Abstract—Besides soluble guanylyl cyclase (GC), the receptor for NO, there are at least seven plasma membrane enzymes that synthesize the second-messenger cGMP. All membrane GCs (GC-A through GC-G) share a basic topology, which consists of an extracellular ligand binding domain, a short transmembrane region, and an intracellular domain that contains the catalytic (GC) region. Although the presence of the extracellular domain suggests that all these enzymes function as receptors, specific ligands have been identified for only three of them (GC-A through GC-C). GC-A mediates the endocrine effects of atrial and B-type natriuretic peptides regulating arterial blood pressure and volume homeostasis and also local antihypertrophic actions in the heart. GC-B is a specific receptor for C-type natriuretic peptide, having more of a paracrine function in vascular regeneration and endochondral ossification. GC-C mediates the effects of guanylin and uroguanylin on intestinal electrolyte and water transport and on epithelial cell growth and differentiation. GC-E and GC-F are colocalized within the same photoreceptor cells of the retina and have an important role in phototransduction. Finally, the functions of GC-D (located in the olfactory neuroepithelium) and GC-G (expressed in highest amounts in lung, intestine, and skeletal muscle) are completely unknown. This review discusses the structure and functions of membrane GCs, with special emphasis on the physiological endocrine and cardiac functions of GC-A, the regulation of hormone-dependent GC-A activity, and the relevance of alterations of the atrial natriuretic peptide/GC-A system to cardiovascular diseases. (Circ Res. 2003;93:700-709.)

Key Words: guanylyl cyclase receptors
surprisingly, targeted disruption of the murine genes for CNP or cGMP-dependent protein kinase II resulted in severe dwarfism as a result of impaired endochondral ossification, demonstrating that the CNP/GC-B system has an essential role in the local stimulation of growth plate chondrocyte proliferation and differentiation through cGMP-mediated activation of PKG II.9,10 GC-C, which contains an extracellular domain with limited sequence similarity to the above two isoforms, is mainly expressed in the intestinal epithelium and represents the receptor for bacterial heat-stable enterotoxins and for two endogenous intestinal peptides, guanylin and uroguanylin.11-13 It mediates the local effects of these peptides on intestinal electrolyte and water transport and epithelial cell growth and differentiation14-16 and possibly also the renal diuretic/natriuretic responses to uroguanylin.17 Additionally, a role of GC-C in liver regeneration has been suggested.18 However, disruption of the GC-C gene in mice has not resulted in a unique phenotype.19 Of the four orphan GC receptors, three are expressed in sensory tissues, GC-E is expressed in the eye and the pineal gland, whereas GC-F expression is confined to the retina.20-22 In the retina, both cyclases are colocalized within the same photoreceptor cells, suggesting that they are involved in the phototransduction cascade.20 Indeed, disruption of the GC-E gene in mice demonstrated an important role in both the survival of cone photoreceptors as well as in the maintenance of vision.23 The expression of GC-D is restricted to a small population of neurons within a single topographic zone in the olfactory neuroepithelium; it may function directly in odor recognition or in modulating the sensitivity of a subpopulation of sensory neurons to specific odors.24,25 GC-G is the last member of the membrane GC form to be identified.26 No other mammalian transmembrane GCs are predicted on the basis of gene sequence repositories. In contrast to the other orphan receptor GCs, GC-G has a broad tissue distribution in the rat, including the lung, intestine, kidney, and skeletal muscle, raising the possibility that there is another yet-to-be-discovered family of cGMP-generating ligands.26

The intracellular region of all membrane GCs consists of a juxtamembraneous protein kinase–homology domain (KHD), an amphipathic α-helical or hinge region, and a C-terminal cyclase–homology catalytic domain (Figure 1).27,29 The function of the KHD is incompletely understood. Although it binds ATP and contains many residues conserved in the catalytic domain of protein kinases, kinase activity has not been detected. It modulates the enzyme activity of the C-terminal cyclase–homology catalytic domain in27,29-31 and may act as a docking site for the direct association of membrane GCs with other proteins, such as protein phosphatase PP5 and HSP90 (GC-A)32 or the intracellular Ca²⁺-binding proteins GCAP-1 and GCAP-2 that regulate GC-E.
ANP, BNP, and Their Receptor, GC-A

