

Review

Myocardial ischaemia and the cardiac nervous system

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Abstract

The intrinsic cardiac nervous system has been classically considered to contain only parasympathetic efferent postganglionic neurones which receive inputs from medullary parasympathetic efferent preganglionic neurones. In such a view, intrinsic cardiac ganglia act as simple relay stations of parasympathetic efferent neuronal input to the heart, the major autonomic control of the heart purported to reside solely in the brainstem and spinal cord. Data collected over the past two decades indicate that processing occurs within the mammalian intrinsic cardiac nervous system which involves afferent neurones, local circuit neurones (interconnecting neurones) as well as both sympathetic and parasympathetic efferent postganglionic neurones. As such, intrinsic cardiac ganglionic interactions represent the organ component of the hierarchy of intrathoracic nested feedback control loops which provide rapid and appropriate reflex coordination of efferent autonomic neuronal outflow to the heart. In such a concept, the intrinsic cardiac nervous system acts as a distributive processor, integrating parasympathetic and sympathetic efferent centrifugal information to the heart in addition to centripetal information arising from cardiac sensory neurites. A number of neurochemicals have been shown to influence the interneuronal interactions which occur within the intrathoracic cardiac nervous system. For instance, pharmacological interventions that modify β -adrenergic or angiotensin II receptors affect cardiomyocyte function not only directly, but indirectly by influencing the capacity of intrathoracic neurones to regulate cardiomyocytes. Thus, current pharmacological management of heart disease may influence cardiomyocyte function directly as well as indirectly secondary to modifying the cardiac nervous system. This review presents a brief summary of developing concepts about the role of the cardiac nervous system in regulating the normal heart. In addition, it provides some tentative ideas concerning the importance of this nervous system in cardiac disease states with a view to stimulating further interest in neural control of the heart so that appropriate neurocardiological strategies can be devised for the management of heart disease. © 1999 Elsevier Science B.V. All rights reserved.

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1. Introduction

The neuronal basis of symptoms elicited during myocardial ischaemia was first presented by Dr. Everard Holm when he discussed Dr. John Hunter's heart disease in 1798 [1]. Therapy directed at restoring myocardial function secondary to compromised local coronary arterial blood supply has undergone considerable modification since that time due to evolving opinions concerning the pathophysiology of myocardial ischaemia [2]. Currently, emphasis is being placed on neuronal 'triggering' of maladaptive events secondary to impairment of local coronary arterial blood supply [3–5]. In order to depict what is known about autonomic neurones from the level of the insular cortex to the heart which comprise the cardiac nervous system, an overview of the hierarchy of neurones

regulating the normal heart is presented. Thereafter, this review focuses on recently acquired data concerning some of the response characteristics of cardiac neurones to myocardial ischaemia. While acknowledging that we do not understand very much about how individual reflexes within this hierarchy affect the normal heart, let alone the ischemic myocardium, this review is presented with the aim of stimulating interest in central and peripheral neuronal mechanisms involved in cardiac regulation so that strategies can be developed to manipulate this nervous system to support the ischemic myocardium. For the purpose of this review, the cardiac nervous system comprises afferent neurones with their associated sensory neurites located in the heart, efferent neurones innervating

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the heart and neurones interconnecting these afferent and efferent cardiac neurones [6].

2. Neurocardiology: anatomical and functional substrates

Afferent neurones with sensory neurites in cardiac tissues are located in nodose and dorsal root ganglia. These centrally projecting cardiac afferent neurones influence, via central interconnecting neurones, parasympathetic and sympathetic efferent preganglionic neurones which synapse with cardiac efferent postganglionic neurones. Intrathoracic cardiac afferent neurones exist which interact with intrathoracic cardiac efferent postganglionic neurones, forming intrathoracic feedback loops (Fig. 1). In order to lay a foundation for a discussion about the function of the cardiac nervous system, an overview of cardiac afferent neurones is presented followed by a discussion of cardiac efferent neurones. A discussion concerning cardiac afferent neuronal interactions with cardiac afferent neurones follows.

2.1. Afferent neurones

Functional evidence indicates that afferent neurones with sensory neurites in cardiac tissues are located not only in nodose and dorsal root ganglia [7,8], but intrathoracic extracardiac [9–11] and intrinsic cardiac [12,13] ganglia. The ventricular sensory neurites of afferent neurones in

each of these various locations display unique functional characteristics when exposed to specific mechanical or chemical stimuli [14]. Langley recognized the importance of visceral afferent neurones. As cardiac afferent neurones in nodose and dorsal root ganglia can give rise to pain, he classified these afferent neurones as somatic in nature. He considered “afferent autonomic fibers those which give rise to reflexes in autonomic tissues” [15]. If one were to follow this historical precedent, then nodose and dorsal root ganglion afferent neurones with sensory neurites in cardiac tissues would be classified as somatic in nature and cardiac afferent neurones in various intrathoracic ganglia which project axons to other intrathoracic neurones (i.e., not to central neurones) as autonomic in nature.

