



ROLE OF ATRIAL NATRIURETIC PEPTIDE IN VARIOUS CONDITIONS

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ABSTRACT

Atrial natriuretic peptide (ANP) was discovered twenty years ago and has a crucial role in regulating blood pressure, body fluid homeostasis and maintaining cardiovascular function. Evidences from animal model reported a decrease in estrogen level via ANP gene inhibition. Estrogen induces ANP release via ER dependent mechanism from the heart and prevents cardiac hypertrophy. It has been reported that mice lacking ANP exhibit high blood pressure due to loss of cGMP (vasodilator). ANP also inhibit L- type Ca^{+2} channel in the heart, induce vasorelaxation in arteries, decrease sympathetic nervous system activity and suppress RAAS. It has been reported that a potent vasoconstrictor (Endothelin) augments ANP secretion and up regulates ANP messenger RNA. Reduced ANP contributes in increased fluid retention in obese individuals. Pro-BNP has shown an independent risk factor for CVD with diabetes. Natriuretic peptides cause augmentation in GFR, thus contributing in glomerular hyperfiltration in diabetic rat heart. ANP improves the attenuated cardioprotective effect of ischemia preconditioning by increasing the activity of NO in diabetic rat heart. Over the past decade, ANP became an essential tool in the management of various metabolic disorders. In this article, we have focused on the physiological effects of ANP referring hypertension, hyperlipidemia, diabetes mellitus, estrogen deficiency, ischemia reperfusion injury, ischemia preconditioning and endothelins.

KEY WORDS: Atrial natriuretic peptide (ANP), estrogen, hypertension, hyperlipidemia



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INTRODUCTION

Atrial Natriuretic Peptide

Every mammalian atrial myocytes have numerous storage granules specified as specific atrial granules. Lot of researches have been going on in the field of atrial natriuretic peptides (ANP) of the rat and human and the same have been rectified, synthesized and sequenced. Atrial natriuratic peptide is also known as atrial natriuretic factor, atrial natriuretic hormone, cardionatrine, cardiodilatine and atriopeptin. ANP are polypeptide in nature and has vasodilator property. They are released by cardiac muscular cells. It also antagonizes aldosterone level and regulates renal function. ANP is a chain of 28 amino acids, secreted by atria in the cardiac environment^{1,2}. Three types of ANP receptors have been

identified namely, Atrial Natriuretic Peptide Receptor A (ANPR-A), Atrial Natriuretic Peptide Receptor B (ANPR-B) and Atrial Natriuretic Peptide Receptor C (ANPR-C). The ANP receptors are biologically active and work via activation of guanylate cyclase³. Calderone *et al.*, in 1998 reported that when ANP exogenously enters in cardiac cells leads to hypertrophy synergized by noradrenaline stimulation in region of ventricular myocytes cell, whereas endogenous ANP negatively affects cardiac myocytes hypertrophy under normal and phenylephrine treated condition via cGMP dependant mechanism⁴. When both nitric oxide (NO) and ANP raise the level of intracellular cGMP, it will slow down the cytosolic calcium level and simultaneously also activates the calcium gated potassium channel.

