Forever Young?

Nerve Growth Factor, Sympathetic Fibers, and Right Ventricle Pressure Overload

Ning Feng, Donald B. Hoover, Nazareno Paolocci

In addition to abnormalities such as structural/metabolic remodeling and Ca\(^{2+}\) mishandling, the failing heart has to cope with the hyperactivation of sympathetic efferent fibers. The latter is part of the more general neuroendocrine disorder typical of this syndrome, and can be because of: 1) reflex changes originating from altered neural inputs (baroreceptors and chemoreceptors); 2) increased levels of circulating hormones such as angiotensin II (Ang II); 3) central factors that may sustain and amplify these responses; and 4) Ang II generated locally within the heart. Although some components of the neuronal loop constituting the sympathetic reflex arc are not fully elucidated yet (for example, it is still unclear what is the afferent component of this circuitry), there is no doubt that norepinephrine (NE) spillover is among the major consequences of sympathetic hyperactivation in CHF. Despite the fact that the NE content of the myocardium from human failing heart is 50% less than that found in normal tissue, in untreated CHF patients the enhanced sympathetic nerve outflow leads to NE plasma concentrations that are 50 times higher than in normal subjects. The NE spillover can be attributed to increased rates of sympathetic fiber discharge and impaired NE reuptake into the sympathetic efferents.

Although increases in sympathetic activity can be beneficial during the early stage of heart failure, providing isotropic support and peripheral vasoconstriction, such compensation becomes maladaptive in the long term, affecting Ca\(^{2+}\) handling to decrease contractility and interfering with L-type calcium channel function to promote arrhythmias and cardiac sudden death. At least in vitro, NE can also act directly on cardiac myocytes to stimulate apoptosis via an action that is mediated by protein kinase A and requires Ca\(^{2+}\) entry via voltage-dependent Ca\(^{2+}\) channels. Accordingly, a tight control on NE synthesis, release and reuptake is necessary to avoid a large increase of NE concentration in the synaptic cleft that in the case of CHF can contribute to both cardiac \(\beta\)-adrenergic receptor downregulation and direct toxic effects on myocytes.

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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Nerve growth factor (NGF), a member of the neurotrophin (NT) family, is prominent among the factors recognized to control NE cycling (and so NE bioavailability) at the level of the nerve-myocyte interface. NGF regulates differentiation, survival and synaptic activity of the cardiac sympathetic nervous system. Overexpression of NGF in mice leads to sympathetic hyperinnervation and cardiac hypertrophy but left ventricular (LV) function remains normal. Preservation of ventricular structure and function in these transgenic mice has been attributed to enhanced NE reuptake associated with hyperinnervation. Increased NGF expression in heart also occurs after myocardial infarction and in early stages of diabetes. Enhanced production of NGF by viable tissue at the perimeter of infarcted myocardium can cause regional sympathetic hyperinnervation, and it has been proposed that the resulting heterogeneous innervation pattern increases risk for ventricular fibrillation and sudden death. Chronic diabetes and CHF, on the other hand, have been associated with NGF deficiency, reduction of cardiac NE levels, and impaired cardiac sympathetic function. Such changes might result from downregulation of crucial proteins required for NE synthesis/reuptake (eg, the NE transporter) or actual regression of noradrenergic nerves. It has been assumed that increased NGF expression in cardiac disease triggers growth of fully functional noradrenergic nerves. Kaye and colleagues were among the first to hypothesize and demonstrate that in CHF, despite cardiac sympathetic overactivity, the concomitant reduced sympathetic innervation could be because of a deficient myocardial production of NGF. In a rat model of CHF, they found a 40% reduction in NGF mRNA expression, associated with a 24% reduction in tissue NGF content. In parallel, a reduced sympathetic innervation was apparent in CHF hearts, as indicated by catecholamine fluorescence and by expression of the neuronal NGF receptor trkA. When isolated cardiac myocytes were challenged with NE, both NGF mRNA and protein expression was reduced, suggesting that NGF downregulation may represent an adaptive response to sympathetic overactivity. In other words, a feed-back between the two signals might occur. Exogenous NGF has been shown to enhance NE reuptake and positively modulate sympathetic transmission between sympathetic neurons and cardiac myocytes. Kreussler and colleagues demonstrated that NGF injection into stellate ganglia normalizes cardiac NE homeostasis in CHF, promoting cardiac NE reuptake through the neuronal norepinephrine transporter (NET). As such, NGF counters the depletion of cardiac NE stores and likely contributes to blunt sympathetic hyperactivation in CHF. All in all, NGF attenuates local cardiac

See related article, pages 1755–1764
sympathetic overdrive of hypertrophic hearts by improving cardiac NE reuptake.

