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Atrial Natriuretic Factor Receptors and Signal Transduction Mechanisms*

MADHU B. ANAND-SRIVASTAVA[1]† AND GEORGE J. TRACHTE[2]

[1]*Department of Physiology, Faculty of Medicine, Groupe de recherche sur le système nerveux autonome, University of Montreal, Montreal, Quebec, Canada, and* [2]*Department of Pharmacology, University of Minnesota-Duluth, School of Medicine, Duluth, Minnesota*

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† M. B. A.-S is the recipient of a Medical Research Council of Canada Scientist award. Address for correspondence: Department of Physiology, Faculty of Medicine, University of Montreal, C. P. 6128, Succursale A, Montréal, Québec, Canada H3C 3J7.

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I. Introduction

ANF‡ was discovered by de Bold et al. (1981, 1982) as 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 actions 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 diuretic, and Richards (1990) reviewed the literature supporting a physiological renal function for ANF. This review will focus on the signal transduction mechanisms mediating biological actions of ANF. We shall emphasize ANF receptors with their associated intracellular signal transduction 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, pathophysiological alterations in these transduction mechanisms will be covered.

The perception of ANF signal transduction pathways 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 some of the biological activities of ANF. These two points represent major deviations from the widely held beliefs that ANF acts solely by stimulating the synthesis of cGMP and that the R_2 receptor is merely a binding protein promoting the clearance of ANF from plasma.

ANF is synthesized primarily in atria as a preprohormone 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). Derivatives of ANF will be presented in this review by their correspondence with the prohormone molecule, such that the circulating form of ANF is designated ANF(99–126). Many other designations for ANF are commonly used, such as atriopeptins, cardionatrin, auriculin, and atrial 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 the fact that they activate GC, promote hypotension 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-Knappe 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 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, 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

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 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 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 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, autoradiographic, ligand-cross-linking, and cloning studies which account 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 binding (K_d) was 129 pM in aortic membranes, identifying only one binding site (Napier et al., 1984). The affinities for other vascular smooth

‡ Abbreviations: ANF, atrial natriuretic factor; ACTH, adrenocorticotropin; ATP, adenosine triphosphate; BNP, brain natriuretic peptide; cANF, des[Gln^{18}, Ser^{19}, Gln^{20}, Leu^{21}, Gly^{22}]ANF_{4-23}; CNP, C-type natriuretic peptide; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; DOCA, deoxycorticosterone acetate; EDRF, endothelium-derived relaxing factor; GC, guanylyl cyclase; G-protein, guanosine triphosphate-binding protein; G_s, stimulatory G-protein; G_i, inhibitory G-protein; G_o, G-protein of unknown functions; GTP, guanosine triphosphate; GTPγS, guanosine 5′-(O-thiotriphosphate); IP_3, inositol trisphosphate; K_d, dissociation constant; K_i, inhibition constant; PT, pertussis toxin; SHR, spontaneously hypertensive rat; WKY, Wistar-Kyoto.

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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 smooth muscle (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 were the following: 100 pM for bovine aorta (Leitman and Murad, 1986), 400 pM for bovine brain (Smith et al., 1988), and 230 pM for rat brain (Ermisch et al., 1991). Only one binding site was identified in all of these studies utilizing radioligand-binding techniques, but later studies with 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 selective for the R_2 receptor. Leitman et al. (1986) found a truncated peptide selective for the R_2 receptor, ANF(103–123), to displace >94% of the ANF binding in bovine aortic endothelial 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., 1990) and rat aortic smooth muscle (Cahill et al., 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 binding by cANF (Bea et al., 1991). Thus, vascular tissues primarily contain the R_2 ANF receptor.

Autoradiographic studies demonstrated ANF binding 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 receptors in vascular tissue have a physiological function. However, they provide no evidence concerning the identity or physiological relevance of the ANF receptor subtypes present.

Cross-linking of ANF to its receptors with separation 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%. Bovine pulmonary artery endothelial cells demonstrated the same abundance of R_2 receptors relative to R_1 receptors, 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 primarily yielded a 130,000 molecular weight receptor with a minority of 65,000 molecular weight sites (Koseki et al., 1986). This irradiation with ultraviolet light may select for the R_1 receptor inasmuch as this technique resulted 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 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 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 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 endothelium. In contrast, rat aortic smooth muscle expressed 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 predominant 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 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 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 a 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 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 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 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 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, 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-binding 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 accounted for only 2% of the total renal binding sites (Suzuki et al., 1987). Autoradiographic studies indicated ANF bind-

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ing in the glomerulus, medulla, and arterial segments (Mantyh et al., 1986; Mendelsohn et al., 1987).

Most of these early studies found a homogeneous population of binding sites for ANF. The introduction of truncated derivatives of ANF provided a mechanism for discriminating binding sites into two types of receptors, labeled B (R_1) for biologically active and C (R_2) for clearance (Maack et al., 1987). These investigators found 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 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 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 ANF derivatives, cANF (Nuglozeh et al., 1990; Martin et al., 1989) or ANF(103–123) (Fethiere and De Lean, 1991), 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 antagonist, 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. This has not been confirmed with cANF at this point. These binding studies have identified ANF receptors in the kidney in 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 disuccinimidyl suberate to covalently link labeled ANF to receptors. The ANF-receptor complex was subjected to sodium dodecyl sulfate-polyacrylamide 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 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., 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 was identified in the rat kidney exhibiting a molecular weight of 180,000 (Ballerman et al., 1988). This receptor probably represents another R_1 receptor subtype inasmuch as it was retained on a GTP-affinity column. These results are consistent with the presence of multiple subtypes of ANF receptors in the kidney.

The final proof for the existence of ANF-binding sites 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 combination of reverse transcriptase and the polymerase chain 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 receptors with biological activity, as will be detailed in later sections. Furthermore, specific renal regions selectively express certain ANF receptors with the R_2 receptor predominating 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., 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 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 (Atarashi et al., 1985).

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 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 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 20% of ANF binding in hamster adrenals (Bianchi et al., 1989), 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 (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 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 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 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 sole presence of an R_1 receptor in the bovine adrenal, an

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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 molecular weight receptor was the predominant receptor present. Unlike Misono et al. (1985), Meloche et al. used labeled ANF and coupled it to membranes with sulfosuccinimidyl suberate. Takayanagi et al. (1987) also found two ANF-binding sites in the porcine adrenal of 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 receptor (Ohashi et al., 1988). Rat adrenal membranes incubated with labeled ANF and irradiated 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 subtypes in adrenal glomerulosa tissue. It appears that the R_1 subtype predominates in rodent adrenal glomerulosa, whereas bovine glomerulosa contains similar amounts of each receptor subtype. Studies examining the 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 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 (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 vasculature endothelium, or mesenchyme but not to myocytes (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). The ventricular 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 to both binding sites was attenuated by cANF, suggesting that they were R_2-binding sites. The ANF-binding sites were 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 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 have not been characterized further by investigating ANF receptor mRNA expression.

5. Lung. Rat lung fibroblasts bound ANF with a K_d of 660 pM (Leitman et al., 1987), whereas a purified ANF 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; 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 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-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). 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 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 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. 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). Autoradiographic 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) after intravenous injection of ANF. These results indicate that ANF is not accumulated to a large extent in the endocrine 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 (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 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 has 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, 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 brain with a K_d of approximately 600 pM (Gibson et al., 1986; Gutkowska et al., 1991). Binding to rat glial cells was

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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 spinal cord bound ANF with a K_d of 54 pM (Simonnet et 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 (Shionoiri et al., 1987; Rathinavelu and Isom, 1988; Toki et al., 1992). Autoradiographic studies revealed ANF binding to most areas of the brain with binding in the olfactory bulb, pineal gland, choroid plexus, and arachnoid mater predominating (Gibson et al., 1986; Mantyh 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), 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 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; Gutkowska et al., 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 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 not investigated in the spinal cord or sympathetic ganglia. Recently, 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 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, suggesting the sole presence of R_1 receptor subtypes (Konrad et 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 accounting for 95% of the binding (Levin et al., 1990). Human pheochromocytomas contained only the 70,000-Da receptor present as a dimer (Shionoiri et al., 1987), whereas rat pheochromocytomas contained both the 70,000- and 130,000-Da receptors (Rathinavelu and Isom, 1988) with 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 nonneuronal. The primary receptor present in the central nervous system is the R_1 subtype. The R_2 receptor is present on pheochromocytoma cells and diencephalic astrocytes.

