Atrial Natriuretic Peptide and Cardiovascular System

V. A. Azizov, S.R. Muradova
2nd Department of Internal Medicine - Azerbajian Medical University, *Baku Azrebajian*

Heart, except it's dynamic function as a pump fforce of cardiovascular apparatus, in whole, fulfills several other purposes. During last years, it has been enlightened that heart has also endocrine function.

First data on secretory granules appeared in literature in 1964 (1, 2) which showed, that mammalian's cardiomyocytes, including human's, have character of specific secretory granules, similar with granules of endocrine organ cells, releasing peptide secrets. Number and density of these granules depend on changes of water and sodium influx, as well as on several experimental manipulations as adrenalectomy and hypertension during adrenal registration. Even, taking in account these morphological findings, it was concluded that cardiomyocytes and mentioned granules had a possible role in regulation of water and sodium homeostasis and volume balance.

The substances of peptic character were isolated and purified from atrial cardiomyocytes and their chemical components and synthesis were then defined. These substances were named as "atrial natriuretic peptide''(ANP). Other definitions –as auriculin, atriopeptin and cardionatrii are used now rarely. As appeared, ANP specifically causes natriuresis and simultaneously controls extracellular liquid volume, water and sodium homeostasis, being thus a regulator of the most important functions of cardiovascular and renal systems.

Secretory granules are ovale bodies with homogenous electron – dense content and limiting membrane, under which one could identify thin ring. They mainly accumulated near nuclei, complex Golgi aggregation zone, where they formed the largest aggregations. Single granules are diffusely spread in cytoplasm (3).

Several works investigated organelles that support endocrine activity of atrial myocytes. It has been shown, that Golgi complexes may be observed at the peripheral cites of cardiomyocyte cells, which is not an intrinsic feature of cardiomyocytes. Entirely, large Golgi complexes, surrounded by large amount of various molecules, well-developed systems of agranular and granular endoplasmic reticulum with accumulation of mitochondria around, formed powerful synthetic complex.

Formation of granules in human myocytes begins with accumulation of moderate density substances in expanded parts of complex Golgi cisterns, sometimes in kind of drop at their ends. These drops are differentiated with surrounded membrane, forming pro-granules with clear electron–transparent well-defined ring under membrane, with bristles on their surface.

Here, in complex Golgi zone, the dissolving granules among mature ones could be revealed (4).

The works of several authors, investigated electron-microscopic features and development of atrial granules, are also attracted attention. It has been found that atrial granules appear in atrial myocytes at the definite stage of heart development. The time of their formation is defined (5) by formation of Golgi apparatus, which is formed at near-nuclei area in close connection with active nuclei membrane.

As Golgi apparatus reaches definite degree of differentiation, the first signs of granular structures formation - peripheral parts become denser with further accumulation of dense substance with microstructure sign - are appeared in their macules.

The investigations of the above-mentioned authors demonstrated that formation of Golgi apparatus starts on the 14th day of embryonic period. Differentiation of its components is accompanied with

the appearance of the single formed granules on the 1st day of the development. Consequently, their amounts are rapidly increased (6).

Further, the hormone secreted by cardiomyocytes, was isolated and its chemical compounds were determined. The amino acid sequence of the factor from atria was established for the first time by Flinn (7).

ANP in cardiomyocytes is synthesized as pro-hormone, consisting of 152 amino acids in rats and 151 amino acids in humans. Human and rat peptides are homologous by their structure, differing only by one amino acid located in 12th position (isoleucine instead of methionine in human factor). Analogous factor, isolated from rat's heart, is also similar in structure. These findings testified on highly conservative structure of ANP in mammalians and humans from one side and on the other - permit to use their similarity for practical purposes (for example animal ANP antibodies could be used for testing of peptide in human blood) (8). Large amount of information on structure of ANP and its precursor, as well as mechanisms of regulation of its synthesis, was obtained while investigation of its gene structure. Human and rat DNA fragments, containing ANP precursor gene and it's primary structures were obtained by gene engineering methods (6, 9).

Specifically, quite original approach, based on features of ANP gene expression –so- called method of differential hybridization of colonies was used for establishing of clones in gene chains that contain ANP gene. Using this method investigators selected clones, containing those DNA fragments, which were expressed in atria, but were inactive in ventricles (10).

