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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.

Contents

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

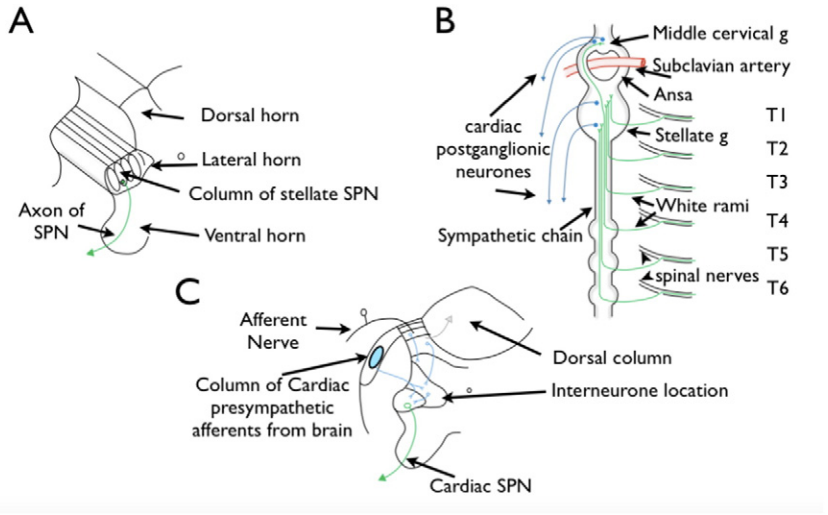

Fig. 1. Diagrammatic representation of the arrangement of the sympathetic nerves to the heart on the left side. A, is an outline of the spinal grey matter at the upper thoracic level indicating the discrete location in the lateral horn, of the column of sympathetic preganglionic neurones which project 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.

probably also in humans (personal observations)(Fig. 1B). There is no reliable evidence that those preganglionic axons described as passing on, to synapse in the superior cervical ganglion contain cardiac destined fibres (see review by Coote, 2013).

An important general principle of organization of neurones in the central nervous system, is the discrete localization of organ specific neurones, at sites throughout the brain and spinal cord. This also applies to spinal sympathetic neurones. The first indication of this came from studies recording ongoing activity in cardiac postganglionic nerves or changes in cardiac activity, and examining the effects of electrical stimulation of nerves originating from different spinal cord segments or by sectioning these nerves in anaesthetized animals. The results indicating the main spinal segment contribution to control of the heart, can be summarized as follows, rats T1–T3 (Pracejus et al., 2015), cats T3–T4 (Kamosinska et al., 1991; Kocsis and Gyimesi-Pelczer, 1998; Ninomiya et al., 1993; Szulczyk and Szulczyk, 1987), dogs T1–T3 (Kostreva et al., 1977; Norris et al., 1974, 1977; humans T1–T3 Randall and McNally, 1960). Thus for all mammalian species studied so far T3 appears as a major contributor to the cardiac sympathetic nerve supply. Furthermore, the population of preganglionic neurones projecting to the stellate ganglion is arranged as a distinct column within the grey matter on both sides of the thoracic spinal cord (Fig. 1A) (Pyner and Coote, 1994) suggesting that this is where cardiac neurones are located. However, perhaps the most interesting question is whether in addition, their location within the column of sympathetic neurones in the spinal cord, depends on a specific cardiac function. This has so far eluded investigators. Evidence up to now has shown that some preganglionic neurones identified electrophysiologically with a pattern of cardiac related discharge in the T3 segments of cat and rat are strongly influenced by activation of cardiac and vascular receptors (Coote and Westbury, 1979; McLachlan and Hirst, 1980; Coote et al., 1981; Lewis and Coote, 1995) but a precise cardiac target was not identified (Gilbey, 1997). Dembowsky et al. (1986) described three types of preganglionic neurones based on their electrophysiological characteristics in the T3 segment of cats but failed to identify if any projected to the heart. However, despite the lack of electrophysiological evidence there must be target specificity since transneuronal tracing has identified preganglionic neurones in the upper thoracic segments, which project to different regions of the dog heart (Hopkins and Armour, 1984) which shows there is topographical distribution, but a selective function of neurones still eludes investigators (Gilbey, 1997). However, the idea of a topographic and functional organization is given credence from the data of several studies in which electrical stimulation of a variety of sites in the brain of cats dogs and monkeys can produce a number of quite distinct pathological electrocardiographic (ECG) changes (Delgado, 1960; Manning and Cotton, 1962; Ueda et al., 1962; Oppenheimer, 1994) which mimic the effects of stimulating the stellate ganglia or branches of the cardiac sympathetic nerves (Yanowitz et al 1966; Szentivanyi et al., 1967; Randall et al., 1968). Additionally, there are numerous clinical observations demonstrating a strong association of brain lesions with distinct sinister ECG abnormalities (Hugenholtz, 1962; Srivastava and Robson, 1964; Fukuda et al., 2015) and no other symptoms.

6. The cardiac postganglionic nerves

The majority of sympathetic postganglionic axons innervating the heart originate from cell bodies in the stellate ganglion (Pardini et al., 1989), or the caudal cervical ganglia (inferior and middle)(Fig. 1B). Postganglionic neurones in these ganglia receive terminals from up to ten preganglionic neurones from the upper thoracic spinal segments via the sympathetic chain and ansal connections. Fine postganglionic nerve trunks pass from these ganglia to enter the heart together with the cardiac vagal branches close to the pulmonary vessels. There is also a fine postganglionic nerve bundle passing from the middle cervical ganglion that joins the vagus low in the neck to form the vago-sympathetic trunk from where it extends into the cardiac area alongside the other cardiac sympathetic nerves (Woollard, 1926; Szentivanyi et al., 1967; Cooper, 1967).

