulating GC activity and tissue-spec
sponses further questions the relationship b
cGMP generation and organ responses to ANF.
Recent pharmacological advances have allowed sponses further questions the relationship between
cGMP generation and organ responses to ANF.
Recent pharmacological advances have allowed critical

ANF in stimulating GC activity and tissue-specific r
sponses further questions the relationship betwee
cGMP generation and organ responses to ANF.
Recent pharmacological advances have allowed critic
tests of these potentia sponses further questions the relationship between
cGMP generation and organ responses to ANF.
Recent pharmacological advances have allowed critical
tests of these potential interactions between ANF recep-
tors and biolog $cGMP$ generation and organ responses to ANF.
Recent pharmacological advances have allowed critic
tests of these potential interactions between ANF receptors
and biological responses. Studies with antagonis
of the GC-coupl Recent pharmacological advances have allowed critical
tests of these potential interactions between ANF recep-
tors and biological responses. Studies with antagonists
of the GC-coupled ANF R_1 receptor revealed that hyp tests of these potential interactions between ANF receptors and biological responses. Studies with antagonists of the GC-coupled ANF R₁ receptor revealed that hypotensive, vascular, and neuronal ANF effects can be dissoc tors and biological responses. Studies with antagonist
of the GC-coupled ANF R_1 receptor revealed that hypo
tensive, vascular, and neuronal ANF effects can be dis
sociated from GC activation. Similarly, heart, various
 of the GC-coupled ANF R_1 receptor revealed that hypotensive, vascular, and neuronal ANF effects can be dissociated from GC activation. Similarly, heart, various endocrine, and platelet effects of ANF are independent of tensive, vascular, and neuronal ANF effects can be dissociated from GC activation. Similarly, heart, various endocrine, and platelet effects of ANF are independent of GC activation. ANF effects on the adrenal, kidney, and sociated from GC activation. Similarly, heart, various hadden endocrine, and platelet effects of ANF are independent of GC activation. ANF effects on the adrenal, kidney, $ARAB$ and potentially the lung appear at this time endocrine, and platelet effects of ANF are independent
of GC activation. ANF effects on the adrenal, kidney,
and potentially the lung appear at this time to be me-
diated by activating the R_1 receptor to enhance cGMP
p of GC activation. ANF effects on the adrenal, kidney,
and potentially the lung appear at this time to be me-
diated by activating the R_1 receptor to enhance cGMP
production. The signal transduction pathway(s) has not
b and potentially the lung appear at this time to be me-
diated by activating the R_1 receptor to enhance GMP A
production. The signal transduction pathway(s) has not
been defined in most tissues, but potential mechanism diated by activating the R₁ receptor to enhance cGM
production. The signal transduction pathway(s) has no
been defined in most tissues, but potential mechanism
other than GC activation could involve the following: (*a*
s production. The signal transduction pathway(s) has not
been defined in most tissues, but potential mechanisms
of a china and attenuates the hormonal inhibition of adenylyl cyclase. J.
been defined in most tissues, but pote other than GC activation could involve the following: (a) suppression of adenylyl cyclase, (b) modulation of phos-
pholipase C activity, or (c) alteration of ion fluxes. The
inhibition of adenylyl cyclase and an activa other than GC activation could involve the following: (a)
suppression of adenylyl cyclase, (b) modulation of phos-
pholipase C activity, or (c) alteration of ion fluxes. The
inhibition of adenylyl cyclase and an activatio suppression of adenylyl cyclase, (b) modulation of phos-

pholipase C activity, or (c) alteration of ion fluxes. The

inhibition of adenylyl cyclase and an activation of phos-

pholipase C appear to be mediated by an inte pholipase C activity, or (c) alteration of ion fluxes. The inhibition of adenylyl cyclase and an activation of phos-
pholipase C appear to be mediated by an interaction with
the R_2 receptor, formerly thought to be dev inhibition of adenylyl cyclase and an activation of phos-

