Sympathetic Nervous System Neuroplasticity

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In human and experimental models of heart failure there is widespread change in the sympathetic nervous system. This involves preferential activation of the sympathetic nervous outflow to the heart, impairment of norepinephrine reuptake by sympathetic nerves, and reduction of the content of norepinephrine in the failing myocardium, attributable in part to sympathetic neuronal rarefaction. Michael Kreusser and colleagues from the University of Heidelberg, in their article in this issue of *Hypertension*, report rapid correction of 2 of these abnormalities—reduced norepinephrine reuptake and depleted cardiac norepinephrine stores—in the rat heart failure model they studied, following injection of a single dose of the neurotrophin, nerve growth factor (NGF), into the left stellate ganglion. The neurotrophins are regulators of neural survival, development, and function that have a key role in vertebrate embryonic life but are increasingly documented to have important influences also in maturity.

The article by Kreusser et al underscores the extraordinary neuroplasticity of the sympathetic nervous system in adulthood, a structural and functional neuronal ebb and flow that is orchestrated in large part by NGF.

Perhaps the most explicit example of human sympathetic neuroplasticity is the regrowth and remodeling of the sympathetic nerves of the heart following cardiac transplantation. With the exception of the sympathetic nerves to the recipient atria, which depending on the surgical technique may be left intact, all cardiac sympathetic nerves are cut at the time of surgical removal of the failing heart. Subsequently, over several years, sympathetic fiber ingrowth leads to substantial reinnervation of the donor heart. By 3 to 5 years post-transplantation this reinnervation is unequivocally demonstrable with neurochemical and scanning methodology. This is evident in the overflow of norepinephrine and its metabolites into coronary sinus venous blood, the restoration of sympathetic neuronal reuptake of norepinephrine in the transplanted heart, and, dependent on this, a return of the capacity of the sympathetic nerves in the donor heart to extract from plasma specific positron emission tomography and single photon emission computerized tomography scanning ligands that are transporter substrates, enabling visualization of the reinnervated myocardium. Sympathetic neural control of the heart returns in concert with these changes, evident in the responses to exercise and experimental mental stress.

It has recently been suggested from a study testing for chimerism in sex-mismatched (female-male) cardiac transplantation that sympathetic reinnervation of the transplanted heart is attributable to neural repopulation by extracardiac progenitor cells rather than neural ingrowth from sectioned sympathetic nerves, but this is unlikely. The sympathetic neurons in the transplanted heart take at least 2 years to appear (this taking place progressively from base to apex), and are under central nervous system control, characteristics not expected with deposition of extracardiac progenitor cells. The extent to which NGF regulates sympathetic reinnervation after heart transplantation has not yet been tested, but could be done with measurement of NGF expression in biopsied myocardium, or with sampling of NGF in coronary sinus venous plasma, given that measurable amounts of NGF overflows from the heart into its venous drainage.

NGF is the prototypic member of a family of neurotrophins. In the periphery NGF plays an important role in the maintenance and survival of both sympathetic and sensory neurons. In the NGF null mouse sympathetic ganglia do not form. Conversely, cardiac-specific NGF overexpression in the mouse causes increases sympathetic innervation density and norepinephrine stores in the heart. An influence of NGF on the sympathetic nervous system is also evident in adult animals. Infusion of NGF into the left stellate ganglion over several weeks in dogs leads to pronounced sympathetic neuronal growth and nerve sprouting in the heart. The relation that exists between myocardial NGF and the sympathetic nerves of the heart seems to involve more than just neural support by the trophin, in that there is evidence of a feedback inhibition of cardiac myocyte production of NGF at high levels of norepinephrine. The release of NGF by cultured cardiac myocytes is inhibited by norepinephrine, and chronic intravenous infusion of norepinephrine in dogs reduces myocardial NGF content. High sympathetic tone in an innervated organ presumably inhibits its NGF production. This concept has been invoked to explain the concurrence in the failing heart of high sympathetic nerve firing rates, low NGF content, and sympathetic neuronal rarefaction.

These ideas are the starting point for the interesting and provocative study by Kreusser and colleagues. In their rat heart failure model they demonstrated that a single injection of NGF into the left stellate ganglion increased the previously reduced neuronal reuptake of norepinephrine and replenished the depleted norepinephrine content. NGF has previously been demonstrated to increase the neuronal reuptake of norepinephrine. The authors’ intriguing observation was that this facilitation of uptake involved a mechanism downstream from the expression of the NET transporter, which was unchanged. They found no increase in myocardial sympathetic nerve density at 32 hours; sympathetic neuronal sprouting does take longer than this. The authors attributed...
the replenishing of cardiac norepinephrine stores they observed to improved neuronal capture of the neurotransmitter by reuptake. This is possible, but may not be correct. Most norepinephrine returned to the nerve cytosol by reuptake is metabolized by monoamine oxidase (MAO) to the intraneuronal metabolite, DHPG, and not sequestered in storage vesicles. Further, in the heart, norepinephrine synthesis rate greatly exceeds the release rate, leaving little scope for reuptake impairment to deplete norepinephrine stores. Might NGF be of importance in other cardiovascular diseases, either (as for heart failure) via a maladaptive feedback between NGF production and high sympathetic nerve firing rates, or even perhaps as a prime mover, causing disease? At present it is uncertain whether a similar linking of reduced NGF production to increased sympathetic nerve firing rates exists in essential hypertension which, as for heart failure, is often accompanied by sympathetic nervous activation. In the Japanese spontaneously hypertensive rate, in which sympathetic stimulation is also well documented, perhaps surprisingly sympathetic hyperinnervation is present, driven by increased expression of NGF. Definitive experiments in essential hypertension have not yet been reported.

The best candidate for a disease in which NGF could be a prime mover, causing disease, might be pure autonomic failure. In this condition there is an inexplicable degeneration of sympathetic nerves throughout the body, leading to loss of sympathetic reflexes manifested primarily as severe postural hypotension and recurrent syncope. Could pure autonomic failure perhaps be due to a permanent loss of the neurotrophic support normally provided in health by NGF? A recent preliminary report describes almost undetectable plasma concentrations and cardiac release of NGF in pure autonomic failure patients, suggesting that this might be so.

A particularly interesting aspect of the article by Kreusser and colleagues was their demonstration that NGF administration improved left ventricular performance in the experimental heart failure model. They attributed this to improvement in neuronal reuptake of norepinephrine and subsequent replenishing of myocardial norepinephrine stores. As the authors discuss, whether NGF administration might be beneficial in human heart failure is problematic. Longer term administration of NGF than used by the authors, in dogs subjected to experimental myocardial infarction, led to sympathetic neuronal sprouting, a three-fold increase in myocardial sympathetic nerve density and an increased rate of ventricular tachyarrhythmias and death. The proven benefit of β-adrenergic blockade in heart failure would seem to argue against the therapeutic prospects of a neurotrophin that, depending on the dosing duration, might increase myocardial sympathetic nerve density and norepinephrine release.

References