NATRIURETIC PEPTIDES AND CARDIOVASCULAR HOMEOSTASIS

De Bold's discovery 16 yr ago of an atrial tissue factor (1) with strong natriuretic activity understandably captured the imagination of renal physiologists seeking the elusive "third factor" (2) and new insights into sodium regulation. However, as well as natriuresis, de Bold's original experiments showed that the atrial extract also caused vasorelaxation and lowered blood pressure—suggesting potentially important actions intrinsic to cardiovascular homeostasis, independent of natriuresis. Subsequent work in the decade after ANP's* discovery has substantiated this view to the extent that some observers regard the physiological actions of natriuretic peptides as primarily cardiovascular, with little if any role for ANP in the day-to-day regulation of sodium excretion in normal health (3,4). Whereas the debate continues to this day on the relative importance of hemodynamic vs renal actions of natriuretic peptides, it is now abundantly clear that a family of hormones, including ANP, brain natriuretic peptide (BNP), and C-type natriuretic peptide (CNP), participate as both paracrine and classical endocrine (ANP and BNP) hormones in the regulation of blood pressure and fluid homeostasis. This view is based on multiple layers of evidence—and in particular on the close coupling of intracardiac pressure with hormone secretion (ANP largely from the atrial myocyte, BNP from the ventricular myocyte) (5), the demonstration of hemodynamic effects of these

*ANP (atrial natriuretic peptide) is synonymous with ANF (atrial natriuretic factor) in this review.
The regulation and actions of natriuretic peptides. Note: atrial and ventricular “receptors” have not as yet been clarified. Brain production of atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and C-type natriuretic peptide (CNP) have paracrine roles in the regulation of systemic blood pressure by the CNS. Other paracrine actions of natriuretic peptide (also indicated by ↑ CNP) on vessel wall, kidney, and so on are omitted for reasons of clarity. BP, blood pressure; aldo, aldosterone; FF, filtration fraction; SNA, sympathetic nervous activity; VSM, vascular smooth muscle. (Modified from Espiner EA. Physiology of natriuretic peptides. J Intern Med 1994;235:527–541, with permission of Blackwell.)

circulating hormones (ANP and BNP) at physiological and pathophysiological concentrations (and which can be inhibited by administration of appropriate hormone antagonists or inhibitors), and more recently the findings from transgenic models amplifying or inhibiting the expression or actions of these hormones.

Before considering the details of cardiovascular action, a broad concept of how the endocrine and paracrine effects of natriuretic peptides mediate cardiovascular homeostasis is needed (Fig. 1). In health, in response to an acute increase in central blood volume/pressure, the secretion of the circulating hormones, particularly ANP (and to a lesser extent BNP), is increased, exerting widespread effects (mediated largely by the guanylyl cyclase receptor NPR-A) (6)—the combined actions of which reduce cardiac filling pressures (preload) and restore hormone secretion toward normal. Although many different tissues contribute, increased natriuresis, increased flux of plasma into the interstitial space, inhibition of renin, and suppression of aldosterone secretion are all clearly demonstrable effects of small (physiological) increments in plasma ANP or BNP concentration. All of these actions, if not themselves primarily “cardiovascular,” importantly affect the integrity of the circulation and must be considered together when interpreting the cardiovascular actions of natriuretic peptides. For example, a sustained natriuretic