Physiological Actions of Atrial Natriuretic Factor

STEVEN A. ATLAS AND JOHN H. LARAGH

Cardiovascular Center and the Department of Medicine, Cornell University Medical College, New York, New York

Effects on the Kidney
Renal hemodynamic actions
Effects on renal excretory function
Effects on renin secretion

Effects on Steroidogenesis
Effects on aldosterone
Effects on glucocorticoids
Effects on gonadal steroids

Effects on Pituitary Hormone Secretion
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Effects on Vascular Tissue
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Present Perspectives

ATRIAL NATRIURETIC FACTOR (ANF) is a recently discovered polypeptide hormone that is synthesized and stored in atrial muscle cells (9, 21, 31, 32, 71, 79). There is evidence that lower levels of ANF are synthesized in several other tissues, including ventricle and brain, but it is presumed that the atrium is the principal source of circulating ANF in mammals. It has been known for nearly 30 years that atrial muscle cells contain secretory granules and a well-developed Golgi apparatus, as found in other hormone-secreting cells (59, 63); such granules are not present in the mammalian ventricle but are present in ventricle and atrium in lower vertebrates (12). Work done in the 1970s suggested that alterations in fluid and electrolyte balance were associated with changes in the density of the atrial granules (29, 75). In 1981 de Bold and coworkers (32) demonstrated that extracts of rat atrium contained a factor that induces a marked increase in sodium excretion when administered to intact rats; subsequent work showed that this factor is associated with the atrial granules (22, 30, 44). More recently it has been shown that ANF comprises a number of structurally related small peptides derived from a 126-amino acid residue precursor (10, 28, 42, 61, 62, 73, 76, 82, 99, 100, 123). The numerous peptides isolated from atrium, ranging between 21 and 35 amino acid residues,
probably resulted in large part from nonspecific proteolysis of the precursor during extraction and purification procedures. Although the precursor is the major storage form in atrium (41), it appears that a 28-residue peptide is the major circulating form (38, 42, 61, 98, 110, 122). Plasma levels of immunoreactive ANF under basal conditions are reported to be on the order of $10^{-12}$ to $10^{-11}$ M in unanesthetized animals and humans (25, 38, 68, 70, 102, 109, 122).

In addition to inducing natriuresis and diuresis, ANF has several actions of potential physiological significance that have been demonstrated in vitro or by administration of the peptide to intact animals. These actions include inhibitory effects on steroidogenesis, most prominently affecting aldosterone biosynthesis, and on the secretion of renin, vasopressin, and possibly ACTH; behavioral effects on thirst and salt appetite; a relaxant effect on contracted vascular smooth muscle; effects on systemic hemodynamics and intravascular volume regulation that may lead to a reduction in blood pressure; and complex renal hemodynamic effects, including an increase in glomerular filtration rate (GFR), which apparently play an important role in its natriuretic and renin-suppressing actions.

Membrane-bound receptors for ANF have been identified on all its potential target tissues; although its exact mechanisms of action remain to be defined, the peptide has been shown to have effects on known cellular intermediates. By activating the particulate (membrane-bound) form of guanylate cyclase, ANF causes striking increases in tissue levels of cGMP (52, 117). In fact, ANF is the only substance of mammalian origin that has been shown to activate this enzyme. In certain target tissues, ANF has also been shown to inhibit adenylate cyclase (4). While some of its actions (e.g., on vascular smooth muscle and adrenal cortex) probably depend ultimately on a reduction in cytosolic calcium, evidence of this has yet to be provided.

This chapter provides an overview of the actions of ANF that may be relevant to the physiological regulation of fluid and electrolyte balance and cardiovascular homeostasis. The potentially important actions of circulating ANF are emphasized, although some of the effects described may also be relevant to the existence of immunoreactive ANF-containing neurons and ANF-binding sites in hypothalamus and other brain regions (58, 87, 92, 95, 104, 109). In some cases, particularly with regard to studies in intact animal preparations, supraphysiological concentrations of the peptide have been employed to demonstrate these effects. A brief consideration of what is known about the regulation of ANF secretion will be useful to place these findings in perspective. However, in the absence of specific antagonists of ANF, only tentative conclusions can be made regarding the physiological significance of these actions.

EFFECTS ON THE KIDNEY

Renal Hemodynamic Actions

In the isolated perfused rat kidney, ANF induces a major increase in GFR accompanied by an increase in renal resistance (10, 18, 71). Increases in GFR