Atrial Natriuretic Peptide: Regulator of Chronic Arterial Blood Pressure

Luis Gabriel Melo, Stephen C. Pang, and Uwe Ackermann

Recent findings in atrial natriuretic peptide (ANP) transgenic and gene knockout mouse models uncovered a tonic vasodilatory effect of this hormone that contributes to chronic blood pressure homeostasis. With elevated salt intake, ANP-mediated antagonism of the renin-angiotensin system is essential for blood pressure constancy, suggesting that a deficiency in ANP activity may underlie the etiology of sodium-retaining disorders.

Atrial natriuretic peptide (ANP) is the most abundant of a family of at least three structurally and functionally related peptide hormones that exert widespread effects on cardiovascular and renal function. Under normal hemodynamic conditions, ANP is predominantly synthesized, stored, and secreted in a regulated fashion by modified myocytes of the cardiac atria. However, in pathophysiological conditions of hemodynamic overload, such as in congestive heart failure, ventricular synthesis of the peptide, which is negligible under normal conditions, is reactivated and contributes significantly to the circulating pool of the peptide. ANP is also synthesized in lesser amounts in some peripheral tissues, in the vasculature, and in central nervous structures, where the peptide may exert autocrine and paracrine modulatory effects on autonomic nervous function and neurohormone release. The biologically active 28-amino acid peptide is cleaved from the carboxy end of a prohormone and released in response to stretch of the secretory myocytes, consequent to an increase in central venous pressure. On release, ANP exerts its biological effects by interacting with a membrane-bound guanylate cyclase-linked receptor (NPR-A) and subsequently stimulating intracellular cGMP synthesis. A second receptor subtype (NPR-C) is the preponderant ANP binding site in most tissues and is primarily involved in clearance of the peptide from the circulation (for a comprehensive review, see Ref. 2).

When administered acutely, ANP elicits potent and short-lasting natriuresis and diuresis and systemic hypotension in a wide variety of mammalian and nonmammalian species (2). The renal excretory effects of the hormone are due, in part, to direct inhibition of tubular sodium reabsorption in the inner medullary collecting duct and to inhibition of salt- and water-conserving mechanisms, such as the sympathetic nervous system, the renin-angiotensin (ANG)-aldosterone hormonal axis, and antidiuretic hormone. The acute hypotensive effect of ANP, on the other hand, is mediated primarily by a renal-independent reduction in cardiac output, consequent to a decrease in intravascular volume. The hypotension is further compounded by attenuation of autonomic reflex compensatory increases in heart rate and vascular resistance. (2).

Despite the extensive characterization of acute cardiovascular/renal actions of ANP, progress in elucidating a role for this hormone in chronic regulation of blood pressure and fluid and electrolyte balance was hampered by the lack of suitable experimental models of ANP-induced disease or selective pharmacological receptor antagonists. These difficulties have been overcome, in part, with the introduction of genetic mouse models expressing life-long alterations in ANP bioactivity. Recent work in these murine models provides evidence that ANP contributes to long-term maintenance of blood pressure constancy and may play an essential role in mediating the cardiovascular and renal adaptations to chronically elevated dietary salt intake. This review summarizes and evaluates the current evidence for a role of ANP in chronic regulation of arterial pressure and fluid-electrolyte balance.

