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Review

Regulation of expression of atrial and brain natriuretic peptide, biomarkers for heart development and disease ☆

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ABSTRACT

The mammalian heart expresses two closely related natriuretic peptide (NP) hormones, atrial natriuretic factor (ANF) and brain natriuretic peptide (BNP). The excretion of the NPs and the expression of their genes strongly respond to a variety of cardiovascular disorders. NPs act to increase natriuresis and decrease vascular resistance, thereby decreasing blood volume, systemic blood pressure and afterload. Plasma levels of BNP are used as diagnostic and prognostic markers for hypertrophy and heart failure (HF), and both ANF and BNP are widely used in biomedical research to assess the hypertrophic response in cell culture or the development of HF related diseases in animal models. Moreover, ANF and BNP are used as specific markers for the differentiating working myocardium in the developing heart, and the ANF promoter serves as platform to investigate gene regulatory networks during heart development and disease. However, despite decades of research, the mechanisms regulating the NP genes during development and disease are not well understood. Here we review current knowledge on the regulation of expression of the genes for ANF and BNP and their role as biomarkers, and give future directions to identify the in vivo regulatory mechanisms. This article is part of a Special Issue entitled: Heart failure pathogenesis and emerging diagnostic and therapeutic interventions.

1. Introduction

The heart of mammals expresses atrial natriuretic factor (ANF, ANP, a-type natriuretic peptide) and brain natriuretic peptide (BNP, b-type natriuretic peptide). Both proteins and their encoding genes have been identified decades ago [1–6], and their various physiological functions and expression in different organs have been studied extensively [7–11]. The overall effect of their function is to lower blood volume, reducing cardiac output and systemic blood pressure. In studies of vertebrate cardiogenesis, ANF and BNP have proven to be very useful and sensitive markers that discriminate chamber myocardium of the atria and the ventricles (positive) from primary, non-chamber myocardium such as the atrioventricular canal and pacemaker tissues (negative) [12]. Use of ANF regulation as a model system has led to the discovery of transcriptional mechanisms that control chamber and conduction system development [11,13].

Ventricular expression of the genes for ANF and BNP is down-regulated after birth (Fig. 1A–D). However, in the adult mammalian heart, their levels strongly increase during hypertrophy and HF (Fig. 1E, F). HF occurs when the heart is unable to provide sufficient pump action to distribute blood flow to meet the needs of the body, and is the end stage of a variety of cardiac diseases. HF is a common, disabling condition that can lead to death. Development of HF can result from hypertension causing increased ventricular wall stress and left ventricular hypertrophy, an important intermediate stage in transition to HF [14]. Other causes of HF include myocardial infarction (MI) and muscle loss, cardiomyopathy (the deterioration of muscle function), valve insufficiency and single-gene mutations [15–24]. Plasma levels of BNP and the N-terminal fragment of its prohormone, NT-proBNP, are used as diagnostic and prognostic markers for hypertrophy and HF [25]. Normal levels rule out acute HF in the emergency setting, whereas increased levels are associated with ventricular dysfunction. ANF is widely used in biomedical research to assess the hypertrophic response in cell culture or the development of HF-related diseases in animal models.

While a large body of knowledge is available on ANF and BNP function, and on conditions in which they are induced, little is known about the actual transcriptional mechanisms responsible for their regulation and induction in the heart. For example, the induction of ANF in the ventricle during hypertrophy is considered to be part of the induction of a fetal gene program [26]. This fetal program is a common feature of different pathological conditions including hypertrophy, ischemia, hypoxia, atrophy, where the heart experiences extensive remodeling and returns from utilization of fatty acids to carbohydrate for energy provision in increased hypoxic conditions. Other hallmarks are the induction of ANF and BNP, early response genes, such as *c-myc* and *c-fos*, and switches in isoform expression of genes for metabolic enzymes and sarcomeric proteins (e.g. induction of *Myh7* and *Acta1* in mouse). Triggered by increased mechanical

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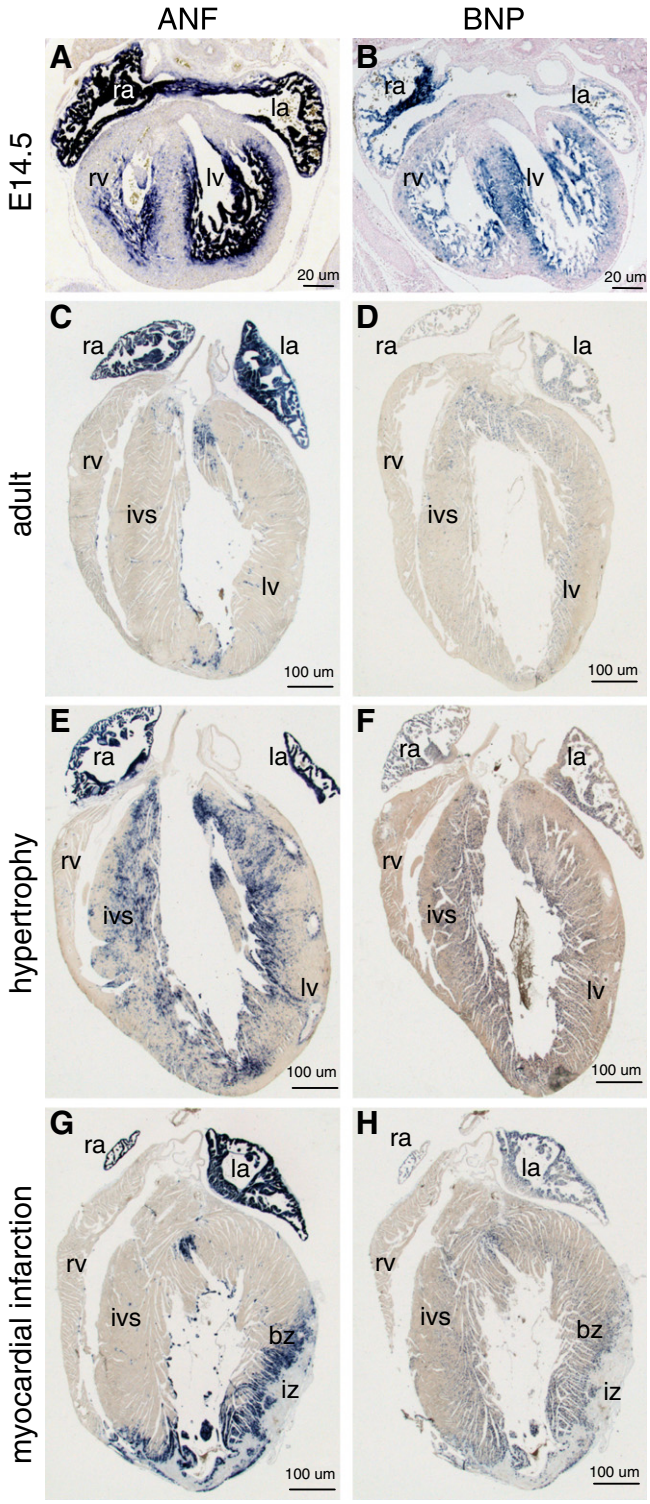

