ATRIAL NATRIURETIC PEPTIDE

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Homeostatic regulation of fluid and electrolyte balance is essential for survival. In the past 30 years there has been tremendous growth in our understanding of intrarenal mechanisms regulating electrolyte balance and blood pressure. In 1959 Kisch (1) has identified endocrine - like granules in cardiac atrial, but not ventricular, tissue. In 1981, the significance of these granules and their relevance to the search for an extrarenal natriuretic mechanism were demonstrated by de Bold and his colleagues (2). These investigators found that the injection of rat atrial homogenates induces a profound natriuresis, diuresis and a decrease in systemic arterial pressure. Considerable effort has focused on the storage and release mechanisms of this substance within cardiac tissue, and on the identification of the circulating form of it. Afterwards, several atrial peptides with potent natriuretic and vasorelaxant properties similar to those of de Bold's crude atrial extracts have been isolated, purified, sequenced and chemically synthesized (3, 4, 5). Various names are used for peptide hormone that is secreted by cardiac atria: such as, atrial natriuretic factor, atrial natriuretic hormone, atrial natriuretic peptide (ANP), atrine, atriopeptin, auriculin and cardionatrin.

The primary atrial peptide synthesized in the atrial tissue is a 152 - amino acid prehormone (4). The disulfide bridge located between positions 129 and 145 of the precursor is essential for both natriuretic and vasorelaxant activities and a minimum of 23 amino acids is required for the expression of complete biologic activity. The 28 - amino acid peptide is the active circulating hormone in man (alpha ANP). Human ANP appears during the very early fetal period (6).

ANP release is stimulated by intravenous volume overloading (7), salt loading (8, 9, 10, 11, 12), exercise (13, 14, 15, 16), vasoconstrictor agents (17) and/or head - out water immersion (5). ANP is secreted into the circulation through the coronary sinus to act on target organs including kidney, adrenal cortex and the vasculature. The physiologic effects of ANPs can be devided into four categories: Effects on renal hemodynamics and sodium excretion, effects on vascular smooth muscle, effects on blood pressure and systemic hemodynamics, and effects on renin - angiotensin - aldosterone system (3, 18, 19).

EFFECTS ON RENAL HEMODYNAMICS AND SODIUM EXCRETION

Detailed studies in the isolated perfused rat kidney (20, 21) and human subjects (22) have shown that ANP administration evokes a definite and sustained increase in glomerular filtration rate (GFR) even when systemic arterial pressure is decreased and renal blood flow is constant or reduced. This may be due to the selective constriction of the efferent arterioles of the glomerulus (3, 18), or ANP may act on the glomerular membranes to oppose angiotensin - II or to directly increase permeability. ANP increases renal sodium and water excretion not only by an increase in GFR, but also by modifying intrarenal distribution of blood flow and thereby increasing medullary blood flow. ANP probably induces a medullary washout, which increases sodium excretion in response to an increased distal delivery of the filtrate. Proposed tubular effects of ANP include distal tubular inhibition, sodium reabsorption thus accounting for remarkable natriuresis and diuresis (3, 4).

ANP is able to ameliorate impaired renal function leading to increased GFR, diuresis, natriuresis in the maintenance phase of glycerol - induced (20) or norepinephrine - induced (21) acute renal failure (ARF). The usefulness of ANP in prevention from ARF in humans has to be elucidated. The plasma levels of human ANP in patients with end - stage renal disease were higher than healthy subjects and patients with advanced renal failure without volume expansion (23, 24, 25). The plasma concentration of ANP falls significantly after hemodialysis (26, 27). This reduction is caused by the decrease of blood volume, but not by removal of the peptide due to dialysis. Alpha - h - ANP with its important role in the regulation of renal function and sodium - water balance, seems to have potential therapeutic value in renal diseases (22, 23, 28).

EFFECTS ON VASCULAR SMOOTH MUSCLE

The vasorelaxant action of ANP has been demonstrated in preconstricted isolated vascular strips. The relaxation mediated by ANP does not require an intact endothelium (29) and occurs concomitantly with an elevation in intracellular cGMP due to an activation of particulate guanylate cyclase. This finding suggests that cGMP may be the second messenger

for ANP (29, 30, 31). ANP is capable of abolishing pressor effects of endogenous substances such as Angiotensin II and norepinephrine (31). The vasodilator potency of atrial peptides is reported to be restricted to the arterioles without affecting venous tone in dogs (32).

