UNIVERSITY OF NIŠ
The scientific journal **FACTA UNIVERSITATIS**
Series: **Medicine and Biology** Vol.5, No 1, 1998 pp. 6 – 11
Editor of Series: Vladisav Stefanović, e-mail: factacivil@medfak.medfak.ni.ac.yu
Adress: Univerzitetski trg 2, 18000 Niš, YU, Tel: (018) 547-095 Fax: (018) 547-950
http://ni.ac.yu/Facta

UDC 612.17

VASOACTIVE NATRIURETIC PEPTIDES AND KIDNEY

Ljiljana Surić-Lambić[1], S. Pleša[1] V. Stojanov[2], D. Avramović[2]

[1] *Department of Nephrology, University Teaching Hospital Zemun, Belgrade*
[2] *Institute of Cardiovascular diseases, Clinical Centre of Serbia, Belgrade, Yugoslavia*

Summary. *The natriuretic peptide family (ANP, BNP, CNP) is responsible for the body fluid homeostasis and blood pressure control. ANP and BNP act on guanylate cyclase-A and CNP on guanylate cyclase-B receptors.The main renal actions of ANP are: 1. direct and indirect effects on the kidney to alter renal hemodynamics, and to increase fluid and electrolyte excretion; 2. functional antagonism of the renin-angiotensin-aldosterone system (R-A-A) by inhibiting synthesis and/or relase of renin and aldosterone, and by antagonising all known effects of angiotensin. ANP increases single nephron GFR in proportion of total GFR due mainly to an increase in glomerular capillary hydrostatic pressure that results from efferent arteriolar constriction and afferent arteriolar dilation. ANP indirectly acts on tubular sites that are targets of R-A-A system, including proximal tubular sites (angiotensin) and distal nephron sites (aldosteron). Regulation of CNP secretion is different from that of ANP and BNP, which are cardiac hormones. The increase of the plasma CNP in chronic renal failure (CNF) can be due to the diminished clearance of CNP in the kidney or due to increase in CNP production that occurs in the renal parenchymal cells. In chronic renal failure (CRF) exists a downregulation of ANP clearance receptors due to exaggerated ANP-stimulated cGMP response in CRF glomeruli. In hemodialysis patients, changes in plasma ANP are greater than in BNP and more responsive to changes in left atrial volume due to ultrafiltration.*

Key words: *Natriuretic peptides, renal disease, haemodialysis*

Introduction

Many investigations have been made to explain the regulation of diuretic-natriuretic function of the kidney. Efforts were focused on the detection of diuretic and natriuretic substances (1,2). A step forward in the research on renal regulation by the heart was made when the first factor from heart atria involved in diuresis was characterized as a peptide (3). In 1981 de Bold et al (1) published the decisive experiment demonstrating that administration of crude acid extract of rat atria to anesthetized rats led to a powerful natriuretic response, sodium excretions increasing more than threefold above baseline levels, whereas a similarly prepared ventricular extract was without effect (3).

Peptides family. – The detection amino acid sequence of this cardiac peptide from rat and porcine atria revealed the atrial natriuretic-diuretic and the vaso-relaxant peptide (4,5) – in the current literature under the names atrial natriuretic factor (*ANF*) or atrial natriuretic peptide (ANP*)*. Subsequent studies resulted in the finding of new substances, and a family of peptides, now designated as the A-type (ANF 28), B-type (BNP 32), C-type (CNP 22) and urodilatin (ANF 32) (3), has been established. Amino acid sequence of ANF 28 and other members of the natriuretic family is shown in Fig. 1 (3).

Atrial natriuretic factor (ANF 28)

Atrial natriuretic factor, a polypeptide hormone of 28 amino acid (*ANF 28*) with potent vasodilator, hypotensive (7) and diuretic activities, has been purified from animal and human atrial extracts (8). Several stimuli for the release of this hormone have been identified, including *volume expansion* associated with increased atrial strech and pressures (4) as well as atrial and ventricular tachyarrhythmias (3,9,10). Stretch-induced release is independent of Ca^{2+}, and that removal of Ca^{2+} from the superfusate increases the rate of ANF 28 release (11).

