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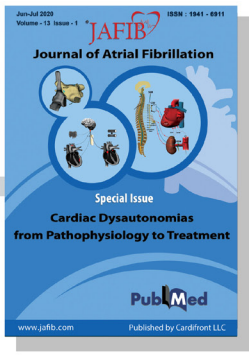

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Cardiac Neuroanatomy for the Cardiac Electrophysiologist

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Abstract

The cardiac neuraxis is integral to cardiac physiology, and its dysregulation is implicated in cardiovascular disease. Neuromodulatory therapies are being developed that target the cardiac autonomic nervous system (ANS) to treat cardiac pathophysiology. An appreciation of the cardiac neuroanatomy is a prerequisite for development of such targeted therapies. Here, we provide a review of the current understanding of the cardiac ANS. The parasympathetic and sympathetic nervous system are composed of higher order cortical centers, brainstem, spinal cord, intrathoracic extracardiac ganglia and intrinsic cardiac ganglia. A series of interacting feedback loops mediates reflex pathways to exert control over the cardiac conduction system and contractile tissue. Further exploration of this complex regulatory system promises to yield neuroscience-based therapeutics for cardiac disease.

Introduction

The autonomic nervous system (ANS) plays a critical role in many facets of cardiac physiology (e.g., modulation of chronotropy, dromotropy, inotropy, and lusitropy) [1]. Historically, the nature of this role has been fervently debated, particularly in the case of cardiac conduction. The Italian physiologist Giovanni Borelli in the 17th century posited the neurogenic origin of the heartbeat, and this notion was widely accepted until Sir Walter Gaskell's experimental work of the late 19th century propelled myogenic theory to the forefront. Furthermore, prior to the advent of direct cardiac interventions such as coronary revascularization for coronary artery disease, nerves were transected to treat angina [2]. In recent years, our understanding of the exquisite control of the ANS in cardiac physiology has significantly improved, and the ANS has increasingly been targeted in cardiovascular diseases including arrhythmia, myocardial infarction and heart failure [3-6].

The ANS has traditionally been characterized as composed of two opposing limbs, the parasympathetic and sympathetic nervous systems, under the influence of the central nervous system (CNS). More extensive study, however, has demonstrated that a series of reflex pathways integrate afferent (sensory) and efferent (motor) information in a complex manner to regulate cardiac excitability and mechanical function (Fig. 1). These reflex pathways involve a cardioneural hierarchy that includes the intrinsic cardiac ganglia, extracardiac intrathoracic ganglia, spinal cord, brainstem, and higher cortical centers. Much of the pharmacologic therapy for heart failure and arrhythmia impact the neurohormonal axis, and neuromodulatory treatment modalities that are currently being explored in pre-clinical and clinical studies include vagal nerve stimulation (VNS), cardiac sympathetic denervation, renal denervation, spinal cord stimulation, baroreflex activation therapy, neurotoxin (botulinum toxin) injection and tragus stimulation [4, 5]. However, these interventions have had varying levels of success. Further understanding of the innervation pathways to the heart and a departure from an overly simplistic view of the sympathetic and parasympathetic nervous systems will promote development of new or improved targeted neuromodulatory therapeutics as alternatives to conventional approaches.

Key Words
Atrial Fibrillation, Neuroanatomy, Electrophysiologist

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The brain-heart axis

The notion of the brain-heart axis typically evokes thoughts of stress-induced cardiomyopathy or 'broken heart syndrome'. Recent data has shown that lower socioeconomic status in patients with stress-induced cardiomyopathy is associated with increased amygdala activity on functional MRI and worse survival [7]. Psychological stress is also associated with arrhythmia, as has been demonstrated in patients with implantable cardioverter-defibrillators or children playing electronic games [8, 9]. However, the importance of this axis is more pervasive, as population studies have demonstrated the link between stress and cardiovascular disease. Increases in cardiovascular events shortly after catastrophic events such as the Northridge earthquake in California in 1994 or the September 11th, 2001 attacks or sporting events such as the 2006 World Cup highlight the importance of the brain-heart axis [10-12].

Cardiac sequalae of CNS insults such as stroke and seizure are multiple and include electrocardiographic changes and arrhythmias such as atrial fibrillation, atrioventricular (AV) block, sudden cardiac death and changes in heart rate variability, a surrogate marker of autonomic tone [13-20].