On reaching the heart the sympathetic nerves show extensive branching with varicose terminals in pericardium, myocardium and endocardium of all four chambers. However, sensitive immunohistochemical or scintigraphic techniques show that the density of these sympathetic terminals varies significantly between regions both across and within the cardiac muscle layers and between the chambers of the heart (Dae et al., 1989, 1991; Wharton et al., 1990; Gordon et al., 1993; Marron et al., 1994; Mitrani and Zipes, 1994; Chow et al., 1995; Crick et al., 1999a, 1999b). In accord, in the rat, measurements of norepinephrine concentration in the heart tissue after selective removal of either stellate ganglion, indicate that the left middle/inferior cervical stellate part of this complex contributes the majority of norepinephrine fibres to the right ventricle (Pardini et al., 1989). Such regional specificity is in accordance with earlier studies using electrical stimulation of the major part of the cardiac postganglionic outflow from each side which has shown that nerves from left stellate ganglion or sympathetic chain cause a significant inotropic response whereas stimulation of the right sympathetics has a predominately chronotropic effect (Randall and Rohse, 1956; Randall et al., 1968; Furnival et al., 1973; Wurster, 1977; reviewed by Van Stee, 1978). This feature was confirmed and extended by a more comprehensive recent study in Andre Ng's lab using an isolated innervated rabbit heart preparation which showed that changes in heart rate were largest with right sympathetic chain stimulation at T2–T3 level (which includes all cardiac sympathetic fibres), whereas changes in left ventricular pressure were greatest with left sympathetic chain stimulation at T1–T2 level. Also shown was that the left sympathetic nerves caused a shortening of left ventricle basal action potential and apical action potential duration (Winter et al., 2012). It is therefore not surprising that there is a strong body of evidence showing that branches of the cardiac postganglionic nerves functionally influence specific and quite localized regions of the heart (Szentivanyi et al., 1967; Randall et al., 1968; Randall 1977; Armour and Randall, 1975; Randall, 1984; Ng et al., 2009). From these studies, which included measurements of heart rate and contractile force in localized regions of the right and left ventricles in the dog and rabbit, during electrical stimulation of different branches of the cardiac postganglionic nerves, we can conclude that specific regions of the heart are selectively controlled by target specified sympathetic neurones in ganglia and probably in the spinal cord. Such an organization was first hinted at by studies in Bob Wurster's lab where it was shown that contractile force recorded from several sites in both ventricles varied according to which of the T1–T5 ventral roots was stimulated (Norris et al., 1974). This raises the question as to whether the cardiac sympathetic supply both peripheral and central is quite functionally discrete. So far this remains unanswered. However, as referred to previously in other examples, it seems to be the case, since stimulation of localized regions within the brain have been shown to selectively elicit sympathetic changes in heart rate or heart rhythm (Fig. 1C)(Lovick, 1987; Cechetto and Saper, 1987; Dampney and McAllen, 1988; Oppenheimer, 1994; Deering and Coote, 2000).

The remarkable differential regional distribution of the postganglionic cardiac nerves of one side with a limited intermingling overlap with nerves from the opposite stellate ganglion leads to the question of how sympathetic preganglionic neurones in the spinal cord coordinate the right and left innervation. However, experiments show that cardiac reflexes can cause sequential participation of selected regions of the heart to augment its activity (Randall, 1977; Wurster, 1977). However, how this is achieved by the sympathetic networks in the spinal cord could have implications to understanding impairments in cardiac performance.

A further characteristic of the heart is that it not only has a dual extrinsic innervation it also has a prominent intrinsic plexus of neurones and networks, which inevitably leads to complex interaction which will modify the effects of each of the nerve inputs alone. This interaction

can produce isolated and selective cardiac regional changes. There is convincing evidence that sympathetic postganglionic neurones interact with intrinsic cardiac plexus neurones in addition to their effects on pacemaker cells, conducting tissue and myocardial cells (Smith, 1999; Armour, 2008). There is also considerable evidence for interaction between sympathetic and parasympathetic terminals in the heart at both the atrial (Levy and Zieske, 1969; Paterson, 2001; Paton et al., 2002; Herring and Paterson, 2009) and ventricle level (Levy and Martin, 1996; Ng et al., 2001, 2007; Brack et al., 2004).

7. Patterns of activity in cardiac sympathetic neurones

Sympathetic nerves innervating the heart are tonically active (Coote, 1988). The basal level of activity varies from moment to moment, but most often it remains synchronized into bursts related to the dominant rhythm. The amplitude and width of this synchronized activity varies according to the number of active neurones, which depends on the integration of excitatory and inhibitory inputs at synapses at each stage of the control system. It is generally accepted that the pattern of activity depends, on integration of various kinds of synaptic input converging onto spinal sympathetic preganglionic neurones, leading to generation of ongoing discharge at a low rate (Coote and Westbury, 1979; McLachlan and Hirst, 1980; Dembowsky et al., 1985; Lewis and Coote, 2008). The pattern of resting ongoing activity depends on the end organ destination. In the third thoracic spinal segment of cats and rats many are destined for the heart and show a distinct cardiac rhythm as well as other oscillations of different frequency, which is faithfully reproduced in cardiac postganglionic neurones, even after passing through the synapses in the stellate ganglion. Statistical analysis of the oscillations shows a number of periodicities from a 2–6 Hz, 10 Hz, a rhythm related oscillating spinal sympathetic networks, a respiratory related rhythm and sometimes a much slower oscillation of 3 cycles per minute, known as Mayer waves (Coote, 1988; Malpas, 1998; Pierce et al., 2010). In general these rhythms are dependent on oscillating networks in the brainstem, and entrainment of afferent inputs from various sources including the spinal cord. The significance is that these rhythms are the basis of physiological drive to the heart that leads to modulation of pacemaker cell activity, conducting tissue and contraction of the myocardial cells. It has been shown that such natural patterning leads to enhanced target organ responses when compared with a similar mean level of continuous activity (Hardebo, 1992; Kishi et al., 1998). Therefore, we could speculate that a disturbance of these rhythms as might occur with an abnormally high frequency burst of afferent input to a select group of presympathetic neurones in the brainstem or even more directly to the spinal sympathetic oscillators would override the natural oscillation. This could result in disruption of transmission. Such an effect has been experimentally demonstrated in other brain systems like those that control urinary bladder emptying (Stone et al., 2015) or movements (Birdno et al., 2008; Deniau et al., 2010) during deep brain stimulation in humans. Here it is suggested that high frequency burst of electrical stimulation imposes an un-physiological pattern resulting in chaotic desynchronisation of network oscillation preventing a pattern of efferent activity in the pathways that normally orchestrate a coordinated response. Such might be the case in 'sympathetic storm' and so lead to breakdown of the normal sequence of transmission to and in the heart and impair cardiac performance. Little attention has been given to this possibility in neural control of the heart.