Determination of the primary structure of ANP gene and surrounding areas showed that it represents typical example of mosaic eukaryotic gene. The ANP precursor structure is encoded in 3 zones: the first coding zone contains information on hydrophobic peptide structure and moreover information on 20 amino acid residuals of intrinsic precursor; the structure of the residual part of ANP precursor, except one human ANP's C-terminal amino acid or three rat's amino acids are encoded in the second block (11).

Formation of m-RNA, that encodes ANP precursor, consisted of 151 amino-acid residuals in humans and of 152 amino acid residuals in rats, takes place after transcription and splicing.

Data on polypeptide precursor structure were acquired mainly by determination of nucleotide sequence of its encoding DNA fragment (12).

The main target organs for ANP action are kidneys, vessels, adrenal glands, several structures in central and sympathetic nervous systems (1, 10). In kidneys, ANP acts on vascular system, excretory and endocrine functions. The most pronounced renal effects are increase in sodium, chloride and water excretion and less one – potassium, calcium, phosphate and magnesium. Despite all efforts, investigators could not yet explain the mechanism of these actions. It is considered that increase in glomerular filtration, changes in parenchymal blood flow and probably – tubule effects on sodium reabsorbtion in tubules and collecting channels play a complex role. Firstly, direct tubule effects of ANP and secondly, relative changes in reabsorbtion due to hemodynamic changes in kidneys could be assumed (11, 13).

ANP has an inhibiting effect on renin production, changes sodium transport or has direct inhibiting effects on renin secretion by juxtaglomerular renal cells (2, 8).

The other system, which is influenced by ANP, is vascular system (14). ANP causes relaxation of vessels, exhibiting constrictive effects of angiotensin II and norepinephrine (15). Its effect on noncontracted arterial bed is markedly less. Reduction of blood pressure, which becomes noticeable after infusion of increased ANP doses, is caused partially by dilation, and partially by decrease in cardiac output due to reduction of venous return and venodilation. Another mechanism, which may play role in blood pressure reduction, is neuromodulating effect of ANP on brain structures, responsible for central regulation of cardiovascular functions (16).

Several investigations also showed that ANP has hypotensive effects due to its influence on other chains, particularly, on the renin-angiotensin-aldosterone system.

ANP binds to the vascular smooth muscle cell's surface receptors, lowering adenylate cyclase, activating guanylate cyclase and increasing c-GMP levels, which plays a role of a secondary messenger in ANP action, leading thus to vessel dilation and reduction of peripheral resistance (17).

During last years it has been demonstrated, that there is a close relationship of ANP with the central and sympathetic nervous system. High ANP concentrations were revealed in central nervous system, and receptors of this peptide - in structures having relation to central regulation of cardiovascular system and water-electrolyte balance. Further, ANP inhibits angiotensin effects and release of antidiuretic hormone from hypothalamic nuclei and neurohypophysis (4).

ANP plays a major role in volume and osmotic balance regulation. Pronounced effects of ANP on natriuresis, diuresis, vasorelaxative and depressor actions, interrelationship with other pressor and antinatriuretic peptides, its effect on central and sympathetic nervous system allow to suppose that this factor plays role in regulation of electrolyte and volume homeostasis, as well as in regulation of pressure balance (18). Accomplishing of volume and osmotic regulation is related to that atria are the ideal place of baro- and osmoreceptors localization, as well as synthesis and release of regulatory substances.

Left atrium plays an important role in volume regulation of extracellular liquid. Increase in blood plasma volume and functional overload of atria (ligation of aorta, physical exercise) stimulate release of ANP into the blood (10). Findings, testified on changes of ANP levels in cardiac pathology, have been acquired recently. It is suggested that change in synthesis affects development of edema. So, atrial extract has the least diuretic and natriuretic activity in Syrian hamsters with spontaneous cardiomyopathy and edemas than in healthy animals (19).

The role of ANP in complex pathogenesis of edematous states and arterial hypertension has more character of adaptive-compensatory changes. However, the effects of ANP in the target organ should not necessary manifest by changes in the number or sensitivity of respective receptors, for example in kidneys (in edematous states) or vessels (arterial hypertension), despite high ANP plasma concentrations (20).