Pre-clinical models and human studies have helped discern important loci within the central nervous system that regulate cardiac function (Fig. 2). In rats, sites implicated in cardiac chronotropic control were found in the insular cortex [21]. Neural tract tracing of the cardiac inputs of the vagus nerves has elucidated that preganglionic parasympathetic neurons origin in the brainstem within in the dorsal motor nucleus and nucleus ambiguus of the medulla oblongata and an intermediate zone between these two structures [22-26] Specifically, functional studies of the cat brainstem has demonstrated that neurons of the dorsal motor nucleus control ventricular contractility while those of the nucleus ambiguus regulate heart rate [27]. A study in human patients demonstrated that strokes impacting the right insular cortex were associated with abnormalities in heart rate variability and increased incidence of complex arrhythmias [28]. Functional MRI has also demonstrated that when the anterior cingulate cortex is impacted in a stroke, autonomic effector function is impacted as demonstrated by changes in heart rate variability [18].

Neuroanatomy of parasympathetic and sympathetic nervous systems

To explore the functional control of the cardiac neuraxis, a firm understanding of the cardiac neuroanatomy is imperative. Myocardial innervation patterns across mammals, including humans, are conserved [29-33], and the cardiac ANS has been categorized into: (1) central; (2) intrathoracic extracardiac; and (3) intrinsic cardiac components (Fig. 1). The intrathoracic extrinsic cardiac nervous system connects the intrinsic cardiac nervous system at the level of the heart to the CNS and is composed of sensory nerves and parasympathetic and sympathetic motor components that exert opposing effects on cardiac electrical and mechanical properties.

Parasympathetic motor neurons

Preganglionic parasympathetic neurons originating in the brainstem as described above traverse the bilateral vagus nerves and multiple intrathoracic cardiopulmonary branches to synapse on efferent postganglionic parasympathetic neurons in the numerous intrinsic cardiac ganglia (Fig. 2) [34, 35]. Interestingly, a small population of sympathetic fibers have also been found to be contained with the vagi [36]. Preganglionic parasympathetic neurons release neurotransmitter acetylcholine to activate the postganglionic neuron via nicotinic and muscarinic cholinergic receptors. Postganglionic neurons in turn secrete acetylcholine to activate muscarinic receptors expressed in the myocardium and coronary vasculature to mediate changes in chronotropy, dromotropy, inotropy and lusitropy.

Sympathetic motor neurons

Sympathetic efferent preganglionic neurons originate in the brainstem reticular formation, including the ventrolateral medulla, and track via the intermediolateral cell column of the spinal cord (Fig. 3). The neurons exit the spinal cord via the bilateral C7-T6 ventral rami to

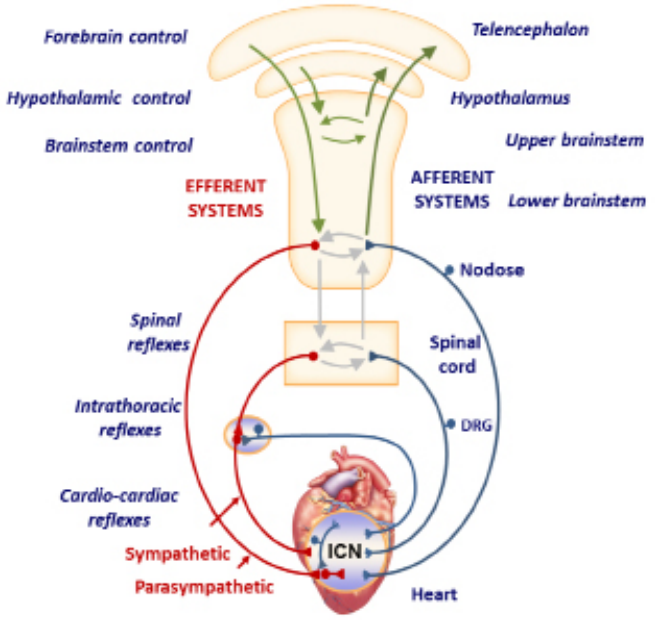

Figure 1: **Neural control of the heart.**

The cardiac autonomic nervous system consists of interacting feedback loops involving afferent (blue), efferent (red) and local circuit (blue and grey) neurons at the intracardiac (level 1), intrathoracic extracardiac (level 2) and central nervous system (level 3) levels. SG, stellate ganglion; DRG, dorsal root ganglion; ICNS, intrinsic cardiac nervous system. (Adapted from Shivkumar et al., 2016)