Fig. 1. Expression of ANF and BNP mRNA in sections of mouse embryonic, adult and diseased hearts. A, B. In E14.5 mouse embryos, ANF and BNP are expressed in both atrial and trabecular ventricular myocardium. The atrioventricular canal and outflow tract myocardium do not express ANF/BNP. C, D. Expression of ANF in the adult heart is restricted to the atria and the Purkinje fibers of ventricular myocardium, whereas BNP is expressed in atrial myocardium and in ventricular myocardium in a transmural gradient from the endocardial side. E, F. ANF and BNP mRNA are upregulated in the ventricles during hypertrophy. G, H. ANF and BNP are reactivated in the border zone after myocardial infarction. ra, right atria; la, left atria; rv, right ventricle; lv, left ventricle; ivs, interventricular septum; iz, infarct zone; bz, border zone.

load and hypoxic environment, all these changes until a certain point ensure cell survival under stress [27]. The regulatory DNA sequences of ANF controlling fetal ventricular expression on the one hand, and induction during disease on the other are different [28,29] and have not yet been identified. As a consequence, the transcriptional mechanisms remain to be elucidated. Insight into these mechanisms will help us to understand the pathology of hypertrophy and HF at the molecular level, and to understand the link between phenotype and ANF/BNP expression to use these molecules as biomarkers for cardiovascular disease more effectively. In this review we will discuss current insight into the expression patterns of ANF and BNP during development and cardiac disease, and the underlying mechanisms of gene regulation, focusing on the regulatory DNA sequences and interacting factors.

2. ANF and BNP expression profiles during development and disease

ANF was the first natriuretic peptide to be identified and purified from atrial extracts in 1981, when it was shown to increase natriuresis, diuresis and vasodilation [30]. But the spectrum of action was not limited to cardiovascular and renal systems. Receptors for ANF were identified in different organs including the kidney, lung, liver, adrenal cortex, and the small intestines, where it could regulate salt and water balance as well [31]. Moreover, ANF receptors [31] as well as bioactive peptide were also found in the brain [32–34]. Extensive work on the purification of a variety of active peptides in the 1980s revealed that in addition to ANF the brain contains another NP, therefore called BNP [2]. One of the actions of NPs in the brain is to inhibit release of adrenocorticotropic hormone, thereby decreasing aldosterone release and enhancing natriuresis. Furthermore, the ANF-ergic neurons inhibit arginine vasopressin release leading to diuresis [35]. Therefore, NPs expressed in the brain also serve to maintain optimal liquid homeostasis. Although isolated from the brain, BNP is predominantly expressed in the heart ventricles and mimics the pharmacological activity of ANF in regulation of blood pressure. Isolated ANF and BNP proteins were found to have a remarkably similar structure [2,30]. These NPs are encoded by *natriuretic peptide A* (*Nppa*) and *-B* (*Nppb*), respectively, which are positioned adjacent to each other and in close proximity (<15 kilo base pairs (kbp) distance) in the vertebrate genome [6,36,37]. Both genes are expressed in specific patterns in the developing and adult heart, and induced in particular cardiovascular pathological conditions.

2.1. Temporal expression patterns of NPs in the heart

Expression of ANF is initiated in the tubular murine heart (mouse embryonic day (E) 8) at the level of the future left ventricle. Thereafter, it is activated in the developing atria and the ventricles of the looping and ballooning heart [12,38]. When compact myocardium of the ventricles begins to form between E10-12, expression of ANF becomes restricted to the trabeculated layer, higher in the left ventricle than in the right. The expression of ANF is limited to differentiating chamber (future working) myocardium. The myocardium flanking the chambers, the sinus venosus, including the sinus node, the atrioventricular canal including the future atrioventricular node, and the outflow tract never express ANF [12]. Because of this property, ANF has been used extensively as a marker for differentiating chamber myocardium during cardiogenesis, which has led to the identification of transcriptional mechanisms for chamber and conduction system development [39]. In human fetuses, ANF mRNA is more abundant in the atria than in the ventricles [40], whereas in the ovine fetal heart atrial expression is lower than that of the ventricles during the last two-third of the gestation period [41].

In mammals during gestation and after birth, ventricular ANF expression decreases from 50% of atrial expression in human and 4% in mouse fetuses to about 1% in adult mammalian hearts [29,42,43].