Journal of Pain & Relief
ISSN: 2167-0846

Kanazawa and Fukuda, J Pain Relief 2016, 5:1
DOI: 10.4172/2187-0846.1000223

Short Communication Open Access

Cardiac Sympathetic Nerve Plasticity and Heart Failure

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Introduction

To establish the treatment strategy for heart failure (HF), progress in the pathophysiological elucidation of HF is important. Recent studies revealed the existence of a cross-talk, which occurs through various humoral factors, between cardiomyocytes and cardiac sympathetic nerves (CSNs). Axon growth, denervation, and functional alteration of sympathetic nerves have been noted in HF cases. By using molecular biological approaches, a new adaptation mechanism involving the autonomic nervous system (ANS) has been developed for HF. In this review, we focus on the concept of cardiac autonomic nerve plasticity in HF.

Anatomy and Function of the CSNs and their Alterations in Diseased Heart

The heart is abundantly innervated, and its performance is tightly controlled by both sympathetic and parasympathetic efferent nerves. The CSNs extending from the sympathetic neuronal body in stellate ganglia uses norepinephrine (NE) as a neurotransmitter and increases the heart rate (chronotropic response) and conduction velocity (dromotropic response), as well as myocardial contraction (inotropic response) and relaxation (lusitrophic response). Sympathetic innervation density, which is the highest in the subepicardium, is stringently regulated in the heart [1].

Cardiac innervation density is altered in diseased hearts, which can lead to unbalanced neural activation and lethal arrhythmias. The pathology of HF involves various abnormalities in the sympathetic nerve terminals. During the transition to overt HF, the sympathetic neural tone is upregulated. On the other hand, there is a paradoxical reduction in NE synthesis concomitant with the downregulation of tyrosine hydroxylase (TH), the rate-limiting enzyme in innervated neurons; NE reuptake into the sympathetic nerve terminals; and decrease in the NE levels in the myocardium [2-4]. This discrepancy between the anatomical or functional integrity and the catecholaminergic properties of the cardiac sympathetic nervous system in HF is long standing. However, the molecular mechanisms underlying the reduction in the catecholaminergic property of the CSN system in HF remain poorly understood.

Factors Regulating the CSN Density

The nerve growth factor (NGF), which is known as a sympathetic nerve regulation factor, is a member of the neurotrophin family [5]. NGF is critical for the differentiation, survival, and synaptic activity of the peripheral sympathetic nerves. The expression of NGF in the target organ is believed to correspond to the sympathetic nerve density [6]. Moreover, NGF is reported to be upregulated in cardiac hypertrophy, leading to sympathetic hyperinnervation [3] NGF upregulation is specifically promoted by endothelin-1 (ET-1), a known cardiac hypertrophic factor. Thus, the ET-1/NGF pathway is critical for the anatomical modulation of the CSNs [7]. In contrast, long-term exposure to high plasma NE concentration caused a reduction in myocardial NGF, and sympathetic nerve fiber loss in severe decompensated HF, resulting in the so-called anatomical denervation due to NGF depletion [8]. A previous report showed that this attenuation of NGF was caused by mechanical stretching and α-1 adrenergic stimulation through the calcineurin-nuclear factor of the activated T-cell signaling pathway [9].

Rejuvenation of CSNs in HF

The genes encoding the fetal phenotype for the β-myosin heavy chain and α-skeletal muscle actin are reported to be upregulated in hypertrophic cardiomyocytes. This rejuvenation phenomenon of cardiomyocytes occurs because of isoform changes that might play a crucial role in the biological defense mechanism. Interestingly, the hyperinnervated sympathetic nerves induced by the upregulated NGF in the hypertrophic heart also express immature neuronal markers such as PSA-NCAM (polysialylated isoforms of neural cell adhesion molecule) and GAP 43 (growth-associated protein 43) [3]. HF leads to the upregulation of various growth factors and cytokines in the heart. LIF (leukemia inhibitory factor) and CT-1 (cardiotrophin-1) are members of the IL-6 (interleukin-6) family, which can induce these fetal genes in the diseased heart [3]. However, a paradoxical deterioration of NE synthesis occurs concomitantly with the downregulation of TH and the reuptake of NE into the sympathetic nerve terminals. Taken together, these results suggest that CSN dysfunction is accompanied by neuronal rejuvenation and the so called"functional denervation due to rejuvenation" mechanism.

