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Review

The sympathetic innervation of the heart: Important new insights

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ABSTRACT

Autonomic control of the heart has a significant influence over development of life threatening arrhythmias that can lead to sudden cardiac death. Sympathetic activity is known to be upregulated during these conditions and hence the sympathetic nerves present a target for treatment. However, a better understanding of the anatomy and physiology of cardiac sympathetic nerves is required for the progression of clinical interventions. This review explores the organization of the cardiac sympathetic nerves, from the preganglionic origin to the postganglionic innervations, and provides an overview of literature surrounding anti-arrhythmic therapies including thoracic sympathectomy and dorsal spinal cord stimulation. Several features of the innervation are clear. The cardiac nerves differentially supply the nodal and myocardial tissue of the heart and are dependent on activity generated in spinal neurones in the upper thoracic cord which project to synapse with ganglion cells in the stellate complex on each side. Networks of spinal interneurones determine the pattern of activity. Groups of spinal neurones selectively target specific regions of the heart but whether they exhibit a functional selectivity has still to be elucidated. Electrical or ischemic signals can lead to remodeling of nerves in the heart or ganglia. Surgical and electrical methods are proving to be clinically beneficial in reducing atrial and ventricular arrhythmias, heart failure and severe cardiac pain. This is a rapidly developing area and we need more basic understanding of how these methods work to ensure safety and reduction of side effects.

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1. Introduction

Abnormalities and alteration in cardiac sympathetic control of the heart are linked to life threatening arrhythmias, congestive heart failure and sudden cardiac death (Fukuda et al., 2015). Recently sympathetic nervous control has been targeted as a means to treat heart disease. So far the clinical approaches have been fairly crude and there is clearly

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a need to improve understanding and treatment. The topic was brilliantly reviewed in 1977 by two outstanding pioneers in this field (Randall, 1977; Wurster, 1977) but much has happened since. Therefore, this review represents a selective overview of literature updating the anatomy and physiology of the spinal cardiac sympathetic neurones and their projection to the heart and relevance to cardiac disease.

2. General features

In mammals including humans the cardiac preganglionic cell bodies are located in the grey matter of the first six segments (T1–T6) of the thoracic spinal cord. Their axons exit the spinal cord by the ventral roots from which they pass into white rami to join the sympathetic chain and subsequently synapse either on postganglionic neurones in ganglia at the segment of spinal origin or travel rostrally into the stellate ganglion and the adjoining inferior/middle cervical ganglion before synapsing with their target postganglionic neurone (Fig. 1). The majority of the cardiac sympathetic innervation arises from these ganglia although a few postganglionic cell bodies have been described in the myocardium. These neurones modulate chronotropy, dromotropy, lusitropy and inotropy functions in all the cardiac chambers.

3. The organization of the T1–T6 sympathetic nuclei

Sympathetic preganglionic neurones lie bilaterally in the intermediate zone of the spinal cord lying most densely in the grey matter but extend into the white matter on its lateral border and medially across to the central canal (Coote, 1988; Jänig, 2006). On each side of the spinal cord these sympathetic neurones form clusters arranged longitudinally in columns (Fig. 1A) with groups of dendrites spreading laterally and medially but most extensively rostro-caudally for up to 1.5 mm to 2.5 mm in the cat spinal cord and probably more in human spinal cord. There is a rich synaptic terminal innervation on these dendrites by both segmental, propriospinal and supraspinal afferent terminals making synaptic contact via an array of neurotransmitters from excitatory amino acids like glutamate or inhibitory amino acids like GABA or glycine as well as monoamines and neuropeptides that have a variety of effects.

4. Interneurones

Of particular importance to spinal organization are interneurones that have been rather ignored but in recent years have been championed by Sue Deuchars whose group has shown the actions of their terminals that richly synapse on the dendrites of sympathetic preganglionic neurones (Deuchars, 2007). Transneuronal labeling studies have identified interneurones within the column of sympathetic cells and in surrounding regions including the inner laminae of the dorsal horn (Strack et al., 1989; Jansen et al., 1995) (Fig. 1C). Intracellular recording from preganglionic neurones have shown that these interneurones provide either excitatory influence in the form of EPSPs or inhibitory influence in the form of IPSPs using a variety of neurotransmitters (Dun and Mo, 1989; Lewis et al., 1993; Spanswick et al., 1994; Deuchars et al., 2005; Deuchars, 2007). The extensive arborization of spinal and supraspinal axons on dendrites of interneurones forming spinal sympathetic networks strongly indicates that interneurones play a large part in shaping the pattern of discharge of the sympathetic preganglionic neurone (Coote, 2001; Staras et al., 2001; Pierce et al., 2010) which is strongly rhythmic and has a key influence on the response of the heart.