EFFECTS ON BLOOD PRESSURE AND SYSTEMIC HEMODYNAMICS

In addition to increases in GFR and sodium excretion, ANP administration consistently has been found to produce dose dependent reductions in arterial blood pressure in various animal species (33) and in human subjects (34). The blood pressure lowering effect of ANP is related to: its natriuretic property, inhibition of the vasoconstriction induced by angiotensin II and norepinephrine and inhibition of renin - angiotensin - aldosterone system (3, 34, 35). ANP also has been shown to reduce blood pressure in several animal models of experimental hypertension (35) and in hypertensive patients (36). The mechanism of the hormone's hypotensive effect appears to differ in high - renin and low - renin forms of hypertension (3). In the high-renin two-kidney Goldblatt hypertension (the renal artery of one kidney is clamped and the opposite is left in place), ANP lowers blood pressure by relaxing the preconstricted arterioles (3, 36) whereas in low-renin hypertension models (as in DOCA-salt treated rats) the hypotensive effect occurs by a reduction in venous return (37, 38). An impaired renal sodium excretion is postulated to be the primary abnormality in essential hypertension. Elevated plasma ANP observed in essential hypertension might be an indication of volume expansion induced by an impaired control of sodium excretion (11). So, the increase of circulating ANP represents a feedback mechanism to compensate for the inefficiency of sodium excretion in the kidney (9, 10, 12, 39). ANP is secreted from cardiac atria presumably by the stimulation of atrial stretch receptors induced by hypervolemia and increase in right atrial pressure (9, 40). ANP is rapidly released into the circulation when sodium or volume is loaded, and the atrial storage of ANP remains depleted for about 1 week (10). Effective antihypertensive therapy reduces elevated levels of plasma ANP in essential hypertension (41). Plasma ANP concentrations are found elevated in various arrhythmias being higher in patients with ventricular tachycardia than with supraventricular tachycardia or atrial fibrillation (42), and in acute versus chronic tachycardia, right atrial pressure (43) rather than ventricular rate determines ANP release during tachycardia. Raised levels of this hormone may be a contributing factor for the polyuria and the hypotension associated with paroxysmal tachycardias (44, 45).

Plasma ANP is found to be elevated in congestive heart failure and directly correlated with the severity of the disease. This suggests a possible role of ANP as a compensatory mechanism in the pathogenesis of congestive heart failure (46). Infusion of synthetic atrial peptide produced benefical hemodynamic effects by counter-balancing the renin - angiotensin - aldosterone system in congestive heart failure (47). Consequently, ANP may be helpful in treating patients with severe congestive heart failure by reducing peripheral vascular resistance and decreasing afterload and thereby improving cardiac performance (46, 47, 48). The elevated ANP concentration in the patients with heart failure decreased after their conditions improved with digoxin and diuretics or with surgical correction. Therefore, the measurement of plasma ANP concentration may provide valuable information in evaluating the presence or absence of heart failure (6). Patients with severe congestive heart failure, who do not respond with natriuresis and diuresis to their high plasma levels of ANP, appear resistant to their endogenous ANP. Whether this is due to target organ insensitivity, alterations in receptor functions or lowered renal blood flow are questions worthy of further exploration (49, 50).

Plasma ANP levels are significantly correlated with pulmonary arterial pressure, cardiac output and with an increase in the intraatrial pressure.

MISCELLANEOUS EFFECTS

An unexplained response noted in experimental animals and man is ability of atriopeptin to increase the cellular component of hematocrit, suggesting that the peptide regulates volume distribution by shifting fluid between the extra and intra vascular compartment (3).

Acute exercise stimulates ANP secretion in proportion to the intensity of exercise (14). This response is modified by subjects sodium status (15). The release of this potent vasoactive substance during exercise initiates events which later contribute to the development of post - exercise hypotension (13). In cardiac patients, the investigators observed an enhanced exercise - induced rise in ANP levels, probably due to hemodynamic impairment, at exercise (16). The estimation of ANP levels in plasma during a standardized ergometer test could turn out to be at least an accessory and noninvasive diagnostic approach in the evaluation of patients suffering from heart diseases.

Not only pharmacological or pathological plasma concentrations but also physiological plasma concentrations of infused synthetic ANP can elicit the renal and hormonal response, proving that ANP is a physiologically important circulating hormone (56). Circulating levels of ANP are elevated during pregnancy (57) and in the human fetus ANP is found to be a circulating hormone (58).