2.1.1. Nodose ganglion cardiac afferent neurones

Anatomical and functional data indicate that one population of atrial and ventricular sensory neurites are connected to cardiac afferent neurones located throughout the right and left nodose ganglia [8]. The ventricular sensory neurites of these afferent neurones are concentrated in the cranial aspects of both ventricles [16]. Most of the ventricular sensory neurites associated with nodose ganglion afferent neurones studied in anesthetized cats or dogs respond to chemical stimuli, fewer responding to mechanical stimuli or to both modalities of stimulation [16,17]. Chemical stimuli induce an order-of-magnitude greater enhancement of their activity than do mechanical stimuli, such enhancement persisting long after (i.e., up to

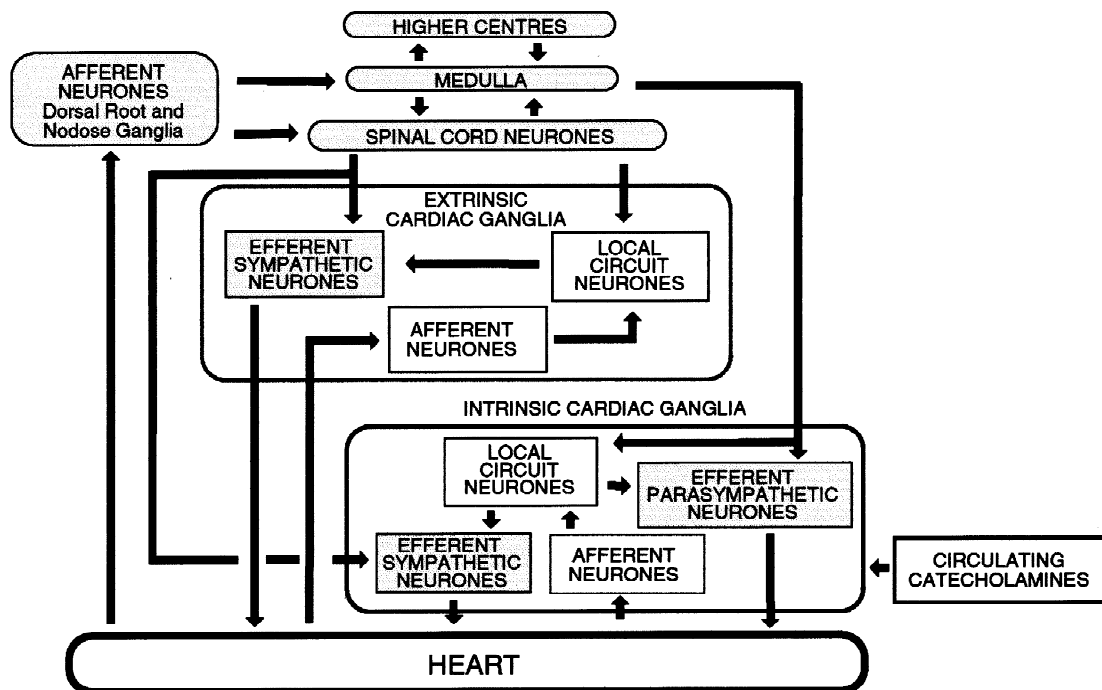


Fig. 1. Diagrammatic representation of the neuronal types and connections between them, purported to exist within the peripheral cardiac nervous system. That circulating catecholamines also influence intrinsic cardiac neurones is depicted by the lower right hand corner.

45 min) removal of chemical as opposed to mechanical stimuli.

2.1.2. Dorsal root ganglion cardiac afferent neurones

The somata of canine afferent neurones connected to ventricular sensory neurites are distributed equally among right and left sided C₆–T₆ dorsal root ganglia [8]. Cardiac afferent neurones in dorsal root ganglia have sensory neurites located throughout both ventricles [18]. Employing extracellular recording techniques, the action potentials generated by dorsal root ganglion cardiac afferent neurones in anesthetized dogs during control states were found to occur at higher frequencies (~10 Hz) than those generated by nodose ganglion cardiac afferent neurones (~0.1 Hz). The sensory neurites of only ~10% of nodose ganglion cardiac afferent neurones are sensitive to mechanical and chemical stimuli [16] while at least 95% of those associated with dorsal root ganglion cardiac afferent neurones are polymodal in nature [18]. This is consistent with the fact that the majority of cardiac sensory neurites associated with afferent axons coursing centrally in sympathetic rami are polysensory in nature [19].

