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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 colleagues¹ 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.² Subsequently, Poche showed, in 1958, that the number of granules present was influenced by changes in food and water intake.³ 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.⁴ 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.⁵ 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.⁶

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^{7, 7a} as well as by radioreceptor assay,^{8, 8a} 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^{9, 10} 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.^{10, 11} Conversely, when dietary sodium intake is decreased, plasma ANP falls and remains depressed as long as the lower dietary sodium intake is maintained.¹¹

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.^{12, 13} Confirmation that atrial peptides are a natriuretic hormone comes from recent studies of the effect in man of administered ANP, which have shown that when given either as a low dose intravenous infusion¹⁴ so that the resulting plasma ANP concentrations are near the physiological range, or intranasally in low dose (0.6 µg/kg),¹⁵ 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.¹⁶ ANP stimulates guanylate cyclase and hence increases the production of the intracellular messenger cyclic GMP,¹⁷ which in renal epithelial cell cultures results in inhibition of amiloride-sensitive sodium transport.¹⁸ Recent work suggests that renal dopaminergic receptors¹⁹ may also be important in modulating the natriuretic effects of ANP infusion on renin secretion.^{20, 21, 22} However, in man ANP appears to inhibit the vasoconstrictive effects of infused angiotensin II²³ and *in vitro*, ANP antagonizes both the basal and stimulated release of aldosterone from the adrenal cortex.²¹ 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 veins²⁴ and *in vivo*, in man, in high concentration, causes dose-dependent reduction in systemic blood pressure.^{20, 22, 25} 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.^{14, 15, 22} However at these low doses, ANP infusion has been found to increase forearm blood flow as well as skin blood flow.^{26, 27} Plasma ANP changes with posture, rising in the supine position.^{28, 29} Whether these elevated levels contribute by vaso-dilatation to reducing 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 hormone, the importance of ANP in neural pathway regulation³⁰ and the local effects of ANP on myocardial 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,^{7, 20, 31, 32, 33} paroxysmal supra-ventricular tachycardia,³⁴ renal failure,^{35, 36} cirrhosis,³⁷ primary hyperaldosteronism, Bartter's and Gordon's syndromes,³⁸ as well as in approximately 50% of patients with essential hypertension.^{39, 40} 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 clearance of the peptides.

It has already been shown that ANP levels fall in association with clinical improvement in cardiac failure.^{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.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 frusemide¹⁴ but without the potassium wasting side effects of currently available loop diuretics,^{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.²⁰ This may be due to high levels of angiotensin II, secondary to the cardiac failure, blocking the effects of ANP, for when ANP was re-infused after the renin system had been blocked with the angiotensin converting enzyme inhibitor captopril,²⁰ a greatly increased natriuresis resulted.

Two developments would greatly increase our understanding of the physiology of ANP, as well as broadening the clinical role of these fascinating peptides. Firstly, inhibitors of ANP are needed to allow direct testing of the importance of ANP in homeostasis of salt and water balance and vasomotor tone. Secondly, human ANP and available synthetic analogues have a short half life in the circulation⁴¹ 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.

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References

1. Henry, J.P., Gauer, O.H. & Reeves, J.L. Evidence of the atrial location of receptors influencing urine flow. *Circulation Res* 1956, **4**: 85–90.
2. Kisch, B. Electron microscopy of the atrium of the heart. *Exp Med Surg* 1956, **14**: 99–112.
3. Poche, R. Submikroskopische Beiträge zur Pathologie der Herzmuskelzelle bei Phosphorvergiftung. Hypertrophie, Atrophie und Kaliummangel. *Virchow's Archiv* 1958, **331**: 165–248.
4. Marie, J.P., Guillemont, H. & Hatt, P.Y. Le degré de granulation des cardiocytes auriculaires. Etude planimétrique au cours de différents apports d'eau et de sodium chez le rat. *Pathol Biol* 1976, **24**: 549–554.
5. De Bold, A.R., Borenstein, H.B., Veress, A.T. & Sonnenberg, H. A rapid and potent natriuretic response to intravenous injection of atrial myocardial extract in rats. *Life Sci* 1981, **28**: 89–94.
6. Needleman, P., Adams, S.P., Cole, B.R. *et al.* Atriopeptins as cardiac hormones. *Hypertension* 1985, **7**: 469–482.
7. Sugawara, A., Nakao, K., Morii, N., *et al.* Alpha-human