postganglionic sympathetic neurons in the superior cervical, middle cervical, cervicothoracic (stellate), and mediastinal ganglia [37, 38]. The preganglionic neurons send signals via acetylcholine, which binds nicotinic cholinergic receptors on the postganglionic neurons. These postganglionic neurons project axons via several cardiopulmonary nerves to the myocardium and limited populations of intrinsic cardiac adrenergic neurons. These neurons release neurotransmitter norepinephrine, which binds α- and β-adrenergic receptors expressed on the myocardium and coronary vasculature to increase chronotropy, inotropy and vasoconstriction.

Parasympathetic-sympathetic interactions

Challenging the dogma that the parasympathetic and sympathetic nervous system act as independent regulators over cardiac function is the body of literature describing interactions between the parasympathetic and sympathetic nervous system in the cardiac neural hierarchy. For example, animal studies have shown that ablation of the RAGP significantly decreases VNS-induced bradycardia but does not impact the indirect influence on stellate ganglia stimulation-induced tachycardia during concurrent VNS [39]. Similarly, ablation of the RAGP and IVC-IA GP mitigated VNS-mediated slowing of AV conduction, but VNS still reduced sympathetic stimulation-induced increases in AV conduction. Furthermore, transecting the bilateral vagi and stimulating the central end of the vagi still mediated effects on heart rate suggesting activation of vagal afferents still impacted central inputs to the heart [40].

Sensory neurons

Cardiac afferents provide beat-to-beat sensory information of cardiac function and microenvironment to the neuraxis, and additional

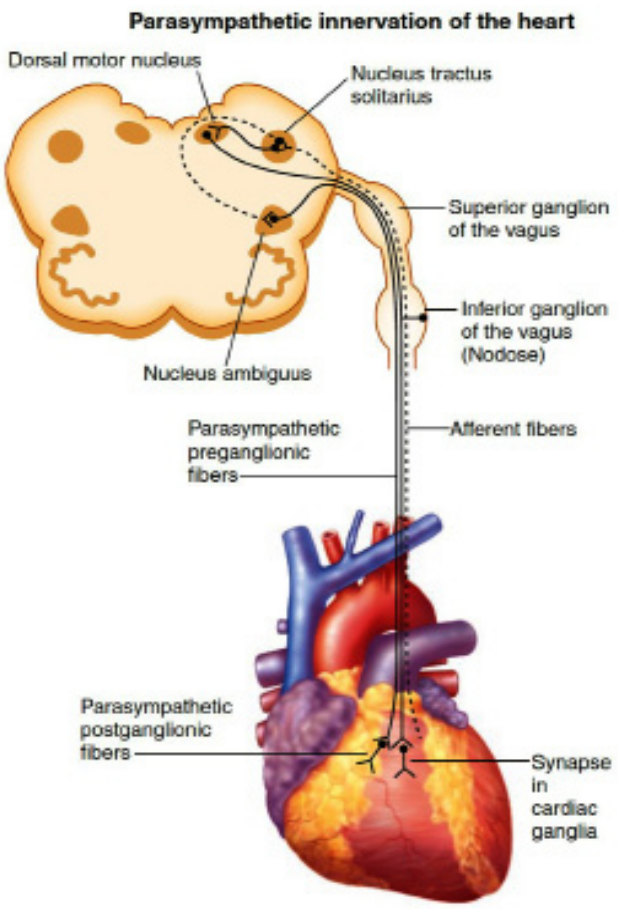

Figure 2: **Parasympathetic innervation of the heart.**

Schematic demonstrating efferent (solid black line) and afferent (dashed black line) pathways to and from the heart, respectively. Preganglionic parasympathetic motor neurons are mainly found in the nucleus ambiguous and the dorsal motor nucleus in the medulla oblongata. Neurons then project via long axons in the vagus nerve to the intrinsic cardiac neurons in the heart. Sensory information is transduced via afferent fibers with cell bodies housed in the nodose ganglia. These neurons synapse in the nucleus tractus solitarius. Interneurons are present between the nucleus tractus solitarius, dorsal motor nucleus and nucleus ambiguus. (Adapted from Rajendran et al., 2017.)