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 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). 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 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 present in 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 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; Schiffrin et al., 1985). After ANF was recognized as a GC 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 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), 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). Conversely, 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 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 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 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. (1989) transfected COS-7 cells with brain GC cDNA and demonstrated increased GC activity and ANF binding following transfection. The cDNA encoded a protein with a predicted molecular mass of 115,852 Da, consistent with the electrophoretic results predicting a molecular mass of 120,000 to 180,000 Da. The data of Chinkers et al. (1989) have been recognized as the strongest evi-

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dence indicating that ANF binds to a receptor containing 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 concentrations 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 generation, although they are presumably mediated by the 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 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 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 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-spanning domain is encoded by exon 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 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 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 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 114,952 Da, similar to the GC-A receptor. The poor 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 (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 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 porcine atrium (Chang et al., 1989). The significance of this GC-B remains to be determined.

D. Atrial Natriuretic Factor R_2 Receptors/cANF Receptors

ANF R_2 receptors, also designated ANF clearance receptors or cANF receptors, are homodimers of a 64- to 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, 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 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 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 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 sequestration and metabolic clearance of ANF and, 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 release; 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 coupled to adenylyl cyclase/cAMP signal transduction pathways and refuted the hypothesis that they were biologically silent. Furthermore, Anand-Srivastava et al. (1991) reported that rat platelets, devoid of particulate GC, respond 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 treatments, suggesting that ANF R_2 receptors couple to the adenylyl cyclase/cAMP system. These results were confirmed 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-Srivastava et al., unpublished observations). In addition, ANF reduced cAMP levels in HeLa cells expressing predominantly 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/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., 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 treatment (Anand-Srivastava et al., 1990). The

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cANF 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 inhibition observed with ANF(99–126), indicating that 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 receptors are not biologically silent but have a physiological role.

The physiological role of the R_2 receptor has been documented by various other studies. Levin and Frank (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 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 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 adenylyl cyclase 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. Very recently, Hu et al. (1992) showed that cANF and nanopiperazine ANF(11–15)NH_2, agents selective for the 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-mediated 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 hypothesis that R_2 receptors elicit physiological responses through their interaction with cAMP signal transduction mechanisms.

Interestingly, Hirata et al., (1989a) showed that ANF and ANF(103–123) stimulate phosphatidylinositol turnover 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 through guanine nucleotide regulatory proteins. Taken together, it is possible that ANF R_2 receptors couple to two different intracellular messengers, cAMP and phosphatidylinositol turnover, or there exists a cross-talk 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 in cultured bovine aortic cells. In other words, the stimulation of phosphatidylinositol turnover by ANF in cultured bovine aortic cells (Hirata et al., 1989a) may 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 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 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 R_2 receptor was isolated from bovine aortic smooth muscle (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 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 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 to 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, 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 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 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 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 reading frame. 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 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 occur in the extracellular binding region of the receptor. One 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 C activities suggests the involvement of inhibitory G-proteins in the coupling of R_2 receptors to adenylyl cyclase inhibition and phospholipase C activation. Receptors coupled to G-proteins typ-

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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 these reservations have been refuted by recent findings that other receptors containing only one transmembrane-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-phosphate receptor coupling to G-proteins as a 14-amino acid segment enriched in basic amino acids. This segment increased GTPγS 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 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 above.

E. Summary

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 receptor is present in almost all cells with the possible exception of central nervous system neurons. All three receptors have been demonstrated to influence biological second messengers. The R_1 receptors elevate cGMP concentrations, 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. Conversely, ANF, cANF, CNP, or BNP interact with R_2 receptors to either suppress cAMP concentrations by 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 activity. The cGMP suppresses cAMP concentrations by activating phosphodiesterases to accelerate cAMP degradation. Both depicted actions of R_2 receptors are mediated by G-proteins.

III. Signal Transduction Mechanisms

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 phospholipase C systems, resulting in the generation of second messengers such as cAMP, cGMP and IP_3, and diacylglycerol, respectively. The signal-transducing enzymes associated with ANF actions are GC, adenylyl cyclase, and phospholipase C. ANF also influences potassium, sodium, and calcium conductances. Finally,

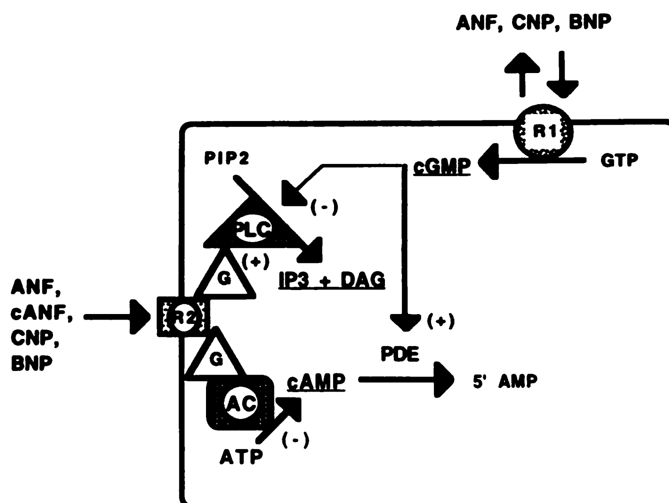

FIG. 1. ANF receptors and signal transduction pathways. ANF and related peptides, CNP and BNP, can interact with an R_1 receptor to stimulate the production of cGMP. The other major type of receptor is the R_2 receptor. ANF, cANF, CNP, and BNP interact with this receptor, promoting coupling to GTP-binding (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 IP_3 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 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 inhibiting adenylyl cyclase activity. The second messengers thought to mediate effects of natriuretic peptides are underlined (i.e., cGMP, cAMP, diacylglycerol, and IP_3). Potentiating or inhibitory effects are indicated by (+) or (−). PIP2, phosphatidylinositol bisphosphate.

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 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 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 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. 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 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 recognition of truncated ANF analogs as R_2 receptor agonists has facilitated evaluation of this receptor in mediating ANF responses.

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B. Guanylyl Cyclase/cyclic Guanosine Monophosphate Signal Transduction System

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 activation of the enzyme. The GCs responding to ANF have molecular masses of 130,000 to 180,000 Da. Other 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. 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., 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 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 R_1 receptors; therefore, they do not respond to ANF with an elevation of GC activity (Anand-Srivastava et al., 1991; Schiffrin et 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 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 mechanism involving increased production of cGMP. 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 also has served as a useful agent to identify effects of 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 effects cannot be attributed to an increased production of cGMP, although renal signal transduction mechanisms for natriuretic actions of ANF have not been differentiated from GC activation.

The relationship between ANF receptor binding and 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 heterodimers with masses of approximately 70,000 and 80,000 Da, as reviewed by Goy (1991). The soluble GC is activated by nitrovasodilators, nitric oxide, and free radicals (Waldman and Murad, 1987). This enzyme is believed to mediate responses to a variety of vasodilators, such as 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 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., 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 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). 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). 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 receptor portion of the molecule to the GC portion.

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 extracellular 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 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 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 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 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 for 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 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 activation of the enzyme by ANF (Marala et al., 1992). Addition of protein kinase C (Ballerman et al., 1988) or phorbol esters, which activate protein kinase C (Nambi

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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, 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; Drewett et al., 1990; Ljusegren et al., 1990). Agents interacting with sulfhydryl groups, such as N-ethylmaleimide, inhibit adenylyl cyclase activity (Ross and Gilman, 1980) but have no effect on GC activity (Sharma 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/Cyclic Adenosine Monophosphate Signal Transduction System

The adenylyl cyclase/cAMP system is one of the best-characterized signal transduction systems mediating physiological responses to a variety of hormones and 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 signal from 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 decreased formation of cAMP, respectively.

The G-proteins are heterotrimeric, consisting of α, β, and γ subunits (Gilman, 1987). The α subunit binds and hydrolyses GTP and confers specificity in receptor and effector interactions (Stryer and Bourne, 1986). Two different forms of the $G_{s\alpha}$ protein, $G_{s\alpha\text{-}45}$ and $G_{s\alpha\text{-}52}$, have been characterized with a third form, $G_{s\alpha\text{-}47}$, recently being identified in heart (Murakami and Yasuda, 1986). These different forms of $G_{s\alpha}$ arise from several species of mRNA, which appear to be products of alternate 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 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 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_s 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, 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 effects to inhibit adenylyl cyclase in response to GTP or receptor activation (Hazeki and Ui, 1981).