- atrial natriuretic polypeptide is released from the heart and circulates. *Biochem Biophys Res Commun* 1985, **129**: 439–446.
- 7a. Richards, A.M., Cleland, J.G.F., Tonolo, G. *et al.* Plasma α natriuretic peptide in cardiac impairment. *Br Med J* 1986, **293**: 409–412.
 8. Burgisser, E., Raine, A.E.G., Erne, P., Kamber, B. & Buhler, F.R. Human cardiac plasma concentrations of atrial natriuretic peptide quantified by radioreceptor assay. *Biochem Biophys Res Commun* 1985, **133**: 1201–1209.
 - 8a. Raine, A.E.G., Erne, P., Burgisser, E. *et al.* Atrial natriuretic peptide and atrial pressure in patients with congestive heart failure. *N Engl J Med* 1986, **315**: 533–537.
 9. Yamaji, T., Ishibashi, M., Takaku, F. Atrial natriuretic factor in human blood. *J Clin Invest* 1985, **76**: 1705–1709.
 10. Sagnella, G.A., Markandu, N.D., Shore, A.C. & MacGregor, G.A. Effects of changes in dietary salt intake and saline infusion on immunoreactive atrial natriuretic peptide in human plasma. *Lancet* 1985, **ii**: 1206.
 11. Sagnella, G.A., Markandu, N.D., Shore, A.C. & MacGregor, G.A. Plasma immunoreactive atrial natriuretic peptide and changes in dietary sodium intake in man. *Life Sci* 1987, **40**: (in press).
 12. Takeda, R., Miyamori, I. & Ikeda, M. Role of atrial natriuretic polypeptides for the pathogenesis of escape from mineralocorticoid excess. In Laragh, J.H. (ed) *Proceedings of the First World Congress on Biologically Active Atrial Peptides*. Raven Press, New York (in press).
 13. Cappuccio, F.P., Markandu, N.D., Shore, A.C., Buckley, M.G. & MacGregor, G.A. Plasma immunoreactive atrial natriuretic peptide during mineralocorticoid "escape" in man. *J Hypertens* 1986, **4**: (in press)
 14. Anderson, J., Struthers, A., Christofides, N. & Bloom, S. Atrial natriuretic peptide: an endogenous factor enhancing sodium excretion in man. *Clin Sci* 1986, **70**, 327–331.
 15. Shoinoiri, H. & Kaneko, Y. Intranasal administration of alpha-human natriuretic peptide produces a prolonged diuresis in healthy man. *Life Sci* 1986, **38**: 773–778.
 16. Koseki, C., Hayashi, Y., Torikai, S., Furaya, M., Ohnuma, N. & Imai, M. Localisation of binding sites for alpha-rat atrial natriuretic polypeptide in rat kidney. *Am J Physiol* 1986, **250**: F210–F216.
 17. Weil, J., Lang, R.E., Suttman, H., Rampf, U., Bidlingmaier, F. & Gerzer, R. Concomitant increase in plasma atrial natriuretic peptide and cyclic GMP during volume loading. *Klin Wochenschr* 1985, **63**: 1265–1268.
 18. Cantiello, H.F., & Ausiello, D.A. Atrial natriuretic factor and cGMP inhibit amiloride-sensitive Na^+ transport in the cultured renal epithelial cell line, LLC-PK₁. *Biochem Biophys Res Commun* 1986, **134**: 852–860.
 19. Pettersson, A., Hedner, J. & Hedner, T. The diuretic effect of atrial natriuretic peptide (ANP) is dependent on dopaminergic activation. *Acta Physiol Scand* 1986, **126**: 619–621.
 20. Tikkanen, I., Fyhrquist, F., Metsarinne, K. & Leidenius, R., Plasma atrial natriuretic peptide in cardiac disease and during infusion in healthy volunteers. *Lancet* 1985, **ii**: 66–69.
 21. Laragh, J.H. Atrial natriuretic hormone, the renin-aldosterone axis, and blood pressure-electrolyte homeostasis. *N Engl J Med* 1985, **313**: 1330–1340.
 22. Biollaz, J., Nussberger, J., Waeber, B. & Brunner, H.R. Clinical pharmacology of atrial natriuretic (3–28) eicosahexapeptide. *J Hypert* 1986, **4**, (suppl 2): S101–S108.
