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Review

Emerging role of neurotensin in regulation of the cardiovascular system

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ABSTRACT

There is increasing evidence in support of an important role played by neurotensin (NT), a tridecapeptide originally found in bovine hypothalamus, in regulation of cardiovascular system. Elevated systemic levels of NT may contribute to pathogenesis of acute circulatory disoders, and predict the risk for cardiovascular morbidity and mortality in population-based studies. Within cardiovascular system, NT-containing neural fibers are found in close contact with atrial and ventricular cardiac myocytes, cardiac conduction system, intracardiac ganglia, as well as coronary vessels in humans and various animal species. The density of NT-immunoreactive innervation is reduced in cardiac disease. NT produces a variety of cardiovascular actions including effects on heart rate, myocardial contractility, systemic blood pressure, coronary vascular tone, venous smooth muscle tone, and regional blood flow in gastrointestinal tract, cutaneous and adipose tissue. NT could trigger cardiovascular reflexes by stimulating primary visceral afferents synaptically connected with preganglionic sympathetic neurons at the spinal cord. Structural determinants of biological activity of NT reside primarily in the C-terminal portion of its molecule which is responsible for receptor activation. NT effects are mediated via activation of NT receptors, or produced indirectly via stimulation of release of various endogenous neuromodulators/neurotransmitters such as histamine, catecholamines and prostaglandins. Three subtypes of NT receptor (NTS_1, NTS_2 and NTS_3) have been shown to be expressed in the myocardium. NTS_1, a high-affinity NT binding site coupled to phospholipase C-inositoltrisphosphate transduction pathway, is thought to mediate NT-induced cardiovascular responses.

Contents

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1. Introduction

There is increasing evidence to demonstrate that autonomic control of the cardiovascular system is not limited to the effects produced by classical neurotransmitters, acetylcholine and noradrenaline, and also includes regulatory actions mediated by various neuropeptides (Herring 2015; Shanks and Herring, 2013). The focus of this review is on neurotensin (NT), a 13 amino-acid peptide, which was originally extracted from bovine hypothalamus (Carraway and Leeman, 1973), and subsequently found in a variety of peripheral tissues including cardiovascular system. Both NT and its larger precursor peptide molecule (proneurotensin 1-117) have been determined at picomolar concentrations in blood samples from healthy human subjects (Bozzola et al., 2012; Ernst et al., 2006; Gullo et al., 1998).

In the brain, NT interacts with different neurotransmitter systems, and is involved in the central control of appetite, endocrine functions, pain modulation, and pathogenesis of mental disorders (Boules et al., 2013). High amounts of NT are also present in endocrine-like cells localized in intestinal mucosa, whereby NT is released upon food intake, and contributes to regulation of gastrointestinal motility and secretion (Kalafatakis and Triantafyllou, 2011). Much less attention has been paid to consider the emerging role of NT in regulation of the cardiovascular system. Nevertheless, recent clinical studies have highlighted the contribution of NT-mediated mechanisms in pathogenesis of various cardiovascular conditions. It has been shown that systemic NT levels are elevated in patients with some circulatory disorders (Liu et al., 2007; Piliponsky et al., 2008), and increased plasma concentrations of NT protein precursor, proneurotensin, are associated with increased risk of cardiovascular morbidity and mortality (Melander et al., 2012). In order to provide a theoretical ground for interpreting these clinical observations, this review updates available published data on the distribution of NT in cardiovascular system, major physiological effects produced by NT in myocardial and vascular tissue, and the mechanisms thereof.

2. NT and cardiovascular innervation

The presence of NT-containing neural fibers in the cardiovascular system has been demonstrated in humans (Onuoha et al., 1999b) and various animal species (Ceconi et al., 1989; Gerstheimer et al., 1988; Onuoha et al., 1999a, 1999b; Reinecke et al., 1982; Weihe et al. 1984). In the heart, these fibers are found in close contact with atrial and ventricular cardiomyocytes as well as neurons of intracardiac ganglia that innervate cardiac conduction system. The density of NT-immunoreactive innervation is higher in atria as compared to ventricles, and higher NT concentrations are found in the right atrium and ventricle as compared to the left side of the heart (Ceconi et al., 1989; Onuoha et al., 1999a, 1999b; Reinecke et al., 1982; Weihe et al., 1984). Importantly, NT is found at picomolar concentrations in samples of coronary effluent collected from isolated, perfused rat heart preparations, thus indicating that it could be released from neural terminals localized in myocardial tissue (Osadchii et al., 2005a).