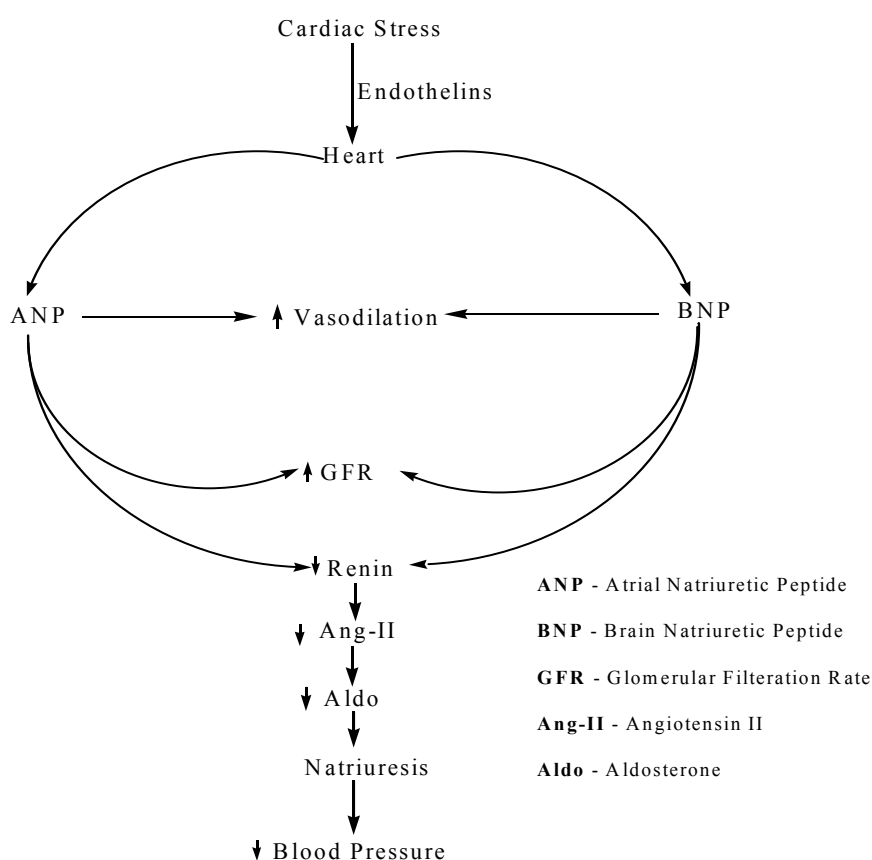


Fig. 1 Cardiovascular and Renal Action of Natriuretic Peptides

Role of ANP in Estrogen deficiency

It basically belongs to a class of steroid hormone that acts through binding membrane as well as intracellular receptor⁵. Estrogen has influencing role in deposition of adipose tissue during later half of female's life cycle⁶. In every postmenopausal woman, the fat mass rises drastically, which leads to experience the chronic diseases like hyperlipidemia and hypertension. ANP has also been reported to decrease the level of visceral adipose tissue during estrogen therapy⁷. At the same

time post menopausal women may experience the elevation of ANP during estrogen therapy⁸. It has been seen under preclinical studies that the estradiol triggers ANP release in isolated perfused rat heart⁹. The estrogen not only manifest a prominent change and protection in the hypertrophic heart, but decreases the infarct size as well¹⁰. Estrogen treatment shows significant protection against ischemia reperfusion injury and reduces edema in myocardial tissues in ovariectomized (ovx) rat heart¹¹. When the treatment of estradiol and its analogues were

given to female OVX rat, they trigger the release of nitric oxide (NO) synthase through guanylate cyclase pathway which elevates intracellular cGMP and protein kinase G. The elevation of intracellular cGMP / protein kinase G controls the myocardial contractility by blocking the L-type calcium channel. L-type calcium channel has concern with the production of action potential¹². During signal transduction events, estradiol works by estrogen receptor α (ER- α) and estrogen receptor- β (ER- β). About 96% ER- β is similar to ER- α in DNA attachment site, position and structure in the opposite N-terminal domain¹³. Lot of observations suggest the involvement of estrogen in vascular cell as well as in cardiac cell, depends on the relative expression of ER- α & ER- β ¹⁴. The level of plasma ANP is raised by estrogen analogues when it was given to female ovariectomized (ovx) rat¹⁵. Many researches prove that estrogen insufficiency block the proliferation and programmed cell death. These processes are regulated by nitric oxide pathway^{16,17}. In female rats the estrogen protects and opposes the formation of fibrosis, resulting in reduction of cardiac related oxidative stress and hypertrophy. This is accompanied by decrease in local synthesis of angiotensin – II, endothelin – I and lipid peroxide in the kidney¹⁸.