information is conveyed by arterial mechano- and chemoreceptors (Fig. 2). Around 80% of the fibers in the vagus nerve are afferents and travel via the nodose ganglia to transduce sensory information to the nucleus tractus solitarius in the brainstem [41-43]. Cell bodies of afferent neurons in 'sympathetic' fibers are in the C7-T4 dorsal root ganglia and synapse on second-order neurons that project to the thalamus via the spinothalamic tract [44,45]. Sensory neurons have also been identified in the intrinsic cardiac ganglia [46,47]. The processing of afferent information at multiple levels, including the intrinsic cardiac nervous system, extracardiac intrathoracic ganglia, spinal cord, brain stem, and higher centers, provides an elegant mechanism of interacting feedback loops that modulate efferent cardiomotor (sympathetic and parasympathetic) signals for maintaining normal rhythm and life-sustaining circulation.

The intrinsic cardiac nervous system

Analogous to the enteric nervous system of the digestive tract, the intrinsic cardiac neurons are found in intramural ganglia and in epicardial fat pads (Fig. 4) [48,49]. While these neuronal somata were identified early in the last century, the location and connections of these neurons remained poorly understood [50]. Subsequent light and electron microscopy studies identified these structures in the human heart [49]. It is now known that the intrinsic cardiac ganglionated plexi contain a distributed network of afferent, motor (parasympathetic and sympathetic) and interconnecting (local circuit) neurons [51]. The ICNS, under the influence of inputs from the brainstem, spinal cord and intrathoracic sympathetic ganglia, is thought to serve as a final coordinator of regional reflexes. Taken together, this neural network at the level of the heart is thought to play an important role in modulating cardio-cardiac reflexes.

While postganglionic neurons in individual ganglionated plexi (GPs) supply both atrial and ventricular tissues, certain GPs influence discrete cardiac regions. Anatomic dissections and functional studies in canines have demonstrated that postganglionic vagal neurons to the sinoatrial (SA) node are found predominantly in a GP next to the right pulmonary vein-atrial junction known as the right atrial ganglionated plexus (GP), while the postganglionic vagal neurons that influence the atrioventricular (AV) node are located predominantly in the region adjacent to the inferior vena cava-inferior left atrium junction [52]. Sympathetic fibers from the right stellate ganglion course through the posterior atrial GP located between the superior vena cava and aorta, while parasympathetic neurons in this GP exerts a negative chronotropic effect on the SAN [53,54]. Parasympathetic neurons in the ventral interventricular GP exert negative ionotropic effects on left ventricular contractility while sympathetic fibers also course through this region [55]. However, while it may be tempting to construe that specific GPs (e.g. the RAGP) within the ICNS may be ablated to affect a particular cardiac region (e.g. the SA node), pleiotropic effects of the GPs on other aspects of cardiac function invite off-target effects if such an approach is adopted (Hanna et al., submitted).

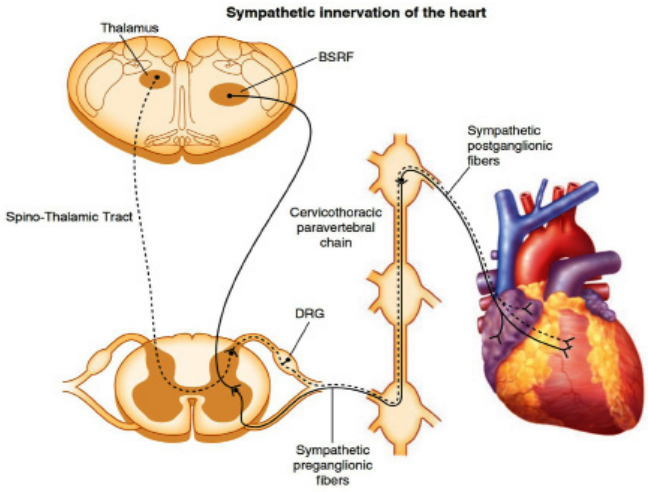

Figure 3: **Sympathetic innervation of the heart.**

Schematic demonstrating sympathetic efferent (solid black lines) and afferent (dashed black lines) pathways to and from the heart. Preganglionic motor neurons originating in the brainstem reticular formation (BSRF), including the rostral ventrolateral medulla, descend the intermediolateral lateral column of the spinal cord and exit via ventral rami to synapse on postganglionic neurons in ganglia of the cervicothoracic paravertebral chain. The postganglionic neurons primarily synapse directly on the heart. Afferent information is conveyed via neurons whose cell bodies are found in the dorsal root ganglia (DRG) and centripetal axons project to the dorsal horn of the spinal cord. Second-order neurons project from the dorsal horn to the thalamus via the spinothalamic tract. (Adapted from Rajendran et al., 2017.)