In 1981, de Bold et al. published a landmark study showing that rat atrial extracts contain a potent diuretic and natriuretic factor, thereby establishing for the first time the connection between the heart and the kidney. This observation led to the isolation of ANP from cardiac tissue. Subsequently, two factors remain unknown.41

Interestingly, a recent report has shown, for the first time, tissue-specific differences in glycosylation of residues located at the N-terminal end of the extracellular domain.40 Glycosylation results in heterogeneity in the size of GC receptors, but the functional consequences remain controversial. In studies with cells overexpressing GC-A, GC-B, or GC-C, removal of carbohydrate residues with endoglycosidase prevented or reduced ligand binding, indicating that glycosylation plays a role in ligand binding. Others suggested that glycosylation functions in folding and/or transport of particulate GCs to the cell membrane.40 Interestingly, a recent report has shown, for the first time, tissue-specific differences in glycosylation of GC-A, namely, the occurrence of a specific, less glycosylated GC-A subtype in the brain; however, the functional implications remain unknown.41

ANP, BNP, and Their Receptor, GC-A

In 1981, de Bold et al. published a landmark study showing that rat atrial extracts contain a potent diuretic and natriuretic factor, thereby establishing for the first time the connection between the heart and the kidney. This observation led to the isolation of ANP from cardiac tissue. Subsequently, two factors have been referred to as NPs, even though they possess a higher potency of human ANP compared with human BNP,49 The plasma half-life of ANP and BNP in humans is 2 to 5 minutes, and elimination occurs by enzymatic metabolism, by cellular internalization by specific receptors, and by urinary excretion. The main triggering factor for the cardiac release/production of ANP and BNP is an increase in wall stretch and/or pressure,46 but neurohumoral factors such as glucocorticoids, catecholamines, arginine vasopressin, angiotensin II (Ang II), and endothelin may also play a role.47 Cardiac ANP and BNP are released into the bloodstream, activate the GC-A receptor, which is expressed in a variety of tissues, and thereby modulate blood pressure/volume (see Table 2). Competitive binding against125I-human ANP on human GC-A established dissociation constants (Kd) in the range of 1.6 pM for ANP and 7.3 pM for BNP.48 The plasma half-life of ANP and BNP in humans is 2 to 5 minutes, and elimination occurs by enzyme metabolism, by cellular internalization by specific clearance receptors (NP receptor-C [NPR-C]; see next section), and (to a limited extent) by urinary excretion. The degradation enzyme is a neutral endopeptidase (NEP 24.11) found in the brush border of the proximal convoluted tubule and also found in the lungs, intestine, seminal vesicles, and neutrophils.49

The important role of the ANP/GC-A system in the physiological regulation of arterial blood pressure/volume has been emphasized in different genetic mouse models. Targeted deletion of the peptide (ANP<sup>-/-</sup>) or its receptor (GC-A<sup>-/-</sup>) leads to severe, chronic arterial hypertension, cardiac hypertrophy, and sudden death.51–54 (Figure 2). In contrast, overexpression of ANP or GC-A elicits a “dose-dependent” fall in arterial blood pressure.55–56 Intriguingly, although BNP and ANP appear to signal through the same receptor, mice without BNP exhibit a different phenotype...
than do ANP-deficient mice. Whereas BNP-deficient mice do not have hypertension or cardiac hypertrophy, they are susceptible to cardiac fibrosis. Thus, gene-deletion experiments suggest that ANP and BNP have distinct physiological roles. Under physiological conditions (in the absence of cardiac pressure or volume overload), the peripheral circulating plasma concentrations of BNP are much lower than the concentrations of ANP. Also, as mentioned above, the affinity of BNP for binding to GC-A is lower than that for ANP. Accordingly, the potency for vasorelaxation is also markedly less. Thus, it is possible that BNP (which is constitutively expressed in cardiomyocytes) mainly acts as a local paracrine antifibrotic factor within the heart (ie, because fibroblasts express relatively high levels of both GC-A and GC-B). However, the following observations suggest that BNP might activate another so-far-unknown receptor: (1) Whereas the amino acid sequences of ANP and CNP are conserved among animal species, the sequence of BNP is highly different between humans, rats, and mice. (2) Some tissues of GC-A−/− mice (ie, the testis and adrenal gland) retain significant high-affinity cGMP responses to BNP. This residual response cannot be accounted for by GC-B or any other known mammalian membrane GC, suggesting that an as-yet-unidentified receptor may exist that specifically recognizes BNP.

