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Neuronal plasticity in the genesis of cardiac arrhythmias due to ischemia

Olivas A, Gardner RT, Wang L, Ripplinger CM, Woodward WR, Habecker BA. Myocardial Infarction Causes Transient Cholinergic Transdifferentiation of Cardiac Sympathetic Nerves via gp130. **J Neurosci 2016; 36: 479-88. http://doi.org/f76m6f**

The nervous control of the heart is produced by the antagonistic or synchronic interaction of the sympathetic and parasympathetic nervous systems. Thus, the sympathetic nervous system releases norepinephrine and increases the heart rate and inotropic state, and the parasympathetic nervous system has opposite effects through the release of acetylcholine. This regulation is based on a neuronal structure tiered in hierarchical functional levels, from intracardiac neurons to the cerebral cortex, allowing a delicate and changing balance between autonomic tones. In a pathological situation, such as myocardial infarction, this balance is altered and the nervous structures undergo changes that lead to dysautonomia. Ischemia damages the nerve terminals and neuronal bodies found in the heart, modifies local neurotransmitter levels and predisposes to arrhythmias and increased myocardial damage. One of the neuronal changes observed in response to myocardial hypoxia is the production of acetylcholine by sympathetic neurons. In response to ischemia, myocytes can release "cholinergic differentiation factors" which modify the phenotypic expression of noradrenergic neurons to cholinergic neurons.

As it is known, postganglionic cardiac sympathetic fibers are derived from the cervicothoracic trunk, which is the most important stellate ganglion, and whose neurons are mainly intended for the heart. With this in mind, Olivas et al. designed this interesting study in an experimental model of myocardial ischemia/reperfusion in mice, demonstrating a transient increase of acetylcholine levels in the remote myocardium to the ischemic area, which returns to baseline values three weeks after the beginning of the event. Coincidentally, in the same period, the expression of specific markers for the synthesis of acetylcholine in the sympathetic neurons of the stellate ganglion was observed by immunohistochemistry. In this way, they demonstrated that the neuronal transdifferentiation of the extracardiac nervous axis that regulates the heart is responsible for the increase in myocardial cholinergic activity in the first weeks after infarction. This initial period of cardiac remodeling is characterized by intense inflammatory activity, with high levels of cytokines and macrophage infiltration. In this sense, the authors observed that the induction of cholinergic genes in the neurons of the stellate ganglion requires the expression of the cytokine receptor gp130, which suggests a mechanism of retrograde signaling from the heart to the nervous system as a trigger for plastic neural changes. To confirm the sympathetic origin of acetylcholine, elevated levels of this neurotransmitter in myocardial ischemia/reperfusion are not observed in transgenic mice that do not express the choline acetyltransferase enzyme in sympathetic neurons. The functional consequences of noradrenaline and acetylcholine co-release from the same sympathetic nerve terminals were studied in isolated rabbit hearts. The authors observed a modification in myocyte membrane potential and intracellular calcium concentration, which generate poor cardiac adaptation to changes in heart rate, predisposing to the onset of severe arrhythmias.

Together with the structural changes of the ventricular myocardium after infarction, there is modifications in the structure and function of the complex network of intracardiac neurons, which is collectively known as cardiac neural remodeling. Distinctive phenomena of this remodeling are nervous destruction in the scar area and disorganized growth of new nerve fibers that generate areas of great electrical instability. Recent studies have shown that this electroanatomical remodeling of the nervous system regulating the heart extends to higher extracardiac levels and generates a complex substrate for arrhythmias in the context of ischemic heart disease. In the present work, it can be seen that this phenomenon based on neuronal plasticity begins at very early stages and needs specific activators, such as proinflammatory cytokines, which could represent future sites of therapeutic blockade to slow down remodeling at the onset of cardiac disease.