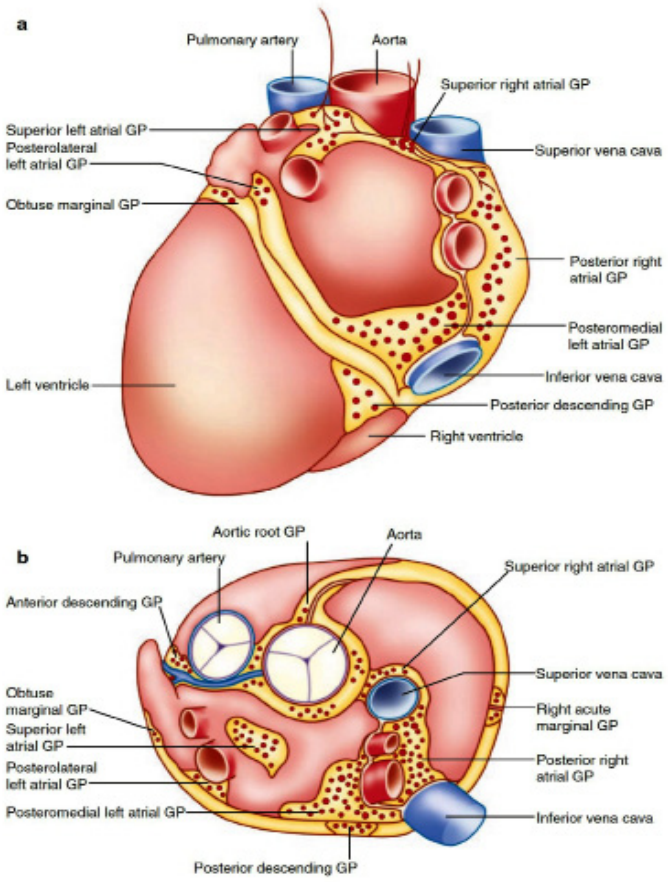

Figure 4: **Intrinsic cardiac nervous system is comprised of several ganglionated plexi (GPs) that are primarily found the heart hilum.**

a Left posterior oblique view of the heart. b Superior view of the heart. (Adapted from Rajendran et al., 2017.)

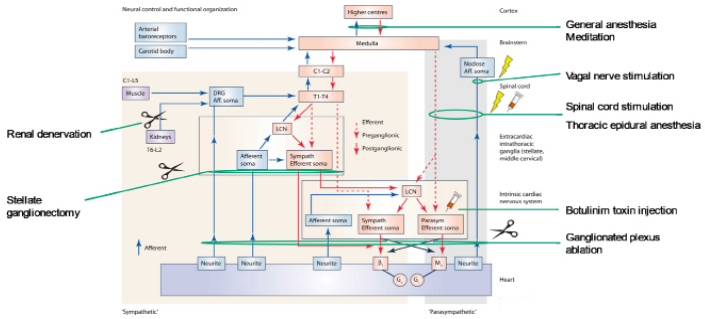

Figure 5: **Schematic of neural control and functional organization of the cardiac ANS.**

Interacting feedback loops within the cardiac neuraxis exert control over the heart. Current neuromodulatory therapies and their sites of action are listed alongside the diagram. Aff, afferent; β1, β-adrenergic receptor; C, cervical; DRG, dorsal root ganglion; Gi, inhibitory G-protein; Gs, stimulatory G-protein; L, lumbar; LCN, local circuit neuron; M2, muscarinic receptor; T, thoracic. Adapted from Shivkumar et al. (2016).

Conclusions

The cardiac ANS regulates all aspects of cardiac electrical activity and mechanical function. Reflex pathways that span the cortex to the ICNS maintain sympathovagal balance. Crosstalk amongst these feedback loops across the neural hierarchy, mixed neuron populations within the ICNS and mixed nerves create a distributed network for autonomic control (Fig. 5). Multiple nexus points for current neurointerventions are found within these pathways. Further study of the cardiac neuroanatomy is necessary for the development of precise neuromodulatory therapeutics for cardiovascular disease.

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