**Endocrine Actions of the ANP/GC-A System Cooperate in Acute and Chronic Regulation of Blood Pressure and Blood Volume**

As depicted in Table 1, the GC-A receptor is expressed in many different organs and cell types and mediates a variety of central and peripheral actions of ANP, which probably all contribute to lower blood pressure (see Table 2). In particular, the renal and sympatholytic actions of ANP probably have a major role in the hypotensive actions of the peptide. In contrast, the relevance of the direct vasodilating ANP effect is controversial, because very variable GC-A levels are expressed in different vascular beds. To characterize this issue, in a recent study, we selectively deleted GC-A in vascular smooth muscle cells (SMC GC-A KO) using Cre-lox technology. Surprisingly, in spite of the clear abolition of the direct vasorelaxing effects of ANP, the resting arterial blood pressure of conscious SMC GC-A KO mice was completely normal (Figure 3A). However, these mice reacted to acute vascular volume expansion with a prompt and marked hypertension, which was never observed in control mice expressing normal GC-A levels (Figure 3B). On the basis of these observations, we suggest that vascular GC-A is dispensable in the chronic but crucial in the acute moderation of blood pressure by ANP.

**Local Cardiac Functions of the ANP/GC-A System**

During chronic hemodynamic overload, the expression levels of ANP and especially BNP in the cardiac ventricles significantly increase. NPs in this situation may act not only as circulating endocrine factors to maintain arterial blood pressure and volume homeostasis but also as local antihypertrophic (ANP) and antifibrotic (BNP) cardiac factors. For example, ANP inhibits growth and proliferation of cultured cardiac myocytes and fibroblasts via GC-A. Also, targeted overexpression of GC-A in cardiomyocytes exerts antihypertrophic effects in vivo. Conversely, mice with a global genetic disruption of the GC-A gene (GC-A−/− mice) not only have increased systemic blood pressure but also display a marked cardiac hypertrophy that is disproportionate to their increased blood pressure and resistant to antihypertensive medication. To test whether ANP locally modulates cardiomyocyte growth and contractility in vivo, we generated mice with selective deletion of GC-A in cardiomyocytes. All endocrine blood pressure and volume-regulating effects of ANP are preserved. Our studies in these mice demonstrate that the ANP/GC-A system indeed plays an autocrine/paracrine role in the heart, which inhibits cardiomyocyte growth and stimulates diastolic relaxation. Furthermore, our results corroborate published studies indicating that ANP inhibits its own synthesis and release via GC-A/cGMP as a negative-feedback mechanism (see Figure 4).
In summary, these observations from various genetic mouse models with global or conditional cell-restricted deletion of GC-A emphasize the importance of the NP/GC-A/cGMP system in the endocrine acute and chronic regulation of arterial blood pressure and blood volume and also its local actions on cardiac growth, remodeling, and contractile functions.

Regulation of ANP/BNP-Dependent GC-A Activity

In some forms of arterial hypertension and as one of the earliest and pathognomonic events in cardiac hypertrophy and insufficiency, the cardiac synthesis and release of ANP and BNP is markedly enhanced, but the GC-A–mediated effects of the NPs are clearly diminished, indicating a receptor or postreceptor defect of GC-A (see next section). Thus, from a clinical and pathophysiological perspective, identifying the specific biochemical and genetic mechanisms involved in the downregulation of GC-A activity has important implications. The present understanding of the regulation of hormone-dependent GC-A activity, derived mainly from in vitro studies using cultured cell lines, is incomplete. Five different mechanisms have been implicated: (1) sequestration of NPs by the clearance receptor (NPR-C), (2) phosphorylation and dephosphorylation of GC-A, (3) receptor internalization, (4) regulation of GC-A signaling activity by extracellular toxicity, and (5) regulation of GC-A at the level of gene transcription.