ANP and chronic regulation of blood pressure

The earliest evidence that ANP may participate in chronic regulation of arterial blood pressure (ABP) originated with the observation that prolonged infusion (3–7 days) of ANP into conscious animals, resulting in plasma levels of the hormone in the high physiological-to-pathophysiological range, causes a sustained reduction in ABP of ~15–20 mmHg (4). Furthermore, the hypotension occurs in the absence of detectable changes in cardiac output, intravascular volume, or absolute...
renal salt and fluid excretion. This indicates that the chronic hypotensive effect of ANP, in contrast to its acute hypotensive effect, is primarily mediated by a reduction in peripheral vascular resistance. This was directly confirmed by measurement of systemic and regional hemodynamics with radiolabeled microspheres, which showed that the chronic ANP-dependent hypotension is mediated by a decrease in vascular resistance in most regional vascular beds (3). These observations have recently been corroborated in genetic mouse models of ANP activity. Transgenic mice constitutively overexpressing a transthrytin-ANP fusion gene (TTR-ANP) in the liver are markedly hypotensive (~25–30 mmHg) relative to their genetically-matched nontransgenic (NT) counterparts, in association with a life-long 8- to 10-fold elevation in basal plasma ANP concentration (1). As expected, the hypotension in the TTR-ANP mice is accompanied by a reduction in total peripheral resistance, in association with vasodilation in most vascular beds (1). In contrast, knockout mice in which synthesis of ANP (6) or its biologically active NPR-A receptor (8, 14) are prevented by targeted homologous disruption of the native genes (–/– ANP mice) develop chronic hypertension in relation to their normotensive wild-type (+/+ ANP) siblings. The hypertension in the –/– ANP mice is associated with an elevation in baseline total peripheral vascular resistance (9) and is accompanied by marked left ventricular hypertrophy (6), which probably develops as compensation for increased ventricular afterload. Thus these findings indicate that ANP exerts a tonic hypotensive effect that is, at least in part, mediated by vasodilation of the resistance vasculature. In the absence of ANP activity, a state of hypertension ensues and is not compensated by other cardiovascular regulatory mechanisms.

The mechanism by which ANP exerts its chronic vasodilatory action in the resistance vasculature has only recently begun to be investigated. Although ANP, at high concentration, is capable of directly relaxing preconstricted large arteries via NPR-A receptor-mediated stimulation of cGMP in vascular smooth muscle, the relative scarcity of these receptors in the resistance vasculature would preclude a direct role for this pathway in ANP-mediated dilation of the microvasculature. In fact, with the possible exception of the renal vascular bed, resistance vessels are insensitive to direct relaxation by ANP (for review, see Ref. 2). These findings imply that the chronic vasodilatory effect of ANP in the resistance vasculature may be mediated by intermediary tonic vasoeffector mechanisms, whose actions would then bring about vasodilation and resultant hypotension. In this regard, ANP has been shown to exert a generalized sympatholytic effect, at least when administered acutely (for review, see Ref. 7). This suggests that ANP-mediated attenuation of cardiovascular sympathetic tone, if tonically active, could be the effector mechanism for the chronic vasodilatory action of this hormone. Indeed, there is indirect evidence that ANP may chronically attenuate cardiovascular sympathetic tone. For example, the hypotensive effect of ANP is exacerbated in animal models characterized by elevated basal sympathetic tone, such as the spontaneously hypertensive rat, and ANP significantly attenuates the hypertension caused by chronic infusion of norepinephrine (2, 7).