Molecular biology of ANF 28 and ANF 32 – The A-types of natriuretic peptides (ANF 28 and ANF 32) are produced by one single gene containing three exons and two introns (12). It is localized on the short-arm position 36.1-3 of chromosome 1 in humans (6). The plasma levels of ANF 28 and the N-terminal fragment of its pro-hormone (termed *N-terminal pro-ANF*) correlate closely with atrial pressure. ANF 28 is rapidly

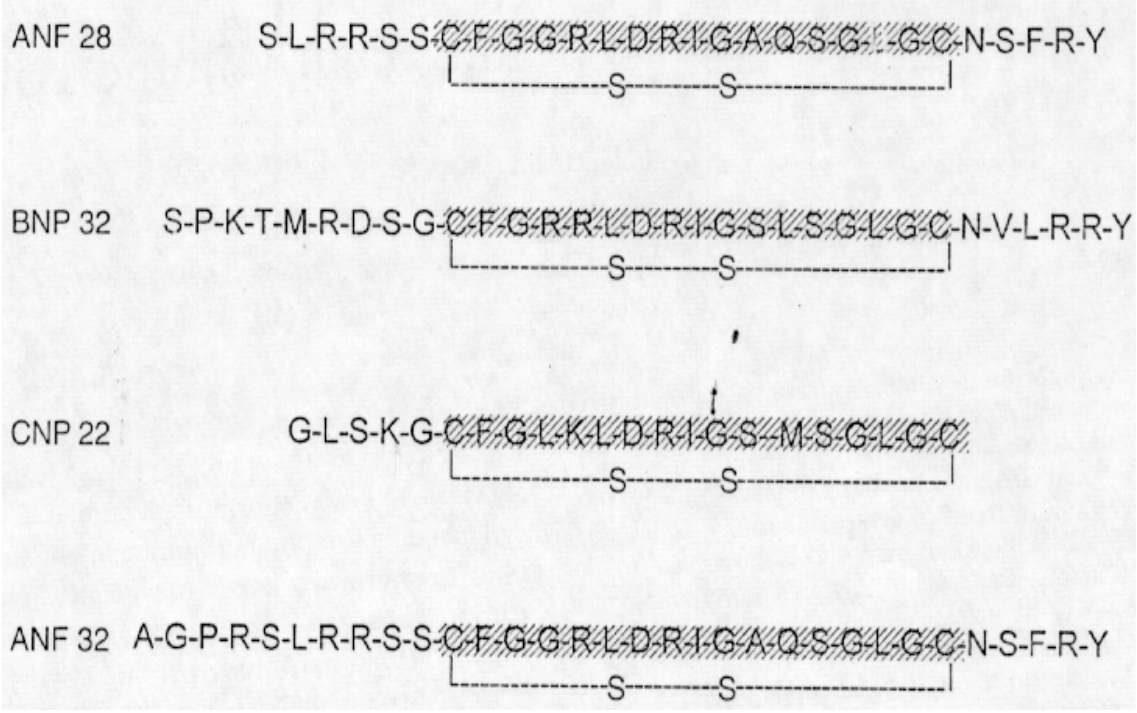

Figure 1. Amino acid sequence of ANF (*ANF 28*) and other members of the natriuretic peptide family. The peptides have a conserved central core between disulfide linked cysteines (shaded) and variable C and N terminals. (Maack T. Role of atrial natriuretic factor in volume controle. Kidney International 1996;49:1732-7).

degraded by lysosomal hydrolases internalization via receptor - mediated endocytosis.

ANF 28 receptors – In the kidney ANF 28 acts on specific receptors. ANF 28 receptors have been identified in the glomerulus (13-16) with the majority (63%) on visceral epithelial cells, 14% on parietal cells, 13% on capillary endothelium and 10% on mesangial cells (13). All vessels of the renal arterial tree have ANF 28 receptors, including the arcuate and interlobular arteries and afferent and efferent arterioles (15), although ANF 28 receptor density appears to be greatest in the glomeruli. Glomerular ANF 28 receptor density is down-regulated when plasma ANF 28 levels are elevated, as in mineralocorticoid escape or in rats on high-salt diet (14).

Renal actions of ANF 28 – The several nephrone sites are targets for ANF 28 (3). ANF 28 increases single nephron (SN) glomerular filtration rate (GFR) in proportion of total GFR (3). The increase is mainly due to an increase in glomerular capillary hydrostatic pressure that results from efferent arteriolar constriction and afferent arteriolar dilation (3). In normal conditions, ANF 28 does not alter or even slightly decrease SN and total renal blood flow (RBF). ANF 28 is the only known endogenous substance that may increase GFR in face of a decrease in blood pressure, and an unchanged or even decreased RBF due to its generic vasorelaxant property (3).

