

**THE CARDIOPROTECTIVE INTENT
OF CARDIAC NATRIURETIC PEPTIDES**

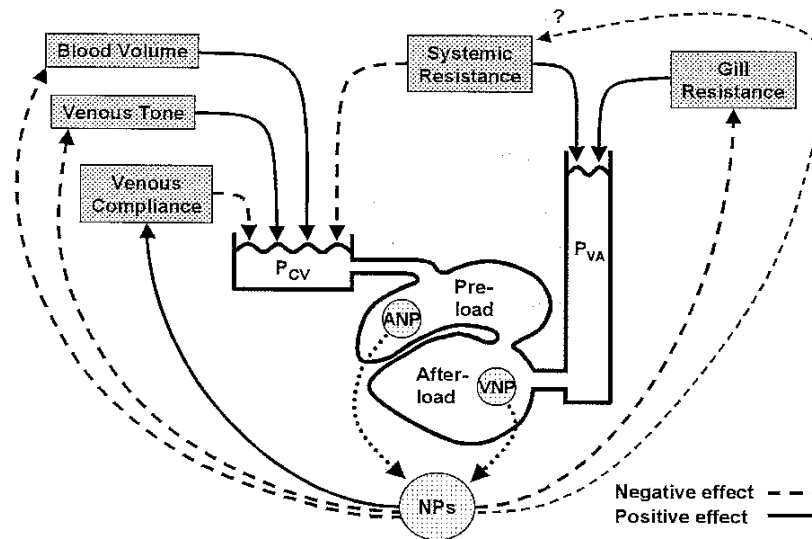
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EXTENDED ABSTRACT ONLY - DO NOT CITE

Vertebrate hearts from fish to mammals secrete peptide hormones with profound natriuretic, diuretic and vasodilatory activity, however, the specific role these cardiac natriuretic peptides (NPs) have in homeostasis is unclear. It has been proposed that cardiac natriuretic peptides (NPs) counter volume expansion in mammals, whereas they mainly prevent salt loading in fish (Brenner et al., 1990; Loretz and Pollina, in press). This review suggests an alternative, and perhaps more universal function of NPs, that is to protect the heart. Our hypothesis is based on several observations. 1. The presence of cardiac NPs appears to be independent of environmental conditions that may variously affect salt and water balance. NP, or NP-like activity is present in all vertebrate hearts, from osmoconforming saltwater hagfish to euryhaline freshwater (volume-loaded/salt-depleted) and saltwater (volume-depleted and salt-loaded) teleosts to volume- and salt-depleted terrestrial mammals (Olson, 1992). 2. Cardiac stretch is one of the most powerful, and apparently universal, NP secretagogues as it has been shown to stimulate NP release from both freshwater and saltwater adapted trout (Cousins et al., 1997), as well as mammals (Brenner et al., 1990). 3. Excessive end-diastolic volume (EDV) compromises the mechanical ability of all vertebrate

hearts. This can occur two ways, by decreasing actin-myosin interaction (length-tension relationships) or through Laplace effects in which case as EDV increases, the wall tension necessary to maintain a constant pressure must also increase. 4. Excessive EDV can be produced by an increased afterload, i.e., factors that decrease cardiac emptying (increased arterial pressure), or by an increased preload, i.e., factors that increase cardiac filling (increased blood volume, increased venous tone, or decreased venous compliance). 5. The major physiological actions of both piscine and mammalian cardiac NPs minimize untoward changes in EDV (Brenner et al., 1990; Olson, 1992; Olson et al., 1997). In fish, NPs promote cardiac emptying by decreasing gill vascular resistance, thereby lowering ventral aortic pressure; higher NP titers also decrease systemic resistance which further reduces ventral aortic pressure. In mammals a similar effect is achieved through pulmonary and systemic vasodilation. NPs also decrease cardiac filling in both vertebrates by decreasing blood volume and increasing venous compliance, the latter producing a rapid fall in central venous pressure.



Several other aspects of NP physiology may provide additional insight on the cardioprotective role of these peptides. First, the presence of NP clearance receptors

in the gill and lung (between the heart and systemic circulation) suggest that these tissues may be exposed to considerably higher NP titers than systemic tissues. Thus a decrease in outflow resistance immediately downstream from the heart may be the first response to increased cardiac distension. Second, vertebrate hearts appear to possess two distinct NPs, one in the atria (ANP) and a second in the ventricle (BNP in mammals and VNP in fish). These peptides may differentially respond to cardiac distension resulting from excess afterload (BNP and VNP) or preload (ANP).

Collectively, these points suggest that the stretch-mediated mechanism of NP release, like that of the Starling response of the heart, had its evolutionary origins in aquatic vertebrates. While NPs have been shown to mediate a variety of homeostatic processes, we propose that their cardioprotective action transcends osmoregulatory considerations. It is also likely that cardioprotection was, from an evolutionary perspective, one of the first and foremost duties of the vertebrate cardiac peptides. An integrated hypothesis for factors affecting NP release by the heart and the resultant physiological consequences is shown in the figure.

Acknowledgments

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