We recently employed TTR-ANP and –/– ANP mice to determine whether alterations in cardiovascular sympathetic tone may underlie the chronic hypotensive effect of ANP. These genetic mouse models of ANP overproduction and underproduction are ideally suited for these studies, insofar as the gene manipulations manifest the predicted cardiovascular phenotypes (i.e., hypotension in TTR-ANP mice and hypertension in –/– ANP mice) without triggering discernible compensatory adjustments by other cardiovascular regulatory systems. Total basal plasma catecholamine concentration and the magnitude of the hypotensive and negative chronotropic responses to acute autonomic ganglionic blockade were measured as indirect indices of underlying cardiovascular sympathetic tone (9, 11) in the different genotypes. We predicted that if the sympathoinhibitory activity of ANP were tonically active, then the absence of this antagonism in the –/– ANP mice would be associated with an elevation in basal cardiovascular sympathetic tone and hypertension, whereas the chronically elevated plasma ANP activity in the TTR-ANP mice would be accompanied by attenuation of sympathetic tone and hypotension. The effect of ganglionic blockade on ABP in the TTR-ANP and –/– ANP mice and their respective wild-type controls (NT and +/+ ANP) is shown in Fig. 1. As expected, ganglionic blockade reduces ABP and heart rate in all genotypes, thereby confirming the contribution of sympathetic tone to basal hemodynamics. However, the hypotensive response is quantitatively smaller in the TTR-ANP mice (Fig. 1A) and greater in the –/– ANP mice (Fig. 1B) than in their respective wild-type controls (11). Furthermore, the differences in the hypotensive response to ganglionic blockade are paralleled by directional differences in basal total plasma catecholamine concentration (11). In addition, the exaggerated depressor response of –/– ANP mice to ganglionic blockade is accompanied by a reduction in calculated total peripheral resistance, without any apparent differences in cardiac performance between mutant and wild-type mice (9). Thus tonic cardiovascular sympathetic tone is inversely related to the chronic level of endogenous ANP activity, suggesting that the chronic hypotensive effect of ANP is, at least in part, dependent on attenuation of sympathetic tone to the resistance vasculature. Indeed, the genotype-dependent differences in ABP between mutant and control mice can be abrogated by ganglionic blockade, suggesting that underlying differences in vascular sympathetic tone per se could account for the differences in blood pressure associated with chronic alterations in ANP activity. The predominance of ANP-dependent alterations in sympathetic tone in mediating the chronic hypotensive effect of this hormone is further strengthened by the observation that neither the synthesizing activity of the vascular endothelium (the other major regulator of basal vascular tone) nor the target cardiovascular effects of vasoactive...
endothelial factors is altered by the chronic level of ANP activity (10), thus excluding a role for this vasoregulatory pathway in mediating the chronic vasodilatory effect of ANP. The mechanism by which ANP exerts its chronic sympatholytic effect has not been fully elucidated. Acutely, ANP inhibits sympathetic nerve activity at all levels of autonomic function, including central attenuation of sympathetic outflow from cardiovascular regulatory areas in the brain stem, as well as inhibition of autonomic ganglion neurotransmission and catecholamine synthesis and release from postganglionic sympathetic nerve terminals and adrenal medulla (2, 7). In addition, ANP has been shown to interfere with the functional expression of α1-adrenergic receptor activity (2, 7). However, the extent to which these interactions may occur chronically is not known. In principle, any of the identified neuromodu-

latory effects of ANP, either singly or in combination, could account for the observed differences in sympathetic tone between the genotypes. We have evidence that the chronic sympatholytic activity of ANP might be mediated at a prejunctional site, since neither the pressor or chronotropic responses to peripheral adrenergic receptor stimulation with norepinephrine nor adrenergic receptor binding differ between the genotypes (11). It could be argued, on the basis of previous evidence (2, 7), that the colocalization of ANP and its NPR-A receptors in the autonomic ganglia may function as a tonically active neuromodulatory unit of sympathetic outflow. In this respect, we note that in humans, ANP-mediated sympatholysis appears to be mediated preferentially by inhibition of autonomic ganglion neurotransmission. It is not known at the moment whether such a mechanism of sympatholysis is operative in the ANP genetic models. Conceivably, the lower vascular resistance in the TTR-ANP mice could be due to tonic ANP-mediated inhibition of sympathetic ganglionic neurotransmission, whereas a lack of such neuromodulation in the −/− ANP mice could account for the high peripheral resistance seen in these animals.

ANP and chronic regulation of fluid and electrolyte balance

Long-term regulation of ABP is ultimately dependent on maintenance by the kidney and auxiliary neural and hormonal salt-regulating mechanisms of salt balance and extracellular fluid volume (ECFV) constancy. As previously mentioned, ANP elicits pronounced natriuresis acutely by directly inhibiting tubular sodium reabsorption and by antagonizing the actions of the major salt-conserving mechanisms, such as the renin-ANG (RAS) system, aldosterone, and the sympathetic nervous system. It may be speculated that such effects of ANP on sodium excretion, if tonically active, could also contribute to the chronic hypotensive effect of the hormone, given the fundamental role played by exchangeable sodium in determining ECFV. On this basis, it may be predicted that a chronic increase in ANP activity would lead to renal salt wasting, thereby resulting in reduction of ECFV and ABP, whereas chronic ANP deficiency would be expected to lead to a reduction in renal salt excretion, resulting in expansion of ECFV and hypertension. This would be particularly evident during increased dietary salt intake, when all salt-conserving mechanisms are deaktivated and the natriuretic activity of ANP is maximized. Obviously, in the long term, salt balance would have to be achieved in both situations to ensure survival, but this would require compensatory adjustments by the other salt-regulating mechanisms.