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 each tissue separately. In addition, the inability of 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, Anand-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% 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 presence of guanine nucleotides, suggesting the involvement 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, 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 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 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 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 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 addition, Umemura et al. (1989) demonstrated that ANF inhibited parathyroid hormone-stimulated increases 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 papillary collecting tubule cells (Ishikawa et al., 1985). However, ANF failed to inhibit adenylyl cyclase activity in whole kidney membranes (Waldman et al., 1984; Anand-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 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 nephron segments (Stokes et al., 1986; Ardaillou

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et al., 1986; Naray-Fejes-Toth et al., 1988; Chabardes et al., 1987). The inability to demonstrate the ANF-mediated 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, 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 apparent K_i between 50 and 1000 pM. These results were confirmed by Barrett and Isales (1988), who demonstrated that ANF inhibited steroidogenesis at physiological concentrations. Furthermore, ANF-mediated inhibition of ACTH-stimulated aldosterone secretion, and cAMP levels has also been reported in adenoma tissue 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 formation and steroidogenesis in response to ACTH in 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 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 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 ventricular cells was 35% with an apparent K_i of 0.1 nM, whereas a 60% inhibition was observed in atrial cardiocytes 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). 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 velocity 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 that ANF receptors coupled to the adenylyl cyclase/cAMP signal transduction system are responsible for these biological effects. ANF inhibited adenylyl cyclase and reduced cAMP concentrations in Purkinje 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.* Resink et al. (1988) demonstrated that ANF inhibited adenylyl cyclase activity in rat lung membrane in a GTP-dependent manner, suggesting that ANF receptors are coupled to adenylyl cyclase in a negative manner through G-proteins. Anand-Srivastava (1989) confirmed these studies and observed a 35% inhibition of adenylyl cyclase by ANF in rat lung membranes.

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-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 adenylyl cyclase could have been due to the high concentrations of GTP (300 μM) 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 cyclase activity is observed at lower concentrations of GTP, whereas 300 μM GTP obliterates the ANF-mediated inhibition.

Obana et al. (1985) also demonstrated that ANF suppressed 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. (1985) showed that ANF decreased cAMP levels in murine Leydig tumor cells in a concentration-dependent manner, which is associated with the inhibition of gonadotropin-stimulated progesterone secretion. These results were confirmed by the studies of Anand-Srivastava

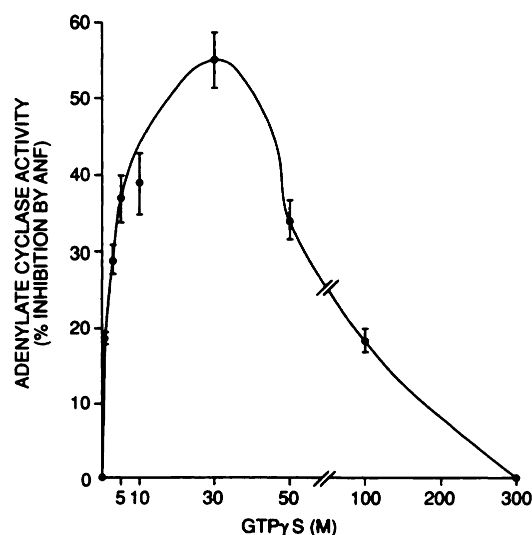

FIG. 2. Dependence on guanine nucleotides of adenylyl cyclase in anterior pituitary homogenates. Adenylyl cyclase activity was determined at various concentrations of GTPγS in the absence and presence of 0.01 μM ANF. The results are presented as percentages of inhibition of adenylyl cyclase by ANF at various concentrations of GTPγS. The basal enzyme activities in the absence and presence of ANF were 60.3 ± 3 and 55.7 ± 7.1 pmol cAMP/(mg protein · 10 min)$^{-1}$, respectively. Values are means ± SEM of three separate experiments.

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et al. (1991) who showed that ANF and cANF inhibited adenylyl cyclase activity, cAMP accumulation, and progesterone secretion in murine Leydig tumor cells. However, Mukhopadhyay et al. (1986) were unable to demonstrate 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 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 levels and progesterone secretion in rat luteal 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 R_2 receptor subtypes (Tseng et al., 1990). The inhibitory effect of ANF or prostaglandin E_2 on parathyroid hormone-stimulated cAMP production was also noted in fetal rat bone cultures (Vargas et 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 inhibitions were 60 to 65% (Anand-Srivastava et al., 1990). However, Geiger et al. (1988) did not observe any inhibition of adenylyl cyclase by ANF in different brain areas, which may be due to the tissue differences and different assay conditions used in their adenylyl cyclase determinations. For example, 8 μM mercaptoethanol used in their enzyme assay could have prevented the inhibition of adenylyl cyclase by ANF.

8. Platelets. ANF and several truncated analogs inhibited 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 dependent on the presence of guanine nucleotides. Furthermore, the inhibition was attenuated by PT or amiloride. ANF reduced both cAMP concentrations and elevations in adenylyl cyclase activity caused by N-ethylcarboxamide adenosine, isoproterenol, and forskolin (Anand-Srivastava 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 techniques. 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 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 ANF on adenylyl cyclase (Anand-Srivastava et al., 1986; Anand-Srivastava and Cantin, 1986). However, Koyama et al. (1992) recently demonstrated the reduction of cAMP levels by oxidized analogs of ANF in HeLa 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-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 or GTPγS required to elicit the maximal inhibition depends on the tissue. For example, in pituitary, the maximal inhibition was observed between 3 and 5 μM, whereas in other tissues, maximal inhibitory effects occurred at 10 μM GTPγS. Above this concentration, the inhibitory effect is decreased, and at higher concentrations, the effect is abolished (fig. 2). In addition, ANF inhibits adenylyl cyclase more effectively in the presence of GTPγS than GTP or GMP-P(NH)P (Anand-Srivastava et al., 1986).

As shown for angiotensin II and other inhibitory hormone 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 factor 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 investigators 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. (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 adenylyl cyclase. This finding supports the involvement of G_i 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 phospholipid-dependent protein kinase (C-kinase) attenuated 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 ANF-mediated inhibition of adenyl cyclase was also attenuated by neurominidase treatment, indicating the involvement of glycoprotein moiety in eliciting the inhibitory response of ANF (Anand-Srivastava, 1992c). Phospholipids were also shown to be involved in the expression of the inhibitory effect of ANF on adenylyl cyclase (Anand-Srivastava, 1992c).

ANF, as reported for other inhibitory hormone receptors, inhibited adenylyl cyclase more effectively as sodium concentrations were increased, whereas potassium

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and lithium suppressed inhibitory effects of ANF (Anand-Srivastava et al., 1992c). Manganese also suppressed 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 indicate that ANF suppresses the adenylyl 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 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 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 pathway in mediating biological responses to ANF is not clearly defined, but results of a number of studies suggest this to be an important signal transduction pathway in cardiac, endocrine, and neuronal tissues, as well as in platelets.

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 intracellular calcium. Resink et al. (1987) and Hirata et al. (1989a) initially observed that ANF stimulated this 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 R_1 receptor. Therefore, phospholipase activation by ANF 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 studies. Conversely, hormone-stimulated phospholipase C activity 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 vasodilator activities of ANF. Currently, ANF is thought 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 has been observed only in vascular tissue (Resink et al., 1988; Hirata et al., 1989a). An inhibitory effect on phospholipase C activity occurred in the kidney (Barnett et al., 1990) and vascular tissue (Rapoport, 1986; Meyer-Lehnert et al., 1988). An absence of ANF effects on phospholipase C activity was reported in the adrenal (Goodfriend et al., 1984) and heart (Cramb et al., 1987). The ultimate significance of ANF actions on phospholipase C activity remains to be established.

E. Altered Ion Conductances

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 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 suggests 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 transmembrane movements of calcium in the heart (Gisbert 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). 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 depletion (Matsuoka, et al., 1987; Rapoport et 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 cotransport 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-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 inhibition to suppress ANF effects suggests a central role for potassium in mediating ANF effects in vascular 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 inhibitors have failed to identify any ANF effect dependent on prostaglandin or thromboxane production. Thus, although ANF can activate eicosanoid synthesis, this action appears to be a phenomenon not required for recognized ANF effects on any organ system. Arachidonic acid is also converted to leukotriene and epoxygenase products. The effect of ANF on leukotriene or epoxygenase production has not yet been investigated and requires further study.

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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 produced 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 augment cGMP concentrations which, then, presumably 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 (Winquist et al., 1984), we conclude that ANF effects are independent of the endothelium.