ANF 28 markedly increases the load of sodium to the base of the inner medullary collecting duct (IMCD), an effect that is essential for a robust natriuretic response, and subsequently disrupt load-reabsorption balance in this nephron segment.The reasons for the increase in sodium load to the IMCD are multiple: increase in GFR, decrease in inner medullary hypertonicity that decreases passive fluid efflux from the thin limbs of Henle′ loop, direct tubular effects of ANP 28 that decrease sodium reapsorption in nephron segments proximal to the IMCD (17).

ANF 28 and end stage renal disease (ESRD)

Basal levels of ANF 28 are increased in both mild to moderate renal insufficiency and ESRD (18). A positive feedback control loop was observed in dialysis patients between *ANF 28* secretion and (1) blood volume level, and (2) atrial dimensions, with *ANF 28* concetration increasing with extracellular fluid volume (ECFV) expansion and decreasing after dialysis ultrafiltration (18).

Molecular forms of ANF 28 (α, β and γ) in plasma of stable haemodialysis (HD) patients differ from those of healthy volunteers. The middle-molecular-weight ANF 28 (β ANF 28) may particularly be secreted in clinically stable HD patients (19).

Plasma levels of ANF 28 and BNP 32 were measured, along with left and right atrial and left ventricular volumes, in patients wirh chronic renal

failure before and after the removal of fluid by ultrafiltration (UF) and again during volume repletion with i.v. NaCl sol. (20). Baseline levels of ANF 28 (46.0 ± 7.5 pmol/L) and BNP 32 (22.0 ± 4.4 pmol/L) were elevated above normal. There was a significant reduction in plasma ANF 28 (26.5 ± 4.7 pmol/L) and *BNP 32* (19.1 ± 4.9 pmol/L, $p < 0.05$) following UF. Changes in plasma ANF 28 during UF correlated significantly with changes in left atrial volume ($r = 0.643$, $p < 0.05$). During volume repletion there was a exaggerated release of ANF 28 (mean level post repletion 71.3 ± 20.8 pmol/L), which was not paralleled by changes in BNP 32. Changes in BNP 32 were small, showing no correlation with atrial or ventricular volumes during UF or volume repletion. Changes in plasma ANF 28 are greater than BNP 32 and more responsive to changes in left atrial volume (20). However, there not yet a consensus as to the significance of a role of BNP compared with results in the Ishizaka et al. study (26).

Hypertensive haemodialysis (HD) patients. – It has been observed that while most hypertensive HD patients normalize their blood pressure (BP) with fluid removal, there is a population of HD patients whose hypertension is refractory to such treatment. The hypotesis is that such patients are still volume overloaded post-HD, and are not at a "true" dry weight. This suggests that: 1) ANF 28 levels are higher in hypertensive than normotensive HD patients. 2) Hypertensive HD patients who normalize their BP with HD, also normalize their ANF 28 levels. 3) Hypertensive HD patients whose BP is refractory to fluid removal do not normalize their ANF 28 levels with volume removal, supporting the hypothesis that these patients remain significantly fluid overloaded after HD (21).

Renal transplatation. – In subjects undergoing renal transplantation, despite an adequate density of glomerular ANF 28 receptors and enhanced cGMP generation, neither renal vasoconstriction nor hypofiltration is alleviated by a progressive elevation of plasma ANF 28 levels in renal transplant recipients with sustained postischemic injury.That means that constricted afferent arterioles are unresponsive to the vasorelaxant action of endogenous ANF 28 in this form of postischemic, acute renal failure (22).

Brain natriuretic peptide (BNP 32)

BNP 32 was first isolated from the porcine *brain*, and it has a stiking similarity to ANF 28 with regard to both its amino acid sequence and pharmacological spectrum (23). BNP 32 is also synthesized in and secreted from the porcine heart (24). Unlike ANF 28, BNP 32 shows species variation in both its structure and tissue distribution.