Sequestration of NPs by NPR-C

Besides GC-A and GC-B, a third specific receptor subtype which triggers the effects of NPs is the C-receptor (NPR-C), a clearance receptor that mainly serves for cellular internalization and degradation of NPs. In many tissues, NPR-C is the most abundant of the NP receptors, and it binds ANP, BNP, and CNP with relatively similar affinities. The extracellular domain shares a high amino acid sequence homology with GC-A and GC-B. However, it has only 37 intracellular amino acids and does not possess GC activity. It may participate in mediating some of the cellular actions of NPs via coupling to Gi proteins and negative modulation of adenyl cyclase activity. However, within the cardiovascular system, the primary action of the NPR-C seems to be the modulation of circulating and local NP concentrations that are available to bind GC-A and GC-B. Hence, changes in GC-A–mediated responses to ANP could theoretically result from changes in the expression levels of NPR-C. Indeed, an upregulation of NPR-C has been described in at least two clinical settings with blunted responses to exogenous ANP: (1) in obesity-related hypertension and (2) in patients with chronic heart failure (see next section). Vice versa, it is conceivable that a downregulation of NPR-C enhances the effects of ANP under specific physiological conditions. For instance, continued exposure of cultured endothelial cells to increased NaCl concentrations resulted in a dramatic loss of NPR-C, which was accompanied with a marked potentiation of ANP/GC-A–induced cGMP accumulation. Although not confirmed in vivo, these observations raise the possibility that changes in extracellular toxicity, in particular, in the kidney, could modulate NPR-C expression levels and thereby the interaction of NPs with GC-A.

Phosphorylation and Dephosphorylation of GC-A

Biochemical studies in transfected GC-A–overexpressing cells showed that phosphorylation of GC-A within the KHD is essential for its activation process. In turn, desensitization and/or inactivation of GC-A probably involves ANP-dependent dephosphorylation of the KHD. On these experiments, the groups of Garbers (Foster et al89) and Potter (Potter and Hunter) constructed a working model of the process of ANP- and BNP-dependent activation and deactivation of GC-A, which is illustrated in Figure 5 (see comprehensive reviews99,99). In the absence of NP, the receptor is highly phosphorylated on at least six amino acid residues located within the KHD, and its GC activity is repressed. On NP binding, a conformational change occurs that facilitates...
three subsequent events. First, the normal inhibitory effect that the KHD has on catalytic activity is relieved. Second, an increased dissociation rate decreases the affinity of the extracellular domain of GC-A for ANP and BNP. Third, a conformational change in the KHD may expose the phosphorylated residues to a specific protein phosphatase. The resulting dephosphorylated receptor is unresponsive to further hormonal stimulation. Unfortunately, the specific kinase(s) and phosphatase(s) involved in the phosphorylation (sensitization) and dephosphorylation (desensitization) of GC-A remain unknown. Notably, a very recent study suggested that cGMP-dependent protein kinase type I (PKG I) might be involved. The authors showed that ANP stimulation of GC-A recruits PKG I to the plasma membrane and simultaneously promotes PKG I activation via ANP/GC-A-generated cGMP. Hence, an ANP-stimulated GC-A–PKG association may represent a novel mechanism for both compartmentation of cGMP-mediated signaling and regulation of receptor sensitivity.

NP-dependent activation of GC-A can be reduced not only by chronic exposure to NPs (homologous desensitization) but also by exposure to agents other than NPs (heterologous desensitization). It has been shown in cell culture systems that Ang II and endothelin decrease the responsiveness of GC-A. This is probably mediated by a protein kinase C–induced dephosphorylation of GC-A. Whether the protein kinase C–dependent dephosphorylation of GC-A results from activation of a protein phosphatase or the inhibition of a protein kinase is not known. However, on the basis of these observations, it is conceivable that increased local concentrations of endothelin, Ang II, or other growth factors such as platelet-derived growth factor and fibroblast growth factor interfere with NP/GC-A signaling under certain pathological conditions in vivo.