The activity generated by canine dorsal root ganglion cardiac neurones recorded using extracellular techniques increases when their associated ventricular sensory neurites are exposed to supramaximal mechanical (about +225%) or chemical (about +500%) stimuli [18]. The ventricular sensory neurites of these afferent neurones, whether they spontaneously generate activity or remain quiescent in control states, are sensitive to purinergic compounds, peptides and/or hydrogen peroxide [18,20,21]. The activity generated by most of these sensory neurites occurs at different frequencies of their power spectra, depending on their sensory characteristics as well as the type and amount of stimuli applied to them (Fig. 2). That is why individual cardiac afferent neurones in the dorsal root ganglia of an animal, display unique activity patterns in response to similar mechanical or chemical stimuli. Presumably the capacity of each cardiac dorsal root ganglion neurone to process multiple stimuli simultaneously reduces the number of cardiac afferent neurones required to project varied information arising from the heart to the spinal cord.

2.1.3. Cardiac afferent neurones in intrathoracic ganglia

Unipolar neurones have been identified in ganglia located in the thoracic cavity, including intrinsic cardiac ganglia [7,13,22–25]. The cardiac sensory neurites of intrathoracic afferent neurones respond to mechanical stimuli as well local application of chemicals such as adenosine, ATP, bradykinin and/or substance P *in situ* [26]. They also are sensitive to local application of veratridine (Fig. 3), a chemical that increases sodium conductance and, as a consequence, induces neuronal hyperpolarization. They are sensitive to the L-type calcium channel activator Bay K8644, but not after local application of nifedipine, an agent which blocks L-type calcium

channels. They are modified by potassium chloride, a chemical which depolarizes neuronal membranes, tetraethylammonium chloride, a chemical which inhibits delayed potassium conductance and the selective ATP-sensitive potassium channel opener cromakalim. These data are mentioned in order to point out that cardiac sensory neurites of intrathoracic afferent neurones utilize a number of ion species *in situ*. The somata of various autonomic neurones employ the same ion channels in the generation of action potentials *in vitro* [27].

2.2. Efferent neurones

Cardiac myocytes and coronary vessels are innervated by sympathetic and parasympathetic efferent postganglionic neurones [28,29]. The two efferent limbs of the autonomic nervous system have long been considered to regulate the heart in a reciprocal fashion. That is, when one efferent limb is activated the other becomes suppressed [30]. The idea that the two efferent limbs of the cardiac nervous system act only in a reciprocal fashion has been revised since it has become evident that both efferent limbs can also be either enhanced or suppressed concurrently [31,32]. Furthermore, a limited population of intrinsic cardiac local circuit neurones receives preganglionic inputs from both efferent limbs of the autonomic nervous system [33–35]. The integrated input of cardiac sympathetic [36] and parasympathetic [37] efferent preganglionic neurones to the intrinsic cardiac nervous system involves complex neuronal processing at the level of the heart [6]. Efferent postganglionic neurones in each part of the intrinsic cardiac nervous system exert control over functionally discrete regions throughout the heart [38].

2.2.1. Sympathetic efferent neurones

Sympathetic preganglionic neurones in the spinal cord that are involved in cardiac regulation project axons via right and left cranial thoracic spinal cord nerves [39] to sympathetic efferent postganglionic neurones in all intrathoracic ganglia [6,14]. Although sympathetic efferent postganglionic neurones have long been considered to be located primarily in paravertebral ganglia (stellate and cranial thoracic sympathetic chain ganglia) [7], recent anatomical and functional evidence indicates that such neurones are also located in middle and superior cervical ganglia, mediastinal ganglia and intrinsic cardiac ganglia [6,14]. That a population of intrinsic cardiac neurones is activated consistently following electrical stimulation of sympathetic efferent preganglionic inputs to them and that such activation no longer occurs following blockade of nicotinic receptors (whole body hexamethonium administration) supports the contention that sympathetic efferent postganglionic neurones are located in the intrinsic cardiac nervous system [33–35]. In agreement with these data, cardiac augmentation induced by electrical stimulation of many intrinsic cardiac sympathetic efferent nerves is