5. Preganglionic neurones

The final output neurones of the spinal sympathetic circuit are the preganglionic neurones which lie in a column on each side of the intermediate region of the spinal cord. The sympathetic preganglionic neurones account for nearly 90,000 efferent neurones in the thoracic spinal cord of humans (Coote, 1988) of which almost a third are in the T1–T3 segments, the third thoracic segment containing more than 11,000 of these. Cardiac sympathetic preganglionic neurones are confined to the T1–T6 spinal segments from where, in mammals (rat, cat, dog, human), their axons project to the stellate ganglion, the main postganglionic efferent sympathetic nerve supply to the heart (Fig. 1B) (Kawashima, 2005). In the dog there are also cardiac postganglionic neurones in the middle cervical ganglion (Armour and Hopkins, 1981; Armour, 1984) which is supplied by axons from the thoracic segments only at least in the rat, rabbit cat and dog (e.g. Langley, 1892) and

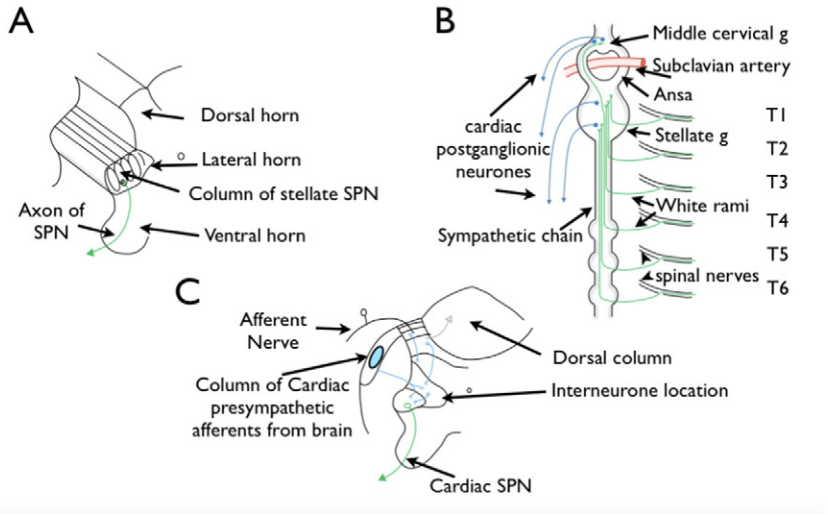

Fig. 1. Diagrammatic representation of the arrangement of the sympathetic nerves to the heart on the left side. A, is an outline of the spinal grey matter at the upper thoracic level indicating the discrete location in the lateral horn, of the column of sympathetic preganglionic neurones which project to the stellate ganglion via their axons which traverse the ventral horn of the spinal cord to pass out in the segmental spinal nerve. B, Schematic of the upper thoracic (T1–T6) showing the path of cardiac sympathetic preganglionic from the spinal cord via the white rami to the sympathetic chain and their synaptic connections in the stellate ganglion and via the ansa subclavia in the middle cervical ganglion. All the cardiac postganglionic neurones lie in these ganglia and project to terminate in different regions of the heart, either as separate nerves or in the vagosympathetic nerve on left and right sides. C, Drawing of a transverse section of upper thoracic spinal cord to illustrate the afferent nerve paths in the dorsal horn and the location of sympathetic interneurones and the relationship to the lateral horn from where the cardiac preganglionic neurones project axons to the sympathetic chain and stellate or middle cervical ganglia. Also shown is an area in blue in the dorsolateral funiculus where axons of neurones descending from the brain project to synapse with cardiac sympathetic neurones in the lateral horn. Dorsal spinal cord stimulation involves electrodes placed close to the dorsal column where the main sensory axons ascend to the brain.

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