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Development of neuropeptide Y-mediated heart innervation in rats

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ABSTRACT

Neuropeptide Y (NPY) plays a trophic role in the nervous and vascular systems and in cardiac hypertrophy. However, there is no report concerning the expression of NPY and its receptors in the heart during postnatal development. In the current study, immunohistochemistry and Western blot analysis was used to label NPY, and Y1R, Y2R, and Y5R receptors in the heart tissue and intramural cardiac ganglia from rats of different ages (newborn, 10 days old, 20 days old, 30 days old, 60 days old, 1 year old, and 2 years old).

The obtained data suggest age-dependent changes of NPY-mediated heart innervation. The density of NPY-immunoreactive (IR) fibers was the least in newborn animals and increased in the first 20 days of life. In the atria of newborn and 10-day-old rats, NPY-IR fibers were more abundant compared with the ventricles. The vast majority of NPY-IR fibers also contained tyrosine hydroxylase, a key enzyme in catecholamine synthesis.

The expression of Y1R increased between 10 and 20 days of life. Faint Y2R immunoreactivity was observed in the atria and ventricles of 20-day-old and older rats. In contrast, the highest level of the expression of Y5R was found in newborn pups comparing with more adult rats. All intramural ganglionic neurons were also Y1R-IR and Y5R-IR and Y2R-negative in all studied animals.

Thus, the increasing of density of NPY-containing nerve fibers accompanies changes in relation of different subtypes of NPY receptors in the heart during development.

1. Introduction

Neuropeptide Y (NPY) is a 36-amino acid peptide, including five tyrosine residues on each molecule and a C terminal amide structure (Tatemoto 1982; Tatemoto et al. 1982). NPY is widely distributed in both the central and peripheral nervous systems and has been functionally related to regulation of blood pressure, circadian rhythms, feeding behavior, anxiety, memory processing, and cognition in the CNS and to vasoconstriction and gastrointestinal tract motility in the PNS (Hodges et al. 2009; Nozdrachev and Masliukov 2011; Kageyama et al. 2012; Masliukov and Nozdrachev 2013).

The various biological effects of NPY and its homologs are mediated by the activation of at least five receptors, known as the Y1R, Y2R, Y4R, Y5R, and Y6R. Among the six NPY receptor subtypes, Y3R subtype has not been cloned, Y4R subtype reacts with pancreatic polypeptide (PP), and Y6R is a nonfunctional receptor in rat and human (Balasubramaniam 1997). Therefore, it seems that Y1R, Y2R, and Y5R are the three major subtypes of NPY receptors that mediate the biological functions of NPY in human and rat. All known NPY receptors belong to the large superfamily of G-protein-coupled, heptahelical receptors (Walther et al. 2011). Actions of NPY on peripheral target-organs are predominantly realized through postsynaptic Y1R, Y5R, and presynaptic Y2R (Balasubramaniam 1997; Michel et al. 1998; Xu et al., 2014).

In the heart, the most prominent source of NPY is postganglionic sympathetic fibers, the majority originating from neurons located in the stellate ganglion (Richardson et al. 2006; Masliukov et al. 2012). In rodents, NPY is also expressed by the parasympathetic neurons of the intrinsic cardiac ganglia (Richardson et al. 2003). Sensory neurons do not produce NPY under physiological conditions (Wakisaka et al. 1991; Valder et al. 2003; Chottová Dvoráková et al. 2008).

NPY can both decrease and increase the contractile response of electrically stimulated rat ventricular cardiomyocytes (Piper et al. 1989; Millar et al. 1991; Allen et al. 2006). The two opposing inotropic effects of NPY in adult rat cardiac myocytes are mediated by different NPY receptor subtypes: positive effects by Y1R and negative effects by Y2R (Protas et al. 2003).

The negative effect, observed in isoproterenol-treated cells, is due primarily to stimulation of the transient outward current (I_{to}) and mediated through an inhibitory G protein/adenylate cyclase pathway (Kassis et al. 1987; Piper et al. 1989; Millar et al. 1991). NPY also activates the slow inward L-type Ca2+ current (Ica_L) and therefore

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