To study the role of ANP in chronic sodium balance, we placed TTR-ANP, −/− ANP, and control mice on either a high-salt (8% NaCl) or low-salt (0.008% NaCl) diet for 2–4 wk and measured daily intake and urinary output of water and electrolytes for the duration of the study. If the above premise is correct, then low dietary salt intake should have aggravated the hypotension in the TTR-ANP and ameliorated the hypertension in −/− ANP mice by reducing ECFV, whereas a high salt intake should have tended to normalize ECFV and ABP in the TTR-ANP mice and to increase ECFV and ABP in the
−/− ANP mice. Surprisingly, there were no differences in fluid and electrolyte excretions, nor was there a differential effect of dietary salt on ECFV and ABP between the TTR-ANP and the control NT mice (15). These findings are not totally unexpected for the animals on the high-salt diet, because the NT mice can presumably increase ANP release sufficiently to allow excretion of the daily salt load. However, the fact that the TTR-ANP mice on the low-salt diet can conserve salt as effectively as the NT mice, despite their inability to reduce their constitutively elevated ANP levels, clearly indicates that the kidneys can compensate for the potentially excessive natriuretic activity of ANP in these mice. The high ANP levels in the TTR-ANP mice remain effective in the kidney because these animals exhibit an exaggerated natriuretic response to acute extracellular volume expansion compared with the NT control mice. Thus the absence of a persistent natriuretic effect of ANP in the TTR-ANP mice is not due to renal insensitivity to the hormone. This implies that ANP-independent salt-conserving mechanisms must be operating in the TTR-ANP mice to override the natriuretic action owing to ANP and bring about salt balance. The nature of the compensatory adaptations that permit salt balance in these animals is not known. One possibility is that the reduction in renal perfusion pressure associated with the systemic hypotension in the TTR-ANP mice opposes the natriuretic activity of ANP by reducing the sensitivity of the pressure natriuresis mechanism, thereby ensuring salt balance at a lower perfusion pressure. An alternative explanation is that ANP-dependent enhancement of the pressure natriuresis mechanism would overcome the counteracting antinatriuretic effect of reduced renal perfusion pressure in the TTR-ANP mice and permit the maintenance of salt balance at the lower perfusion pressure. However, the pressure natriuresis mechanism in these mice has not yet been characterized. These findings, therefore, support the premise that the chronic hypotensive effect of ANP is due primarily to direct cardiovascular actions of the hormone, occurring independently of changes in absolute renal sodium excretion and ECFV.

Like the TTR-ANP mice, the −/− ANP mice are also fully capable of maintaining salt balance even on the high-salt diet (12). However, prolonged high-salt feeding exacerbates the hypertension in these mice but has no effect on ABP in the +/+ ANP mice (13), indicating that a salt-sensitive component of ABP development in response to reduced or absent endogenous ANP activity. This suggests that normal ANP activity is essential for the cardiovascular and renal adaptations that are necessary for long-term maintenance of ABP constancy during elevated dietary salt intake. In fact, plasma ANP concentration is known to increase in parallel with salt intake, and high dietary salt content potentiates the vasorelaxant action of ANP in the renal vasculature (for review, see Refs. 2 and 15). These are generally considered to be appropriate adaptations for the renal handling of increased dietary salt. How does a decrease in endogenous ANP activity lead to salt-sensitive hypertension in the −/− ANP mouse? In principle, the sensitization of ABP to salt in the −/− ANP mice could be caused by increased reabsorption of sodium from the inner medullary collecting duct, given that normal ANP-induced natriuresis in this tubular segment is absent in these animals. Alternatively, the development of salt sensitivity of ABP in the −/− ANP mice may be due to failure to adequately downregulate the activity of salt-conserving mechanisms that, under normal physiological conditions, are antagonized by ANP (i.e., RAS activity). With respect to the first possibility, we have previously reported that, although the −/− ANP mice have an inherently reduced capacity for renal salt excretion (5), these mice maintain salt balance in the absence of changes in ECFV (12). This indicates that the lack of ANP-dependent natriuretic activity is adequately compensated for by some other mechanisms. Regarding the second possibility, we found that the −/− ANP mice fail to reduce plasma renin activity (PRA) in response to high salt intake (Fig. 2B), whereas the +/+ ANP mice respond to the increase in dietary salt with an appropriate reduction in PRA (15). These findings suggest that the sensitization of ABP to salt in the −/− ANP mice is due to a failure to adequately downregulate PRA.
Indeed, the fact that the salt-induced difference in ABP between the –/– ANP and +/+ ANP mice is fully abrogated by chronic inhibition of the ANG II AT-1 receptor activity with losartan (12) (Fig. 3) underscores the functional dependency of salt sensitivity of ABP in the –/– ANP mice on the underlying elevated basal ANG II activity. Thus it can be concluded from these observations that ANP-dependent antagonism of RAS activity is essential for the chronic adaptation of ABP to high salt intake and that, in the absence of such physiological antagonism, an ANG II-mediated salt-sensitive component of ABP develops as a consequence of removal of the inhibitory effect of ANP on renin synthesis.