Myocardial NT levels are altered in cardiac disease. In the rat model of monocrotaline-induced cardiac hypertrophy, the amount of NT was significantly decreased in all cardiac chambers, especially on the right side (Ceconi et al., 1989).

NT-immunoreactive fibers also contribute to vascular innervation. Numerous evenly distributed NT-containing fibers are detected in peri- and paravascular plexuses innervating coronary vessels (Reinecke et al., 1982). These fibers are found at the adventitia-media border in all segments of the coronary vasculature, but coronary arteries are more densely innervated than veins. Abundant NT-containing neural fibers are also present in the adventitia of ascending aorta, aortic arch, and pulmonary vein (Onuoha et al., 1999b; Reinecke et al., 1982).

3. Cardiovascular effects of NT

3.1. Basal heart rate

The presense of dense NT-immunoreactive cardiac innervation suggests that NT is involved in regulation of myocardial performance. In support of this notion, NT administration is associated with heart rate acceleration in rat (Bachelard et al., 1992; Chahl and Walker, 1981; Rioux et al., 1982a, 1982b), guinea-pig (Bachelard et al., 1985, 1987; Kerouac et al., 1981; Nisato et al., 1994; Rioux et al., 1982a; Rioux and Lemieux, 1992), and cat (Pokrovsky and Osadchiy, 1995).

Heart rate acceleration induced by NT upon systemic administration (Kerouac et al., 1981; Rioux et al., 1982a) or following its infusion in isolated, perfused guinea-pig hearts (Bachelard et al., 1985) is not abolished by ganglion blocking agents or antagonists of β-adrenoreceptors, H_2-histamine and 5-hydroxytryptamine receptors, thus indicating a direct effect of NT on sinoatrial node. Alternatively, NT-induced positive chronotropic responses could be mediated via stimulation of substance P and/or calcitonin gene-related peptide release from cardiac primary sensory neurons (Rioux et al., 1988). On the other hand, NT-induced tachycardia in rat (Bachelard et al., 1992; Rioux et al., 1982b) is abolished by β-adrenoreceptor blockers, reserpine pretreatment or adrenalectomy, suggesting that NT effect is mediated via release of adrenal catecholamines. Consistent with these findings, plasma adrenaline levels have been increased by about 4-fold following systemic NT administration in anesthetized rats, an effect suppressed after adrenalectomy (Oishi et al., 1983).

3.2. Myocardial contractility

NT at nanomolar concentrations increases contractility of isolated rat and guinea-pig atria (Bachelard et al., 1987; Nisato et al., 1994; Quirion et al., 1980a; Rioux et al., 1988), an effect preserved following blockade of β-adrenoreceptors, but significantly reduced by chronic pretreatment with capsaicin, a neurotoxin depleting substance P and calcitonin gene-related peptide stores in primary sensory neurons (Bachelard et al., 1987; Rioux et al., 1988). NT-induced inotropic responses are also abolished after prior administration of SR 48692, a nonpeptide NT receptor antagonist (Nisato et al., 1994). Therefore, cardiostimulatory responses induced by NT are ascribed to NT receptor-mediated stimulation of substance P and/or calcitonin gene-related peptide release from cardiac capsaicin-sensitive afferent neurons (Bachelard et al., 1987; Rioux et al., 1988). Importantly, NT-induced atrial inotropic responses are partly reduced by cimetidine, an H_2-histamine receptor antagonist (Quirion et al., 1980a), thus indicating that NT effect on atrial muscle may be partially attributed to the stimulation of histamine release from cardiac mast cells. In support of this mechanism of action, the stimulatory effect of NT on the myocardial histamine release has been demonstrated in isolated, perfused heart preparations (Rioux et al., 1984). NT-induced stimulation of histamine release is likely to play a role in myocardial responses observed in stressful conditions. Indeed, cardiac mast cell degranulation provoked by acute immobilization stress in rats, has been found to be abolished by SR 48692, a specific NT receptor antagonist (Pang et al., 1998). These findings raise a possibility that in acute stress, endogenous NT could be released from cardiac autonomic neural fibers that are located in close apposition to the myocardial mast cells, and produce stimulatory paracrine effects