8. Sympathetic changes and impairments in cardiac performance

Since the heart is regulated by sympathetic and parasympathetic innervations, in order to understand the complexity of autonomic neural events associated with cardiac disease it is worth briefly outlining the effects of sympathetic and parasympathetic actions directly on the myocardial cells. In the normal heart sympathetic stimulation typically increases sinus rate and shortens A-V nodal conduction. It shortens action potential duration and reduces transmural dispersion of repolarization (Winter et al., 2011, 2012). In concordance myocardial contractile function and oxygen consumption in pig hearts is improved by bilateral stellate ganglion stimulation (Liu et al., 2012). In contrast, in heart failure or in hearts showing long QT characteristics, sympathetic stimulation can enhance dispersion of repolarization and generate afterdepolarizations of excited cells and thus is most likely to generate arrhythmias (Shen and Zipes, 2014). These actions are similar for cells in all heart chambers. In contrast parasympathetic fibres have different effects in ventricles compared to atria in which they decrease action potential duration in atria and reduce effective refractory period (ERP), and enhance spatial electrophysiological heterogeneity. These parasympathetic actions in the ventricle have a potent anti-arrhythmic effect. Other actions such as those on conduction and inotropy are similar in both atria and ventricles.

A dynamic balance of activity in cardiac sympathetic activity with cardiac parasympathetic activity ensures healthy regulation of cardiac function. Abnormal alterations in stellate ganglion discharge or even in sub-branches can lead to abnormal ECG (Yanowitz et al., 1966), and can predispose to arrhythmias (Tan et al., 2008; Ng et al., 2009; Arora, 2012). More controversially, it has been suggested on the basis of changes in the autospectra of R-R oscillations that the onset of atrial fibrillation may also result from unusually large simultaneous increases in sympathetic and parasympathetic nerves (Amar et al., 2003; Tomita et al., 2003).

Unsurprisingly thoracic sympathectomy removing either one or both stellate ganglia, has proved of benefit for anti-arrhythmic therapy (Shen and Zipes, 2014). This procedure is considered to be widely successful in high-risk patients with long QT syndrome, with a range of arrhythmias and structural heart disease (Bourke et al., 2010; Schwartz, 2010; Coleman et al., 2012; Vaseghi et al., 2014). A problem with such a procedure is that it removes normal sympathetic control throughout the heart (Schwartz, 2010). It clearly would be best for a more targeted approach. This has become possible as knowledge of the selective functions of the sympathetic outflow via white rami in each spinal segment improves. Recent studies have already shown the possibility, by using a limited surgically targeted approach, whereby a rather crude stepwise decentralization of the stellate ganglion in anaesthetized dogs and pigs was achieved (Buckley et al., 2016; Wu et al., 2016). These studies indirectly recorded changes in heart rate, QRS, QT intervals, ERPs in atria and ventricles and conduction times. They showed it was feasible to remove inputs to the paravertebral chain and parts of the stellate ganglion on each side without causing a significant impairment of non-cardiac viscera supplied by the upper thoracic sympathetic nerves. However, unfortunately they do not provide information of the selective target-specified regional projection to the heart of different segmental preganglionic neurones. Nonetheless, it is encouraging to see that attempts to limit the extent of surgical intervention and side effects of denervation in humans are being explored (Raskin et al., 2016). We are using our isolated innervated rabbit heart preparation (Ng et al., 2001; Winter et al., 2012) to explore more thoroughly the influence of function specific thoracic sympathetic preganglionic neurones on heart rate, conduction and heart rhythm. Further developments were communicated as a Poster at 'Physiology 2016' meeting of the American Physiological Society and The Physiological Society in Dublin (Chauhan et al., 2016).

9. Dorsal spinal cord stimulation

The foregoing data reviews the anatomical location and evidence for safe transmission of signals from sympathetic preganglionic neurones as well as via the extensive interneurone connections. Why is it then, that a non focused electrical stimulation of the dorsal spinal cord can suppress atrial fibrillation (Wang et al., 2016), reduce symptoms of angina pectoris (Foreman et al., 2000), reduce ventricular arrhythmias (Grimaldi et al., 2012) and partially restore ventricular function in

heart failure (Tse et al., 2015)? The technique applies high frequency electrical pulses to stimulate the dorsal aspect of the T1–T4 spinal cord via electrodes placed epidurally, one in the midline and the other laterally on the left side. This improves myocardial perfusion and oxygen consumption and reduces the suppression of the ST segment of the ECG associated with cardiac ischaemia in patients with angina pectoris (Sanderson et al., 1992, 1994) as well as removing the cardiac pain (Hautvast et al., 1998). The question was addressed by an excellent but technically demanding study in anaesthetized dogs (Foreman et al., 2000). This study recorded atrial ganglion neuron action potentials during dorsal spinal cord stimulation and showed that the spinal cord stimulus reduced their frequency of firing. The effect was abolished by sectioning the right and left subclavian ansae, effectively removing connections between the heart and intra thoracic ganglia. Therefore, it was concluded that the influence of spinal cord neurones on the intrinsic cardiac nervous system occurs primarily via axons (afferent and efferent) in the intrathoracic nervous system. This appears to suggest that activity of sympathetic postganglionic fibres suppresses activity in intrinsic cardiac plexus neurones and in some way is anti-ischaemic and antiarrhythmic. The local mechanisms involved in the latter actions is unknown but a suggestion is that dorsal spinal cord stimulation causes a remodeling of the membrane and synaptic properties of autonomic neurones, possibly due to release of neuropeptides from the postganglionic nerve terminals (Smith et al., 2016). A further feature of this procedure which might be important is that the electrical stimulus used was strong enough to activate many myelinated dorsal root afferents (Croom et al., 1997) some of which operate spinally via the dorsal horn, and some which travel in the dorsal columns to the brain. An action via the latter can be dismissed since the effect of dorsal spinal cord stimulation remains unaffected after transection of the cervical spinal cord. In the thoracic segments, the larger afferents synapse with interneurones not directly with sympathetic preganglionic neurones (which do not have monosynaptic spinal reflex connections). Thus the actions of dorsal spinal cord stimulation could not be an effect of high frequency current directly interfering with the normal pattern of sympathetic activity. Additionally the strength of the current used in the Foreman et al. (2000) study and subsequent studies, is deliberately adjusted to avoid activating the large diameter myelinated afferent fibres but the current used would include the small afferents like those myelinated cardiac afferents described by Malliani et al. (1973) that can excite or inhibit sympathetic preganglionics. However, since it appears that the cardiac effects are due to increases in postganglionic cardiac nerve activity it would appear that afferents that inhibit preganglionic neurones are not affected by the dorsal spinal cord current. Why this might be, is interesting and presently unclear. The explanation provided by the Foreman et al. (2000) study is therefore still incomplete.