How does the increase in ANG II synthesis sensitize ABP to salt in the –/– ANP mice? Although the direct vasoconstrictor activity of ANG II may contribute to the hypertensive effect of salt, there is also evidence that ANG II exerts a widespread sympathoexcitatory effect that may play a major role in maintaining hypertension in the salt-fed –/– ANP mice. We have shown that the salt-fed –/– ANP mice have inappropriately elevated sympathetic tone (12), as indicated by an almost 10-fold elevation in total plasma catecholamine concentration and by higher basal heart rates compared with similarly maintained +/+ ANP mice (Fig. 3, B and C). Interestingly, the differences in plasma catecholamine concentration and heart rate are abolished by treatment with losartan (Fig. 3, B and C), showing the dependency of the elevated sympathetic tone on ANG II activity (12). Thus these findings imply that the sensitization of ABP to salt in the –/– ANP mice is, at least in part, due to tonic potentiation of sympathetic nerve activity by ANG II. It is likely that these two vasoregulatory and salt-conserving mechanisms interact synergistically, given the agonist effect that they exert on one another. A possible sequence of events in this dysregulation is that the increase in basal ANG II activity initially potentiates sympathetic nerve activity. The resultant increase in sympathetic tone would then maintain elevated PRA and support the hypertensive effect of salt. The elevated ANG II levels, in turn, would sustain the elevation in basal sympathetic tone.

The remaining question is how do the –/– ANP mice maintain salt balance on the high dietary salt intake against such a powerful background of antinatriuresis? The antinatriuretic action of increased ANG II and sympathetic nerve activity per se is largely attributed to a decrease in the sensitivity of the pressure natriuresis mechanism, suggesting that any compensatory adjustments in cardiovascular/renal function must be directed at overcoming the reduced sensitivity of this mechanism. Therefore, we suggest that the increase in renal perfusion pressure that follows the salt-induced elevation in ABP in the –/– ANP mice may operate to counteract the heightened antinatriuretic activity in these animals, thereby permitting long-term salt balance. In fact, if this were not the case, then the marked fall in ABP that is observed in the salt-fed –/– ANP mice with losartan treatment (Fig. 3A) would have been expected to lead to relative salt retention. However, these animals maintain salt balance despite the fall in ABP (12), thus supporting the contention that the primary role of the salt-induced increase in ABP in the –/– ANP mice is to overcome the reduced sensitivity of the pressure natriuresis mechanism. In this context, it is noted that ANP has been shown to increase the sensitivity of the pressure natriuresis mechanism, in part, by inhibiting ANG-II-mediated sodium reabsorption in the proximal tubule (for review, see Ref. 2). Thus the salt-induced elevation of ABP and renal perfusion pressure in the –/– ANP mice may be seen as compensation for the absence of ANP-dependent antagonism of the antinatriuretic action of ANG II.

