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Deepening the Knowledge of the Cardiac "Brain"

Navickaite I, Pauziene N, Pauza DH. Anatomical evidence of non-parasympathetic cardiac nitrergic nerve fibres in rat. **J Anat. 2021;238(1):20-35. https://doi.org/10.1111/joa.13291.**

Cardiac autonomic innervation can be divided into an extrinsic cardiac nervous system (ECNS) and an intrinsic cardiac nervous system (ICNS). The extrinsic portion consists of sympathetic and parasympathetic preganglionic neurons of the central nuclei and their preganglionic fibers, same as the postganglionic neurons that form the cervical and thoracic autonomic ganglia. On the other hand, the ICNS is composed of thousands of sympathetic and parasympathetic postganglionic neurons and afferent and interconnecting neurons grouped in subepicardial nervous ganglia. These ganglia, in an approximate number of 700 to 1600, are tightly interconnected between them, forming a fibrillar and ganglionic network known as subepicardial plexus. In turn, this nervous network connects with a second deeper network without ganglia, called subendocardial plexus. The ICNS has some degree of functional autonomy, but it is strongly interconnected with superior centers through the cardiac nerves, and thus, the cardiac nervous system regulates regional cardiac dynamic functions. Regional cardiac regulation is possible thanks to the subdivision of the epicardial plexus into different subplexuses which are distributed in defined myocardial territories to which specific ganglia contribute efferent and afferent fibers. It is known that autonomous neurons synthetize and release acetylcholine (ACh) and noradrenaline as neurotransmitters. However, cardiac neurons are phenotypically more complex and express other very important neurotransmitters, as the vasoactive intestinal peptide (VIP), neuropeptide Y (NPY), substance P, the calcitonin gene-related peptide and nitric oxide (NO). Neuronal nitric oxide synthase (nNOS)-derived nitric oxide (NO) fulfills a very important role in the neural control of circulation, as well as in different cardiovascular diseases, as hypertension, myocardial infarction and arrythmias. Nevertheless, the profound mechanisms through which NO achieves these functions are not clearly understood.

In this work, Navickaite et al. performed an interesting study to establish the origin of nitrergic nerve fibers innervating the heart. They used a combination of immunohistochemical markers in sections of rat spinal cord, medulla oblongata, vagal nerves, dorsal spinal root ganglia, and cardiac nerves and ganglia. They observed that the greatest proportion of nitrergic neuronal soma is found in the vagal nodose ganglion, and is also seen in the nucleus of the solitary tract, suggesting that NO participates in cardiac parasympathetic afferences. They also found a lower proportion of nitrergic neuronal soma in the ambiguus nucleus and the dorsal nucleus of the vagus nerve, but in these cases, they were biphenotypic neurons, which in addition are cholinergic. The presence of these biphenotypic fibers in the vagus nerve pathway and the cardiac nerves suggests their participation in the efferent parasympathetic innervation of the heart. An abundant number of nNOS-positive neuronal soma indicates an important role of NO in preganglionic sympathetic regulation. On the contrary, very few neurons or fibers of the stellate ganglion or spinal dorsal root ganglia were positive for nNOS, demonstrating that these fibers do not directly contribute NO to cardiac innervation.

Previous works showed the presence of an important number of nitrergic fibers in ICNS, but their origin was not well demonstrated. This outstanding study of Navickaite et al. contributes to its understanding, by showing that an important number of cardiac nerve fibers expressing nNOS arise from vagal ganglia, and could participate not only in efferent cardiac regulation, but also in cardiac afferences involved in complex physiological and abnormal neural reflex mechanisms. Experimental studies observed a decreased activity of cardiac neural nNOS in hypertension. Also, nNOS-derived NO is capable of reducing ventricular myocardial excitability in arrhythmias. In addition, it is necessary to consider that the whole cardiac neuroaxis undergoes functional and structural changes as a consequence of neural remodeling due to ischemic heart disease and heart failure. These are some of the examples of the autonomous nervous system participation in cardiovascular diseases, but the spectrum is much wider. Selective innervation of the cardiac conduction system and regional myocardial distribution of epicardial nervous plexuses, as well as the topographic communication of ICNS and ECNS at specific sites of the cardiac hilum open the path in the field of selective catheter ablation of atrial arrhythmias. The ICNS is a yet not completely studied group of very complex neural networks, which has been called the "little brain of the heart". A better understanding of cardiac neuroanatomy, and its neurochemistry and function, could improve the widespread use of neuromodulation techniques and the specific pharmacological management of dysautonomia-based cardiovascular diseases.