Subsequent studies using dorsal spinal cord stimulation on experimental animals reveal that in addition to sympathetic involvement the effect of cardiac parasympathetic nerves is enhanced particularly so after several weeks of dorsal spinal cord stimulation (Olgin et al., 2002; Smith et al., 2016). It was also shown there was a reduction in resting heart rate, and a potentiation of bradycardia and atrial repolarization induced by stimulation of the cervical vagus nerve. These effects on the vagus are dependent on altered synaptic behavior of intrinsic cardiac plexus neurones as well on the presence of cardiac postganglionic sympathetic nerves from the stellate ganglion (Foreman et al., 2000; Cardinal et al., 2006). As a result the dorsal spinal cord phenomenom is explained as due to two factors one is inhibiting sympathetic remodeling (Ajijola et al., 2013; Smith et al., 2016; Wang et al., 2016) the other is enhancing intrinsic nerve effects both consequent on reversing the effects of remodeling. Remodeling can be defined as a response to nerve injury that may be caused by local hypoxia or ischemia due to changes in coronary perfusion or damage to the nerve axons or synapses in ganglia or the cns. It can consist of nerve sprouting or changes in the electrophysiology of the nerve membrane as well as flow of neurotransmitter precursors like neuropeptide Y, galanin or neuropeptide transcription in the cell body of ganglion cells (Pirola and Potter, 1990; Revington et al., 1990; Herring and Paterson, 2009). As a consequence there may be global hypo- or hyper-innervation or even greater neurotransmitter release and target cell super-sensitivity or depression of cardiac parasympathetic activity. Dorsal spinal cord stimulation has been suggested to modify these changes. An extensive and comprehensive study in rabbits indicated that dorsal spinal cord stimulation applied preemptively, reduces the size of an infarcted area (coronary artery occlusion) by increasing the release of catecholamines, and galanin (Sutherland et al., 2007). Therefore spinal cord stimulation undoubtedly has a wide range of actions in the heart. However, an explanation of the actions of dorsal spinal cord in general is still unsatisfactory in some aspects particularly we think because there is still much that is unknown of the extent to which the intrinsic cardiac plexuses interact with the extrinsic autonomic nerves. It also seems at variance with the induction of cardiac pathologies related to sudden increases in sympathetic activity (sympathetic storm). Furthermore the very high stimulation frequency needed (used) is puzzling.

10. Conclusion

Huge increases in knowledge of the anatomy and physiology of cardiac nerves have led to massive improvements in translating this into beneficial clinical interventions. However, there are still many gaps that need to be filled as treatments move away from pharmaceuticals towards surgical ablation or electrical stimulation therapies. It seems likely that sympathetic preganglionic neurones selectively target particular cardiac regions and have a specific functional effect. Conclusive evidence for a functional specificity has so far proved elusive. However, new technical developments look promising and may lead to clinical benefits. Recent results using dorsal spinal cord stimulation, a technique rather crude and ill-understood, show a remarkable degree of effectiveness in treating several different functional cardiac impairments. How this works is still a puzzle. Clearly more basic experimental studies are needed to improve understanding of spinal sympathetic control of the heart. The innervated isolated whole heart preparation we are using in Professor Ng's lab in Leicester (Ng et al., 2001) is already helping to address these shortcomings in knowledge.

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References

Ajijola, O.A., Yagishita, D., Patel, K.J., Vaseghi, M., Zhou, W., Yamakawa, K., So, E., Lux, R.L., Mahajan, A., Shivkumar, K., 2013. Focal myocardial infarction induces global remodeling of cardiac sympathetic innervation: neural remodeling in a spatial context. Am. J. Phys. 305, H1031–H1040.

Amar, D., Zhang, H., Miodownik, S., Kadish, A.H., 2003. Competing autonomic mechanisms precede the onset of postoperative atrial fibrillation. J. Am. Coll. Cardiol. 42, 1262–1268.

Armour, J.A., 1984. Physiological studies of small mediastinal ganglia in the cardiopulmonary nerves of dogs. Can. J. Physiol. Pharmacol. 62, 1244–1248.

Armour, J.A., 2008. Potential clinical relevance of the 'little brain' on the mammalian heart. Exp. Physiol. 93, 165–176.

Armour, J.A., Hopkins, D.A., 1981. Localization of sympathetic postganglionic neurons of physiologically identified cardiac nerves in the dog. J. Comp. Neurol. 202, 169–184.

Armour, J.A., Randall, W.C., 1975. Functional anatomy of canine cardiac nerves. Acta Anat. 91, 510–528.

Arora, R., 2012. Recent insights into the role of the autonomic nervous system in the creation of substrate for atrial fibrillation implications for therapies targeting the atrial autonomic nervous system. Circ. Arrhythm. Electrophysiol. 2, 850–859.

Birdno, M.J., Kuncel, A.M., Dorval, A.D., Turner, D.A., Grill, W.M., 2008. Tremor varies as a function of the temporal regularity of deep brain stimulation. Neuroreport 19, 599–602.

Bourke, T., Vaseghi, M., Michowitz, Y., Sankhla, V., Shah, M., Swapna, N., Boyle, N.G., Mahajan, A., Narasimhan, C., Lokhandwala, Y., Shivkumar, K., 2010. Neuraxial modulation for refractory ventricular arrhythmias: value of thoracic epidural anesthesia and surgical left cardiac sympathetic denervation. Circulation 121, 2255–2262.