Plasma BNP 32 before and after hemodialysis. – In patients before HD, a 14 to 2.300-fold increase in plasma level of immunoreactive (ir-) BNP 22 was observed when compared to normal controls. A ratio of BNP 32 to pro-BNP in plasma from the patients was much larger than that in plasma from normal subjects, indicating that the high plasma level of ir-BNP level in the patients on HD largely results from a marked increase in BNP 32. Hemodyalisis significantly ($p < 0.01$) lowered the plasma levels of both BNP 32 and pro-BNP, with a greater reduction in BNP 32 than in *pro*-BNP. Whereas, ANF 28 was a main molecular form of plasma ANF in both pre- and post-HD plasma. These suggest that plasma BNP 32 plays an important role in the sodium-fluid balance and that secretion and metabolism of BNP 32 may differ from those of ANF 28 in the HD patients (25).

In the other study, BNP 32 was measured in 40 patients on HD and in 12 healthy subjects. The mean (±SD) plasma BNP 32 level in the patients before HD (18.4 ± 3.4 fmol/mL) was markedly higher than that in the control group (0.39 ± 0.08 fmol/mL). The plasma BNP 32 level was significantly decreased by HD from 18.4 ± 3.4 fmol/mL to 10.5 ± 2.2 fmol/mL, $p < 0.001$), but the latter value was still higher than the upper limit of the normal range (26). The correlation was not observed between the plasma BNP 32 level and mean blood pressure. Ultrasound studies in 13 patients revealed correlations between the ANF 28 level before HD and the interventricular septal thickness index ($r = 0.68$, $p < 0.05$) and between the change in BNP 32 levels and left atrial diameter ($r = 0.806$, $p < 0.001$). In conclusion, BNP 32 and ANF 28 levels correlated with several parameters of volume change and cardiac status (26), which is in contrast to results in Corboy et al. study (20).

C-type natriuretic peptide (CNP 22)

The third member of the natriuretic peptide family, CNP 22, recently has been isolated from the porcine brain and is reported to act principally as a neuropeptide (27) and is also produced in cultured vascular endothelial cells (28,29). CNP 22 is known to act via two types of receptors, natriuretic peptide receptors B and C (30). The former of these is linked to guanylate cyclase, causeing accumulation of cGMP; the latter produces several effects including inhibition of cAMP synthesis (31). Suga et al. (32) reported the *in vivo* gene expression of CNP 22 and its specific receptor, guanylate cyclase-B (GC-B) receptor, in *intact vessels*. CNP 22 can induce relaxation and growth-inhibition of vascular smooth muscle cells as a novel endothelium-derived relaxing peptide (33).

The differences of the potency of CNP 22, ANF 28 and BNP 32 can be partly attributed to the differences in the distribution of GC-A receptors, which show a high affinity to ANF 28 and BNP 32, and GC-B receptors which are specific to CNP 22 (32). GC-A is widely distributed in humans and predominantly exists in the lung, kidney and blood vessels, which are the target

organs of intravenous-administered natriuretic peptides, wheras GC-B expression in those organs is less abundant (32).

In contrast with ANF 28 and BNP 32, CNP 22 appears to be secreted predominantly from the vascular endothelium (28). The *diuretic* and natriuretic effects of CNP 22 are limited in comparison with ANF 28 and BNP 32 (34).

CNP 22 is involved in the local regulation of the vascular renin-angiotensin system. It inhibits the vasoconstrictor effect of angiotensin I more than it inhibits the vasoconstrictor effect of angiotensin II. This suggests an important role for CNP 22 as a paracrine endogenous regulator of vascular ACE activity (35). ACE activity in cultured endothelial cells is stimulated by cAMP and by agents that increase its production but is not affected by cGMP, suggesting that CNP 22 may act via natriuretic peptide receptor C to reduce cAMP production and inhibit ACE activity (35).

CNP 22 and hemodialysis therapy. – To investigate the significance of CNP 22 as an endothelium-relaxing peptide in renal functions in humans, the plasma CNP 22 level in chronic renal failure (CRF) patients (n = 7), who were under hemodialysis therapy, was examined (36). The significant increase of the plasma CNP 22 level (3.0 ± 0.4 fmp/ml) in patients with CRF vs healthy humans (1.4 ± 0.6 fmol/ml) can be partly due to the diminished clearance of CNP 22 (36). However, another possibility remains; an incraese in CNP 22 production may occur in the renal parenchymal cells, leading to elevated plasma CNP 22 (37).