IV. Biological Actions of Atrial Natriuretic Factor

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 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 bolus injections uniformly cause a decrease in total peripheral 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 exchange (Huxley and Meyer, 1990) and occurs in nephrectomized animals (Almeida et al., 1986). This ANF effect on vascular permeability affects water and electrolytes but does not involve an increased permeability to 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 (Meyer and Huxley, 1992). This review will concentrate 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 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 intact in the presence of the R_2 receptor agonist, cANF (Elmquist and Trachte, 1992). The signaling pathway for ANF remains unknown, although a number of potential mediators of the relaxant effect are influenced by ANF. Interestingly, the antimitogenic effect of ANF appears to be mediated by the ANF R_2 receptor because cANF prevents the antimitogenic activity of ANF in vascular smooth muscle (Cahill and Hassid, 1991). The 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 adenylyl 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 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 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 muscle by an activation of soluble GC (Murad, 1988). This correlative evidence among ANF, cGMP, and vasodilation 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 vasodilatory and cGMP responses. ANF(103–125) relaxed rabbit aortic rings without stimulating GC (Budzik et al., 1987), whereas Willenbrock et al. (1989) observed an oxidized derivative, oxidized Met^{110} 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 in relaxing aortic rings (Budzik et al., 1987). A GC inhibitor, LY83583, also prevented the GC response to ANF but not the vasodilation (Gupta et al., 1989). Similarly, a linear ANF analog with two cysteine residues

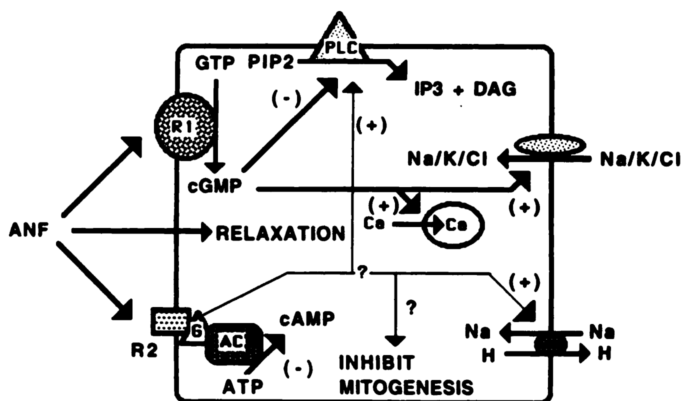

FIG. 3. Vascular signal transduction pathways for ANF. ANF acts on the R_1 receptor to generate cGMP which can inhibit phospholipase C (PLC) activity. The cGMP also activates a sodium-potassium-chloride exchange or an uptake of calcium in cellular organelles. ANF probably interacts with the R_2 receptor to inhibit adenylyl cyclase (AC) 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 pathways described. The antimitogenic effect of ANF is mediated by the R_2 receptor. Potentiating or inhibitory effects are indicated by (+) or (−). DAG, diacylglycerol; PIP2, phosphatidylinositol bisphosphate.

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modified by various alkyl groups antagonized cGMP accumulation, but not vasorelaxation, in response to ANF (Kitajima et al., 1989). Finally, a R_1 receptor antagonist, A74186, inhibited the activation of GC, but not the depressor response, to infused ANF (von Geldern et al., 1990). Another recently developed R_1 receptor antagonist, 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 relaxed the rings in the presence of R_1 receptor antagonists (Elmquist and Trachte, 1992).

Most recently, HS-142-1 was observed to slightly antagonize ANF vasodilatory responses in rabbit aorta at concentrations that essentially abolished GC activation (Imura et al., 1992). HS-142-1 antagonized BNP dilatory 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 acts as a vasodilator via an increase in GC activity. Further work with selective agonists or antagonists should clarify the role of cGMP in mediating vascular responses to ANF.

2. Inhibitory effects of atrial natriuretic factor on vascular adenylyl cyclase. ANF inhibited vascular smooth muscle adenylyl cyclase activity (Anand-Srivastava et 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 ANF vasodilator effect appears to be independent of both adenylyl cyclase inhibition and R_2 receptor interactions. The vasoconstriction elicited by ANF(103-125) in coronary arteries (Wangler et al., 1985) may be mediated through an inhibition of the adenylyl cyclase/cAMP signal transduction 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 phospholipase C. Surprisingly, the initial reports of ANF effects 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). Both of these studies measured modulatory effects on basal unstimulated phospholipase C activity. Later experiments examining phospholipase C activity after stimulation by contractile agonists uncovered an inhibitory ANF effect on IP_3 generation (Rapoport, 1986; Meyer-Lehnert et al., 1988; Winquist and Hintze, 1990). The inhibition of phospholipase C activity was associated with the generation of cGMP, and cGMP analogs mimicked the ANF effect (Rapoport, 1986). Phospholipase C activation results in the generation of IP_3 and a protein kinase C stimulant, diacylglycerol. The increase in protein 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 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 on vascular phospholipase C activity remains unknown, and no clear evidence supports this pathway as a major 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 sodium entry into the cells and to decrease calcium concentrations 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 accumulated sodium in the presence of ANF by a mechanism 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 bovine carotid endothelial cells (Fujita et al., 1989), presumably by a cGMP-dependent mechanism. The activation was measured as intracellular ^{86}Rb uptake 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 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 sodium homeostasis have not been elucidated. For example, the potential involvement of G-proteins in these responses has not been assessed with PT. The ANF receptor mediating these effects also has not been ascertained.

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; 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 (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 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 vascular smooth muscle of calcium and presumably

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reduce contractions. Dibutyryl cGMP mimicked the 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 homeostasis to alter vascular tone, a hypothesis consistent with the accepted preeminence of calcium in mediating smooth muscle contractions. However, the 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 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 transduction 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 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 and Owen (1986a) also indicated that ANF increases potassium influx by stimulating sodium-potassium-chloride 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 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. Calcium-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 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 potassium channel activation is not a requirement 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-derived relaxing factor production in the vasculature. ANF stimulated the release of arachidonic acid 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 sustained in the presence of ANF (Tamm et al., 1990). Cyclooxygenase inhibitors were ineffective in altering the vasodilatory response to ANF (Garcia et al., 1984); 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 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 al., 1987) but routinely inhibited dilator responses to EDRF. 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 factor 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 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 potential pathways are depicted in figure 3. ANF can enhance or suppress phospholipase C activity, activate sodium-hydrogen exchange, facilitate sodium-potassium-chloride cotransport and calcium efflux by both sodium-calcium exchange and calcium extrusion via a calcium pump, inhibit adenylyl cyclase activity, and promote 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 effect has not been clarified further but represents one of the few 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 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 associated 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 (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). 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. Established intracelluar actions of ANF in renal cells are shown in figure 4. They include activation of GC and reductions in adenylyl cyclase activity, phospholipase C activity, sodium influx, and calcium concentrations.

1. Role of renal guanylyl cyclase. The stimulatory effect

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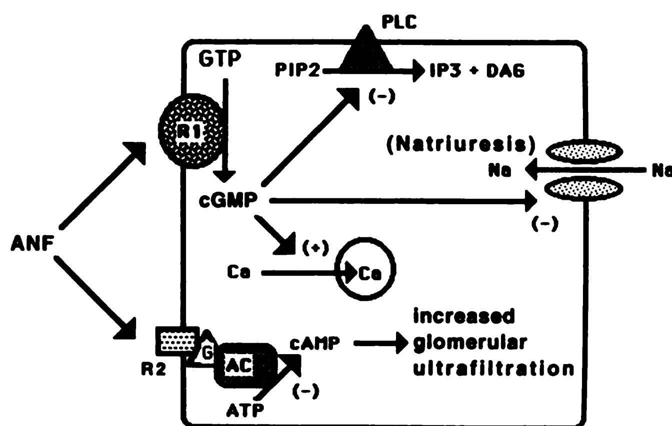

FIG. 4. Renal signal transduction pathways for ANF. ANF can act on either of two receptors, R_1 or R_2. The R_1 receptor generates cGMP in response to ANF, and the cGMP can act to suppress phospholipase C (PLC) activity or sodium channel opening. The cGMP also can decrease intracellular calcium concentrations. ANF suppresses adenylyl cyclase (AC) activity, but the functional significance of this response 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 bisphosphate.

of ANF on GC was found initially in the kidney (Hamet et al., 1984; Waldman et al., 1984). The augmentation of renal 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 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 GC response to ANF in the proximal tubule of rabbits. 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 renal function and correlated 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 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 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 and Ausiello, 1986; Mohrmann et al., 1987; Light et al., 1989). Inhibitors of cGMP phosphodiesterase potentiated 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 of cANF, a specific R_2 receptor-binding peptide (Maack et al., 1987; Anand-Srivastava et al., 1990), to alter renal function in vitro. Furthermore, cANF failed to alter renal effects of 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 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 observations 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. This putative pathway is depicted in figure 4. The ANF effect on blood pressure was unaltered by A74186 and only slightly modified by HS-142-1, suggesting that the depressor action of acutely infused ANF is not necessarily mediated by renal mechanisms.