In the current issue of Circulation Research, Kimura and colleagues report that in a drug (monocrotaline)-induced pulmonary hypertension, right ventricle (RV) hypertrophy and impaired RV function develop while NGF protein levels in RV freewall are increased by greater than 4-fold. In spite of the elevation of NGF, tyrosine hydroxylase (TH) activity and the density of TH positive fibers were significantly decreased in the RV wall. Similarly, RV NE content and the uptake of radiolabeled NE were decreased. Nevertheless, the authors also present novel evidence for the presence of new sympathetic and sensory nerve processes (neuron rejuvenation) which they identified by immunostaining for markers that are expressed during development and nerve regeneration (ie, polysialylated neural cell adhesion molecule, PSA-NCAM). The sympathetic and sensory nature of these nerve processes was suggested on the basis of staining for TH and calcitonin gene-related peptide, respectively.

The present study is provocative in that it appears to challenge some of the most established concepts regarding the impact of NGF on sympathetic fiber-myocyte interactions. At the same time, it suggests the necessity of performing additional experiments to define the pathophysiological impact of the new findings. First and foremost, the functional status of these “rejuvenated” nerve processes needs to be established. This is especially true for the sympathetic fibers that require two additional enzymes for the synthesis of NE, vesicular monoamine transporter 2 (VMAT2) for storage of NE, and NET for the reuptake of NE after release. Differential regulation of these critical noradrenergic proteins is not well described but is crucial to understanding the functional status of old and new sympathetic fibers. In a more teleological perspective, what is the significance of having a heart that is hyperinnervated by rejuvenated nerve fibers? Are these nerves going to positively or negatively impact the progression of CHF? The authors propose that the discovery of “neuron rejuvenation” may provide “a possible explanation for the dissociation of anatomical hyperinnervation and functional depression”, but it remains to be established, first, whether sympathetic rejuvenation occurs in additional experimental models, and above all in human CHF. Second, is sympathetic rejuvenation affecting the progression from hypertrophy to overt (dilated) failure? Along the same line, given the nature of the model chosen, it remains to be assessed whether the rejuvenation process is reversible. If so, will it ultimately lead to a sort of “nerve rarefaction” again? Another relevant finding of the Kimura’s article is that elevated levels of NGF might cause downregulation of TH in some of the original sympathetic nerves, which populated the RV freewall (ie, decreased TH fiber density and TH activity at 30 days) or promote regression of these nerves. Simultaneous staining for other noradrenergic markers (eg, VMAT2 and NET) might aid in resolving these options and would certainly help define the functional repertoire of the rejuvenated sympathetic fibers. Alternatively, this model of pulmonary hypertension might cause upregulation of other unknown factors that cause sympathetic nerve regression in the presence of NGF. Indeed, it appears that there is no rejuvenation process reported in the cardiac-specific NGF overexpressor. In cardiomyocytes, endothelin (ET-1) and Ang II are among the most important triggers of fetal genes expression, particularly in CHF conditions. In the present study, ET-1 positively modulated cardiomyocyte-derived NGF expression, and Ang II is an additional important regulator of sympathetic nerves activity in failing hearts. Whether these factors are involved in the process of rejuvenation or sympathetic nerve regression in the presence of NGF and who is the primary offender requires further investigation. Yet, regardless to the number of factors involved, the present study offers another intriguing new perspective. Stimuli that target one region of the heart (RV in this case) are able to selectively influence NGF generation and release within that cardiac region by local actions or selective reflexes. In this monocrotaline-induced model of pulmonary hypertension, the specific stimuli that, in addition to ET-1, likely trigger NGF upregulation and localized sympathetic dysfunction beg for more studies.

The study of Kimura and colleagues reiterates the necessity of understanding much more about the nature and the clinical relevance of cardiac sympathetic remodeling in cardiac disease. In the present case, one literary analogy can be used in the attempt of posing the right questions for future studies. In addition to cardiac myocytes, also sympathetic efferent fibers appear to be victims of the “Peter Pan syndrome” that invests the heart during the transition from hypertrophy to failure. If so, will the rejuvenated sympathetic fibers (and heart) defeat Captain Hook (ie, pressure overload) and leave Neverland to finally become an adult?

The story continues...


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