Role of ANP in hypertension

Cardiovascular disease remains the biggest reason of mortality worldwide. Approximately 17 million people died from this disorder yearly and more than 9.4 million deaths occurred due to major cardiovascular risk factor i.e. hypertension globally. Hypertension is responsible for at least 45% of deaths due to ischemic heart disease and 51% of deaths by stroke. Hypertension is often a silent killer. Most people with hypertension do not experience any symptoms. Earlier this disorder is diagnosed, greater is the prospect for its cure. Wiinber N *et al.*, reported that hypertension is more prominent in men than premenopausal women as endogenous estrogens regulate vasodilatation in women and thus control blood pressure. Loss of estrogen production in post menopause, women is accompanied by elevated blood pressure as compared to man¹⁹. The increment of hypertension renal failure leads to be severe in case of post menopause women as estrogen has a protective effect over renal hypertension²⁰. Nishikimi T *et al.*, 2009 reported that ANP has antifibrotic effect in mice. It was immersed in NPR-C and NPR-A activation that elevates kidney cGMP level, activates transforming growth factor beta (TGF- β) and reduces collagen I & III content²¹. Many evidence found that ANP has an antihypertensive effect via activation of kidney NO synthase & cardiovascular activity^{22,23}. ANP protects smooth muscle cell of aorta through generation of ROS^{24,25}. It has been proved that ANP decreases the cardiovascular oxidative stress in hypertension. Endothelin is secreted by endothelin dependent releasing factor (EDRF) and is responsible for ANP activation²⁶. Endothelin stimulates nitric oxide (NO) secretion and up-regulates ANP messenger RNA in perfused rat heart. It has been reported that the antagonist of endothelin receptor

attenuates the effect of ANP to atrial stretch²⁷. High atrial pressure of (8-10 mmHg) is responsible for ANP secretion (30- 60 min) as compared to low atrial pressure.

Role of ANP in Hyperlipidemia

Obesity is a major contributor to global burden and a big challenge for clinical and medical research. It is responsible for various cardiovascular diseases in postmenopausal women and causes hypertension via salt retention in human body²⁸. Framingham reported that obesity is directly linked to 65% of hypertension in female²⁹. Cardiovascular diseases are responsible for the deaths in postmenopausal women. Obesity is developed by glucose intolerance, high lipid profile and is responsible for insulin resistance³⁰. In the female rat, high fat diet produces the chances of ventricular arrhythmia by increasing high lipid level in the body. High lipid diet induces obesity and ultimately leads to hypertension^{31,32}. Researchers reported that obesity increases the renin angiotensin pathway mechanism³³. Natriuretic peptides are important regulators for neurohormonal activation, which are impaired in obesity. Experimental data suggest that ANP level falls down in obese people³⁴. Low ANP leads to reduced lipolysis and lipid mobilizing action. Some author suggests that ANP type C-NPR is abundant in rats & human tissue. Obese people have low circulating ANP level that contributes for hypertension related disorders.

Role of ANP in Diabetes mellitus

In year 2008, world health organization (WHO) reported an estimated 347 million people with diabetes. Its prevalence is growing in developing countries. In 2012, this disease was the direct cause of 1.5 million deaths, with more than 80% of those occurring in low and middle income countries. WHO declared that diabetes would be the 7th leading cause of death in 2030. In the course of experimental diabetes, increase in renal blood flow rate as well as glomerular filtration rate (GFR) takes place, which is a cardinal feature of the primary pathogenesis^{35,36}. Streptozocin produces intrarenal vasodilation with increase glomerular flow rate in nephron in rats^{37,38}. ANP stimulates diuresis i.e. sodium is excreted out. Evidences found that intravenous infusion of ANP manifested the increase in glomerular filtration rate³⁹. It has been reported that ANP reduces the pressure of afferent arterioles and rises the glomerular pressure. The experiment was carried out during micro puncture studies⁴⁰. The associated problems like increase in plasma aldosterone and renin level were reduced during the treatment.^{41,42}. Features of diabetic state like systemic vasodilation are similar to the effect of ANP^{43,44}. ANP infusion results in enlargement of P_{GC} , GFR, suppression of rennin activity and aldosterone release⁴⁵. It has been reported that the endogenous ANP concentration is increased in moderately hyperglycemic diabetic rats due to dietary mineralocorticoid excess. ANP level normalization in normoglycemic diabetic rats has shown normal volume and concentration because of tight metabolic control. Glucagon-like peptide-1 (GLP-1)

is a hormone derived from the gut after ingestion of meal⁴⁶. GLP-1 has favorable effects on the vasculature along with anti-hyperglycemic actions. Long term treatment of GLP-1 receptor agonist has shown improvement in lowering blood pressure in type 2 diabetic patients⁴⁷. Recently, it is reported that ANP might be essential for GLP-1 stimulated smooth muscle relaxation regulating anti-hypertensive effect in rodents.