Receptor Internalization

Another process that may account for ANP-dependent down-regulation of GC-A is the internalization of ligand-receptor complexes. So far, this phenomenon has been shown only in stably transfected 293 cells expressing a very high density of recombinant GC-A receptors. Most of the internalized ANP and GC-A was degraded. But a portion of the internalized ligand-receptor complexes dissociated intracellularly, escaping the lysosomal degradative pathway and recycling back to the plasma membrane.

Regulation of GC-A Signaling Activity by Extracellular Tonicity

Studies in various cultured cell types have shown that hyperosmolality acutely inhibits GC-A whereas chronic exposure results in elevated GC-A activity. Chen and Gardner demonstrated in primary cultures of rat inner medullary collecting duct cells that both the expression and cGMP-synthesizing activity of GC-A are stimulated by increased extracellular tonicity and that this process seems to involve the activity of p38 mitogen-activated protein kinase. Thus, changes in extracellular tonicity, in particular in the kidney, might modulate the diuretic/natriuretic responses to ANP at the level of the expression and also the sensitivity of both GC-A and NPR-C.

Regulation of GC-A at the Level of Gene Transcription

In addition to these short-term posttranscriptional mechanisms, regulation of GC-A gene transcription also plays a role in the regulation of receptor activity. Several studies have shown that GC-A mRNA and receptor number are reduced in cultured cells stimulated for a prolonged period of time with ANP. Functional analysis of the GC-A gene promoter revealed a putative cGMP-responsive element, suggesting that the ANP-dependent downregulation of GC-A mRNA is cGMP dependent. However, other studies could not reproduce this result.

Two recent in vitro studies have indicated that GC-A gene transcription might be inhibited by Ang II and endothelin. It has been suggested that local endothelin production mediates the effects of changes in extracellular tonicity on GC-A expression in the kidney. Again, the relevance of these experiments to the in vivo situation needs to be confirmed.

In summary, the regulation of hormone-dependent GC-A activity is complex and surely involves different processes at both the posttranscriptional and transcriptional level. Which of these processes accounts for the termination and physiological as well as pathophysiological modulation of effects of NP in vivo remains an open and important question. It is also likely that different types of tissues and cells rely on different mechanisms to regulate GC-A activity.

Relevance of Alterations in the ANP/GC-A System to Cardiovascular Diseases

The findings summarized in the present review indicate that the ANP/GC-A system is not only critical in the regulation of blood pressure/volume but also locally involved in moderating the cardiac growth response to hypertrophic stimuli, suggesting that some forms of hypertension and/or cardiac hypertrophy in humans are explained in part by inappropriate secretion of ANP or diminished expression and/or responsiveness of GC-A.

Quantitative alterations in gene expression governed by polymorphisms in noncoding sequences seem to contribute to the genetic susceptibility to complex diseases, such as essential hypertension (EH) and cardiac hypertrophy. Many of such variations have been published within the human genes for ANP, GC-A, and NPR-C, and some interesting examples will be mentioned here. An HpaII-polymorphism in intron 2 of the ANP gene is more frequently observed in salt-sensitive hypertensive African Americans (50%) compared with normotensive subjects (3%) or with white patients with EH (15%). For GC-A, the association between a functional deletion mutation in the promoter region of the human GC-A gene, decreased receptor expression, and EH as well as ventricular hypertrophy has been shown in the Japanese population but not in European patients with EH. Knowles et al recently identified 10 additional polymorphic sites in the noncoding sequence of GC-A and, by transient expression analysis, demonstrated that they can alter...
GC-A expression as much as 2-fold. Last, a promoter variant
of the NPR-C gene has been shown to be associated with
lower ANP levels and higher blood pressure in obese
hypertensives.113

Apart from these genetic variations, functional alterations
of ANP or GC-A might also be involved in some forms of
EH. Inappropriate ANP secretion was reported in salt-
sensitive hypertensive black patients manifesting a paradox-
ical decrease in ANP secretion under conditions of high salt
intake.114 On the other hand, blunted vasodilating and diuret-
ic/natriuretic responses to exogenous ANP have been
reported in EH,111 in Cushing’s disease,115 and in hypertensive
obese patients.83 The latter group has been shown to exhibit
a lower GC-A/NPR-C mRNA ratio in adipose tissue as well
as diminished plasma ANP levels, suggesting enhanced
sequestration and clearance of ANP by NPR-C in adipocytes.