Conclusions and perspectives

The work reviewed in this article provides evidence that ANP plays a determining role in long-term regulation of arterial pressure, inasmuch as chronic reduction in ANP activity leads to systemic hypertension that remains uncompensated by other homeostatic pressure-regulating mechanisms.
Under conditions of normal salt intake, ANP by itself is not the determining factor in renal regulation of salt excretion but only one of several redundant natriuretic mechanisms, whose activity may not be absolutely essential in isolation. However, as seen in the −/− ANP mice, a salt-sensitive component of hypertension develops during high salt intake, due to the failure to adequately downregulate the activity of RAS. Thus these findings conclusively establish that ANP-mediated antagonism of RAS is essential for the cardiovascular and renal adaptations to chronically elevated dietary salt intake.

Deficiencies in ANP activity and/or target organ responsiveness have been observed in several experimental and natural variants of salt-sensitive hypertension, as well as in other sodium-retaining disorders such as cirrhosis and congestive heart failure. Whether a deficit in ANP activity plays a pathological role in the etiology of these disorders remains somewhat controversial. In congestive heart failure, there is marked renal hyporesponsiveness to ANP despite greatly elevated plasma levels of the hormone. The hyporesponsiveness can be corrected by inhibition of ANG II activity, suggesting that in this condition the ANP-mediated antagonism of RAS is attenuated. This defect, in turn, could partly account for the elevated sympathetic tone that is characteristic of this disorder. When fed on a high-salt diet, Dahl salt-sensitive rats display a dysregulation of PRA and sympathetic nerve activity that is strikingly similar to that of −/− ANP mice. Interestingly, the development of salt sensitivity of ABP in these rats is effectively prevented by exogenous ANP gene delivery, implying that a deficiency in ANP activity may be an underlying cause of the salt sensitivity in this genetic hypertensive model.

On the basis of the evidence reviewed here, we propose the following working model of chronic regulation of arterial blood pressure by ANP (Fig. 4). Some of the concepts are speculative and await experimental confirmation. Accordingly, the chronic ANP hypotensive effect is determined by tonic inhibitory influences of this hormone on a single or on multiple sites in the sympathetic nervous system and in the RAS cascade. Centrally, locally derived ANP may potentiate sympahtoinhibitory neurotransmission from the nucleus tractus solitarius to the rostral ventrolateral medulla, the site of origin of peripheral sympathetic outflow. In the area postrema, a region in the circumventricular area that is devoid of blood-brain barrier, systemic ANP may antagonize the central sympathoexcitatory activity of circulating ANG II. Peripherally, locally produced ANP may inhibit cholinergic sympathetic ganglionic transmission, and at the neuroeffector junction ANP may reduce norepinephrine synthesis in sympathetic nerve terminals by inhibiting tyrosine hydroxylase. In the kidney and other tissues expressing RAS, ANP inhibits renin synthesis and ANG-converting enzyme activity, thereby decreasing the vasoconstrictor potential of ANG II.

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References


Regulation of Mammalian Gene Expression by Glucose

Guy A. Rutter, Jeremy M. Tavaré, and D. Gail Palmer

Glucose regulates gene transcription in mammals. As one of the primary nutrients, glucose is sensed by specialized cells that express glucose transporters.

The sensing of glucose in mammalian tissues occurs within a network of cells that are specialized for sensing glucose levels. These cells are located in the pancreas (β-cells) and the hypothalamus (glucose-sensitive neurons).

β-cells are the primary site of glucose sensing in mammals. They respond to changes in glucose levels to regulate the release of insulin. In contrast, glucose-sensitive neurons in the hypothalamus respond to changes in glucose levels to regulate feeding behavior and energy expenditure.

Recent evidence suggests that glucose sensing is not only limited to the pancreas and hypothalamus, but that other tissues also respond to glucose levels. This has led to a reevaluation of the role of glucose sensing in regulating energy metabolism and disease.

β-cells secrete insulin when blood glucose rises, whereas glucose-sensitive neurons in the ventromedial hypothalamus (VMH) modulate feeding behavior in response to changes in glucose levels.

The hypothalamus is a region of the brain that plays a critical role in the regulation of energy metabolism. The VMH is a sub-region of the hypothalamus that is involved in the regulation of feeding behavior. It is sensitive to changes in glucose levels and modulates feeding behavior in response to these changes.

In conclusion, glucose sensing is a fundamental process that is critical for the regulation of energy metabolism and disease. Further research is needed to determine the mechanisms by which glucose sensing is regulated and how it is affected by disease.