Role of ANP in Ischemic Preconditioning (IPC)

A new situation has developed to change heart condition in accordance with ischemic preconditioning. The mechanism deals with the degree of reduction in cell injury and prolongs time ischemic damage. The intermittent episode of reperfusion and ischemia for a short span of time diminishes infarct size and prevents the heart from long term ischemic insult⁴⁸. Ischemic preconditioning is a biphasic phenomenon which has two types - The early phase or classical preconditioning and the delay phase or late phase. Classical preconditioning starts within minutes and immediately diminishes within 2 to 3 hours, whereas late phase preconditioning responds in 12 to 24 hour and lasts up to 3-4 days. The late phase is also known as protection of second window⁴⁹. Cohen *et al.*, reported that preconditioning enhances the

improvement in contractile function of myocardial region in rabbits. Preconditioning also has a beneficial effect on acute recovery of contractile function via delaying ischemic cell death. Infarct size and enzyme leakage are the parameters that are associated with functional recovery⁵⁰. Kitakaze *et al.*, reported that ischemic preconditioning elevates adenosine release and 5'-nucleotidase activity in the dog heart. This study contributed valuable information in the effects of I/R on purine catabolism. Downey & coworker *et al* hypothesized that the activation of protein kinase C (PKC) occurs via stimulation of G protein coupled receptors that, in turn leads to the PKC translocation, where it phosphorylates ATP-sensitive K⁺ channel, that further provides resistance to ischemia. This evidence shows that the protective effect of IPC is short term and the last for more than 2 hour. However, a delayed IPC has been shown in many species that occur 24 hours after preconditioning and last for 48 hours. Delayed IPC is mediated by the activation of antioxidant enzymes and heat shock proteins⁵¹. A delayed anti-arrhythmic effect has been reported following preconditioning⁵². It is concluded that ANP improves the attenuated cardioprotective effect of ischemia preconditioning by increasing the activity of NO in diabetic rat heart⁵³.

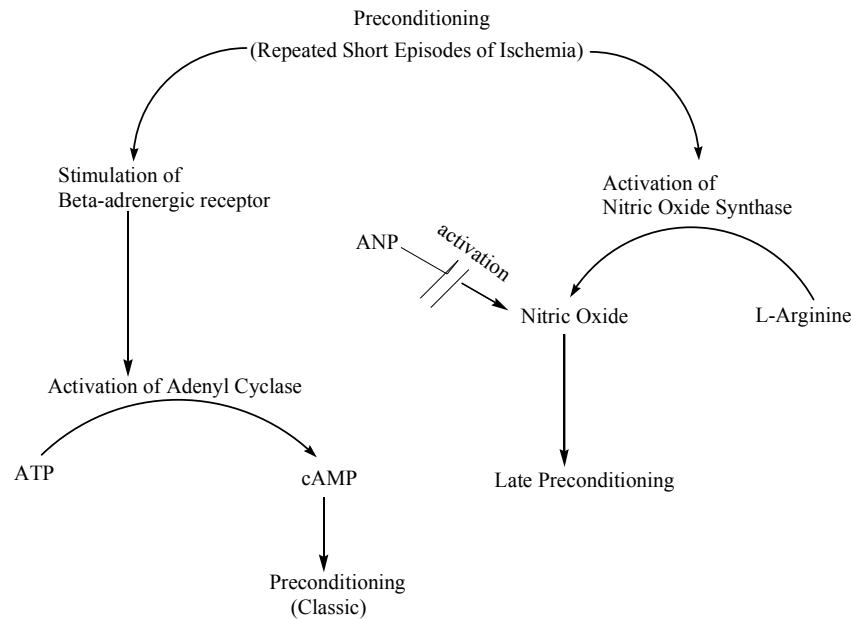


Fig. 2 Correlation of Nitric Oxide and ANP during IPC

ANP - Atrial Natriuretic Peptides
 ATP - Adenosine Triphosphate
 cAMP - Cyclic Adenosine Monophosphate

Role of ANP in Ischemic reperfusion (I/R)