The discovery of ANP succeeded in bringing together nephrologists, endocrinologists, cardiologists, physiologists, pharmacologists, pediatricians, etc., in attempts to define the pharmacology and physiology of this peptide (17).

Although the research to date suggests that ANP may be the key component of a new cardiovascular

regulatory system, there is still much to learn about this hormone. The exciting pharmacologic profile for ANP has offered promise for the therapy of cardiovascular disorders involving volume overload elevated vascular resistance, and renal disease states. Although a vast amount of information has accumulated over the past 6 years, a more complete understanding of the role of ANP and synthesis of specific antagonists are needed before it is possible to determine the therapeutic potential of this new exciting hormone.

REFERENCES

1. *Kisch B. Electron microscopy of the atrium of the heart. Exp Med Surg 1956; 14: 99 - 112.*
2. *De Bold AJ, Borenstein HB, Veress AT, Sonenberg HA. Rapid and potent natriuretic response to intravenous injection of atrial myocardial extracts in rats. Life Science 1981; 28: 89 - 94.*
3. *Laragh HJ. Atrial natriuretic peptides. Pharmacology 1987; 1: 33 - 39.*
4. *Needleman P, Currie GM, Geller MD, et al. Atriopeptins: potential mediators of an endocrine relationship between heart and kidney. TIPS 1984; Dec: 506 - 509.*
5. *Needleman P. The expanding physiological roles of atrial natriuretic factor. Nature 1986; 321: 199 - 200.*
6. *Kikuchi K, Nishioka K, Ueda T, et al. Relationship between plasma atrial natriuretic polypeptide concentration and hemodynamic measurements in children with congenital heart disease. Jour of Ped 1987; 3: 335 - 342.*
7. *Kihara M, Nakoa K, Morii N, et al. Responses of plasma atrial natriuretic polypeptide to isotonic volume expansion in conscious spontaneusly hypertensive and chronically Guanethidine - treated rats. Jour of Hypertension 1986; 4, supp: 3: 321.*
8. *Gibbs DM. Noncalcium - dependent modulation of in vitro atrial natriuretic factor release by extracellular osmolality. Endocrinology 1987; 120: 1091 - 1094.*
9. *Salazar FJ, Granger JP, Joyce MLM, et al. Effect of hypertonic saline infusion and water drinking on atrial peptide. Am J Physiol 1986; 251: 1091 - 1094.*
10. *Kato J, Kida O, Nakamura S, Sasaki A, Takiguishi K, Tanaka K. Dissociation between plasma and atrial content of atrial natriuretic polypeptide following sodium load in rats. Life Science 1986; 39: 2624 - 2627.*
11. *Wambach G, Götz S, Bönner G, Kaufmann W. Plasma levels of atrial natriuretic peptide are raised in essential hypertension during low and high sodium intake. Klin Wochenschr 1987; 65: 232 - 237.*
12. *Lang RE, Thölgen H, Ganten D, Luft FC, Ruskuaho H, Unger T. Atrial natriuretic factor: a circulating hormone stimulated by volume loading. Nature 1985; 21: 264 - 268.*