pholipase C appear to be mediated by an interaction with

the R_2 receptor, formerly thought to be devoid of any

coupling to an intracellular signal transducti pholipase C appear to be mediated by an interaction with
the R_2 receptor, formerly thought to be devoid of any
coupling to an intracellular signal transduction pathway.
This R_2 receptor couples to inhibitory G-prote the R_2 receptor, formerly thought to be devoid of any
coupling to an intracellular signal transduction pathway.
This R_2 receptor couples to inhibitory G-proteins to
suppress adenylyl cyclase and mediates neuronal an coupling to an intracellular signal transduction pathway.
This R_2 receptor couples to inhibitory G-proteins to
suppress adenylyl cyclase and mediates neuronal and
platelet effects of ANF. Furthermore, the R_2 recepto tissues. ppress adenylyl cyclase and mediates neuronal and
atelet effects of ANF. Furthermore, the R_2 receptor
obably mediates ANF effects in at least some endocrine
sues.
The receptor or signal transduction mechanism in-
lved platelet effects of ANF. Furthermore, the R_2 receptor probably mediates ANF effects in at least some endocrine tissues.
The receptor or signal transduction mechanism involved in vascular or adrenal responses to ANF are

probably mediates ANF effects in at least some endocrine $\frac{\text{ANAP}}{\text{hypothesis}}$
tissues.
The receptor or signal transduction mechanism in-
volved in vascular or adrenal responses to ANF are not
known and further experiments wi tissues.
The receptor or signal transduction mechanism involved in vascular or adrenal responses to ANF are not
known and further experiments with the novel ANF
receptor antagonists are essential for a better resolution
of The receptor or signal transduction mechanism in-
volved in vascular or adrenal responses to ANF are not
known and further experiments with the novel ANF
receptor antagonists are essential for a better resolution
of ANF m volved in vascular or adrenal responses to ANF are not
known and further experiments with the novel ANF $_{\text{arct}}^{\text{ANAN}}$
receptor antagonists are essential for a better resolution
of ANF mechanisms of action in this tissu known and further experiments with the novel AN
receptor antagonists are essential for a better resolutio
of ANF mechanisms of action in this tissue. Potassius
and sodium channels also are involved in ANF effects i
renal, receptor antagonists are essential for a better resolution
of ANF mechanisms of action in this tissue. Potassium
and sodium channels also are involved in ANF effects in
renal, adrenal, and endocrine tissues. The signaling of ANF mechanisms of action in this tissue. Potassium
and sodium channels also are involved in ANF effects in
a dimension of action and sodium channels also are involved in ANF effects in
a dimension of all interior recept and sodium channels also are involved in ANF effects in
renal, adrenal, and endocrine tissues. The signaling path-
way initiated by ANF may directly affect these channels
via a G-protein or may be mediated by the generatio renal, adrenal, and endocrine tissues. The signaling path-
way initiated by ANF may directly affect these channels
via a G-protein or may be mediated by the generation of
 GMP or suppression of cAMP concentrations way initiated by ANF may directly affect these channels
via a G-protein or may be mediated by the generation of
cGMP or suppression of cAMP concentrations. These
pathways must be investigated in greater detail to define
th via a G-protein or may be mediated by the generation of cGMP or suppression of cAMP concentrations. These pathways must be investigated in greater detail to define the actual sequence of events leading to biological respon cGMP or suppression of cAMP concentrations. These $\frac{1}{AB}$
pathways must be investigated in greater detail to define $\frac{1}{AB}$
the actual sequence of events leading to biological re-
sponses in individual tissues. Effect pathways must be investige
the actual sequence of every
sponses in individual tissue
states on signal transduction
investigated further also.
The major point of the e actual sequence of events leading to biological re-
onses in individual tissues. Effects of various disease $\frac{1}{48}$
attes on signal transduction pathways for ANF must be
vestigated further also.
The major point of th

sponses in individual tissues. Effects of various disease
states on signal transduction pathways for ANF must be
investigated further also.
The major point of the reviewed work is that ANF
must act via multiple signaling states on signal transduction pathways for ANF must be
investigated further also.
The major point of the reviewed work is that ANF
must act via multiple signaling pathways including the
 R_2 receptor to produce its biolo investigated further also.
The major point of the reviewed work is that ANF
must act via multiple signaling pathways including the
 R_2 receptor to produce its biological responses. The ac-
tivation of GC as a result of The major point of the reviewed work is that ANF
must act via multiple signaling pathways including the
 R_2 receptor to produce its biological responses. The ac-
tivation of GC as a result of R_1 receptor interactions must act via multiple signaling pathways including the R_2 receptor to produce its biological responses. The activation of GC as a result of R_1 receptor interactions occurs in the vast majority of tissues but often c

account for biological actions of ANF.
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excellent secretarial help.
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