Editorial

Is atrial natriuretic peptide really a hormone?

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Since the 1950s when granules were first observed histologically within the atrial wall there has been intense interest in their function. Two early key papers were those of Marie *et al*¹ and de Bold,² who showed that the granulation was related to the water/electrolyte balance, although a first time reader's starting point should be the meticulous histological investigation of Jamieson and Palade.³

On pages 302-16 of this issue of the *British Heart Journal* Genest gives an excellent historical account of this exciting research, much of which has been conducted at the Clinical Research Institute of Montreal.

There has been remarkably rapid progress in biochemical knowledge about atrial natriuretic peptides and perhaps now is the time to pause and take stock of the evidence about their postulated physiological functions.

Because in humans and in rats the atrial natriuretic factor is elaborated and localised in the granules of the atrial cardiocytes and is released in the blood, it is suggested that the atrial natriuretic factor is "a true circulatory hormone".⁴ But is there any evidence for the usual process of secretion from the atrial muscle cell? Certainly there is no evidence that the plasma concentrations attained during applied physiological stimuli (such as stretch of left atrial wall) can evoke acute responses. There is only evidence that large doses or large infusions that produce pharmacological concentrations of atrial natriuretic peptide have effects on the blood vessels (arteries, arterioles, veins), causing relaxation, particularly of pre-contracted muscle, and on the kidneys, causing natriuresis and diuresis.

Little is yet known of the biosynthesis and processing of atrial natriuretic peptide in, and its release from, the cardiocytes. Interpretation of the observed changes in granulation in relation to changes in fluid balance^{1,2} is at present difficult in view of studies^{5,6}

which suggest that granulation is dependent on release rather than synthesis, with low granularity apparently indicating high biosynthesis and turnover; also, in cultured cardiocytes there was an inverse relation between granulation and release of atrial natriuretic peptide.⁷ It seems likely, however, that in some circumstances low granularity will be associated with low biosynthesis. Exocytosis has not been seen despite specific attempts to detect it in several electron microscope studies,^{3,7} so it is still not certain that the cardiocytes secrete atrial natriuretic peptides by mechanisms analogous to those found in established endocrine organs. Low molecular weight forms are, however, found in plasma and again controversy is rife, evidence being presented both for the release of the high molecular weight form, for the later cleavage in plasma,^{8,9} and for the release of the low molecular weight form.¹⁰

Few studies have considered quantitatively the problem of the possible physiological stimuli for release and in these no evidence has been provided of a causative relation between stimuli within the physiological range, a rise in the plasma concentration of atrial natriuretic peptide, and the response of natriuresis and diuresis. For instance, the secretion of atrial natriuretic peptide and a causative relation have been implied¹¹ in the diuresis and natriuresis arising from stimulation of receptors in the atria—the so-called volume receptors.¹² Stimulation of atrial receptors is known reflexly to cause a water diuresis and small natriuresis¹³ but afferent nerves in the vagi are necessary for these responses to occur. When a large balloon was distended in the left atrium of anaesthetised¹⁴ or unanaesthetised dogs¹⁵ to stretch it and raise left atrial pressure to the top end of the pressure range in this animal (12-15 mm Hg) the plasma concentration of atrial natriuretic peptide increased by about 24 and 80 fmol/ml respectively (60 and 200 pg/ml, assuming $M_r = 2.5$ K daltons), with increases of the same magnitude whether or not the hearts were innervated. Knapp *et al*, however, obtained no natriuresis

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when this intervention was performed after atrial receptor denervation,¹⁶ indicating that the diuresis and natriuresis resulting from stimulation of atrial receptors¹⁷ were *not* caused by atrial natriuretic peptide. We suggested that such evidence must call seriously into question the claim that atrial natriuretic peptides are released into plasma in sufficient concentration for natriuresis to be a normal physiological function of these substances.