Evidence opposing a mediating role of cGMP in promoting 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 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 oxidized Met^{110}-ANF produced diuresis and hypotension, 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 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, 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 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 generation of cGMP. The two studies dissociating cGMP production from some renal effects of ANF (Willenbrock et al., 1989; von Geldern et al., 1990) emphasize the 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 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 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 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 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; 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 accumulation induced by hormonal agonists, such as glucocorticoids (Aboud et al., 1979), enhanced single nephron glomerular filtration rate and whole kidney glomerular filtration rate (Baylis and Brenner, 1978). Thus, it may be suggested that lowered intraglomerular cAMP concentrations cause increased ultrafiltration. The presence of ANF R_2 receptors, combined with the ability of 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 isolated rat kidney using the R_2-selective agent, cANF. 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 on cortical collecting 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 the effect of the ANF. The major argument 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). The R_1 receptor antagonist should dissociate the renal actions of ANF from an inhibition of adenylyl cyclase. It is possible that a suppression of adenylyl cyclase activity could be involved in the diuretic action of ANF, but the 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 C activity. ANF had no effect on basal phospholipase C 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 stimulator of GC, also reduced angiotensin effects on phospholipid turnover. A stimulatory effect of ANF on phospholipase C activity was also found in the shark rectal gland, with an increase in sodium and chloride secretion (Ecay and Valentich, 1991). The ultimate relationship 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 recognized actions of ANF is an alteration of sodium excretion, 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 mimicked by dibutyryl cGMP (Light et al., 1989). Furthermore, ANF stimulated GC activity. Therefore, ANF could act to reduce sodium conductance in the inner medulla by a signal transduction pathway involving 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 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 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 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, 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 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 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 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 interaction of ANF with calcium fluxes was investigated in mesangial cells, where ANF suppressed intracellular calcium concentrations from 110 to 60 nM with an EC_{50} of 100 pM (Lermioglu et al., 1991). However, ANF (100 pM) failed to stimulate GC activity. Nevertheless, 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 relevant to the effect on sodium channels inasmuch 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 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 from the

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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 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., 1990), although the eicosanoid synthesis 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 suppress eicosanoid synthesis as well as stimulate it. Three reports dissociate renal effects of ANF from eicosanoid synthesis (Keeler, 1982; Garcia et al., 1984; Rodriguez-Puyol et al., 1986). These studies demonstrated 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 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, or intracellular calcium accumulation have all been proposed as important signal transduction pathways. 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

Sodium excretion by the kidney is controlled by renal transport processes including one influenced by aldosterone, 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 of 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 actions of ANF and aldosterone to explore ANF effects 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 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 be physiologically significant and account for natriuretic effects. Established ANF effects within adrenal glomerulosa cells are shown in figure 5. They include an activation of GC, potassium channels, and L-type calcium channels, whereas T-type calcium channels conductance and adenylyl cyclase activity are depressed.

1. Guanylyl cyclase involvement in adrenal effects of

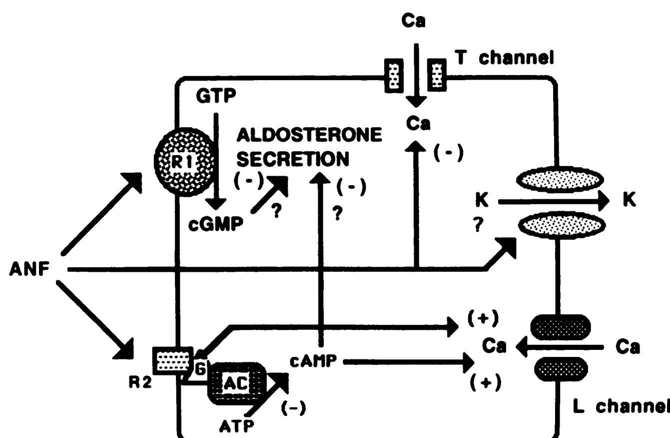

FIG. 5. Adrenal signal transduction pathways for ANF. ANF acts on at least two receptors in the adrenal. It augments cGMP production, but cGMP has not been identified as a second messenger for any adrenal response (?). ANF inhibits adenylyl cyclase (AC) activity via an interaction with the R_2 receptor and a G-protein (G). The significance 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 fluxes might be increased by ANF. The mechanisms accounting 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 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; Naruse et al., 1987). This correlative evidence for cGMP suppressing aldosterone secretion was challenged 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 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 R_1 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 R_1 receptors mediate ANF effects to suppress aldosterone 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 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 not alter cGMP responses to ANF (Horng et al., 1991). These findings led the authors to hypothesize the existence of a GC-uncoupled receptor that suppressed aldosterone synthesis when stimulated. Obviously, the ANF

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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 ANF derivative, ANF(106–121), failed to alter aldosterone synthesis at 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 aldosterone secretion and, by exclusion, support a role for R_1 receptors. 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 precedent for R_1 receptors to act independently of cGMP; therefore, the ultimate mediator of ANF effects in the adrenal gland is unestablished but may be cGMP. Future experiments using selective ANF R_1 or R_2 receptor-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 adenylyl cyclase activity in the adrenal glomerulosa in all studies examining this effect (Anand-Srivastava et al., 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 cyclase activity in bovine adrenals occurred at concentrations of ANF approximating plasma levels. The EC_{50} varied from 10 to 100 pM (Anand-Srivastava et al., 1985b; Barrett and Isales, 1988). ANF also inhibited the prostaglandin E_1, ACTH, and forskolin stimulation of both adenylyl cyclase activity and steroidogenesis, suggesting that the adenylyl cyclase/cAMP pathway may account for the 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. PT did not alter ANF effects on aldosterone synthesis but eliminated the suppression of adenylyl cyclase activity (Barrett and Isales, 1988; MacFarland et al., 1991). Furthermore, truncated ANF derivatives such as ANF(106–121) failed to suppress aldosterone secretion 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 study of MacFarland et al. (1991) suggested that 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 mechanism probably does not solely mediate the suppression of adenylyl cyclase activity caused by ANF, because ANF acts on adenylyl cyclase at concentrations failing to alter GC activity. Furthermore, truncated ANF derivatives such as ANF(106–121) are full agonists on adenylyl cyclase at concentrations that do not stimulate cGMP production. Therefore, the R_2 receptor appears to 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 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 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 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 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 mechanism of ANF action being the most investigated. Most of the initial studies found no effect of ANF on ^{45}Ca influx (Goodfriend et al., 1984; Elliott and Goodfriend, 1986; Isales et al., 1992), although Chartier and Schiffrin (1987) observed ANF to inhibit ^{45}Ca influx in response to high concentrations of potassium, angiotensin II, or ACTH. Intracellular calcium concentrations were unaffected by ANF (Apfeldorf et al., 1988; Isales et al., 1992); therefore, ANF was thought to act by mechanisms unrelated 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 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 depolarizations of the membrane presumably because 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 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 the activation of L-type channels is mediated either by the ANF R_2 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 alterations in calcium fluxes as the mediator of ANF effects in the adrenal glomerulosa.

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Potassium is another ion that can profoundly affect aldosterone synthesis and release. Elevations in potassium concentrations in plasma represent one of the most potent stimuli for aldosterone production. The ANF 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 production only in the presence of potassium. Alternatively, 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 further by using potassium channel inhibitors 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.

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 investigated. Negative results with these agents in other systems suggest that they are unlikely candidates as second 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 receptor. Because adrenal effects of ANF have been dissociated from cGMP actions, the exact mechanism of action is unresolved, potentially involving signal transduction 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, 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 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, suggesting an important role for potassium. The adrenal 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 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 cardiac contractility (Wangler et al., 1985; Burnett et al, 1987; Yanagisawa et al., 1987; Bohm et al., 1988; Hutter, 1991), whereas a slight, but statistically significant, suppression of myocardial contractility caused by ANF has also been 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 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 the exact signaling pathways have not been discerned. The intracellular actions of ANF in cardiocytes 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 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 myocardial cells (McCall and Fried, 1990). Meulemans et al. (1988) found dibutyryl cGMP and sodium nitroprusside 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 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 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 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 relevance to the GC activation. Furthermore, PT prevented the

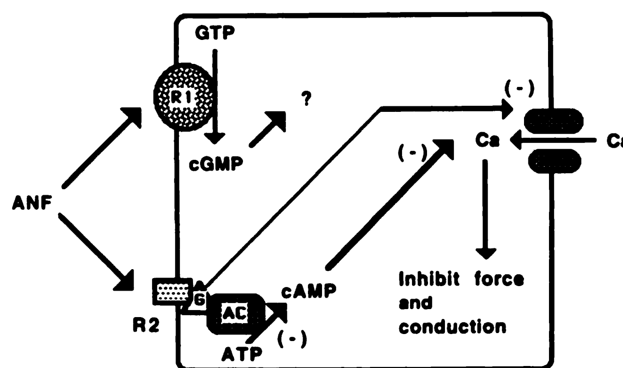

FIG. 6. Cardiac signal transduction pathways for ANF. As with previously described tissues, ANF acts on R_1 receptors to promote cGMP formation and probably interacts with the R_2 receptor to inhibit adenylyl cyclase (AC) activity via a G-protein (G). The inhibitory pathway involving cAMP apparently (?) mediates the suppression of cardiac contractility, potentially by an inhibitory effect on calcium influx. The influence on calcium conductance could be mediated by a suppression of cAMP concentrations or a G-protein interaction with a calcium channel. cGMP does not appear to be involved in the negative inotropic effect of ANF. –, inhibitory effects.

