Cardiac sympathetic nerve terminal function in congestive heart failure

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Introduction

It has been long recognized that cardiac norepinephrine (NE) is depleted in patients with congestive heart failure (1, 2). Early studies have shown that NE depletion is associated with increased release of cardiac NE secondary to heightened sympathetic nervous activity and decreased synthesis of NE in patients with congestive heart failure (2-5). It was thought initially that the heightened sympathetic activity was an important adaptive mechanism to support the failing myocardium, and that the subsequent depletion of cardiac NE stores contributed to the progressive deterioration of cardiac function, and the decreased myocardial contractility seen in chronic heart failure. However, it was later discovered that the intrinsic contractility of heart muscle remains normal after depletion of myocardial NE by reserpine treatment or cardiac denervation (6). Thus, normal cardiac stores of NE are not essential for maintaining the intrinsic myocardial contractility, and NE depletion does not account for the myocardial depression in heart failure. However, as overwhelming majority of NE is stored in the intraneuronal storage vesicles, tissue content of NE does not accurately reflect myocardial interstitial NE concentration which is elevated in heart failure. Recent studies from my laboratories and others have provided new insight on cardiac sympathetic nerve terminal function in heart failure, and suggest that abnormal NE uptake in the sympathetic nerve ending plays an important pathophysiologic role in dilated cardiomyopathy. The findings further indicate that the change in NE uptake in chronic heart failure is maladaptive, and may be a novel therapeutic target in the treatment of congestive heart failure.

Reduction of NE Uptake Transporter in Heart Failure

Myocardial uptake of NE is known to be reduced in the failing heart. In experimental heart failure produced by aortic constriction, Spann et al. (7) showed that intravenous infusion of NE resulted in a much smaller increase in cardiac NE in guinea pigs with heart failure than normal animals, but the increase of NE in the kidneys did not differ between the two groups of animals. They attributed the organ-specific difference of tissue NE uptake to a diminished number of sympathetic nerves and/or binding sites in the failing heart. We now know that the primary defect is caused by reduction of neuronal NE transporter (NET) density at the sympathetic nerve endings (8). Since the NE uptake mechanism is responsible for a rapid removal of interstitial NE after sympathetic release of NE, this defect of NE uptake has been used to explain, at least in part, the selective

increase of cardiac washout of NE. The amount of NE in the myocardial interstitial space is also expected to increase, and causes greater actions on the postsynaptic adrenergic receptors. NET, a 617 amino acid protein, comprises of 12 transmembrane domains at the sympathetic nerve endings (9). It is a member of the Na^+ and Cl^- dependent family of neurotransmitter transporters. It takes up NE from the interstitial space back to the adrenergic nerve terminals with the stoichiometric exchange of Na^+ and Cl^- against their electrochemical gradients (10).

My laboratories have studied the pre- and post-synpatic function of the cardiac sympathetic nerves for many years. Fan in my group (11) was the first to demonstrate a chamber-specific reduction of myocardial ß-receptors in the failing right ventricle of dogs with right-heart failure produced by tricuspid avulsion and progressive pulmonary artery constriction. Chamber-specific reduction of myocardial ß-receptor density was later confirmed in the failing human right ventricles associated with primary pulmonary hypertension (12). The decrease of myocardial ß-adrenoceptor density in heart failure animals is linked to reduced NE uptake activity, NET density (13, 14), and increased interstitial NE (15). In contrast, the contralateral nonfailing left ventricle is relatively spared without reductions of myocardial ß-receptor or NET density. Nor did NET change in the kidneys of the heart failure animals. These findings suggest that the change in NET is produced by a local mechanism, and is organ- and chamber-specific, occurring only in the failing ventricle.

The functional importance of the NE uptake site was further studied in rabbits at various time intervals after the start of rapid ventricular pacing (16). We found that rapid ventricular pacing caused early sympathetic nervous system activation, followed in sequence by reduced myocardial NE uptake, loss of neuronal NE, and down-regulation of myocardial ß-adrenoceptors. However, there was no significant reduction of protein gene product 9.5, a panneuronal marker, suggesting that the anatomic integrity of the cardiac sympathetic nerves probably is intact, and the changes of sympathetic neurotransmitters within the nerve endings are caused by functional abnormalities that are potentially reversible with either effective therapy or removal of a primary insult that causes heart failure. The interdependence of increased sympathetic stimulation, decreased cardiac NE uptake, and myocardial ß-adrenoceptor down-regulation is further borne out by a study by Leineweber et al. (17), who found that neurohumoral activation is essential for the reduction of myocardial ß-receptors in the hypertrophied right ventricle produced by monocrotaline, which, similar to our earlier studies in right-heart failure, is characterized by a chamber-specific reduction of myocardial NE uptake sites (18).

The physiological significance of the NE reuptake mechanism in the regulation of myocardial ß-receptor density and post-synaptic ß-adrenergic inotropic responsiveness was further studied in heart failure animals treated with desipramine (19) and selegiline (20). Desipramine is a NET inhibitor. It increased myocardial interstitial NE in heart failure, and caused further reductions of myocardial ß-adrenoceptor density and ß-adrenergic subsensitivity. In contrast, selegiline, which is a central α_2-agonist with a neuroprotective effect, attenuated the increase in plasma NE and the decrease of myocardial ß-receptor density and improved cardiac mechanical function in pacing-induced cardiomyopathy. These findings support the concept that interstitial NE is a modifiable variable, important in the mediation of agonist-induced post-synaptic events seen in heart failure.