Brack, K.E., Coote, J.H., Ng, G.A., 2004. Interaction between direct sympathetic and vagus nerve stimulation on heart rate in the isolated rabbit heart. Exp. Physiol. 89, 128–139.

Buckley, U., Yamakawa, K., Takamiya, T., Andrew Armour, J., Shivkumar, K., Ardell, J.L., 2016. Targeted stellate decentralization: Implications for sympathetic control of ventricular electrophysiology. Heart Rhythm. 13, 282–288.

Cardinal, R., Page, P., Vermeulen, M., Bouchard, C., Ardell, J.L., Foreman, R.D., Armour, J.A., 2006. Spinal cord stimulation suppresses atrial tachyarrhythmias induced by mediastinal nerve stimulation in canines. Am. J. Phys. 291, R1369–R1375.

Cechetto, D.F., Saper, C.B., 1987. Evidence for a viscerotopic sensory representation in the cortex and thalamus in the rat. J. Comp. Neurol. 262, 27–45.

Chauhan, R.A., Coote, J.H., Wake, E., Brack, K.E., Ng, G.A., 2016. Differential Effects from Left and Right Sympathetic Nerve Stimulation on Ventricular Electrophysiology and Arrhythmic Inducibility. Physiology 2016 Dublin, p. PCA 030.

Chow, L.T., Chow, S.S., Anderson, R.H., Gosling, J.A., 1995. The innervation of the human myocardium at birth. J. Anat. 187, 107–114.

Coleman, M.A., Bos, J.M., Johnson, J.N., Owen, H.J., Deschamps, C., Moir, C., Ackerman, M.J., 2012. Videoscopic left cardiac sympathetic denervation for patients with recurrent ventricular fibrillation/malignant ventricular arrhythmia syndromes besides congenital long-QT syndrome. Circ. Arrhythmia. Electrophysiol. 5, 782–788.

Cooper, T., 1967. The functional significance of the cardiac nerves. Ann. Intern. Med. 66, 440–442.

Coote, J.H., 1988. The organisation of cardiovascular neurons in the spinal cord. Rev. Physiol. Biochem. Pharmacol. 110, 147–285.

Coote, J.H., 2001. Multiple oscillators in autonomic control. J. Physiol. 533, 313.

Coote, J.H., 2013. Myths and realities of the cardiac vagus. J. Physiol. 591, 4073–4085.

Coote, J.H., Westbury, D.R., 1979. Functional grouping of sympathetic preganglionic neurones in the third thoracic segment of the spinal cord. Brain Res. 179, 367–372.

Coote, J.H., Macleod, V.H., Fleetwood-Walker, S., Gilbey, M.P., 1981. The response of individual sympathetic preganglionic neurones to microelectrophoretically applied endogenous monoamines. Brain Res. 215, 135–145.

Crick, S.J., Anderson, R.H., Ho, S.Y., Sheppard, M.N., 1999a. Localisation and quantitation of autonomic innervation in the porcine heart II: endocardium, myocardium and epicardium. J. Anat. 195, 359–373.

Crick, S.J., Sheppard, M.N., Ho, S.Y., Anderson, R.H., 1999b. Localisation and quantitation of autonomic innervation in the porcine heart I: conduction system. J. Anat. 195, 341–357.

Croom, J.E., Foreman, R.D., Chandler, M.J., Barron, K.W., 1997. Cutaneous vasodilation during dorsal column stimulation is mediated by dorsal roots and CGRP. Am. J. Phys. 272, H950–H957.

Dae, M.W., Herre, J.M., O'Conell, J.W., Botvinick, E.H., Newman, D., Munoz, L., 1991. Scintigraphic assessment of sympathetic innervation after transmural versus nontransmural myocardial infarction. J. Am. Coll. Cardiol. 17, 1416–1423.

Dae, M.W., O'Connell, J.W., Botvinick, E.H., Ahearn, T., Yee, E., Huberty, J.P., Mori, H., Chin, M.C., Hattner, R.S., Herre, J.M., 1989. Scintigraphic assessment of regional cardiac adrenergic innervation. Circulation 79, 634–644.

Dampney, R.A., McAllen, R.M., 1988. Differential control of sympathetic fibres supplying hindlimb skin and muscle by subretrofacial neurones in the cat. J. Physiol. 395, 41–56.

Deering, J., Coote, J.H., 2000. Paraventricular neurones elicit a volume expansion-like change of activity in sympathetic nerves to the heart and kidney in the rabbit. Exp. Physiol. 85, 177–186.

Delgado, J.M., 1960. Circulatory effects of cortical stimulation. Physiol. Rev. 4, 146–178.

Dembowsky, K., Czachurski, J., Seller, H., 1985. An intracellular study of the synaptic input to sympathetic preganglionic neurones of the third thoracic segment of the cat. J. Auton. Nerv. Syst. 13, 201–244.

Dembowsky, K., Czachurski, J., Seller, H., 1986. Three types of sympathetic preganglionic neurones with different electrophysiological properties are identified by intracellular recordings in the cat. Pflugers Arch. - Eur. J. Physiol. 406, 112–120.

Deniau, J.M., Degos, B., Bosch, C., Maurice, N., 2010. Deep brain stimulation mechanisms: beyond the concept of local functional inhibition. Eur. J. Neurosci. 32, 1080–1091.

Deuchars, S.A., 2007. Multi-tasking in the spinal cord–do 'sympathetic' interneurones work harder than we give them credit for? J. Physiol. 580, 723–729.

Deuchars, S.A., Milligan, C.J., Stornetta, R.L., Deuchars, J., 2005. GABAergic neurons in the central region of the spinal cord: a novel substrate for sympathetic inhibition. J. Neurosci. 1063–1070.

Dun, N.J., Mo, N., 1989. Inhibitory postsynaptic potentials in neonatal rat sympathetic preganglionic neurones in vitro. J. Physiol. 410, 267–281.

Foreman, R.D., Linderoth, B., Ardell, J.L., Barron, K.W., Chandler, M.J., Hull Jr., S.S., TerHorst, G.J., DeJongste, M.J., Armour, J.A., 2000. Modulation of intrinsic cardiac neurons by spinal cord stimulation: implications for its therapeutic use in angina pectoris. Cardiovasc. Res. 47, 367–375.