Patients with cardiac hypertrophy and/or congestive heart
failure (CHF) have elevated plasma levels of ANP and BNP,
with these peptide levels being highly related to the severity
of the disease.116 However, the cardiovascular and cGMP
responses to exogenous ANP or BNP are markedly attenu-
ated, indicating a downregulation or impaired receptor or
postreceptor responsiveness of GC-A (as demonstrated by
Hirooka et al117 and many others). Some studies have
suggested that the decreased biological responses to ANP
are partly due to an upregulation of NPR-C receptors in periph-
eral tissues, leading to increased sequestration and degrada-
tion of ANP.84 Other studies have even indicated a down-
regulation of NPR-C receptors.118 Thus, the mechanisms
accounting for a diminished NP-dependent stimulation of
GC-A in patients with severe CHF are poorly understood.
The aforementioned processes of downregulation and/or ho-
omologous/heterologous desensitization of GC-A may be
involved. Using various methodologies, such as “real-time”
quantitative reverse transcription–polymerase chain reaction
and stimulation of cGMP production, we recently determined
the level of transcripts of both GC-A and NPR-C as well as
ANP-stimulated GC-A activity in explanted hearts from CHF
patients subjected to cardiac transplantation. Compared with
“nonfailing” hearts, the cardiac GC-A/NPR-C mRNA ratios and
ANP-dependent GC-A activities were significantly de-
creased in both ischemic and dilated cardiomyopathy (au-
thor’s unpublished observations, 2003). Our studies in mice
with cardiomyocyte-restricted deletion of GC-A indicate that
an inhibition of the local cardiac ANP effects might accelera-
te the progression of cardiac hypertrophy and insufficiency79
and support further work to assess the importance of the
ANP/GC-A system in human cardiovascular diseases and, in
particular, its systemic but also local cardiac alterations.

Future Directions
The findings described in the present review open several
new directions for study. First, they demonstrate the potential
utility and power of the Cre-lox approach in dissecting out the
tissue-specific functions of ANP and GC-A. This is important
because the GC-A receptor is widely distributed in many
different cell types and mediates the effects of ANP and BNP
in many biological functions. In addition to its role in blood
pressure control, recent reports have indicated that GC-A
might be critical in the regulation of other completely differ-
ent physiological processes, such as cellular growth in the
brain and kidney,60 angiogenesis,119 liver regeneration,120
or even lipolysis in adipose tissue.121

Second, an important and still unresolved issue is whether
cGMP production by different membrane-bound versus sol-
able GCs is compartmentalized. For instance, it has been
shown that GC-A, but not soluble GC, has potent effects on
plasma membrane control of the calcium ATPase pump.122
Interestingly, a very recent study has demonstrated that
ANP/GC-A, but not NO/soluble GC, stimulates the translo-
cation of PKG I to the plasma membrane.82 Hence, the
mechanisms for compartmentation of cGMP-mediated sig-
naling within different cell types remain an intriguing issue.

Third, the present review also demonstrates that the pro-
cesses regulating GC-A activity and responsiveness in vivo
are largely unknown. In view of the many clinical studies
showing that in some forms of hypertension and in all forms
of cardiac insufficiency the GC-A–mediated effects of ANP
and BNP are greatly diminished, clarification of the respon-
sible GC-A receptor or postreceptor defects and identification
of proteins that regulate the activity of GC-A may have
important pathophysiological implications. This could lead
to the development of drugs that could revolutionize the treat-
ment of some forms of cardiac disease. Even more, because
synthetic BNP (Nesiritide) and ANP (Anaritide) have been
proven to be clinically highly beneficial in the acute treatment
of CHF,123 an understanding of the mechanisms involved in
the ligand-dependent desensitization of GC-A might also be
important from this therapeutical perspective.

As a final point, additional work may uncover other
receptor GCs. Although seven have been identified in mam-
mals, 29 genes encode putative GCs in Caenorhabditis
elegans, even though the nematode genome is only 1/30 that
of the mammalian genome.124 Clearly, there is an exciting
field of physiological and putative clinical importance with
more questions than answers.

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