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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 data refute the hypothesis that ANF acts on cardiac tissue via the GC signal transduction pathway. Alternatively, Le Grand et al. (1992) found that ANF suppresses calcium currents in human atria in the presence of GTP but not GTPγS. They interpreted this finding to indicate that cGMP formation from GTP is essential for the inhibitory actions of ANF on calcium fluxes that ultimately results in negative inotropic effects.

2. Role of adenylyl cyclase inhibition in cardiac responses to atrial natriuretic factor. The ANF influence on cardiac adenylyl cyclase activity has been variable, depending on the investigators performing the studies. 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 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-dependent decrease in cAMP concentrations following the 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 Fried, 1990). Furthermore, PT prevented both the decrease in cAMP concentrations and the negative inotropic 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 (Gisbert and Fischmeister, 1988). Thus, current evidence supports an inhibitory action of ANF on cardiac 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 adenylyl 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 no ANF effect in rabbit ventricular myocytes (Cramb et al., 1987). Obviously, this potential ANF signal transduction pathway should be investigated further, but currently there is no evidence supporting a critical role for 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. ANF 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, 1988). As mentioned above, this inhibition of calcium currents could have been mediated by alterations in cAMP concentrations. PT inhibited ANF effects in rat myocardial cells (McCall and Fried, 1990), suggesting the involvement 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 differentiate between the two potential pathways. Human atrial cells failed to respond to ANF in cells exposed to GTPγS 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 ANF on calcium fluxes. The effects of ANF on other ionic fluxes have not been determined in cardiac tissue.

5. Atrial natriuretic factor effects on cardiac endothelium-derived relaxing factor or eicosanoid synthesis. Surprisingly, 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 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 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 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 the 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 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 transduction pathway involved has not been elucidated but may involve a suppression of adenylyl cyclase mediated by a G-protein, as depicted in figure 6. The negative inotropic 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; Potvin and Varma, 1989) and ciliary paralysis (Tamaoki 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 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 effects of ANF, only guanylyl and adenylyl cyclase will be discussed as potential pulmonary signal transduction pathways. Effects of ANF within pulmonary cells are

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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 response to a variety of ANF congeners capable of stimulating GC (Ishii and Murad, 1989). In contrast, ANF(103–123) neither stimulated GC nor relaxed tracheal 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 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 and elevated cGMP concentrations, and these activities were augmented by an inhibitor of cGMP phosphodiesterase, 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 evidence is consistent with ANF effects in the lung being mediated by cGMP. No studies have used ANF R_1 receptor 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 (Anand-Srivastava et al., 1988; Resink et al., 1988) or rabbit (Tkachuk et al., 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 be an unlikely mediator of ANF relaxant effects. Whether this ANF effect mediates other pulmonary responses to ANF, such as suppressed ciliary motility, is unestablished.

3. Conclusions regarding pulmonary transduction pathways. ANF effects in the lung appear to be mediated by 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 thoroughly, and these conclusions require additional investigations into receptor subtypes, PT sensitivity, and influences on ionic fluxes and phospholipase activities. The rudimentary pathways described thus far for ANF effects in pulmonary tissues are presented in figure 7.

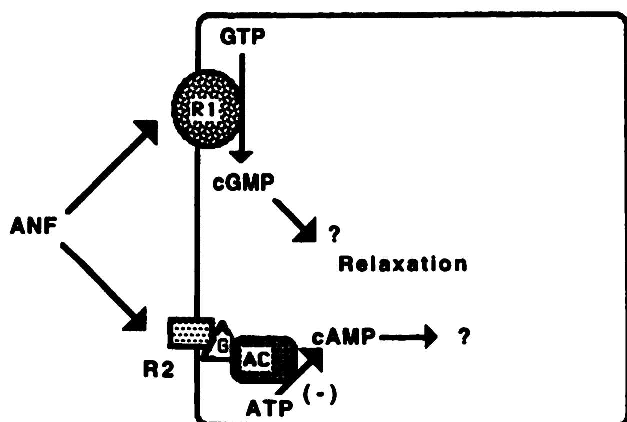

FIG. 7. Pulmonary signal transduction pathways for ANF. ANF can act on R_1 receptors to stimulate cGMP formation, and the cGMP apparently (?) mediates the relaxant effect. ANF also inhibits adenylyl cyclase (AC), presumably by an interaction with the R_2 receptor and coupling via a G-protein (G). The significance of the modulatory effect on adenylyl cyclase in bronchodilation has not been determined.

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 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 luteinizing 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 also exists for alterations in potassium currents 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 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 effect. We shall present evidence for ANF effects on GC, adenylyl cyclase, and ion channels, and their potential for mediating ANF effects on hormone release. Effects of ANF within endocrine cells are presented in figure 8.

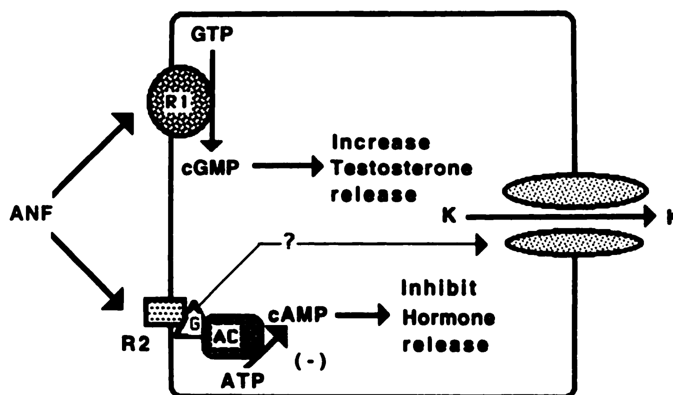

FIG. 8. Endocrine signal transduction pathways for ANF. ANF activates R_1 receptors to accelerate cGMP formation. The cGMP apparently mediates an enhanced release of testosterone from the testis. ANF also presumably interacts with R_2 receptors to inhibit adenylyl cyclase (AC) activity by a mechanism 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 channels via the G-protein to inhibit hormone release also (?). The cGMP action in endocrine tissue is believed to be mediated by promiscuous activation of a cAMP-dependent protein kinase. –, inhibitory effects.

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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 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 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 could potentially attenuate ACTH secretion. 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 effects on ACTH release from an activation of GC. Another anterior pituitary hormone, luteinizing hormone, was released in greater amounts in the presence of ANF (Horvath et al., 1986; Steele, 1990), but the potential involvement of cGMP has not been investigated.

The most recognized effect of ANF on the posterior pituitary gland is decreased antidiuretic hormone secretion (Samson, 1985). The addition of ANF to the posterior pituitary gland elevated cGMP concentrations (Obana et al., 1985); however, the significance of this action is unknown. The locus of ANF actions to reduce antidiuretic 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 present. These results indicate that cGMP production was enhanced and antidiuretic hormone release was reduced, indicating the potential for a cause and effect 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 thyroglobulin (Tseng et al., 1990) release. The inhibition of thyroglobulin release from cultured human thyroid cells occurred at ANF concentrations having no effect on cGMP concentrations. 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.

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 al., 1986b). A recent report indicates that ANF augments testosterone production by elevating cGMP concentrations to activate protein kinase A, resulting in increased testosterone secretion (Schumacher et al., 1992). Another ANF effect in the testis was a suppression of progesterone formation, but this effect of ANF was more potent, occurring at an EC_{50} of 100 pM (Pandey et al., 1986b). Thus, the suppressed progesterone synthesis presumably occurred independently of GC activation.

ANF decreased renin secretion to inhibit the generation 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 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 angiotensin II concentrations to lower arterial pressure. The inhibitory effect on renin release occurred at physiological 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 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 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 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 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 significantly alter cGMP generation. Nevertheless, these authors 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 nitroprusside, 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 effects on renin release and cGMP production.

2. Atrial natriuretic factor effects on adenylyl cyclase activity in endocrine tissues. ANF suppressed cAMP concentrations in the majority of reports regarding endocrine tissues. ANF and cANF reduced the adenylyl cyclase activity in the anterior pituitary (Anand-Srivastava 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 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., 1987). The importance of ANF effects on adenylyl cy-

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clase in endocrine organs has not been determined in most tissues. The EC_{50} of ANF to suppress ACTH release (King and Baertshci, 1989) and adenylyl cyclase activity (Anand-Srivastava et al., 1985a) in the pituitary was 10 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 cyclase activity (Tseng et al., 1990). Furthermore, dibutyryl cAMP prevented the inhibitory effect of ANF on thyroglobulin release. Therefore, ANF could affect thyroid secretions by depressing adenylyl cyclase activity. The R_2 receptor apparently mediated this effect because it was the only receptor identified in the thyroid cells utilized (Tseng et al., 1990). No information exists concerning 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 adenylyl 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 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 Campbell, 1980), indicating that a reduction in its intracellular concentration could reduce renin secretion. Unfortunately, critical experiments utilizing PT have not been 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 activity is a causative factor in this response. Similarly, no results with the R_2 receptor ligand, cANF, are available to confirm or refute the involvement of the R_2 receptor in the suppression of renin release.

