

## Mutual Homeostatic Regulation Between Natriuretic Peptides And Mineralocorticoids In The Cardiovascular System

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**Abstract:** The two natriuretic peptides, A-type Natriuretic peptide (ANP), B type Natriuretic peptide (BNP) are released by the heart while C-type natriuretic peptide (CNP) is mostly expressed in the brain but also by the endothelial cells and heart and they induce natriuresis and have vasodilatory actions. On the other hand, aldosterone released by the adrenal cortex may regulate the release of natriuretic peptides by acting on specific receptors in the heart and increasing the circulating sodium and ECF levels. This article examines the mutually homeostatic regulatory role of natriuretic peptides and aldosterone in maintaining cardiovascular system and other possible biological roles. This may be more relevant in cardiovascular disorders like hypertension and cardiac failure.

**Keywords:** ANP, BNP, CNP, Aldosterone, heart, expression, receptor

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### I. Introduction:

Atrial natriuretic peptide is a cardiac-derived hormone with natriuretic, diuretic, and vasodilatory properties [1]. Atrial natriuretic peptide is also an endogenous inhibitor of the renin-angiotensin-aldosterone system, due in part to suppression of aldosterone secretion from the adrenal glands [2,3]. ANP is mostly expressed and stored in granules in the atria, although it is present at lower concentrations in other tissues, such as the ventricles and kidney. The current data suggests that primary stimulus for ANP release is atrial wall stretch resulting from increased intravascular volume [3-4] (Fig.2) or cardiac transmural pressure which may promote ANP expression and biosynthesis in the ventricles in conditions such as heart failure(HF). While BNP was initially purified from porcine brain extracts and hence defined brain NP [5]. However, it was subsequently found in much higher concentrations in cardiac ventricles from patients or animals undergoing cardiac stress such as congestive HF or myocardial infarction [6]. On the other hand, aldosterone regulates various cellular functions through classical mineralocorticoid receptor (MR)-mediated gene regulation, and by MR-independent non-genomic actions [7]. It is a key regulator of blood pressure and electrolyte balance. Aldosterone, in the presence of high salt, has been shown to induce cardiac fibrosis in animal models [8]. Further, aldosterone has been shown to induce hypertrophy and re-expression of the fetal gene ANP in isolated cardiomyocytes [9-10], and its continuous infusion induces cardiac hypertrophy and fibrosis in animal models [11]. Aldosterone has also been shown to induce activation of NF- $\kappa$ B and AP-1 and pro-inflammatory cytokine expression in hearts [12-14].

It has also been demonstrated that aldosterone-induced cardiac hypertrophy and fibrosis are associated with increased TRAF3IP2 expression and enhanced NF- $\kappa$ B/p65 and AP-1/c-Jun activation in LV tissues of WT mice, whereas TRAF3IP2 gene deletion markedly attenuates aldosterone-induced NF- $\kappa$ B and AP-1 activation, and cardiac hypertrophy and fibrosis, in a manner that is independent of increased blood pressure [15].

The interactive relationship of aldosterone and natriuretic peptides is shown in Fig.1. It appears that the aldosterone induced proteins like the ENaC and Na<sup>+</sup>K<sup>+</sup>ATPase may be also contributing in a homeostatic balance with the natriuretic peptides in regulating cardiovascular system. Aldosterone by its direct actions on specific aldosterone cardiac receptors and induced proteins like the ENaC and Na<sup>+</sup>K<sup>+</sup>ATPase regulates natriuretic peptide release from the heart and modulates its effects in patho-physiological states.

**Natriuretic peptides and heart:** ANP and BNP have direct effects on the heart. Mice lacking ANP or NPR-A have enlarged hearts [16], whereas animals which overexpress ANP have smaller hearts. Initially, it was unclear whether the cardiac hypertrophy observed in the knockout animals resulted from prolonged exposure to systemic hypertension or from the loss of a local inhibitory effect on heart growth; it is likely that both processes lead to cardiac hypertrophy. The first evidence supporting a local effect involved NPR-A knockout mice that were treated with anti-hypertensive drugs from birth. These animals were normotensive but still had cardiac hypertrophy [17]. The selective transgenic replacement of NPR-A in the heart of NPR-A knockout animals

reduced cardiomyocyte size without affecting hypertension [18]. Pre-clinical data have demonstrated the ability of ANP to inhibit cardiomyocyte hypertrophy thus displaying cardioprotective effect.

**NT-pro fractions of natriuretic peptides:** The plasma measurement of N terminal fractions of the peptide has been complicated by the fact that the endocrine heart seems much more endocrine than initially assumed, meaning that post-translational processing of both proatrial natriuretic peptide and NT-proBNP results in the existence of multiple peptide species, rather than just one active hormone the B-type natriuretic peptide and one inert fragment i.e the NT-proBNP. NT-pro fragments may be possible clinical markers for cardiovascular and metabolic disorders.

