Atrial Natriuretic Factor: A Hormone Produced by the Heart

Adolfo J. de Bold

Summary. Systematic studies on the significance of the secretory-like morphological characteristic of cardiac atrial muscle cells of mammals led to the finding that these cells produce a polypeptide hormone. This hormone, described in 1981 as atrial natriuretic factor (ANF), is diuretic (natriuretic), hypotensive, and has an inhibitory effect on renin and aldosterone secretion. Thus, ANF probably intervenes in the short- and long-term control of water and electrolyte balance and of blood pressure. Phylogenetically, ANF appears early, suggesting different functions for this peptide in accordance with each species' environment. Knowledge of the properties of the hormone should provide insights into the pathophysiology of important clinical entities and lead to the development of new pharmaceutical products.

The homeostatic control of body sodium and water and of blood pressure involves a complex interaction of hormonal and neural mechanisms. The major determinants include central and autonomic nervous function, cardiac output, blood vessel tonicity, renal function, the renin-angiotensin-aldosterone system, catecholamines, and antidiuretic hormone.

It was recently found that the heart atrial muscle produces a polypeptide hormone—atrial natriuretic factor (ANF)—that interacts with several of the above determinants allowing for both long- and short-term regulation of salt and water balance and of blood pressure. The properties of ANF include potent diuretic (natriuretic) and hypotensive actions as well as an inhibitory effect on renin and aldosterone secretion (*1–3*).

A substance with some of the properties of ANF has long been sought on theoretical grounds deriving from physiological and pathophysiological observations. The discovery of ANF, however, derived from functional morphological studies of the cardiac muscle cell. These studies are important to obtaining a full understanding of ANF.

Functional-Morphological Overview

Most of the muscle cells (cardiocytes) forming the atrial and ventricular muscle of the mammalian heart are differentiated for mechanical work. Morphologically this is evident from their large content of contractile elements. The rest of the cardiocytes do not share this morphological differentiation to the same degree. In 1893, Kent (*4*) described a muscular connection between atria and ventricles, which were known to be otherwise separated from each other by connective tissue. Kent's observations led to studies by other investigators, who established that the microscopic appearance of cardiocytes forming the conducting system of the heart differs markedly from that of the cardiocytes making up the bulk of the myocardium. The morphology of the sinoatrial node was aptly described by Keith and Flack (*5*) in 1907 as "a remarkable remnant of primitive fibers." In 1910 Lewis *et al.* (*6*) showed that these fibers were the source of electrical events in the heart and thus defined the cardiac pacemaker.

The cardiocyte population of the mammalian heart is now regarded as a group of cells showing an essentially continuous spectrum of differentiation (*7*) from the primitive-looking cardiocyte found in the sinoatrial node to the cardiocyte fully differentiated as a special type of striated muscle cell. In more general terms, the cardiocyte population of the mammalian heart displays to different degrees the expression of three basic properties: excitability, conductivity, and contractility. These properties are used to explain the physiological and physiopathological phenomena associated with the heart as an organ that plays the central role in blood circulation. However, in 1956, B. Kisch (*8*) pointed out a morphological difference between atrial and ventricular cardiocytes in the heart of the guinea pig that could not be fitted into the functional framework then established. He observed, as others did subsequently, that atrial cardiocytes in mammals, unlike ventricular cardiocytes, have morphological features of secretory cells (*9, 10*). The most obvious expression of this differentiation is the presence of membrane-bound storage granules—the specific atrial granules—which, after conventional processing for electron microscopy, display an electron-dense core and measure 250 to 500 nanometers (Fig. 1). These granules are more concentrated in the central sarcoplasmic core of atrial cardiocytes. Often, the granules are found associated with a prominent Golgi complex from which they arise. Numerous profiles of rough endoplasmic reticulum are also normally found. These features of the central sarcoplasmic core of the mammalian atrial cardiocyte are more common in the general population of cardiocytes found in the auricles. Cardiocytes in the sinoatrial node and in specialized path of conduction are far less developed in this sense so that the expression of a secretory function is most often associated with cells that are also differentiated for contraction. Yet cells differentiated for contraction in ventricular muscle do not show elements of secretory cells. However, ventricular as well as atrial cardiocytes in nonmammalian vertebrates, including reptiles, amphibians, birds, teleost fishes, and elasmobranchs, do appear to have a dual contractile-secretory function even though, morphologically, this duality is most obvious in mammals. Even in mammals there are variations in the morphological expression of the secretory function. Small rodents, for example, have far more atrial granules—up to 4 percent of the cardiocyte volume—than large mammals such as cattle, which have very few granules per cardiocyte. Human cardiocytes have an intermediate content. In rats, granule content varies with age. It doubles between ages 6 and 10 weeks and, although the number plateaus at adulthood, morphometric procedures show significant variations in animals of the same age (*11*).