Fukuda, K., Kanazawa, H., Aizawa, Y., Ardell, J.L., Shivkumar, K., 2015. Cardiac innervation and sudden cardiac death. Circ. Res. 116, 2005–2019.

Furnival, C.M., Linden, R.J., Snow, H.M., 1973. Chronotropic and inotropic effects on the dog heart of stimulating the efferent cardiac sympathetic nerves. J. Physiol. 230, 137–153.

Gilbey, M.P., 1997. Fundamental Aspects of the Control of Sympathetic Preganglionic Neuronal Discharge. In: Jordan, D. (Ed.), Central Nervous Control of Autonomic Function. Harwood Academic Publishers, UK, pp. 1–28.

Gordon, L., Wharton, J., Gaer, J.A., Inglis, G.C., Taylor, K.M., Polak, J.M., 1993. Quantitative immunohistochemical assessment of bovine myocardial innervation before and after cryosurgical cardiac denervation. Cardiovasc. Res. 27, 318–326.

Grimaldi, R., de Luca, A., Kornet, L., Castagno, D., Gaita, F., 2012. Can spinal cord stimulation reduce ventricular arrhythmias? Heart Rhythm. 9, 1884–1887.

Hardebo, J.E., 1992. Influence of impulse pattern on noradrenaline release from sympathetic nerves in cerebral and some peripheral vessels. Acta Physiol. Scand. 144, 333–339.

Hautvast, R.W., DeJongste, M.J.L., Staal, M.J., Van Gilst, V.H., Lie, K.L., 1998. Spinal cord stimulation in chronic intractable angina pectoris: a randomized, controlled efficacy study. Am. Heart J. 136, 114–120.

Herring, N., Paterson, D.J., 2009. Neuromodulators of peripheral cardiac sympatho-vagal balance. Exp. Physiol. 94, 46–53.

Hopkins, D.A., Armour, J.A., 1984. Localization of sympathetic postganglionic and parasympathetic preganglionic neurons which innervate different regions of the dog heart. J. Comp. Neurol. 229, 186–198.

Hugenholtz, P.G., 1962. Electrocardiographic abnormalities in cerebral disorders. Report of six cases and review of the literature. Am. Heart J. 63, 451–461.

Jänig, W., 2006. The Integrative Action of the Autonomic Nervous System: Neurobiology of Homeostasis. Cambridge University Press, Cambridge, UK, pp. 1–610.

Jansen, A.S., Wessendorf, M.W., Loewy, A.D., 1995. Transneuronal labeling of cns neuropeptide and monoamine neurons after pseudorabies virus injection into the stellate ganglion. Brain Res. 683, 1–24.

Kamosinska, B., Nowicki, D., Szulczyk, A., Szulczyk, P., 1991. Spinal segmental sympathetic outflow to cervical sympathetic trunk, vertebral nerve, inferior cardiac nerve and sympathetic fibres in the thoracic vagus. J. Auton. Nerv. Syst. 32, 199–204.

Kawashima, T., 2005. The autonomic nervous system of the human heart with special reference to its origin, course, and peripheral distribution. Anat. Embryol. 209, 425–438.

Kishi, E., Ootsuka, Y., Rong, W., Terui, N., 1998. Functional significance of the 10 Hz rhythmic discharges in sympathetic nerves. Clin. Exp. Pharmacol. Physiol. 25, 464–467.

Kocsis, B., Gyimesi-Pelczer, K., 1998. Spinal segments communicating resting sympathetic activity to postganglionic nerves of the stellate ganglion. Am. J. Phys. 275, R400–R409.

Kostreva, D.R., Zuperku, E.J., Cusick, J.F., Kampine, J.P., 1977. Ventral root mapping of cardiac nerves in the canine using evoked potentials. Am. J. Phys. 232, H590–H595.

Langley, J.N., 1892. On the origin from the spinal cord of the cervical and upper thoracic sympathetic fibres, with some observations on white and grey rami communicantes. Philos. Trans. R. Soc. Lond. B 183, 85–124.

Levy, M.N., Martin, P.J., 1996. Autonomic Control of Cardiac Conduction and Automaticity. In: Shepherd, J.T., Vatner, S.F. (Eds.), Nervous Control of the Heart. HAP, United Kingdom, pp. 201–225.

Levy, M.N., Zieske, H., 1969. Autonomic control of cardiac pacemaker activity and atrioventricular transmission. J. Appl. Physiol. 27, 465–470.

Lewis, D.I., Coote, J.H., 1995. Chemical mediators of spinal inhibition of rat sympathetic neurones on stimulation in the nucleus tractus solitarii. J. Physiol. 486, 483–494.

Lewis, D.I., Coote, J.H., 2008. Electrophysiological characteristics of vasomotor preganglionic neurons and related neurons in the thoracic spinal cord of the rat: an intracellular study in vivo. Neuroscience 152, 534–546.

Lewis, D.I., Sermasi, E., Coote, J.H., 1993. Excitatory and indirect inhibitory actions of 5-hydroxytryptamine on sympathetic preganglionic neurones in the neonate rat spinal cord in vitro. Brain Res. 610, 267–275.

Liu, Y., Yue, W.S., Liao, S.Y., Zhang, Y., Au, K.W., Shuto, C., Hata, C., Park, E., Chen, P., Siu, C.W., Tse, H.F., 2012. Thoracic spinal cord stimulation improves cardiac contractile function and myocardial oxygen consumption in a porcine model of ischemic heart failure. J. Cardiovasc. Electrophysiol. 23, 534–540.

Lovick, T.A., 1987. Differential control of cardiac and vasomotor activity by neurones in nucleus paragigantocellularis lateralis in the cat. J. Physiol. 389, 23–35.

Malliani, A., Recordati, G., Schwartz, P.J., 1973. Nervous activity of afferent cardiac sympathetic fibres with atrial and ventricular endings. J. Physiol. 229, 457–469.

Malpas, S.C., 1998. The rhythmicity of sympathetic nerve activity. Prog. Neurobiol. 56, 65–96.

Manning, J.W., Cotton, M.D.V., 1962. Mechanism of cardiac arrhythmias induced by diencephalic stimulation. Am. J. Phys. 203, 1120–1124.