To study the mechanism responsible for the NE uptake inhibition in heart failure, experiments have been conducted in my laboratories to show that the reductions of cardiac sympathetic transmitters and NET can be induced by exogenous NE (21, 22), and inhibited by desipramine (19, 23) and antioxidants (22, 24) in intact animals. Studies also have been conducted in cultured rat neuroblastoma cell (PC) 12 cells, showing that NE reduces NE uptake activity and NET protein in a dose-dependent fashion (25), most likely due to endoplasmic reticulum stress and reduced glycolyation and trafficking of NET to the cell membrane (26). There is also evidence that this effect of NE is associated with an increase in reactive oxygen species, and can be attenuated by the free-radical scavenger mannitol, or antioxidant enzymes superoxide dismutase and catalase. The findings suggest that the cardiac sympathetic nerve terminal dysfunction is probably caused by increased interstitial NE in heart failure, and the neuronal damaging effect of NE involves the uptake of NE or its oxidative metabolites into the sympathetic nerve endings.

Myocardial MIBG Scintigraphy and Its Clinical Utility in Heart Failure

Recently, radio-iodinated metaiodobenzylguanidine (^{123}I-MIBG), a structural analogue of NE, has been used to study the integrity and function of the cardiac sympathetic nervous system. MIBG shares the same reuptake mechanism and storage site with NE. Thus, its uptake into the myocardium reflects both the distribution of cardiac sympathetic innervation and the extent of neuronal NE uptake activity. The failing heart is characterized by reduced distribution and washout of MIBG (27). Abnormal MIBG uptake also correlates with reduced myocardial contractile reserve in patients with dilated cardiomyopathy (28). Similarly, c-11-HED, a PET-based NE analog, is significantly correlated to the NET density, and has been used to demonstrate regional variations of NE content in cardiomyopathy (29). Thus, the MIBG and HED-PET patterns can be used as a noninvasive means to investigate the changes of cardiac sympathetic innervation in the hearts of

cardiomyopathic patients. Studies have now shown that cardiac sympathetic nerve innervation as demonstrated by MIBG scintigraphy is an independent predictor for adverse clinical outcome including mortality in patients with heart failure (30). Improvements in MIBG patterns also have been shown to occur in patients who respond favorably to carvedilol (31), metoprolol (32), spironolactone (33), and enalapril (34). In contrast, bucindolol therapy, which showed only marginal survival benefits (35), did not improve the sympathetic nerve function as measured by MIBG (36).

Therapeutic Implications

Long-term ß-blocker therapy is now widely accepted as a pillar in the treatment of systolic heart failure. Effective utilization of the ß-receptor blockers can not only improve left ventricular systolic function but also increase survival in patients with chronic heart failure secondary to left ventricular systolic dysfunction (37-40). Given the overwhelming success of the ß-adrenoceptor blocker therapy, attempts have been made to determine if similar or greater beneficial effects can be derived from potent sympatholytic agents such as moxonidine which has been shown to decrease peripheral sympathetic outflow and circulating plasma NE by stimulating the brain stem imidazoline-1 receptor (41). Unfortunately, despite early enthusiasm with the centrally acting sympatholytic agents (42, 43), moxonidine therapy was considered detrimental, because it tended to increase mortality and morbidity in chronic systolic heart failure in a large clinical trial (44). Thus, the sympathetic nervous system activation can be both adaptive and maladaptive, depending on the degree of basal sympathetic activation and the extent of sympatholysis or ß-receptor blockade. Furthermore, generalized sympathetic nervous system inhibition probably has limited therapeutic utility, and localized adrenergic inhibition at the cardiac receptor level is the preferred mode of therapy heart failure.

Alternatively, results of several recent studies suggest that without directly affecting central sympathetic drive, cardiac function in heart failure may be modified by agents or interventions that upregulate the neuronal NET in the myocardium. Kreusser et al. (45) reported that injection of nerve growth factor into stellate ganglia of rats with heart failure produced by transverse aortic constriction improved NE uptake, repleted cardiac NE stores, and increased left ventricular fractional shortening. The number of cardiac sympathetic nerves, however, was unaffected. In a separate study (46), adenoviral gene transfer was used to overexpress NET in the myocardium of rabbits with pacing-induced cardiomyopathy. This resulted in increased NE uptake capacity and reversal of ß-receptor downregulation in the cardiac tissue. Local overexpression of cardiac NET also improved the systolic function and contractile reserve of the cardiomyopathic hearts. These

findings not only confirm the importance of NET in the initiation or progression of cardiomyopathy, but also suggest that cardiac NET may be a novel therapeutic target in the treatment of congestive heart failure. Future research should be directed to development of pharmacological agents or interventions that reduce the cardiac noradrenergic drive while preserving the integrity and NE reuptake function of the sympathetic nerve terminals.

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