The dual secretory-contractile function of atrial cardiocytes in the rat is suggested from autoradiographic studies

The author is associated with the Department of Pathology, Queen's University and Hotel-Dieu Hospital, Kingston, Ontario, Canada K7L 3H6.

after these cells are exposed to [^{3}H]leucine (*12*). There is a striking difference in the stable protein-labeling pattern of mitochondria and myofibrils as compared with the rapid turnover of activity of the Golgi complex and specific atrial granules. The labeling of atrial granules shows kinetics similar to that found in cells producing polypeptide hormones. No such labeling pattern is found associated with any cell compartment of ventricular cardiocytes. Histochemically, atrial granules display properties in common with polypeptide hormone–containing granules. The selective staining of these granules with lead-hematoxylin-tartrazine and the relatively large sampling size afforded by the light microscope have been used to develop an unbiased morphometric procedure to measure the degree of granulation of atrial cardiocytes (*11*). These measurements were carried out because many experimental procedures were reported to affect the number of granules (*10, 13*). This approach demonstrated unequivocally that some experimental maneuvers leading to changes in water and electrolyte balance significantly altered the specific atrial granule population in the rat (*14*). These and other histochemical observations led to the hypothesis that the specific atrial granules stored a basic polypeptide containing tryptophan and sulfur amino acids and that this polypeptide was involved in the regulation of water and electrolyte balance. The experimental testing of this hypothesis led to the finding that atrial extracts contained a factor of proteinaceous nature that elicited natriuresis and a hypotensive effect when injected into rats (*1, 2*). This factor was named atrial natriuretic factor.

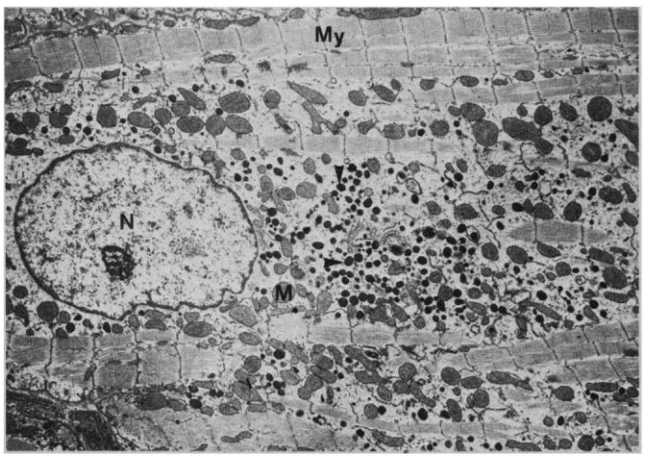

Fig. 1. Electron microscopic view of a rat atrial cardiocyte. *N*, nucleus; *M*, mitochondria; *My*, myofibrils. The central sarcoplasmic core displays morphological features associated with secretory cells that include a large number of storage granules (arrowheads), referred to as specific atrial granules (×3400).

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Met Gly Ser Phe Ser Ile Thr Lys Gly Phe Phe Leu Phe Leu Ala Phe
 1

Trp Leu Pro Gly His Ile Gly Ala Asn Pro Val Tyr Ser Ala Val Ser
                               25

Asn Thr Asp Leu Met Asp Phe Lys Asn Leu Leu Asp His Leu Glu  Glu

Lys Met Pro Val Glu Asp Glu Val Met Pro Pro Gln Ala Leu Ser Glu

Gln Thr Asp Glu Ala Gly Ala Ala Leu Ser Ser Leu Ser Glu Val Pro

Pro Trp Thr Gly Glu Val Asn Pro Ser Gln Arg Asp Gly Gly Ala  Leu

Gly Arg Gly Pro Trp Asp Pro Ser Asp Arg Ser Ala Leu Leu Lys Ser

Lys Leu Arg Ala Leu Leu Ala Gly Pro Arg Ser Leu Arg Arg Ser Ser
                                        123

Cys Phe Gly Gly Arg Ile Asp Arg Ile Gly Ala Gln Ser Gly Leu  Gly
└──────────────────────────────────────────────────────────────┘

Cys Asn Ser Phe Arg Tyr Arg Arg
└──┘                  150
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Fig. 2. Rat prepro-ANF sequence. Cardionatrin IV begins at Asn^{25} and ends at Tyr^{150}. This carboxyl terminus is shared by cardionatrin I (underlined) which begins at Ser^{123}. These peptides appear to be the major storage and release products, respectively, of ANF. The disulfide bond indicated between Cys^{129} and Cys^{145} is essential for biological activity.