13. *Somers VK, Anderson JV, Conway J, Sleight P, Bloom SR. Atrial natriuretic peptide is released by dynamic exercise in man. Horm Met Res 1986; 18: 871 - 872.*
14. *Tanaka H, Shindo M, Gutkowska J. Effect of acute exercise on plasma immunoreactive atrial natriuretic factor. Life Sciences 1986; 39: 1685 - 1693.*
15. *Richards AM, Tonolo G, Cleland GF, et al. Plasma atrial natriuretic peptide concentrations during exercise in sodium replete and deplete normal man. Clin Science 1987; 72: 159 - 164.*
16. *Petzl DH, Hatter E, Osterode W, Böhm H, Wolosczuk W. Atrial natriuretic peptide release due to physical exercise in healthy persons and in cardiac patients. Klin Wochenschr 1987; 65: 194 - 196.*
17. *Winquist R. Pharmacological effect of atrial natriuretic peptide. End Met Clin Nortn America 1987; 16: 163 - 181.*
18. *Flier J, Underhill LH, Laragh HJ. Atrial natriuretic hormone: the renin - aldosterone axis and blood pressure - electrolyte homeostasis. New Eng J Med 1985; 21: 1330 - 1340.*
19. *Palluk R, Gaida W, Hoefke W. Minireview atrial natriuretic factor. Life Sciences 1985; 36: 1416 - 1425.*
20. *Heidbred E, Schafferhans K, Götz RS, Heidland A. Toxic renal failure in the rat: Beneficial effects of atrial natriuretic factor. Klin Wochenschr 1986; 64, suppl 4: 78 - 82.*
21. *Schafferhans K, Heidbreder E, Heidland A. Human atrial natriuretic factor prevents against norepinephrine - induced acute renal failure in rat. Klin Wochenschr 1986; 64, supp 4: 73 - 77.*
22. *Kuribayashi T, Nakatazo M, Tanaka M, et al. Renal effects of human alpha atrial natriuretic polypeptide. New Eng J Med 1985; 30: 1456 - 1457.*
23. *Walker GR, Swainson P, Yandle T, Nicholls G, Espiner A. Exaggerated responsiveness of immunoreactive atrial natriuretic peptide to saline infusion in chronic renal failure. Clin Science 1987; 72: 19 - 24.*
24. *Rascher W, Tulassay T. Atrial natriuretic peptide in plasma of volume - overloaded children with chronic renal failure. Lancet 1985; 10: 303 - 305.*
25. *Yamamato Y, Higa T, Kitamura K, Tanaka K, Kangawa K, Matsuo H. Plasma concentration of human natriuretic polypeptide in patients with impaired renal function. Clin Neph 1987; 27: 84 - 86.*
26. *Kojima S, Inoure I, Hirata Y, et al. Plasma concentrations of immunoreactive - atrial natriuretic polypeptide in patients on hemodialysis. Nephron 1987; 46: 45 - 48.*
27. *Larochelle P, Beroniade V, Gutkowska J, et al. Influence of hemodialysis of plasma levels of the atrial natriuretic factor in chronic renal failure. Clin Invest Med 1987; 10: 350 - 354.*
28. *Tulassay T, Rascher W, Lang R, Seyberth W, Scharer K. Atrial natriuretic peptide and other vasoactive hormones in nephrotic syndrome. Kidney Int 1987; 31: 1391 - 1395.*
29. *Winquist JR. Modulation of vascular tone by atrial natriuretic factor. Blood Vessels 1987; 24: 128 - 131.*
30. *Casto R, Hilbig J, Schroeder G, Stock G. Atrial natriuretic factor inhibits central angiotensin II pressor responses. Hypertension 1987; 9: 473 - 477.*