The high concentration of ANP in dependence on stage of decompensation has been shown in congestive heart failure (21). Gradual compensation of congestive heart failure was accompanied by the reduction of high ANP plasma concentrations. The direct correlation of ANP plasma concentration with right atrial and pulmonary arterial pressures and its relative correlation with cardiac index were confirmed (22). Depressor and natriuretic actions of ANP hypothetically allow suggesting, that its insufficient synthesis might be one of the causes of arterial hypertension.

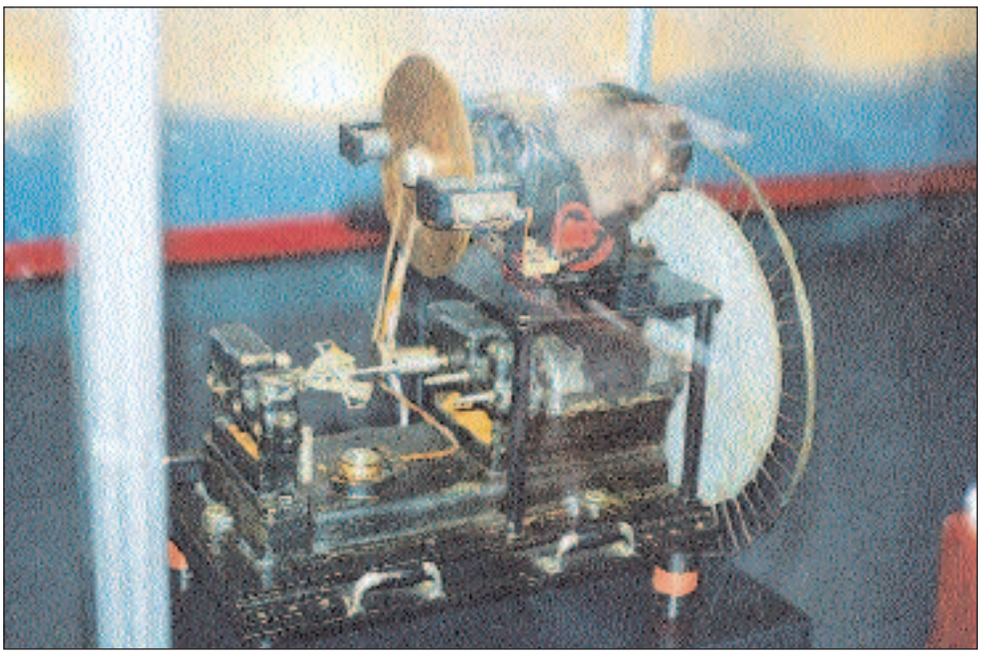
Angiotensin II and atrial natriuretic peptide are considered as functional antagonists in the regulation of liquid volume homeostasis and electrolyte content and arterial pressure as well. In order to investigate in detail the relationship of two hormones, the effects of low doses of angiotensin II on plasma ANP concentration and influences of ANP release on renal and hormonal reactions of angiotensin II were studied. These investigations were carried out in the conditions of continuous sodium load and inhibition of angiotensin-converting enzyme. It has been established that during increase of liquid volume in dogs angiotensin II may promote release of renin independently of changes in atrial pressures and systemic hemodynamics. This allows concluding, that angiotensin II may have significant modulating effect on ANP secretion.

In conclusion, it should be noted, that ANP as regulatory factor has marked effects, participating in regulation of the most physiological processes in organism through interrelationship with the most important regulatory systems as renin-angiotensin-aldosterone, sympathetic and kallikrein-kinin systems. In this connection, further investigations of its structural-functional interrelationships have undoubtedly theoretical and practical meaning.