Collectively, these endocrine studies indicate a potential role for R_2 receptors in mediating an inhibitory ANF effect on adenylyl cyclase and hormone secretion.

3. Atrial natriuretic factor effects on ion conductance in endocrine tissue. ANF suppressed ACTH release from isolated rat anterior pituitary cells in a concentration-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 activation in ANF effects have been reported. The frequency of potassium channel involvement in other ANF effects is suggestive of this mechanism being of potential importance in endocrine organs as well.

ANF failed to influence the influx of ^{45}Ca in juxtaglomerular cells (Kurtz et al., 1986). Moreover, the intracellular calcium concentrations were unchanged, indicating that ANF must act independently of calcium to 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 endocrine systems. The descriptive nature of most experiments in endocrine tissues precludes definitive conclusions regarding the involvement of ANF signal transduction mechanisms. ANF stimulates cGMP formation, and this second messenger conceivably could mediate ANF effects. ANF also inhibits adenylyl cyclase activity fairly consistently in endocrine 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 linkage 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 cells, suggesting that ANF alters potassium currents to mediate its effects. Further work is urgently needed to critically test 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 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 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 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 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; 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 relevance of this effect has not been ascertained. The EC_{50} for the effect in isolated adrenergic tissue is about 30 pM (Drewett 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 ANF acts as an antimitogenic agent. ANF suppresses proliferation of astroglial cells from rat diencephalon (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, an-

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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 follow are consistent with a role for the R_2 receptor in mediating neuromodulatory influences of ANF as well, although GC activation via the R_1 receptor also occurs. 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 responses to atrial natriuretic factor. As with most tissues, neuronal tissue responded to ANF with an elevated synthesis 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_{50} 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-rich cultures from the mouse brain (Simonnet et al., 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 cGMP were found to inhibit adrenergic neurotransmission, indicating the potential for cGMP to mediate ANF neuromodulatory effects (Drewett et al., 1989). Additional critical tests of this hypothesis involved the effects of PT, R_2-binding 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, the R_2 receptor-selective agonist, cANF, reduced evoked catecholamine release without affecting GC activity (Drewett et al., 1990). Both of these results dissociated 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), indicating that these conclusions are not limited to cultured PC12 cells. Finally, R_1 receptor antagonists lacked an effect on ANF neuromodulatory influences in the rabbit vas deferens (Trachte, 1993), leading to the rejection of the cGMP hypothesis of ANF action in peripheral neurons.

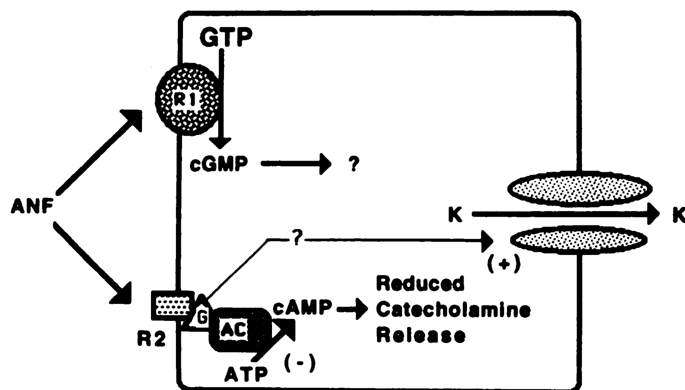

FIG. 9. Neuronal signal transduction pathways for ANF. ANF activates R_1 receptors to increase cGMP production. The significance of this effect in peripheral neurons is undetermined. ANF interacts with R_2 receptors to inhibit adenylyl cyclase (AC) by a pathway mediated by a G-protein (G). The reduction in cAMP appears to reduce the evoked secretion of neurotransmitter. The G-protein also may couple to potassium channels to increase the efflux of potassium from the cell (?). −, inhibitory effects; +, potentiating effects.

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) 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 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 by R_2 receptors in tissues associated with neurons in the 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 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 concentrations but by a mechanism involving an activation of a cGMP-dependent phosphodiesterase at high ANF concentrations (1 μM). PT blocked inhibitory effects of ANF and cANF on both adenylyl cyclase and neurotransmission (Drewett et al., 1990), but not stimulatory effects 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 (Drewett et al., 1992). These data are 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 is probably not valid for ANF actions in the central nervous system. Numerous studies have identified 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 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 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 which ANF affects neuro-

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transmitter release could include inhibitory effects on nicotinic 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 ANF with an inhibition of acetylcholine nicotinic currents (Borman et al., 1989). However, this inhibitory effect of ANF only occurred at concentrations exceeding 1 μM, a concentration five orders of magnitude higher 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 effect on potassium transport in rat brain astrocytes (Beaumont and Tan, 1990) or rat superior cervical ganglia (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 neuronal 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 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 prostaglandin 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 deferens. These data indicated no role for prostaglandins in mediating ANF effects in neuronal tissue. Other eicosanoids, such as leukotrienes or epoxygenases, have not been investigated as mediators of ANF actions thus far.

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 pathway appears to involve interactions with R_2 receptors leading to a suppression of both adenylyl cyclase and neurotransmitter release with a G-protein mediating the effect. Potassium channels also may be activated to suppress neurotransmission. These putative 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-Srivastava et al., 1991; Schiffrin et al., 1991). Thus, it is devoid of the R_1 receptor (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, suggesting that they represented R_2 receptors. However, some of the high molecular weight receptors were not converted to low 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 aggregation in response to thrombin and epinephrine (Loeb and Gear, 1988). The biological activity of ANF in the absence of R_1 receptors suggests that ANF acts via R_2 receptors in platelets. The only established intraplatelet action of ANF is a suppression of adenylyl cyclase activity, 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 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 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 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 of atrial natriuretic factor. ANF inhibited adenylyl cyclase with an EC_{50} of 100 to 500 pM (Anand-Srivastava et al., 1991), consistent with the ability of low concentrations of ANF to alter aggregatory responses to epinephrine and thrombin (Loeb and Gear, 1988). PT (5 μg/ml) or amiloride (100 μM) 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 present 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 factor actions

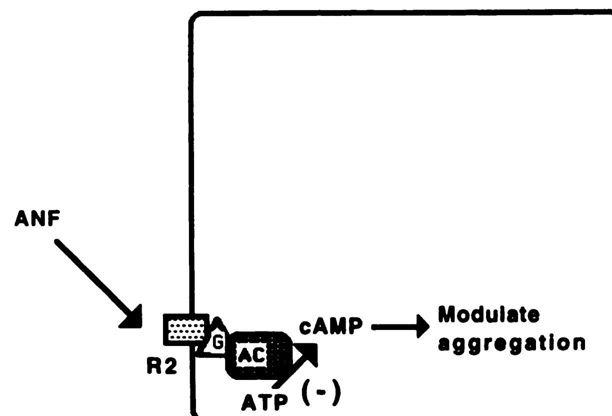

FIG. 10. Platelet signal transduction pathways for ANF. ANF activates only R_2 receptors in the platelet, resulting in an inhibition of adenylyl cyclase (AC) activity. This suppression involves a G-protein (G) and apparently mediates the proaggregatory effects of ANF. −, inhibitory effects.

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in platelets. ANF has a slight stimulatory effect on platelet aggregation despite a complete absence of R_1 receptors. ANF inhibits adenylyl cyclase activity with an EC_{50} 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 transduction 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

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 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 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 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), 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 plasma clearance of natriuretic peptides actually generated selective 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 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 concentrations of 10 μM. 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 to ANF with a half-maximal effect at 100 nM. Another similar agent, A71915 (1 μM; von Geldern et al., 1990), inhibited cGMP production in response to ANF (Trachte, 1993). Anantin, a product of the microorganism *Streptomycetes coerulescens* (Weber et al., 1991), consists of a cyclic region of eight amino acids with a nonapeptide tail (Wyss et al., 1991). Anantin has weak antagonistic activity, suppressing cGMP generation in response to ANF at antagonist concentrations exceeding 100 μM (Weber et al., 1991). Anantin also suppressed adenylyl cyclase activity, suggesting that it is an R_2 receptor agonist (Trachte, 1993). The most recently discovered 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 residues esterified with capronic acid. HS-142-1 reduced ^{125}I-ANF binding by 50% at 10 μM and suppressed cGMP generation in response to ANF with a half-maximal effect at 1.8 μg/ml (Ohyama et al., 1992), essentially eliminating cGMP production at 100 to 1000 μg/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 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 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 the R_1 receptor. Nevertheless, they currently provide the best 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 antagonistic activity. Abell et al. (1989) observed an ANF metabolite to be a partial agonist; it both stimulated 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 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 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 ANF in vascular smooth muscle. These modified cysteinyl 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 compounds provide no obvious advantages over the other antagonists mentioned above. However, if ANF metabolites function as ANF antagonists, then metabolite profiles could be extremely important in defining physiological activities of ANF. The metabolizing enzymes could serve a dual function of inactivating an agonist and generating an antagonist simultaneously. Pharmacologically, 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 natriuretic peptides are mediated by cGMP and the R_1 receptor (von Geldern et al., 1990; Sano et al., 1992). Similarly, adrenal effects of ANF on aldosterone synthesis were reversed by HS-142-1 (Oda

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et al., 1992) but not by R_2-selective binding agents (Sessions 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 more effectively, suggesting a greater affinity of HS-142–1 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; Elmquist and Trachte, 1992). Curiously, the hypotensive effect 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 actions 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 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 more selective and potent ANF receptor antagonists should improve dramatically this analysis of receptor involvement in ANF effects.