In the other study, plasma CNP 22 levels were greatly elevated in patients with CRF [non-dialysed, 13.0 ± 4.2 fmol/L, n=9, $p < 0.01$ compared with normal subjects (4.4 ± 0.4 pmol/L, n = 26); hemodialysis 16.1 ± 2.1 pmol/L, n=13, $p < 0.01$], but non in patients with congestive heart failure (CHF, NYHA class II-IV) (3.0 ± 0.7 pmol/L, n=11, $p > 0.05$). Plasma ANF 28 and BNP 32 levels were elevated both in patients with CHF and in HD patients with CRF. These findings suggest that CNP 22 is a non-cardiac circulating hormone and participates in the cardiovascular regulation in a different manner from ANF 28 and BNP 32 (38).

Renal natriuretic peptide - urodilatin (ANF 32)

The different natriuretic peptides (NPs) were recognized to be mainly important as cardiovascular regulatory hormones. Several observations led to the conclusion that in extracardiac NP systems, namely that of the kidney, may exist NP-immunoreactive substances that were demonstrated by immunohistochemistry in tubular epithelial cells of the kidney. Actually, it is known that A-type (39) and C-type (40) natriuretic peptides are localized in kidney cells of the distal tubules. These peptides can be measured by radioimmunoassay in kidney tissue. Isolation and amino acid sequence analysis of the urinary form of the A-type NP resulted in the discovery of A-new factor – ANF 32 (urodilatin) (6, 41).

In contrast to the circulating form of A-type NP with its 28 amino acid containing chain (ANF 28), urodilatin represent a peptide of 32 amino acids (ANF 32) lengthened at the N-terminus of the cirulating form by Thr-Ala-Pro-Arg. It is postulated that the peptides are derived from the common gene in chromosome 1. (Fig. 1) (6).

The mechanism how the exact synthesis of ANF 32 happens is still unclear. Two hypothesis (6) may be proposed: (1) ANF 32 is processed from minor quantities of circulating cardiogenic precursor which is sufficient when cleared from the circulation and cleaved in the kidney, and (2) the produced ANF 32 is really synthesized in distal tubular cells and cleaved there from the precursor (6,42,43). ANF 32 is a typical paracrine factor regulating intrarenal functions (5) and resistant to degradation by the endoprotease (EC 24.11) (6).

Physiology. – Receptors of the collecting ducts may be the target under physiological conditions. The natriuretic peptid luminal receptors B (NPR-B) are physiologically the only targets for ANF 32. Recently, it has been shown by polymerase chain reaction that urodilatin-sensitive receptors are expressed in the human kidney (44). ANF 32 binds to renal receptors (45) and activates the targets via cyclic guanosine monophosphate (cGMP) increase. Its tubular effect is a result of its interaction with the amiloride-sensitive sodium channels.

ANF 32 peptide closely relates to diurnal rhythm of natriuresis and intermitent water-sodium load, dietary sodium changes and renal sodium excretion (46), and reduction of natriuresis during microgravity (47). The regulation of ANF 32 peptide secretion is unclear, but may be triggered by a humoral factor induced among other things by brain salt *load* reaching the kidney by means of a humoral pathway (6).

Clinical application

Acute renal failure. – It has been shown in animal experiments that natriuretic peptides may prevent or attenuate ischemic renal failure. In animal experiments, ANF 32 peptide in contrast to sodium nitroprusside improves the state of acute renal failure (48).

Cardiac transplantation. – Some investigators observed significant benefits using a 4-day infusion of *ANF 32* peptide after heart (49, 50) or liver and heart transplantations (51).

Bone marrow transplantation. – Acute renal failure was imminent in an 18-month-old male infant 20 days after unrelated bone marrow transplantation (BMT). The infant was treated with urodilatin and furosemide infusions. After seven days of urodilatin (ANF 32) treatment diuresis was normal, the serum

creatinin level had decreased, and furosemide was reduced. No side effects were observed (52).

Liver transplantation. – Eight patients who developed acute renal failure (ARF) after liver transplantation and fulfilled requirements for hemodialysis / hemo-filtration were treated. After low dose ANF 32 (urodilatin) infusion was started, renal function improved and all patients developed a strong diuresis and natriuresis within 2-4 h. The study shows that continuous low dose ANF 32 infusion may present a new concept for treatment of postoperative acute renal failure resistant to conventional therapy (53).