References

1. Genest J. The atrial natriuretic factor. Br Heart J 1986: 56; 302-16.
2. Laragh J.H. Atrial natriuretic peptides. Pharmacology, 1987; 21: 33-8.
3. Mikhailov IB, Chukhlovina ML. Natriuretic peptides–biologically active substances. Eksp Klin Farmakol. 1995; 58: 63-5. Russian.
4. Postnov AI, Gor'kova SI, Vikhert AM. Morphological characteristics of the secretion of natriuretic peptide by atrial cardiomyocytes in spontaneous hypertension in rats. Biull Eksp Biol Med 1987; 104: 116-8. Russian.
5. Chervova IA, Pavlovich ER. Morphology of the main parts of conduction system in rats. Arch Anat Hist Embryol 1979; 8: 67-77.
6. Ballermann BJ, Brenner BM. Role of atrial peptides in body fluid homeostasis. J Circ Res 1986: 58 ; 619-30.
7. Ferrari P, Ferrier CP, Franscini L, Saxenhofer H. Atrial natriuretic factor and autonomic nervous system func-

tion in man. Eur J Clin Pharmacol 1990 : 38 ; 25-30.
8. Cherniaev AL, Bolshakova GB. Atrial natriuretic peptide in human and animal pathology. Arkh Patol. 1987; 49: 88-92. Review. Russian.
9. Clemo H, Baumgarten C, Ellenbogen K, Stambler B. Atrial natriuretic peptide and cardiac electrophysiology: autonomic and direct effects. J Cardiovasc Electrophysiol 1996: 7; 149-62.
10. Gellai M, Allen DE. Contrasting views on the action of atrial peptides: lessons from studies of conscious animals. Federation proceedings. 1986: 45; 2387-90.
11. Gerzer R, Heim JM Cellular mechanisms of action of atrial natriuretic factor. Klin Wochenschr 1987: 65; 109-14.
12. Takemura G., Fujiwara H., Mukoyama M., Saito Y. Immunohistochemical localization and semi-quanti-fication of atrial natriuretic polypeptide (ANP) in formalin-fixed-paraffin-embedded normal human hearts Comparative study with radioimmunoassay. Jap Circulat J 1989 ; 53: 686-94.
13. Volpe M., Atlas S.A., Sosa R.E., Marion D.E. Angiotensin II-induced atrial natriuretic factor release in dogs in not related to hemodynamic responses. Circ Res 1990; 67: 774-9.
14. Takemura G., Fujiwara H., Horike K., Mukoyama M. Ventricular expression of atrial natriuretic polypeptide and its relations with hemodynamics and histology in dilated human hearts. Immunohistochemical study of the endomyocardial biopsy specimens. Circulation. 1989: 80; 1137-47.
15. Tikkanen I., Metsarinne K. Plasm atrial natriuretic peptide in cardiac disease and during infusion in healthy volunteers. The Lancet 1985; 13: 66.
16. Atlas S, Kleinert H, Camargo M, et al. Structure and biological effects of atrial natriuretic peptide. Kardiologiia 1986; 26: 20-7. Russian.
17. Baturova EA, Suvorov IA. The role of atrial natriuretic peptide in the regulation of the activity of the cardiovascular system. Kardiologiia. 1991; 31: 91-3. Russian.
18. Bobrov VA, Shershnev VG, Polivoda SN, Konoshevich SN. Structural-functional state of the hypertensive heart and atrial natriuretic peptide during treatment with nifedipine. Kardiologiia. 1991; 31: 9-11. Russian.
19. Nozuki M., Mouri T. Plasma concentrations of atrial natriuretic peptide in various diseases. J Exp Med 1986: 148; 439-47.
20. Atlas A. S, Kleinert H.D., Camargo M.J., Januszewicz A. Purification, sequencing and synthesis of natriuretic and vasoactive rat atrial peptide. Nature 1984: 309; 717-9.
21. Almazov VA, Khirmanov VN, Shcherbak AI, Krutikov AN, Danilchenko AR, Kireenkov IS. Natriuretic hormones (atrial and digitalis-like) in patients with arterial hypertension during exercise. Kardiologiia. 1992; 32: 56-60. Russian.
22. Bilchenko AV, Vasilev IM. Atrial natriuretic peptide in patients with hypertension. Kardiologiia. 1991; 31: 64-7. Russian.



Eindhoven tarafından kullanılan ilk elektrokardiyograf.
Avrupa Kardiyoloji Derneği'nin 50. yıldönümü, XXII. Avrupa Kardiyoloji Kongresi, Amsterdam 2000.