 23. Anderson, J.V., Struthers, A.D., Payne, N.N., Slater, J.D.H. & Bloom, S.R. Atrial natriuretic peptide inhibits the aldosterone response to angiotensin II in man. *Clin Sci* 1986, **70**: 507–512.
 24. Winquist, R.J., Faison, E.P. & Nutt, R.F., Vasodilator profile of synthetic atrial natriuretic factor. *Eur J Pharmacol* 1984, **102**: 169–173.
 25. Richards, A.M., Nicholls, M.G., Ikram, H., Webster, M.W.I., Yandle, T.G. & Espiner, E.A. Renal, haemodynamic and hormonal effects of human alpha atrial natriuretic peptide in healthy volunteers. *Lancet* 1985, **i**: 545–549.
 26. Muller, F.B., Erne, P., Raine, A.E.G. *et al.* Atrial antipressor natriuretic peptide release mechanisms and vascular actions in man. *J Hypert* 1986, **4** (Suppl 2): S109–S104.
 27. Brüssien, J.P., Biollaz, J., Waeber, B. *et al.* Dose-dependent effect of atrial natriuretic peptide on blood pressure, heart rate and skin blood flow of normal volunteers. *J Cardiovasc Pharmacol* 1986, **8**: 216–220.
 28. Hollister, A.S., Tanaka, I., Imada, T., *et al.* Sodium loading and posture modulate human atrial natriuretic factor plasma levels. *Hypertension* 1986, **8**: (Suppl II): II 106–111.
 29. Solomon, L.R., Atherton, D.C., Bobinski, H. & Green, R. Effect of posture on plasma immunoreactive atrial natriuretic peptide concentrations in man. *Clin Sci* 1986, **71**: 299–305.
 30. Shiono, S., Nakao, K., Morii, N. *et al.* Nature of atrial natriuretic polypeptide in rat brain. *Biochem Biophys Res Commun*. 1986, **135**: 728–734.
 31. Nakaoka, H., Imataka, K., Amano, M., Ishibashi, M. & Yamaji, T. Plasma levels of atrial natriuretic factor in patients with congestive heart failure. *N Engl J Med* 1985, **313**: 892–893.
 32. Katoh, Y., Kurosawa, T., Takeda, S. *et al.* Atrial natriuretic peptide levels in treated congestive heart failure. *Lancet* 1986, **i**: 851.
 33. Singer, D.R.J., Shore, A.C., Markandu, N.D., Buckley, M.G. & MacGregor, G.A. Atrial natriuretic peptide levels in treated congestive heart failure. *Lancet* 1986, **i**: 851.
 34. Tikkanen, I., Metsarinne, K. & Fyhrquist, F. Atrial natriuretic peptide in paroxysmal atrial tachycardia. *Lancet* 1985, **ii**: 40–41.
 35. Rascher, W., Tulassey, T. & Lang, R.E. Atrial natriuretic peptide in plasma of volume-overloaded children with chronic renal failure. *Lancet* 1985, **ii**: 303–305.
 36. Wilkins, M.R., Wood, J.A., Adu, D., Lote, C.J., Kendall, M.J. & Michael, J. Change in plasma immunoreactive atrial natriuretic peptide during sequential ultrafiltration and haemodialysis. *Clin Sci* 1986, **71**: 157–160.
 37. Gerbes, A.L., Arendt, R.M., Ritter, D., Jungst, D., Zahringer, J. & Paumgartner, G. Plasma atrial natriuretic factor in patients with cirrhosis. *N Engl J Med* 1985, **313**: 1609–1610.
 38. Tunny, T.J. & Gordon, R.J. Plasma atrial natriuretic

- peptide in primary aldosteronism (before and after treatment) and in Bartter's and Gordon's syndromes. *Lancet* 1986, **i**: 272–273.
39. Arendt, R.M., Stangl, E., Zahringer, J., Liebisch, D.C., & Herz, A. Determination and characterization of α -human atrial natriuretic factor in human plasma. *FEBS letters* 1985, **189**: 57–61.
 40. Sagnella, G.A., Markandu, N.D., Shore, A.C. & MacGregor, G.A. Raised circulating levels of atrial natriuretic peptides in essential hypertension. *Lancet* 1986, **i**: 179–181.
 41. Yandle, T.G., Richards, A.M., Nicholls, M.G., Cuneo, R., Espiner, E.A. & Livesey, J.H. Metabolic clearance rate and plasma half life of alpha-human atrial natriuretic peptide in man. *Life Sci* 1986, **38**: 1827–1833.