Reperfusion (recirculation of blood flow) in ischemic tissue is beneficial for myocardial infarction. Early reperfusion protects the myocardium from damage, yet reperfusion after a prolonged ischemic insult causes tissue injury that is called ischemia reperfusion (I/R)

injury⁵⁴. I/R injury is influenced by microvascular dysfunction that further suppress endothelial dependent relaxing factor (EDRF) such as nitric oxide (NO) and prostacyclin that will ultimately result in reduced perfusion, capillary constriction, elevated leukocyte plugging and cellular extravasation. Inadequate supply of

oxygen to endothelial cell induces neutrophil adherence⁵⁵. Ischemia inadequately supports oxidative phosphorylation in mitochondrial cells due to inappropriate oxygen supply⁵⁶. In clinical models, ischemia may be followed by reperfusion i.e. re-supply of metabolic substrates and oxygen. Many experiments have been reported to support ischemia reperfusion injury on animals as no other therapy has been established to reduce infarct size^{57,58,59}. Currently studies suggest that anti-CD18 and anti-C5 inhibit the inflammatory mediators in reperfusion injury^{60,61}. Myocardial apoptosis, reperfusion injury and neutrophil activation leads to infarct area expansion and left ventricular dysfunction⁶². It has been reported that

noradrenaline concentration affects the mortality and morbidity in patients suffering with acute myocardial infarctions. ANP is atria releasing circulatory hormone with many biological effects like vasodilation and diuresis. It also suppresses aldosterone synthesis. Owen P *et al.*, reported that increased glucose uptake in patients with myocardial ischemia results in decreased myocardial enzyme release and improved cardiac function. In cardiac myocytes of rat, ANP addition has shown increased uptake of glucose during the hypoxic condition. In Ischemic heart and ischemia/reperfusion injury, the metabolic effect of ANP may contribute in cardioprotection⁶³.

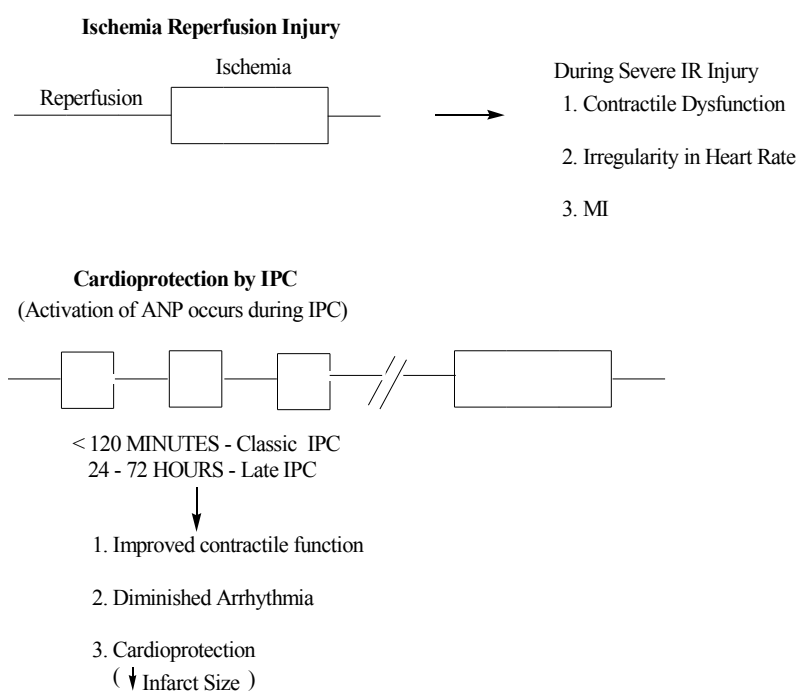


Fig. 3 ANP mediated Cardioprotection during IPC

CONCLUSION

Atrial Natriuretic Peptide is the polypeptide protein of cardiac origin and help in regulating intravascular blood volume. The plasma concentration of ANP elevates in heart failure and is considered to compensate this failure because of their vasodilating effect. There are three types of ANP receptor - ANPR-A, ANPR-B and ANPR-C which control the renal function and has inhibitory effect on rennin and aldosterone system. It has been reported that estrogen treatment in ovariectomized rat prevents cardiac damage by increasing the cGMP level via NO synthase. Estrogen receptors found in heart are responsible for ANP release. ANP activate renal NO synthase that act as antihypertensive. During high blood pressure, ANP decreases cardiovascular oxidative stress. ANP shows lipolytic effect in hyperlipidemia by inhibiting renin angiotensin pathway. It has been reported that in diabetic rat heart, ANP restore the

cardioprotective effect of IPC by increasing the expression of eNOS. ANP addition increases uptake of glucose during hypoxic conditions in cardiac myocytes of rats. In ischemia/reperfusion injury, the metabolic effect of ANP may contribute in cardioprotection.

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CONFLICT OF INTEREST

Conflict of interest declared none.

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