Marron, K., Wharton, J., Sheppard, M.N., Gulbenkian, S., Royston, D., Yacoub, M.H., Anderson, R.H., Polak, J.M., 1994. Human endocardial innervation and its relationship to the endothelium: an immunohistochemical, histochemical, and quantitative study. Cardiovasc. Res. 28, 1490–1499.

McLachlan, E.M., Hirst, G.D., 1980. Some properties of preganglionic neurons in upper thoracic spinal cord of the cat. J. Neurophysiol. 43, 1251–1265.

Mitrani, R.D., Zipes, D.P., 1994. Clinical Neurocardiology: Arrhythmias. In: Armour, J.A., Ardell, J.L. (Eds.), Neurocardiology. Oxford University Press, New York, pp. 365–395.

Ng, G.A., Brack, K.E., Coote, J.H., 2001. Effects of direct sympathetic and vagus nerve stimulation on the physiology of the whole heart – a novel model of isolated Langendorff perfused rabbit heart with intact dual autonomic innervation. Exp. Physiol. 86, 319–329.

Ng, G.A., Brack, K.E., Patel, V.H., Coote, J.H., 2007. Autonomic modulation of electrical restitution, alternans and ventricular fibrillation initiation in the isolated heart. Cardiovasc. Res. 73, 750–760.

Ng, G.A., Mantravadi, R., Walker, W.H., Ortin, W.G., Choi, B.R., de Groat, W., Salama, G., 2009. Sympathetic nerve stimulation produces spatial heterogeneities of action potential restitution. Heart Rhythm. 6, 696–706.

Ninomiya, I., Malpas, S.C., Matsukawa, K., Shindo, T., Akiyama, T., 1993. The amplitude of synchronized cardiac sympathetic nerve activity reflects the number of activated pre- and postganglionic fibers in anesthetized cats. J. Auton. Nerv. Syst. 45, 139–147.

Norris, J.E., Foreman, R.D., Wurster, R.K., 1974. Responses of the canine heart to stimulation of the first five ventral thoracic roots. Am. J. Phys. 227, 9–12.

Norris, J.E., Lippincott, D., Wurster, R.D., 1977. Responses of canine endocardium to stimulation of the upper thoracic roots. Am. J. Phys. 233, H655–H659.

Olgin, J.E., Takahashi, T., Wilson, E., Vereckei, A., Steinberg, H., Zipes, D.P., 2002. Effects of thoracic spinal cord stimulation on cardiac autonomic regulation of the sinus and atrioventricular nodes. J. Cardiovasc. Electrophysiol. 13, 475–481.

Oppenheimer, S.M., 1994. Neurogenic cardiac effects of cerebrovascular disease. Curr. Opin. Neurol. 7, 20–24.

Pardini, B.J., Lund, D.D., Schmid, P.G., 1989. Organization of the sympathetic postganglionic innervation of the rat heart. J. Auton. Nerv. Syst. 28, 193–201.