References

1. de Bold AJ, Borenstein HB, Veress AT, Sonneberg H. A rapid and potent natriuretic response to intravenous injection of atrial myocardial extract in rats. Life Sci 1981; 28: 89-94.
2. Sonnenberg H, Cupples WA, de Bold AJ, Veress AT. Intrarenal localization of the natriuretic effects of cardiac atrial extract. Can J Physiol Pharmacol 1982; 60: 1149-1152.
3. Maack T. Role of atrial natriuretic factor in volume control. Kidney Int 1996; 49: 1732-1737.
4. Burnett JCJr, Kao PC, Hu DC, et al. Atrial natriuretic peptide elevation in congestive heart failure in the human. Science 1986; 231: 1145-1147.
5. Forssmann WG, Hock D, Lottspeich F, et al. The right auricle of the heart is an endocrine candidate. Anat Embryol (Berl) 1983; 168: 307-313.
6. Forssmann WG. Urodilatin (Ularitide,INN): A renal natriuretic peptide. Nephron 1995; 69: 211-222.
7. de Bold AJ Atrial natriuretic factor: a hormone produced by the heart. Science 1985; 230: 767-770.
8. Cantin M, Benchimol S, Castonguay Y, Berlinguet J-C, Huet M. Ultrastructural cytochemistry of atrial cells. Characterization of specific granules on the human left atrium. J Ultrastruct Res 1975; 52: 179-192.
9. Nicklas JM, Dicarlo LA, Koller PT, et al. Plasma level of immunoreactive atrial natriuretic factor increase during supraventricular tachycardia. Am Heart J 1988; 112: 923-928.
10. Ellenbogen KA, Rogers R, Walsh M, Monhatny PK. Increased circulating atrial natriuretic factor (ANF) release during induced ventricular tachycardia. Am Heart J 1988; 116: 233-238.
11. De Bold M I. and De Bold A J. Effect of manipulations of Ca^{2+} environment on atrial natriuretic factor release. Am J Physiol 1989; 256: H1588
12. Oikawa S, Imai M, Tanaka S, et al. Cloning and sequence analysis of cDNA encoding a precursor for human natriuretic polypeptide, Nature 1984; 309: 724-726.
13. Bianchi C., Gutkowska J., Thibault G. et al. Distinct localization of atrial natriuretic factor and angiotensin II binding sites in the glomerulus. Am J Physiol 1986; 251 (Renal Fluid Electrolyte Physiol 20) : F 594
14. Ballermann BJ.,Hoover RL., Karnovsky MJ. and Brenner BM. Physiologic regulation of atrial natriuretic peptide receptors in rat renal glomeruli. J Clin Invest 1985; 76: 2049
15. Healy DP. and Fanestil DD. Localiyation of atrial natriuretic peptide binding sites within the rat kidney. Am J Physiol 1986; 250 (Renal Fluid Electrolyte Physiol 19) : F 573
16. Koseki C., Hayashi Y., Torikai S. et al. Lokalization of binding sites for α-rat atrial natriuretic polypeptide in rat kidney. Am J Physiol 1986; 250 (Renal Fluid Electrolyte Physiol 19) : F 210
17. Ballermann BJ, Zeidel ML, Gunning ME, Brenner BM. Vasoactive peptides and the kidney. In Brenner BM, Rector FC: The Kidney, 4th ed. Philadelphia : W.B.Saunders Comp, 1991: 510-583
18. London G., Marchais S. Guerin AP. Blood pressure control in chronic hemodialysis patients. In Jacobs C.,Kjellstrand CM., Koch KM., Winchester JF (Eds): Replacment of Renal Function by Dialysis, 4th ed. Dordrecht: Kluwer Academic Publ 1996; 966-989.
19. Akiba T, Ando K, Marumo F. Changes in molecular pattern of atrial natriuretic peptide in hemodialysis patients. Int J Artif Organs 1994; 17: 585-590.
20. Corboy JC, Walker RJ, Simmonds MB, et al. Plasma natriuretic peptides and cardiac volume during acute changes in intravascular volume in haemodialysis patients. Clin Sci Colch 1994; 87: 679-684.
21. Fisbane S, et al. Atrial natriuretic peptide (ANP) and subtypes of hypertension in hemodialysis (HD) patients (abstract). 27th Annual Meeting American Society of Nephrology. Orlando (USA), 1994.
22. Vinot O, Bialek J, Canaan-Kuhl S, et al. Endogenous ANP in postischemic acute renal allograft failure. Am J Physiol 1995; 269 (1 Pt 2): F125-33.
23. Sudoh T, Kangawa K, Minamino N, Matsuo H. A new natriuretic peptide in porcine brain. Nature 1988;332:78-81.
24. Hasegawa K, Fujiwara H, Itoh H, et al. Light and electron microscopic lokalization of brain natriuretic peptide in relation to atrial natriuretic peptide in porcine atrium: immunohisto-cytochemical study using specific monoclonal antibodies. Circulation 1991; 84: 1203-1209.
25. Ishizaka Y, Yamamoto Y, Tanaka M, et al. Molecular forms of human brain natriuretic peptide (BNP) in plasma patients on hemodyalisis (HD). Clin Nephrol 1995; 43: 237-242.
26. Ishizaka Y, Yamamoto Y, Fukunaga T, et al. Plasma concentration of human brain natriuretic peptide in patinets on hemodialysis. Am J Kidney Dis 1994; 24: 461-472.
27. Sudoh T, Minamino N, Kangawa K, Matsuo H. C-type natriuretic peptide (CNP): A new member of natriuretic peptide family identified in porcine brain. Biochem Biophys Res Commun 1990; 168: 863-870.
28. Suga S, Nakao K, Itoh H, et al. Endothelial production of C-type natriuretic peptide and its marked augmentation by transforming growth factor-β – Possible existence of "vascular natriuretic peptide system". J Clin Invest 1992; 90: 1145-1149.
29. Komatsu Y, Nakao K, Itoh H, Suga S, Ogawa Y, Imura H. Vascular natriuretic peptide. Lancet 1992; 340: 622.
30. Nakao K, Ogawa Y, Suga S, Imura H. Molecular biology and biochemistry of the natriuretic peptide system.II: natriuretic peptide receptors. J Hypertens 1992; 10: 1111-1114.
31. Levin ER. Natriuretic peptide C-receptor more than a clearance receptor. Am J Physiol 1993; 264: E483-489.
32. Suga S, Nakao K, Itoh H, et al. Receptor selectivity of natriuretic peptide family, atrial natriuretic peptide, brain natriuretic peptide and C-type natriuretic peptide, Endocrinology 1992; 130: 229-239.
33. Itoh H, Pratt RE, Dzau VJ. Atrial natriuretic polypeptide inhibits hypertrophy of vascular smooth muscle cells. J Clin Invest 1990; 86: 1690-1697.
34. Hunt PJ, Richards AM, Espiner EA, et al. Bioactivity and metabolism of C-type natriuretic peptide in normal man. J Clin Invest 1994; 78: 1428-1435.
35. Davidson NC, Barr CS, Struthers AD. C-type natriuretic peptide. Circulation 1996; 93: 1155-1159.
36. Igaki T, Itoh H, Suga A, et al. C-type natriuretic peptide in chronic renal failure and its action in humans.Kidney Int 1996; 49 (Suppl. 55): S144-S147.
37. Mattingly M,Brandt R, Heublein D, Wei C, Nir A, Burnett J Jr. Presence of C-type natriuretic peptide in human kidney and urine. Kindny Int 1994; 46: 744-477.
38. Tosune K, Takahashi K, Murakami O, et al. Elevated plasma C-type natriuretic peptide concentrations in patients with chronic renal failure. Clin Sci (Colch) 1994; 87: 319-322.
39. Figueroa CD, Lewis HM, MacLver AG, Mackenzie JC, Bhoola KD. Cellular localization of atrial natriuretic factor in the human kidney. Nephrol Dial Transplant 1990; 5: 25-31.
40. Suzuki E, Hirata Y, Hayakawa H, et al. Evidence for C-type