These investigations also support the contention that the plasma concentrations of atrial natriuretic peptide that evoke responses after infusion are much higher than those attained by stretching the atria or in disease. Normal endogenous basal concentrations of atrial natriuretic peptide are reported to be below 40 fmol/ml (100 pg/ml)^{14 15 18 19} and raised concentrations after intervention or in pathological conditions are generally < 200 fmol/ml.^{14 15 18-23} Even grossly unphysiological volume expansions of 30-40% of blood volume produced increases of only 4, 11, and 100 fmol/ml respectively.^{18 24 25}

From the evidence of Goetz¹⁵ it is possible to put the data from infusions of atrial natriuretic peptide into the context of these very low endogenous levels. Goetz reported plasma atrial natriuretic peptide concentrations of 170 and 300 fmol/ml in conscious dogs after infusions of atriopeptin III of 10.3 and 20.6 pmol/kg/min respectively¹⁵; thus infusions as low as 10.3 pmol/kg/min (25.8 ng/kg/min) would give plasma concentrations of far in excess of most of the reported endogenous concentrations. Yet Goetz reported no natriuresis or diuresis at these concentrations¹⁵; he found that a minimum infusion rate of 412 pmol/kg/min (1030 ng/kg/min) was necessary to produce natriuresis. Similar analysis of infusions in man leads to comparable values with infusions of about 50 ng/kg/min resulting in plasma concentrations of atrial natriuretic peptide^{21 26 27} in the pathological range. Very few published reports used infusion rates as low as those of Goetz¹⁵; most reports of the effects of atrial natriuretic peptide used doses within the pharmacological range and are thus unlikely to be useful in elucidating its physiological function.

The use of various high levels of infusion probably goes some way to explain the many contradictions that have emerged about the postulated functions and mechanisms of action of atrial natriuretic peptide, and these are exacerbated by the fact that most reviewers in discussing mechanisms of action still include early studies in which impure atrial extracts were used. These controversies include: disagreements about the site or sites of action in the kidney²⁸⁻³¹; the apparent paradox of *in vitro* vasodilatation and *in vivo* falls in blood pressure with the findings *in vivo* of an increase in peripheral

resistance,³² for which the current explanations are falling cardiac output and changes in capacitance³²; the finding that vascular selectivity is only partly related to vascular receptor binding³³; that the vascular effects are endothelium independent in contrast with other hormonal vasodilators³³; and the dissociation of excretion of sodium from the levels of cyclic guanosine monophosphate in plasma and urine.²⁸ The fact that high concentrations of atrial natriuretic peptide are found in patients with severe heart failure²² but are not associated with diuresis and natriuresis leads to claims that such patients may be resistant to the renal effects of endogenous atrial natriuretic peptide or that other factors (for example the renin-angiotensin-aldosterone system) may counteract the polyuric action of atrial natriuretic peptide in cardiac failure. But the high concentrations of the peptide could be incidental.

The excitement created by the discovery of atrial natriuretic peptides is understandable. The search for the postulated natural natriuretic substance has continued relentlessly for decades; and ever since the early experiments of Henry *et al* in 1956 in which they showed that distension of the left atrium by a balloon results in diuresis,³⁴ the atria have been seen as being important in fluid regulation. The possibility of tying these two strands together has been too much for the theorists.^{11 35} That alterations in fluid balance result in changes in atrial natriuretic peptide both in the atria and plasma is not in dispute and it does suggest a role that is linked with volume regulation. The suggestion that atrial stretch alone, that is without nerves being involved, is an adequate stimulus to raise the plasma concentration sufficiently to evoke responses, however, has not yet been demonstrated. It is difficult to understand how this postulated system of control of fluid balance may be working; stretching that causes leakage of atrial natriuretic peptide from atrial muscle seems an unlikely stimulus for a complex hormonal system that controls blood volume. At present it is impossible to determine whether the concomitant changes in atrial natriuretic peptide and fluid balance indicate a role in control of fluid homeostasis or whether the observed changes are secondary to fluid imbalance. The reported changes in endogenous concentrations appear to be too small to be important in short term control but it is possible that in the long term small but prolonged changes in the concentration of atrial natriuretic peptide have a role in the control of body sodium—a hypothesis that it may be too difficult to test.

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