Specific Atrial Granules and ANF

Various methods have shown that ANF is stored within specific atrial granules. The net specific natriuretic activity of atrial extracts is highest for animals with the highest number of granules (*15*). In addition, both atrial and ventricular homogenates of nonmammalian vertebrate hearts have natriuretic activity. Tissue fractionation studies show that the highest natriuretic activity is associated with fractions containing purified granules (*16*) and immunocytochemical studies with antisera directed against ANF peptides clearly localize ANF within the atrial granules (*17–19*).

Immunocytochemical studies and radioimmunoassay techniques have suggested extracardiac localizations of ANF, notably in the central nervous system and kidney (*19*), but quantitatively the main store of ANF in mammals is the atria and the amount of ANF precursor messenger RNA (mRNA) is highest in this tissue (*20*). In other tissues, ANF mRNA is orders of magnitude lower, although this does not necessarily reflect its importance relative to function. In nonmammalian species ANF synthesis may also occur in ventricular muscle, and the extracardiac site of production may be quantitatively different from that found in mammals.

ANF peptides isolated from atrial muscle show molecular sizes of 2500 to 13,000 daltons. Purification and sequencing of peptides with 21 to 31 residues have been carried out in various laboratories (*21–25*). Evidence exists that some of these peptides are artifactual cleavage products generated during isolation (*21*). However, biological testing of these peptides has helped to establish that a disul-

fide-looped sequence of 17 amino acids plus various COOH- and NH_2-terminal extensions are necessary for biological activity.

Cloning and sequence analysis of complementary DNA encoding the ANF precursor have provided a more complete understanding of ANF peptides (*20, 21, 24, 26, 27*) (Fig. 2). From these studies it has been established that ANF is synthesized in a prepro form containing 152 amino acids in the rat and 151 amino acids in the human. A high degree of homology exists between the rat and human sequences. These precursors contain 24– and a 25–amino acid putative signal sequences, respectively. It is the COOH-terminal portion of this molecule that contains the biologically active sequences.

The main form of ANF in rat atrial homogenates and in isolated granules is a 126–amino acid peptide called cardionatrin IV (*17, 21*) or γ rat atrial natriuretic peptide (*27*). It is derived from prepro-ANF by removal of the signal peptide and residues 151 and 152, which are arginines. The absence of these residues in the peptides so far isolated indicates early removal after biosynthesis. The circulating form of ANF appears to be cardionatrin I (*22, 28*) or α rat atrial natriuretic peptide (*27*), a 28–amino acid peptide that comprises residues 123 to 150 of prepro-ANF. This peptide is also the major form detected in perfusates of isolated atria (*29*), so that it is likely that the 126-residue peptide is processed to the 28–amino acid peptide before release from cardiocytes. A similar process may take place in human atria from which an α human natriuretic peptide has been isolated (*24*). The latter shares 27 of 28 amino acids with rat cardionatrin I.

Plasma levels of ANF measured by radioimmunoassay vary widely from approximately 25 to 100 picograms per milliliter of plasma in humans and 100 to 1000 pg/ml in rats. Differences in species, measuring techniques, and sampling protocols account for some of this variability. It is not clear what stimulates ANF secretion from atria, but in vitro investigations indicate that adrenaline, arginine vasopressin, acetylcholine, and atrial distension all lead to increase in ANF release (*30*). The peptides have a half-life on the order of minutes in blood. Binding to specific receptors in known target organs, including kidney, blood vessels, and adrenal cortex has been demonstrated. Several additional binding sites have been described but are not as yet clearly defined as specific receptor sites (*31*).

The main systemic effects ascribed to ANF result from observations in vitro and in vivo. In the whole animal, these effects include a potent and rapid diuretic and natriuretic action of short duration accompanied by hypotension and, often, bradycardia as well as depressant effects on aldosterone and renin secretion. The cellular or molecular basis of these systemic effects are not clearly understood. Whether renal hemodynamic or tubular mechanisms account for the natriuretic action of ANF is unknown, and a possible role for both these mechanisms has been suggested (*32*). The effect of ANF on aldosterone and renin, as well as on smooth muscle, pertains to phenomenological knowledge, although some of these effects are clearly related to activation of guanylate cyclase, elevation of guanosine 3′,5′-monophosphate, and inhibition of adenylate cyclase (*33*). The finding that dopamine receptor antagonists interfere with the natriuretic response to ANF suggests that the autonomic nervous system might mediate the actions of ANF (*34*).