**Mineralocorticoid receptors in heart :** Perrier et al[19] showed an excellent correlation between aldosteronaemia and calcium channel activity (iCal) in cardiomyocytes isolated from experimental models of pseudo-hyperaldosteronism i.e the knock-out mutation of the epithelial sodium channel [ENaC], hypoaldosteronism i.e the activating mutation of ENaC, or chronic administration of aldosterone. It was recently shown that administration of aldosterone in mice increases the release of calcium from the sarcoplasmic reticulum because of an abnormally prolonged opening of ryanodine receptors. Cardiac expression of MRs is increased in hypertension, myocardial infarction, and diastolic heart failure. Increased MR activation could occur in the presence of normal aldosterone and glucocorticoid levels because of increased local expression of MRs [20].

**Interaction between natriuretic peptides and aldosterone:** There is evidence that natriuretic peptides have an inverse relationship with aldosterone. ANP directly inhibits aldosterone production in the adrenal glomerulosa adrenocorticotrophic hormone, [ACTH]-stimulated, Ang-II-stimulated and basal aldosterone levels [21-23]. Atrial natriuretic peptide is also an endogenous inhibitor of the renin-angiotensin-aldosterone system, due in part to suppression of aldosterone secretion from the adrenal glands. Given the inverse relationship between elevated aldosterone and decreased natriuretic peptide levels, the addition of chronic GC-A agonists with aldosterone antagonists for e.g Spirololactone may be important for further clinical experiments and a co-therapeutic approach could finally be clinically useful [24].

Fig.1: Natriuretic peptide and aldosterone interaction

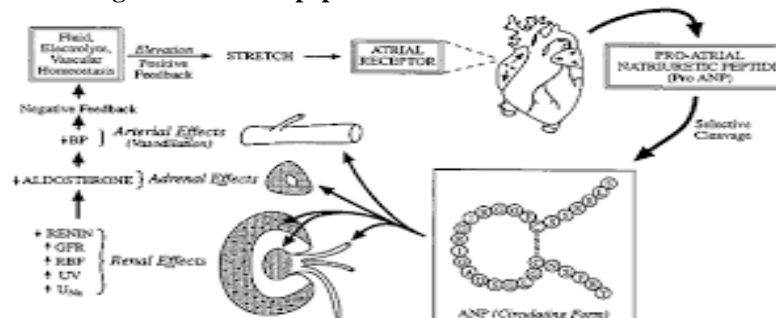
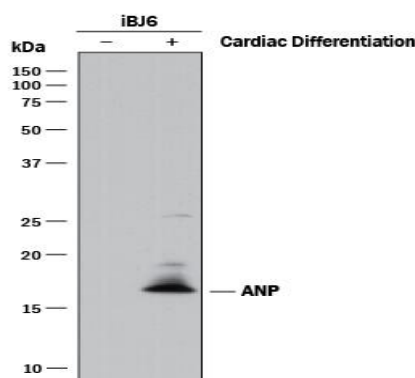


Fig.2 : Western blotting identifying the natriuretic peptide



**Detection of Human Atrial Natriuretic Peptide/ANP by Western Blotting:** Simple Western lane view shows lysates of iBJ6 human induced pluripotent stem cell line untreated (-) or differentiated to cardiomyocytes (+),

loaded at 0.2 mg/mL. A specific band was detected for Atrial Natriuretic Peptide/ANP at approximately 21 kDa using 10 µg/mL of Goat Anti-Human Atrial Natriuretic Peptide/ANP Antigen Affinity-purified Polyclonal Antibody (Courtesy ; R and D Systems, USA).

**Table 1:** Effect of natriuretic peptides in DOCA salt (40mg/kg) treated hypertensive albino rat heart

Serial #	Treatment	GC activity/10min/mg	% change
1)	Control	72.5 pmoles	
2)	ANP	89.5 pmoles	18.9
3)	BNP	92.7 pmoles	21.8

## II. Conclusion:

The secretion of ANP and BNP from cardiac chambers signifies the heart as one of the endocrine organs involved in the fluid and salt balance by interacting with RAAS and aldosterone. Natriuretic peptides, particularly ANP and BNP are released from the heart and regulated by the mineralocorticoid aldosterone via its effects on the receptors in the heart and also the aldosterone induced proteins, apart from the aldosterone floating in the blood circulation. There appears to be a mutually homeostatic regulatory balance between natriuretic peptides and aldosterone and it is suggested from the cumulative research data that both these molecules may be affecting each other's release. ANP can also affect cardiac hypertrophy. Thereby this interaction may be more relevant in cardiovascular disorders like hypertension and cardiac failure.

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