Paterson, D.J., 2001. Nitric oxide and the autonomic regulation of cardiac excitability. Exp. Physiol. 86, 1–12.
Paton, J.F., Kasparov, S., Paterson, D.J., 2002. Nitrous oxide and autonomic control of heart rate: A question of specificity. Trends Neurosci. 25, 626–631.
Pierce, M.L., Deuchars, J., Deuchars, S.A., 2010. Spontaneous rhythmogenic capabilities of sympathetic neuronal assemblies in the rat spinal cord slice. Neuroscience 170, 827–838.
Pirola, F.T., Potter, E.K., 1990. Vagal action on atrioventricular conduction and its inhibition by sympathetic stimulation and neuropeptide Y in aneasthetized dogs. J. Auton. Nerv. Syst. 31, 1–12.
Pracejus, N.H., Farmer, D.G., McAllen, R.M., 2015. Segmental origins of cardiac sympathetic nerve activity in rats. Auton. Neurosci. 187, 45–49.
Pyner, S., Coote, J.H., 1994. Evidence that sympathetic preganglionic neurones are arranged in target-specific columns in the thoracic spinal cord of the rat. J. Comp. Neurol. 342, 15–22.
Randall, W.C., 1977. Sympathetic Control of the Heart. In: Randall, W.C. (Ed.), Neural Regulation of the Heart. Oxford University Press, New York, pp. 45–94.
Randall, W.C., 1984. Nervous Control of Cardiovascular Function. Oxford University Press, New York.
Randall, W.C., McNally, H., 1960. Augmentor action of the sympathetic cardiac nerves in man. J. Appl. Physiol. 15, 629–631.
Randall, W.C., Rohse, W.G., 1956. The augmentor action of the sympathetic cardiac nerves. Circ. Res. 4, 470–475.
Randall, W.C., Szentivanyi, M., Pace, J.B., Wechsler, J.S., Kaye, M.P., 1968. Patterns of sympathetic nerve projections onto the canine heart. Circ. Res. 22, 315–323.
Raskin, J.S., Liu, J.J., Sun, H., Nemecek, A., Balaji, S., Raslan, A.M., 2016. Minimal access posterior approach for extrapleural thoracic sympathectomy: a cadaveric study and cases. World Neurosurg. http://dx.doi.org/10.1016/jwneu 2016.06.072.
Revington, M., Potter, E.K., McCloskey, D.I., 1990. Prolonged inhibition of cardiac vagal action following sympathetic stimulation and galanin in anaesthetized cats. J. Physiol. 431, 495–503.
Sanderson, J.E., Brooksby, P., Waterhouse, D., Palmer, R.B., Neubauer, K., 1992. Epidural spinal electrical stimulation for severe angina: a study of its effects on symptoms, exercise tolerance and degree of ischaemia. Eur. Heart J. 13, 628–633.
Sanderson, J.E., Ibrahim, B., Waterhouse, D., Palmer, R.B., 1994. Spinal electrical stimulation for intractable angina–long-term clinical outcome and safety. Eur. Heart J. 15, 810–814.
Schwartz, P.J., 2010. Efficacy of left cardiac sympathetic denervation has an unforeseen side effect: medicolegal complications. Heart Rhythm. 7, 1330–1332.
Shen, M.J., Zipes, D.P., 2014. Role of the autonomic nervous system in modulating cardiac arrhythmias. Circ. Res. 114, 1004–1021.
Smith, F.M., Vermeulen, M., Cardinal, R., 2016. Long term spinal cord stimulation modifies canine intrinsic neuronal properties and ganglionic transmission during high-frequency repetitive activation. Phys. Rep. 4 (13), e12855. http://dx.doi.org/10.14814/phy2.12855.
Smith, F.M., 1999. Extrinsic inputs to intrinsic neurons in the porcine heart in vitro. Am. J. Phys. 276, R455–R467.
Spanswick, D., Pickering, A.E., Gibson, I.C., Logan, S.D., 1994. Inhibition of sympathetic preganglionic neurons by spinal glycinergic interneurons. Neuroscience 62, 205–216.
Srivastava, S.C., Robson, A.O., 1964. Electrocardiographic abnormalities associated with subarachnoid haemorrhage. Lancet 2, 431–433.
Staras, K., Chang, H.S., Gilbey, M.P., 2001. Resetting of sympathetic rhythm by somatic afferents causes post-reflex coordination of sympathetic activity in rat. J. Physiol. 533, 537–545.
Stone, E., Coote, J.H., Lovick, T.A., 2015. Effect of electrical vs. chemical deep brain stimulation at midbrain sites on micturition in anaesthetized rats. Acta Physiol. Scand. 214, 135–145.
Strack, A.M., Sawyer, W.B., Hughes, J.H., Platt, K.B., Loewy, A.D., 1989. A general pattern of CNS innervation of the sympathetic outflow demonstrated by transneuronal pseudorabies viral infections. Brain Res. 491, 156–162.
Sutherland, E.M., Milhorn, D.M., Foreman, R.D., Linderoth, B., DeJongste, M.J.I., Armour, J.A., Subramanian, V., Singh, M., Singh, K., Ardell, J.L., 2007. Preemptive, but not reactive spinal cord stimulation mitigates transient ischemia-induced myocardial infarction via cardiac adrenergic neurons. Am. J. Phys. 292, H311–H317.
Szentivanyi, M., Pace, J.B., Wechsler, J.S., Randall, W.C., 1967. Localized myocardial responses to stimulation of cardiac sympathetic nerves. Circ. Res. 21, 691–702.
Szulczyk, A., Szulczyk, P., 1987. Spinal segmental preganglionic outflow to cervical sympathetic trunk and postganglionic cardiac sympathetic nerves. Brain Res. 421, 127–134.
Tan, A.Y., Zhou, S., Jung, B.C., Ogawa, M., Chen, L.S., Fishbein, M.C., Chen, P.S., 2008. Ectopic atrial arrhythmias arising from canine thoracic veins during in vivo stellate ganglia stimulation. Am. J. Phys. 5, H691–H698.
Tomita, T., Takei, M., Saikawa, Y., Hanaoka, T., Uchikawa, S., Tsutsui, H., Aruga, M., Miyashita, T., Yazaki, Y., Imamura, H., Kinoshita, O., Owa, M., Kubo, K., 2003. Role of autonomic tone in the initiation and termination of paroxysmal atrial fibrillation in patients without structural heart disease. J. Cardiovasc. Electrophysiol. 14, 559–564.
Tse, H., Turner, S., Sanders, P., Okuyama, Y., Fujiu, K., Cheung, C., Russo, M., Green, M.D.S., Yiu, K., Chen, P., Shuto, C., Lau, E.O.Y., Siu, C., 2015. Thoracic spinal cord stimulation for heart failure as a restorative treatment (SCS heart study): first-in-man experience. Heart Rhythm. 12, 588–595.
Ueda, H., Sugimoto, T., Murao, S., Goto, H., Kato, K., Katayama, S., Ito, K., 1962. Changes in cardiac rate and rhythm produced by electrical stimulation of the brain stem of dogs. Jpn. Heart J. 3, 455–475.
Van Stee, E.W., 1978. Autonomic innervation of the heart. Environ. Health Perspect. 26, 151–158.
Vaseghi, M., Gima, J., Kanaan, C., Ajijola, O.A., Marmureanu, A., Mahajan, A., Shivkumar, K., 2014. Cardiac sympathetic denervation in patients with refractory ventricular arrhythmias or electrical storm: intermediate and long-term follow-up. Heart Rhythm. 11, 360–366.
Wang, S., Zhou, X., Huang, B., Wang, Z., Zhou, L., Chen, M., Yu, L., Jiang, H., 2016. Spinal cord stimulation suppresses atrial fibrillation by inhibiting autonomic remodeling. Heart Rhythm. 13, 274–281.
Wharton, J., Polak, J.M., Gordon, L., Banner, N.R., Springall, D.R., Rose, M., Khagani, A., Wallwork, J., Yacoub, M.H., 1990. Immunohistochemical demonstration of human cardiac innervation before and after transplantation. Circ. Res. 66, 900–912.
Winter, J., Brack, K.E., Ng, G.A., 2011. The acute effects of cardiac contractility modulation (CCM) are connected with action potential shortening and mediated by $ß_1$ adrenergic signaling. J. Mol. Cell. Cardiol. 51, 252–262.
Winter, J., Tanko, A.S., Brack, K.E., Coote, J.H., Ng, G.A., 2012. Differential cardiac responses to unilateral sympathetic nerve stimulation in the isolated innervated rabbit heart. Auton. Neurosci. 166, 4–14.
Woollard, H.H., 1926. The innervation of the heart. J. Anat. 60, 345–373.
Wu, G., DeSimone, C.V., Suddendorf, S.H., Asirvatham, R.S., Asirvatham, S.J., Huang, C., Chen, P.S., Cha, Y.M., 2016. Effects of stepwise denervation of the stellate ganglion: novel insights from an acute canine study. Heart Rhythm. 13, 1395–1401.
Wurster, R.D., 1977. Spinal Sympathetic Control of the Heart. In: Randall, W.C. (Ed.), Neural Regulation of the Heart. Oxford University Press, New York, pp. 211–246.
Yanowitz, F., Preston, J.B., Abildskov, J.A., 1966. Functional distribution of right and left stellate innervation to the ventricles. Production of neurogenic electrocardiographic changes by unilateral alteration of sympathetic tone. Circ. Res. 18, 416–428.