Atrial natriuretic peptides: clues to their physiological and clinical importance

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The idea that the heart might be important in the control of salt and water balance is not new, for Gauer and his colleagues had shown in the 1950s that atrial distension caused a diuresis and, in 1956, by the new technique of electron microscopy, dense, homogenous granules were described in the atria but not in the ventricles. Subsequently, Poche showed, in 1958, that the number of granules present was influenced by changes in food and water intake. However, it took a further 18 years before the influence of diet was explored again, Marie and colleagues finding that changes in both salt and water intake had independent effects on the numbers of granules in the atrial cardiac muscle cells. De Bold then performed the critical experiment in 1981. He found that injection of atrial but not ventricular extracts caused striking increases in urinary sodium and water excretion. It was only a further 2 years, with the new techniques available to molecular biologists, before the structure of atrial peptides was first reported and by 1984, several groups had independently sequenced and synthesized potent natriuretic and vasoactive atrial peptides.

Two years later, it is now possible to consider to what extent the initial excitement in these peptides has been justified. The first question of interest is whether there is now sufficient evidence to confirm in man that the atrial peptides are a natriuretic hormone. Many studies in man have now shown, by radio immunoassay as well as by radioreceptor assay, that atrial natriuretic peptides (ANP) are secreted in active form by the heart and circulate in measurable amounts in the plasma. Secondly, the level of plasma ANP in man changes rapidly in response to acute and chronic changes in sodium balance. Following saline infusion there is a rapid rise in plasma ANP which precedes the increase in natriuresis. With an increase in dietary sodium intake, there is a rise in plasma ANP within 24 hours, which is associated with an increase in urinary sodium excretion. The levels of ANP then remain elevated as long as the high salt diet is continued. Conversely, when dietary sodium intake is decreased, plasma ANP falls and remains depressed as long as the lower dietary sodium intake is maintained.

Studies of mineralocorticoid escape have shown that in plasma ANP rises on mineralocorticoid treatment, reaching a maximum at the time of escape and remaining elevated as long as fludrocortisone supplements are continued. Confirmation that atrial peptides are a natriuretic hormone comes from recent studies of the effect of man of administered ANP, which have shown that when given either as a low dose intravenous infusion so that the resulting plasma ANP concentrations are near the physiological range, or intranasally in low dose (0.6 μg/kg), there is an increase in urinary excretion of sodium and water.

The mechanism for the natriuresis caused by ANP is unclear. There is an extensive network of renal receptors for ANP, predominantly on the glomeruli, the collecting tubules and the renal artery. ANP stimulates guanylate cyclase and hence increases the production of the intracellular messenger cyclic GMP, which in renal epithelial cell cultures results in inhibition of amiloride-sensitive sodium transport. Recent work suggests that renal dopaminergic receptors may also be important in modulating the natriuretic effects of ANP infusion on renin secretion. However, in man ANP appears to inhibit the vasoconstrictive effects of infused angiotensin II and in vitro, ANP antagonizes both the basal and stimulated release of aldosterone from the adrenal cortex. There is therefore evidence for direct effects by ANP on the kidney as well as indirect effects on the renin-angiotensin-aldosterone axis (RAA).

In vitro, ANP causes endothelium-independent relaxation of aortic rings and peripheral veins and in vivo, in man, in high concentration, causes dose-dependent reduction in systemic blood pressure. More recent studies suggest that these vaso-active properties of ANP are pharmacological, with little...
effect on blood pressure when ANP is administered to
man in doses near the physiological range.\textsuperscript{14, 15, 22}
However at these low doses, ANP infusion has been
found to increase forearm blood flow as well as skin
blood flow.\textsuperscript{26, 27} Plasma ANP changes with posture,
rising in the supine position.\textsuperscript{28, 29} Whether these
elevated levels contribute by vaso-dilatation to reduc-
ing the increased venous return to the heart which
occurs in this position, complementing the diuresis
which later ensues, must remain speculative until
inhibitors of ANP become available.

Other potential physiological roles for ANP which
remain unclear are interactions between ANP and
other peptidergic systems, such as anti-diuretic hor-
mone, the importance of ANP in neural pathway
regulation\textsuperscript{30} and the local effects of ANP on myocar-
dial function.

Increasing knowledge of the physiology of atrial
peptides may lead to improved understanding of the
pathophysiology of disorders of salt and water
balance, as well as cardiac and renal disease. Indeed,
raised plasma ANP levels have been reported in
cardiac failure,\textsuperscript{2, 28, 31, 32, 33} paroxysmal supra-ven-
tricular tachycardia,\textsuperscript{24} renal failure,\textsuperscript{25, 26} cirrhosis,\textsuperscript{27}
primary hyperaldosteronism, Bartter's and Gordon's
syndromes,\textsuperscript{28} as well as in approximately 50% of
patients with essential hypertension.\textsuperscript{30, 39} These raised
ANP levels may be compensating for sodium and
water retention caused by the primary disorders and it
may be that without these raised ANP levels, there
would be considerably greater salt and water overload.
However, a contributing factor for plasma ANP
elevation particularly in cardiac disease and renal and
hepatic failure may be impaired catabolism and
clarity of the peptides.

It has already been shown that ANP levels fall in
association with clinical improvement in cardiac
failure.\textsuperscript{32, 33} In addition, it has been found, in end-stage
renal failure, that the high basal plasma ANP levels
fall in association with fluid removal by haemodialysis.\textsuperscript{36}
These findings suggest that plasma ANP measurement may prove useful in assessing
response to treatment in these and other conditions in
which salt and water homeostasis is abnormal.

The discovery that atrial peptides are powerful
diuretic agents, 1000 times more potent, on a molar
basis, than frusemide\textsuperscript{14} but without the potassium
wasting side effects of currently available loop diuretics,\textsuperscript{20, 22, 25}
suggested that they might be clinically useful in the treatment of salt and water overload and
there are now several studies underway of the
therapeutic effects of ANP. However, in a study of
intravenous infusion of ANP, patients with untreated
cardiac failure were relatively unresponsive to an
infusion rate that caused a marked natriuresis in
normal subjects.\textsuperscript{20} This may be due to high levels of
angiotensin II, secondary to the cardiac failure, block-
ing the effects of ANP, for when ANP was re-infused
after the renin system had been blocked with the
angiotensin converting enzyme inhibitor captopril,\textsuperscript{20}
a greatly increased natriuresis resulted.

Two developments would greatly increase our un-
derstanding of the physiology of ANP, as well as
broadening the clinical role of these fascinating pep-
tides. Firstly, inhibitors of ANP are needed to allow
direct testing of the importance of ANP in homeo-
sis of salt and water balance and vasomotor tone.
Secondly, human ANP and available synthetic
analogue has a short half life in the circulation\textsuperscript{41}
and they have to be given parenterally because these
peptides are rapidly denatured in the gut. Therefore,
long-acting analogues, particularly if stable when
given orally, would greatly increase the therapeutic
potential of these powerful agents. With the rapidly
increasing insight which is being acquired into the
physiology of atrial natriuretic peptides, it should
become possible to improve our understanding, and
therefore management, of many disorders of salt and
water balance.

Acknowledgements

DRJS is a British Heart Foundation Junior Research Fellow.

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Postgrad Med J 1987 63: 1-4
doi: 10.1136/pgmj.63.735.1