Conclusion

Although much remains to be learned about the systemic actions of ANF and factors that affect the release of ANF from atrial cardiocytes, several mechanisms link the atria and, possibly ANF, to plasma volume regulation. This link may be demonstrated, for example, by maneuvers leading to changes in atrial distension and intrathoracic blood volume, which, in turn, influence renal and cardiovascular function and the renin-angiotensin-aldosterone system in a way that mimics the effects of ANF. The polyuria associated with paroxysmal atrial tachycardia has been linked with increased plasma ANF (*35*). Both long-term and short-term variation in extracellular volume affect the atrial stores, synthesis, or circulating levels of ANF. Moreover, the inability of the kidney to bring about an escape from the sodium-retaining state accompanying chronic cardiac failure may be viewed as related to ANF. All of this evidence, although multifactorial, can be extrapolated to indicate a physiological role for ANF in the regulation of sodium and water balance and thus to allow the development of new therapies for clinical entities such as hypertension and heart failure.

The finding of secretory-like morphological characteristics in heart muscle cells in all species studied, together with the highly conserved nature of the known sequences of ANF peptides, hints at a fundamental evolutionary strategy used to maintain water and electrolyte balance. In sharks, for example, ANF stimulates chloride secretion from the rectal gland (*36*). It is reasonable to conclude that ANF plays regulatory roles in accordance with each species' strategy for maintaining water and salt balance as well as with the ionic environment to which the species is exposed.

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The Action of Oncogenes in the Cytoplasm and Nucleus

Robert A. Weinberg

Summary. As many as 40 distinct oncogenes of viral and cellular origin have been identified to date. Many of these genes can be grouped into functional classes on the basis of their effects on cellular phenotype. These groupings suggest a small number of mechanisms of action of the oncogene-encoded proteins. Some data suggest that, in the cytoplasm, these proteins may regulate levels of critical second messenger molecules; in the nucleus, these proteins may modulate the activity of the cell's transcriptional machinery. Many of the gene products can also be related to a signaling pathway that determines the cell's response to growth-stimulating factors. Because some of these genes are expressed in nongrowing, differentiated cells, the encoded proteins may in certain tissues mediate functions that are unrelated to cellular growth control.

Oncogene research has changed substantially over the past several years. Initial emphasis concerned the identification of oncogenes present in tumor virus genomes and in the genomes of a number of different types of tumor cells. Together, various experimental routes have led to the characterization of at least 30 different oncogenes originating from the cellular genome and 10 or more found in the genomes of DNA tumor viruses (*1*). Having catalogued these genes and their structures, workers are now moving into a new phase in which mechanistic problems are confronted: how do oncogenes and their encoded proteins convert normal cellular metabolism to that of a tumor cell? What regulatory pathways are perturbed by oncogenes, and how can their various modes of action be interrelated?

This review attempts to synthesize much of the currently available data on these issues. It is written with the belief that much of the information about oncogenes will eventually be understandable in terms of a small number of mechanisms and that the outlines of some of these are gradually becoming apparent. Much of the present discussion concerns the modes of activation of cellular oncogenes and the effects that these genes have on cellular physiology. The implications of all this for tumorigenesis involves less discussion, because we still understand relatively little about the connections between oncogene action and the outgrowth of tumors in vivo.

The author is at the Whitehead Institute for Biomedical Research, 9 Cambridge Center, Cambridge, Massachusetts 02142, and in the Department of Biology, Massachusetts Institute of Technology, Cambridge 02139.

Nuclear and Cytoplasmic Oncogenes

The existence of the 40 and more oncogenes provokes an obvious question: do they represent as many as 40 distinct mechanisms of transformation, or can they be grouped into a small number of functional classes on the basis of shared functional properties? One such classification that has arisen in recent years groups oncogenes on the basis of the nuclear or cytoplasmic localization of their gene products (Table 1). Perhaps surprisingly, this crude classification scheme correlates with similarities of function within each group. The terms used to label these as "nuclear" or "cytoplasmic" oncogenes are a bit misleading, in that they imply the location of the genes rather than the site of action of their gene products. I will use the terms here nevertheless.

Among the nuclear oncogenes of special interest are several cellular genes or variants thereof (*myc*, N-*myc*, *myb*, and Ela) that exhibit some structural homology with one another (*2, 3*). These and several other nuclear oncogenes (*p53*, polyoma large T, and SV40 large T) exhibit similarities of function, although no one of them behaves precisely the same as any other in all respects (*4–6*). Among the most readily measured of these traits is that of immortalizing ability—the power to convert a tissue culture cell of limited replicative potential in vitro into one that can be passaged without limit in culture.

Associated with this immortalizing ability are often other functions that may affect the altered growth properties of tumor cells in vivo. For example, a recent characterization of the *myc* oncogene (*6*) revealed that this oncogene also allows embryo fibroblasts to grow at lower serum concentrations and at lower density in monolayer culture, echoing similar results obtained with some other oncogenes of this group. These nuclear oncogenes tend to be weak in their ability to induce anchorage independence of fibroblasts, in contrast to cytoplasmic