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 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 antagonists involves the use of R_2-selective binding agents in conditions of heart failure or hypertension to accentuate renal and cardiovascular effects of endogenous ANF. These R_2-binding agents often are combined with neutral endopeptidase inhibitors to elevate more 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. 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 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 levels; therefore, the effects of sodium loading, ANF, angiotensin II, progesterone and estrogen administration, 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 been obtained in renal, adrenal, and vascular tissues and platelets. In general, conditions elevating ANF concentrations tend to decrease ANF receptors.

B. Hypertension

The hypotensive effect of ANF is well established in 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; 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 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 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 elevated (Hirata et al., 1984; Garcia et al., 1985). On the other hand, atrial and plasma ANF levels are not significantly different in stroke-prone SHRs from those of 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 smooth muscle cells from SHRs as compared to WKY rats, whereas Resink et al. (1989) and Nakamura et al. (1988) confirmed the increased receptor density but found a decreased affinity for ANF in SHRs. In contrast, ANF effects on cGMP concentrations were diminished in vascular smooth muscle 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) and one-kidney, one-clip hypertensive rats (Schiffrin, 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 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 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 cGMP response to ANF suggests a selective reduction of R_1 receptors while R_2 receptors are up-regulated. Al-

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ternatively, postreceptor events could be modified by hypertension.

Pulmonary hypertension induced by a single injection of monocrotaline resulted in right ventricular hypertrophy with elevated ventricular levels of ANF. Cardiac and renal binding sites for ANF were decreased significantly by the monocrotaline as judged by autoradiography (Oehlenschlager et al., 1989). Unfortunately, signal transduction pathways were not tested for alterations.

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 effect on renal adenylyl cyclase activity was not studied. Renal ANF receptor number was reduced in 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., 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.

Glomerular ANF receptors increased in prehypertensive 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 and 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-clip hypertensive rats, whereas no change or decreased glomerular ANF 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 increased 2-fold 24 h after unclipping of one-kidney, one-clip hypertensive rats (Garcia et al., 1988). The unclipping was associated with a marked increase in plasma ANF concentrations. Interestingly, injected ANF decreased blood pressure in both one- and two-kidney forms of renal hypertension but only elevated urinary cGMP concentrations in the two-kidney form (Garcia et al., 1985). These results suggest differential changes in receptor number in the different forms of renal hypertension 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 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 established hypertension.

3. Adrenal. Adrenal diseases, such as aldosteronoma or Cushing adenoma, are associated with drastic changes 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 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 young and adult SHRs (Saavedra 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 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 Czarnecki, 1991). These data indicate the potential for alterations of ANF receptors in the central nervous 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 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, 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 production 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 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 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 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 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 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 pressures slightly higher than age-matched normotensive control rats, whereas no strain difference in ANF-binding sites was observed in either the choroid plexus or area postrema.

5. Platelets. Maximal ANF binding was unaltered in

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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), 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.

Similarly, fewer ANF receptors occurred in SHR spleen and thymus compared to tissues from normotensive WKY controls (Khurihara et al., 1987). However, the stimulation of cGMP production caused by ANF in isolated thymocytes or spleen cells from SHRs was unaltered (Khurihara et al., 1987). These data indicate that 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 to ANF is also attenuated 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 vasculature and a selective reduction of R_2 receptors in thymus and spleen. Platelet R_2 receptors were reduced also. Both R_1 and R_2 receptors were reduced in DOCA salt hypertensive kidneys and vasculature. Other models 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 eliminated in platelets. These data suggest either that vascular and cardiac ANF R_2 receptors are up-regulated in hypertension or that postreceptor signaling mechanisms are amplified in hypertension.

C. Congestive Heart Failure

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 (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 heart failure have not been studied in detail. Bianchi et al. (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 severe heart failure. Furthermore, Tsunoda et al. (1988) reported decreased ANF binding in rat inner renal medulla in proportion to the ventricular dysfunction in heart failure. Abassi et al. (1991) demonstrated increased ANF effects on cGMP concentrations in glomeruli from rats with chronic aortocaval fistulas, an experimental model of congestive heart failure, but did not examine ANF receptor binding in these rats. No change in the ANF receptor-binding sites was observed in zona glomerulosa (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-regulated in heart failure. A reduction of ANF receptors 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 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 show any difference in the number of ANF platelet receptors or their affinity for ANF in patients with congestive heart 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 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 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 Natriuretic Factor Receptor Regulation

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 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 (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 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 decrease 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 additional maneuvers to alter ANF concentrations in plasma. Dehydration reduced plasma ANF concentrations (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 receptors (Kollenda et al., 1990). Alternatively, sodium loading increased plasma ANF concentrations and suppressed ANF binding to glomerular receptors (Ball-

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erman et al., 1985; Gauquelin et al., 1988; Kollenda et 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 R_2 receptors (Katafuchi et al., 1992). Sodium deprivation increased 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 as ANF concentrations increase in plasma. The mechanism of the homologous regulation is unknown, but stable cGMP analogs selectively reduce ANF R_2 receptors in bovine endothelial cells (Kato et al., 1991), and stable cAMP analogs increase ANF binding to neuroblastoma receptors (Delporte et al., 1991). Because ANF both elevates cGMP concentrations and reduces cAMP concentrations, either mechanism could function in the homologous regulation of ANF receptors.

In addition to the homologous regulation of ANF receptors 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 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. (1988) actually observed an increased production of 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 unaffected or only slightly reduced in number. Gauquelin et al. (1991) confirmed this conclusion directly by observing a selective reduction of ANF R_2 receptors in the 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 estrogen 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 ANF-binding sites and eliminated binding to the R_1 receptor (Potvin and Varma, 1991). These results suggest that 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 desensitization 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 involves an apparently selective reduction in ANF R_2 receptors, whereas progesterone selectively down-regulates ANF R_1 receptors. Finally, the heterologous sensitization of ANF responses by estrogen involved an apparent up-regulation of both general types of ANF receptors. The mechanisms accounting for alterations in receptor regulation have not been elucidated.

VII. General Conclusions

Much of the data presented in this review is summarized 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 requires ANF concentrations of two to three orders of magnitude greater to achieve half-maximal activation. The cardiovascular and pulmonary effects of ANF correlate well with GC activation, although the cardiovascular effects have 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 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 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 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. 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 suggest a prominent role of ANF receptors coupled to adenylyl cyclase in the majority of tissues studied. The differential potencies of

TABLE 1

*EC_{50} for various ANF responses at the level of the organ, GC, and adenylyl cyclase**

Organ	EC_{50} (pM)		
	Response	GC	Adenylyl cyclase
Kidney (natriuresis)	20	10,000	500
Adrenal	30	100,000	10
Vasculature	30,000	30,000	500
Cardiac	>10,000	>100,000	500
Pulmonary	4,200	>30,000	5,000
Endocrine			
ACTH	300	5,000	100
Antidiuretic hormone	?	?	10
Thyroglobulin	100	–	100
Progesterone	100	6,000	100
Testosterone	6,000	6,000	100
Renin	10	100,000	<100
Neurons	35	10,000	21
Platelet	10	–	300

* The numbers represent reported concentrations of ANF producing a half-maximal response (EC_{50}) in a measured variable such as a whole organ response, GC, or adenylyl cyclase inhibition. References for the values presented are provided in the text under the section for each organ. –, no response; ?, no data concerning the response indicated.

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ANF in stimulating GC activity and tissue-specific responses 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 receptors and biological responses. Studies with antagonists 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 GC activation. ANF effects on the adrenal, kidney, and potentially the lung appear at this time to be mediated by activating the R_1 receptor to enhance cGMP production. The signal transduction pathway(s) has not been defined in most tissues, but potential mechanisms other than GC activation could involve the following: (*a*) suppression of adenylyl cyclase, (*b*) modulation of phospholipase C activity, or (*c*) alteration of ion fluxes. The inhibition of adenylyl cyclase and an activation of phospholipase 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-proteins to suppress adenylyl cyclase and mediates neuronal and 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 not known and further experiments with the novel ANF 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 pathway 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 the actual sequence of events leading to biological responses 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 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 cannot account for biological actions of ANF.

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