natriuretic peptide production in the rat kindney. Biochem Biophys Res Commun 1993; 192: 532-538.
41. Schulz-Knappe P, Forssmann K, Herbst F, Hock D, Pipkorn R, Frossmann WG. Isolation and structural analysis of "urodilatin", a new peptide of the cardiodilantin (ANP), extracted from human urine. Klin Wochenschr 1988; 66: 752-759.
42. Ritter D, Needlemann P, Greenwald JE. Synthesis and secretion of atriopeptin-like protein in rat kidney cell culture. J Clin Invest 1990; 87: 208-212.
43. Greenwald JE, Needlemann P, Wilkins MR, Schreiner GF. Renal syntgesis of atriopeptin-like protein in physiology and pathophysiology. Am J Physiol 1991; 260: F602-607.
44. Kruhoeffer M, Bub A, Ekhlasi M, Klingenberg M, Forssmann WG. Natriuretic peptide B receptor is predominantly expressed in renal papilla. Exp Clin Endocrinol 1994; 102(Suppl. 1): 122.
45. Valentin JP, Sechi LA, Qiu C, Schambelan M, Humphreys MH. Urodilantin binds to and activates renal receptors for atrial natriuretic peptide. Hypertension 1993; 21: 432-438.
46. Heer M, Drummer C, Baisch F, Gerzer R. Long-term elevations of dietary sodium produce parallel increases in the renal excretion of urodilantin and sodium. Pfluegers Arch 1993; 425: 390-394.
47. Drummer C, Heer M, Dressendoerfer RA, Strasburger CJ, Gerzer R. Reduced natriuresis during weightlessness. Clin Invest 1993; 71: 678-686.
48. Weidmann P, Hellmueller B, Uehlinger DE, et al. Plasma levels and cardiovascular, endocrine and excretory effects of atrial natriuretic peptide during different sodium intakes in man. J Clin Endocrinol Metab 1986; 62: 1027-1036.
49. Hummel M, Kuhn M, Mann B, et al. Urodilantin, ein humanes renales Peptid zur Orophylaxe des akuten Nierenversagens nach Herztransolantation. Z Hearz Thorax Gefaesschir 1993; 7: 90-98.
50. Hummel M, Kuhn M, Bub,A, et al.Urodilantin, a new therapy to prevent kidney failure after heart transplantation. J Heart Transplant 1993; 12: 209-218.
51. Cedidi C, Kuse ER, Meyer M, et al. Treatment of acute postoperative renal failure after liver and heart transplantation. Clin Invest 1993; 71: 435-436.
52. Laws HJ, Kropp S, Meyer M, Forssmann WG, Burdach S. Treatment of acute renal failure with urodilatin after unrelated bone marrow transplantation. Bone Marrow Transplant 1995; 16: 307-310.
53. Cedidi C, Meyer M, Kuse ER, et al. Urodilatin: a new approach for the treatment of therapy-resistant acute renal failure after liver transplantation. Eur J Clin Invest 1994; 4: 632-639.