As CSNs are mediated by changes in cardiac-derived humoral factors, cardiac sympathetic properties are also altered in chronic HF. Less dense TH-positive neurons were observed in an experimental animal model and in autopsy specimens from patients with HF [10]. Furthermore, many neurons in the sympathetic ganglion and left ventricle express parasympathetic markers such as choline transporter and choline acetyltransferase. This was thought to represent the cholinergic transdifferentiation of cardiac adrenergic neurons into cholinergic neurons, which were induced by cardiac-derived IL-6-related cytokines such as the LIF and CT-1 [10]. Thus, we confirmed that sympathetic neuron-specific gene targeting of glycoprotein (gp) 130, an IL-6 cytokine family receptor, revealed that sympathetic nerves do not undergo cholinergic transdifferentiation in the left ventricle. More interestingly, control mice had significantly improved survival rates and ventricular functions than sympathetic nerve-specific gp130-deficient mice, suggesting that this phenomenon might be an adaptive response that protects the heart from excessive sympathetic discharge. Taken together, these results indicate that the IL-6 family of cytokines secreted from the failing myocardium act as negative modulators of sympathetic function by means of rejuvenation and cholinergic differentiation through a gp130 signaling pathway.10)

Plasticity of the CSNs

Both cardiac sympathetic and parasympathetic nerves are known to develop from a neural crest cell with same genetic origin. The ability

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Received November 30, 2015; **Accepted** January 19, 2016; **Published** January 21, 2016

Citation: Kanazawa H, Fukuda K (2016) Cardiac Sympathetic Nerve Plasticity and Heart Failure. J Pain Relief 5: 223. doi:10.4172/2187-0846.1000223

of cardiac sympathetic neurons to change their function in HF suggests that sympathetic neurons exhibit diverse plasticity that enables them to adapt to changes in the environment. The functional alterations in CSNs that occur in HF are believed to be associated with pluripotent potentials (dedifferentiation and transdifferentiation) that are based on their plasticity. From a cardioprotective perspective, this phenomenon is a notable concept for the elucidation of sympathetic abnormalities in HF. However, the rationale for the functional and anatomical changes in CSNs that occur in HF is difficult to explain. The complicated pathogenesis of HF includes many factors, such as disease phase and etiology, which contribute to its spatial and temporal complexity (Figure 1).

HF and the Parasympathetic Nerves

The parasympathetic nerve function reportedly starts declining in the early stages of HF [11]. As a result of the reduced parasympathetic nerve function, the heart rate increases, which works as a compensatory mechanism for HF. However, this also reduces the threshold for the development of fatal arrhythmia. As a result, the reduced parasympathetic nerve function promotes the progression of HF, and worsens the prognosis. The muscarinic 2 (M2) receptor is well recognized among the muscarinic receptors distributed in the myocardium. Recently, however, it has been reported that the M3 receptor is also present in the myocardium and that its expression increases during HF [12]. Additionally, the stimulation of the M3 receptor is reported to protect the myocardium by signaling the promotion of antioxidative and antiapoptotic activities as well as the defense mechanisms against ischemia [13]. It also improves the cardiac function, prevents remodeling, and improves the prognosis after HF or after myocardial infarction by activating the vagus nerve [14]. Acetylcholine has been shown to exert antiarrhythmic effects by inducing expression of the hypoxia-inducible factor HIF-1α, suppressing apoptosis, and reducing cytotoxicity [15], as well as by improving the function of connexin 43 [16]. On the basis of the results of previous studies, direct and indirect stimulations of the parasympathetic nerve functions during HF, which increase cardioprotective effects, are initiated through various mechanisms. Furthermore, the changes in the expression of the muscarinic receptors during HF, as well as the previously mentioned functional changes in the cholinergic nerves of the CSNs, are possibly a generalized purposive adaptation.

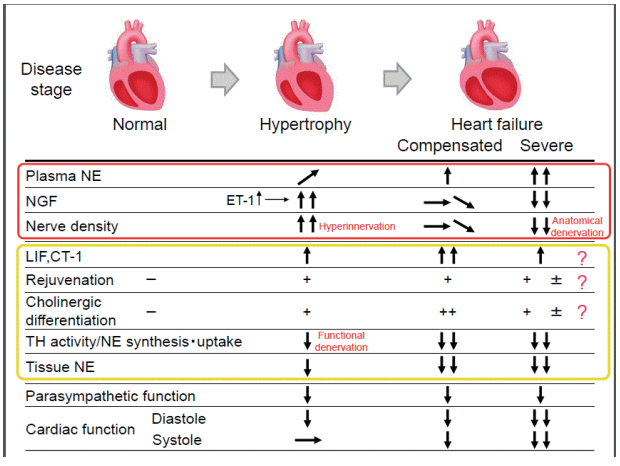

Figure 1: Temporal alterations of cardiac sympathetic nerves and mediators with the progression of heart failure; NE: Norepinephrine; NGF: Nerve Growth Factor; ET-1: Endothelin-1; LIF: Leukemia Inhibitory Factor; CT-1: Cardiotrophin-1; TH: Tyrosine Hydroxylase.

Conclusions

The upregulation of the CSN activity observed in HF is a primitive but important compensatory mechanism. However, this adaptive reaction causes further myocardium damage, decreases cardiac function, and promotes fatal arrhythmia, all of which contribute to poor prognosis [17,18]. Therefore, several compensatory mechanisms should exist to maintain homeostasis electrophysiologically and cardioprotectively. We expect that further elucidation of the molecular mechanism of CSN plasticity should eventually result in a new treatment strategy for HF.

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