

## Editorial

### Heart – the source and target of “hypothalamic neurohormones”: Do they provide a delicate regulation complementary to the conduction system in the heart?

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The discovery of **hypothalamic factors controlling pituitary** functions was a critical step in understanding the functioning of the nervous and endocrine systems as one integral neuroendocrine unit. Isolation of the hypothalamic hypophysiotropic neurohormones, *thyrotropin releasing hormone (TRH)* as the first (1969) and later on *corticotropin-releasing hormone – CRH, gonadotropin-releasing hormone GnRH or LHRH, growth hormone releasing hormone – GHRH and growth hormone inhibiting hormone – somatostatin*, peptides produced by the hypothalamic neurones and secreted into hypophyseal portal blood, provided tools to examine the interaction of the nervous and endocrine systems at the molecular level. Soon, it could be demonstrated that these factors are present not only in various areas of the brain, but also outside the nervous system, in the gastrointestinal tract, reproductive organs, placenta, milk etc.

**The heart** has been recognized as a target of the classical neurotransmitters (e.g. catecholamines, serotonin) for a long time. Only with the discovery of atrial natriuretic peptide (ANP, Flynn et al. 1983) and its synthesis in the heart did become obvious that this organ is also an important endocrine gland. “Hypothalamic releasing peptides” were discovered in the heart in the 90s. Elucidation of the role of CRH in the heart attracted the attention of surprised physiologists (Samson 1996). Muglia et al. (1994) proved that there is synthesis of CRH and its receptors (Lovenberg et al. 1995) in the heart. CRH stimulates cardiac secretion of ANP and increases the content of cAMP in the cardiomyocytes (Heldwein et al. 1996). TRH is synthesized in atrial but not in ventricular cardiomyocytes (Shi et al. 1996) but its receptors are present in ventricles (Wilber and Xu 1998). Also LHRH and its receptor are synthesized in the heart (Kakar and Jennes 1995). So releasing hormones controlling pituitary–adrenal, pituitary–thyroid and pituitary–gonadal functions and their respective receptors are synthesized in the heart. Hypothalamic peptides controlling somatic growth are also present in the heart. Somatostatin is concentrated in the atrioventricular node and atria of different species including man (Day et al. 1985; for review see Osadchii and Pokrovskii 1998). Somatostatin receptors are present in rat heart coronary artery smooth muscle cells (Lesczynski et al. 1993) and somatostatin may inhibit proliferation of these cells.

Characteristics of the **cardiac effects**: Releasing hormones – peptides amidated at the C terminal are **generally stimulating**: LHRH has a positive inotropic effect on isolated cardiac muscle (Hasegawa et al. 1989). TRH has a positive inotropic effect on contractility of the isolated rat heart (Socci et al. 1996), ventricular contractility of open-chested dog preparation, and in *ex vivo* ventricular myocytes (Wilber and Xu 1998). CRH exerts a positive inotropic effect on the isolated rat heart and increases coronary blood flow and aortic pressure (Grunt et al. 1990). Growth hormone releasing hormone has a positive inotropic effect in the guinea pig cardiac muscles *in vitro* (Hasegawa et al. 1988). Somatostatin (growth hormone inhibiting hormone) with an intact C terminal is **generally inhibiting**: It has negative inotropic and chronotropic effects (for review Osadchii and Pokrovskii 1998) and restores sinus rhythm in patients with supraventricular cardiac arrhythmia (Ghirlanda et al. 1986; Webb et al. 1986). Treatment of acromegalic patients with a slow-release somatostatin analogue caused regression of their left ventricular hypertrophy (Hradec et al. 1999).

It is clear that peptides, originally isolated as hypothalamic hypophysiotropic hormones, are equipped to play a physiological role in the heart. Some of them (somatostatin) are part of the conductive system; the others (LHRH, TRH, CRH) are produced in, and act at myocytes either at the place of their release or after having been transported from the atria to the ventricles. By modulation of myocardial contractility and relaxation they presumably play a role in the cardiac regulatory system. An important message emerges from these observations: all these peptides are synthesized as high molecular weight precursors. Processing of prohormones produces, in addition to mature hormones, a group of peptides with an incompletely delineated function which may prove to be extremely important for normal cardiac activity. Are “hypothalamic peptides” a delicate complementary conductive system in the heart or do they have more powerful undiscovered functions? Molecular biology and cardiovascular physiology may soon provide striking findings and ideas.

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