VASOAKTIVNI NATRIURETIČKI PEPTIDI I BUBREG

Ljiljana Surić-Lambić[1], S.Plješa[1] V. Stojanov[2], D. Avramović[2]

[1] KBC Zemun, Nefrološko odeljenje Internističke službe, Beograd
[2] Institut za kardiovaskularne bolesti Kliničkog centra Srbije, Beograd, Jugoslavija

Kratak sadržaj: *Porodica natriuretskih peptida odgovorna je za homeostazu telesne tečnosti i kontrolu krvnog pritiska. ANP i BNP deluju preko gvanilat-ciklaza A a CNP preko gvanilat-ciklaza B receptora. Glavna dejstva ANP su: 1 .neposredni i posredni uticaj na hemodinamske promene u bubregu, čime je povećano izlučivanje tečnosti i elektrolita; 2.suprotstavljanje funkciji renin-angiotenzin-aldosteron (RAA) sistema putem inhibicije stvaranja i/ili oslobađanja renina i aldosterona, i neutralisanjem svih poznatih efekata angiotenzina. ANP povećava glomerulsku filtraciju (GF) u svakom pojedinačnom nefronu zavisno od ukupne GF uglavnom na račun povećanja hidrostatskog pritiska u kapilarima glomerula regulisanim konstrikcijom eferentne i dilatacijom aferentne arteriole. ANP posredno deluje na mestima uticaja RAA sistema u tubulima uključujući proksimalni (angiotenzin) i distalni (aldosteron) tubul. Mehanizam nastanka CNP je različit od mehanizma nastanka hormona srca-ANP i BNP. U hroničnoj bubrežnoj insuficijenciji (HBI), smanjeno uklanjanje CNP u bubregu ili povećano stvaranje CNP od strane bubrežnih parenhimskih ćelija, dovodi do povećanja nivoa CNP u plazmi. Uz to, u HBI smanjuje se broj receptora za ANP zbog povećanja nivoa cGMP u glomerulima nastalog kao posledica povišenih vrednosti ANP u plazmi.U bolesnika na hemodijalizi (HD), promene nivoa ANP u plazmi veæe su nego nivoa BNP i reaktivnije na promene volumena leve pretkomore u toku HD.*

Ključne reči: *Natriuretički peptidi, bubrežne bolesti, hemodijaliza*

Received: September 18, 1997