Sympathetic Nervous System Neuroplasticity

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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 uptake of norepinephrine and replenished the depleted norepinephrine content. NGF has previously been demonstrated to increase the neuronal uptake 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, or even perhaps as 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 might be beneficial in human heart failure. 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