31. *O'Donnel EM, Owen N. Role of cyclic GMP in atrial natriuretic factor stimulation of Na, K, Cl cotransport in vascular smooth muscle cells. J Biol Chem 1986; 261: 15461 - 15466.*
32. *Holtzo J, Stewart DJ, Elsner D, Babenge E. In vivo atrial peptide venodilation minimal potency relative to nitroglycerin in dogs. Life Sciences 1986; 39: 2177 - 2184.*
33. *Dunn R, Ichikawa I, Pfeffer M, Troy LJ, Brenner BM. Renal and systemic hemodynamic effect of synthetic atrial natriuretic peptide in anaesthetized rat. Circ Res 1986; 59: 237 - 246.*
34. *Cusson RJ, Hamet P, Gutkowska J, et al. Effects of atrial natriuretic factor on natriuresis and cGMP in patients with essential hypertension. J Hypertension 1987; 5: 435 - 443.*
35. *Garcia R, Cantin M, Geneset J, Gutkowska J, Thibault G. Body fluids and plasma atrial peptide after its chronic infusion in hypertensive rats. Proc Soc Exp Biol Med 1987; 185: 352 - 358.*
36. *Edwards B, Schwab RT, Zimmerman RS, Heublein MD, Burnett JC. Cardiovascular, renal and endocrine response to atrial natriuretic peptide in angiotensin II mediated hypertension. Circ Res 1986; 59: 664 - 667.*
37. *Schiffrin EL, Louis J. Decreased density of vascular receptors for atrial natriuretic peptide in DOCA - salt hypertensive rats. Hypertension 1987; 9: 504 - 512.*
38. *Tikkanen T, Tikkanen I, Fhyrquist F. Plasma atrial peptide in DOCA NaCl treated rats. Acta Physiol Scand 1987; 129: 151 - 155.*
39. *Kohno M, Yasunari K, Murakawa K, Kanayama Y, Matsura T, Takeda T. Effects of high - sodium and low - sodium intake on circulating atrial natriuretic peptides in salt sensitive patients with systemic hypertension. Am J Cardio 1987; 59: 1212 - 1213.*
40. *Akabane S, Kojima S, Igarahi Y, Kawamura M, Matsushima Y, Ito K. Release of atrial natriuretic polypeptide by graded right atrial distension in anesthetized dogs. Life Sciences 1987; 40: 119 - 125.*
41. *Kohno M, Yasunari K, Matsuura T, Murakawa K, Takeda T, Osaka MD. Circulating atrial natriuretic polypeptide in essential hypertension. Am Heart J 1987; 113: 1160 - 1163.*
42. *Crozier I, Nicholls GM, Ikram H, Espiner EA, Yandle TG. Atrial natriuretic peptide in spontaneous tachycardia. Br Heart J 1987; 58: 96 - 100.*
43. *Niclas JM, Dicarlo AL, Koller TP, et al. Plasma levels of immunoreactive atrial natriuretic factor increase during supraventricular tachycardia. Am Heart J 1986; 112: 923 - 930.*
44. *Kojima S, Akabane S, Ohe T, et al. Plasma atrial natriuretic polypeptide and polyuria during paroxysmal tachycardia in Wolf Parkinson White Syndrome patients. Nephron 1986; 44: 249 - 253.*
45. *Roy D, Paillard F, Cassidy D, et al. Atrial natriuretic factor during atrial fibrillation and supraventricular tachycardia. JACC 1987; 9: 509 - 514.*
46. *Riegger GAJ, Kromer PE, Kochsiek K. Human atrial natriuretic peptide: Plasma levels, hemodynamic, hormonal and renal effects in patients with severe congestive heart failure. J Cardiovasc Pharm 1986; 8: 1107 - 1112.*
47. *Crozier IG, Ikram H, Gomez HJ, Nicholls MG, Espiner EA, Warner NJ. Hemodynamic effects of atrial peptide infusion in heart failure. Lancet 1986; 29: 1242 - 1245.*
48. *Kokubu T, Nagae A, Hdawa K, Katanazi Y, John T, Matsuo H. Pulmonary arterial pressure and plasma concentration of atrial natriuretic factor in patients with heart disease. Jpn Heart J 1986; 27: 791 - 794.*
49. *Tikkanen T, Tikkanen I, Fhyrquist F. Elevated plasma atrial natriuretic peptide in rats with myocardial infarct. Life Sciences 1987; 40: 659 - 663.*
50. *Lee RW, Gay GR, Moffett C, Johnson GD, Goldman S. Atrial natriuretic peptide levels during development of chronic heart failure after myocardial infarction in rats. Life Sciences 1987; 40: 2025 - 2030.*
51. *Wambach G, Hannekum A, Kaufman W, Dalichau H. Erhöhte konzentrationen des atrialen natriuretischen peptids im plasma und im Herzvorhof bei patienten mit aorten und mitralvitien im vergleich zu patienten mit koronarer herzkrankheit. Z Kardiol 1987; 76: 76 - 80.*
52. *Naruse K, Naruse M, Honda T, et al. Atrial natriuretic peptide correlates with pulmonary arterial pressure and cardiac output. Peptides 1987; 8: 285 - 290.*
53. *Koller P, Grekin R, Nicklas J. Paradoxical response of plasma atrial natriuretic hormone to pericardiocentesis in cardiac tamponade. Am J Cardiology 1987; 15: 491.*
54. *Hirata Y, Isii M, Suggmoto T, et al. Relationship between the renin aldosterone system and atrial natriuretic polypeptide in rats. Clin Science 1987; 72: 165 - 170.*
55. *Lappe WR, Todt AJ, Robert WL. Effects of atrial natriuretic factor on the vasoconstrictor actions of the renin - angiotensin system in conscious rats. Circ Research 1987; 61: 134 - 140.*
56. *Anderson J, Struthers A, Christofides N, Bloom S. Atrial natriuretic peptide: an endogenous factor enhancing sodium excretion in man. Clin Science 1986; 70: 327 - 331.*
57. *Cusson RJ, Gutkowska J, Rey E, Michon N. Plasma concentration of atrial natriuretic factor in normal pregnancy. New Eng J Med 1985; 7: 1230.*
58. *Yamaji t, Hirai N, Ishibashi M, Takaku F, Nakayama T. Atrial natriuretic peptide in umbilical cord blood: Evidence for a circulating hormone in human fetus. J Clin End Met 1986; 63: 1414 - 1416.*

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