Origin and Determinants of ANF and BNP Production by the Heart under Normal and Pathophysiological Conditions

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The endocrine function of the heart in adult mammals, including humans, resides on the ability of the striated cardiac muscle cells (cardiocytes) of the atrial wall to produce in a regulated manner the polypeptide hormones atrial natriuretic factor (ANF or ANP) and brain natriuretic peptide (BNP), which are referred to as natriuretic peptides (NP). Their general function is to modulate cardiac preload and afterload by their effect on water and electrolyte balance and cardiovascular growth (For review see (6)). There is some confusion in the literature as to the precise cell type where this secretory function resides, as well as to the peptide storage form and the location of the secretory function, which, of late, is often quoted as being the ventricular muscle for BNP. Some confusion also exists with nomenclature when referring to ANF or ANP. ANF remains the agreed upon name for the peptide referred to as ANP (4).

All cardiocytes found in the auricles display a dual contractile-secretory phenotype, albeit to different extents. In the right atrium, cells of the sino atrial node do not contain storage granules but all cells anterior to the crista terminalis, i.e. the cells making up the auricle, do so. At the microscopic level, this phenotype is mainly manifested by the abundance of rough sarcoplasmic reticulum, a highly developed Golgi complex and storage granules known as *specific atrial granules*, which co-store both ANF and BNP. Following the convention of assigning residue number beginning at the amino terminus of their respective prohormones, the peptides that are stored in the atrial granules are mainly ANF_{1-126} and BNP_{77-108}

Microscopic studies of ANF immunoreactivity and mRNA presence by *in situ* hybridization in ventricular muscle reveal that there are storage granules containing ANF and a strong ANF mRNA signal in the ventricular portion of conducting system of the heart in the rabbit and in the rat (1),(our unpublished observations) .

The biochemical evidence further supports an overwhelming atrial source of NP. In the rat atria for example, the concentrations of ANF and BNP are about 30,000 and 300 pmol/g respectively. In the ventricle NP concentration for ANF and BNP is about 5 and 0.5 pmol/g respectively. There are three clear conclusions that may be drawn from these data. Firstly, not

only BNP but also ANF is present in the ventricles. Secondly, in both atria and ventricles, ANF is more abundant than BNP. Thirdly, even taking into account the differences in mass between the atrial and ventricular chambers (approximately 1:10) it is not possible to conclude that BNP might be a ventricular hormone. Similar conclusions can be reached when evaluating transcript abundance for atrial and ventricular ANF and BNP (2; 9).

The expression of both ANF and BNP increases in atria and in ventricles in conditions of chronic pressure or volume overload. In deoxycorticosterone acetate (DOCA)-salt hypertension, left ventricular hypertrophy induced by a 5-week treatment, increases left ventricular BNP content from about 1.5 pmol/g in control animals to about 5 pmol/g in DOCA-salt treated animals while ANF increases from about 5 pmol/g to 70 pmol/g. Following DOCA-salt stimulation, left atrial ANF content decreases presumably reflecting an increase in demand over supply from storage even though both atrial ANF and BNP mRNA abundance increases. In a fashion similar to the atria, ventricular ANF and BNP transcript abundance increases (9).

Recent cardiac catheterization data in humans with left ventricular hypertrophy suggest that the abnormal circulating levels of NP are significantly derived from atrial sources (7). Importantly, in humans, replacement of the failing ventricle (5) as it is done in orthotopic heart transplantation, does not result in normalization of either BNP or ANF plasma levels even after normalization of intracardiac pressures and the renin angiotensin aldosterone system occurs. From the pathophysiological point of view, these findings show that while there may be a good correlation between parameters such as ventricular hypertrophy or failure or ischemic events and NP secretion, the influence of these parameters on atrial function and hence, on atrial NP production should not be ignored.

The determinants of NP production in the heart are both humorally and hemodinamically determined (3). In a study of ANF and BNP synthesis and secretion in the aortic- banded rat treated with dosage schedules of the angiotensin converting enzyme (ACE) inhibitor Ramipril that result in the prevention or regression of both hypertension and hypertrophy (high dosage) or in the regression of hypertrophy alone with persistent hypertension (low dosage) it can be demonstrated that NP production and secretion is independently related to increased blood pressure and hypertrophy. Regression of ventricular hypertrophy in the presence of hypertension only partially decreases circulating levels of NP even though this regression is accompanied by normalization of ventricular NP gene expression (8). Administration of an endothelin type A receptor antagonist to DOCA-salt or Goldblatt hypertensive rats with left ventricular hypertrophy as well as ACE inhibition in aortic banded rats, normalizes ventricular NP gene expression but does not affect atrial NP gene

expression suggesting that there significant differences in the mechanisms controlling NP production between atrial and ventricular cardiocytes, the latter appearing to be dependant on humoral factors to a significant degree but certainly not to wall tension alone.

The above findings clearly demonstrate that both ANF and BNP are hormones originating in the atria even when the peptide or transcript abundance is considered relative to tissue weight. In comparative terms, the level of expression of NP in the normal ventricle is negligible compared to that of the atria. In addition, as in the atria, ventricular ANF is more abundant than ventricular BNP. This holds true for the normal as well as for the pathological condition. The circulating levels of both ANF and BNP rise following appropriate hemodynamic or neuroendocrine stimuli and whereas the BNP increases relatively more than the ANF, it does so without changing the concept that circulating ANF is more abundant than circulating BNP and that the increase observed in circulating levels of either NP does not entirely reflect ventricular production. Given these considerations, the recently developed notion that BNP is a ventricular hormone appears to be unfounded.

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