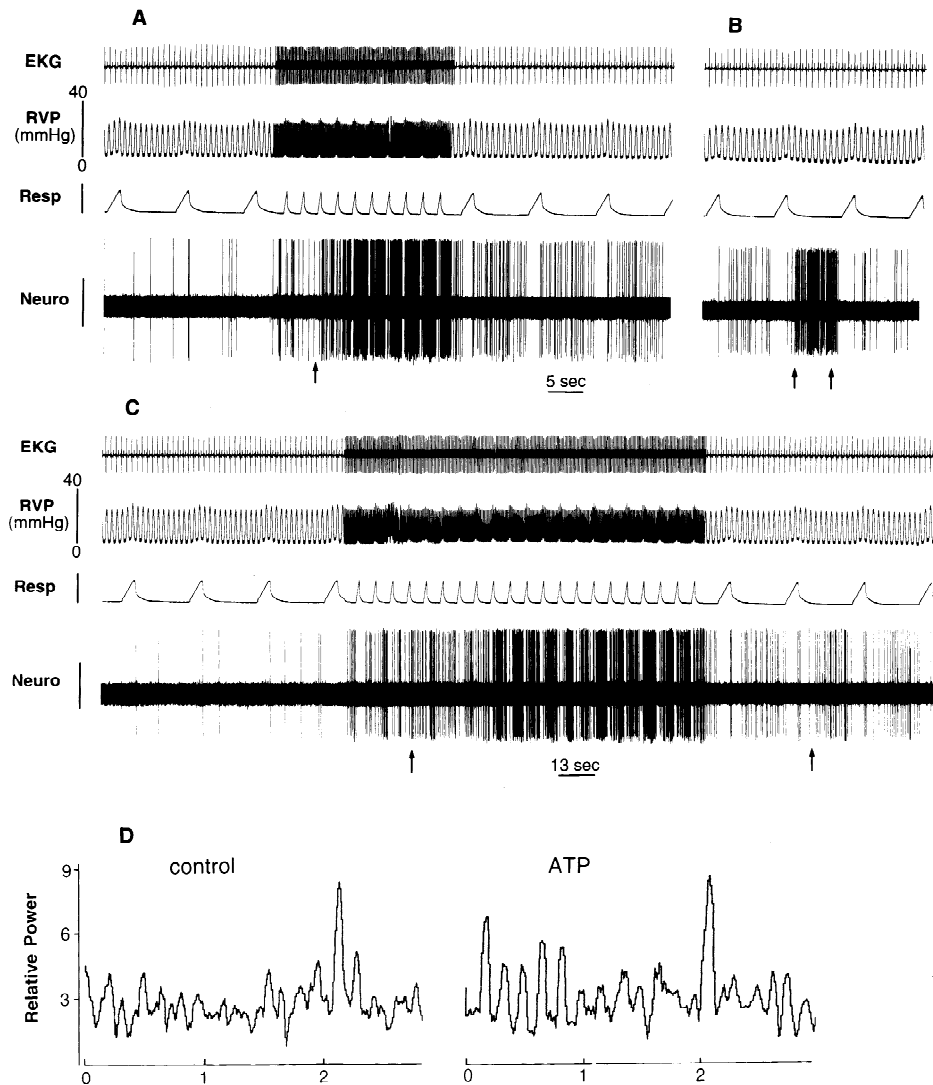


Fig. 2. Activity generated by a mechanical- and chemical-sensitive afferent neurone in a right T₂ dorsal root ganglion associated with right ventricular conus sensory endings. (A) Afferent neuronal activity increased from 4 to 22 Hz when substance P (10 μM) was applied to its sensory field (between arrows below) even though cardiac variables were unchanged. Note that a respiratory related activity rhythm was evident when substance P was tested. (B) Gently touching its sensory field (between arrows below) excited this neurone. (C) Application of ATP (10 μM, between arrows below) to its epicardial sensory field increased the activity that this neurone generated. The estimated conduction velocity of its axon was 2.4 m/s. Vertical calibration bars beside neuronal activity=0.2 mV. (D) Power spectral analysis of the activity generated by this neurone displayed one peak at about 2 Hz, which concurred with the heart rate. When its sensory neurites were exposed to ATP (right panel), activity also developed in the lower power range (presumably the multiple peaks represent harmonics of the respiratory derived one).

modified following whole body administration of hexamethonium [40]. Taken together, these data indicate that intrinsic cardiac nervous system contains, in addition to parasympathetic efferent postganglionic neurones, sympathetic efferent postganglionic neurones [6].

Adrenergic neurones have been identified in the intrinsic cardiac nervous system [23,41,42], some of which display catecholamine synthesizing properties [43–45]. One population of small intensely fluorescent (SIF) cells (10–20 μm diameter) displays tyrosine hydroxylase immunoreactivity [41,42], projecting axons to principal intrinsic cardiac neurones [23,46]. In accord with these observations, mRNA and protein enzymes involved in catechol-

amine biosynthesis have been associated with a population of intrinsic cardiac neurones [47]. That some intrinsic cardiac neurones possess β-adrenoceptors [48] or α-adrenoceptors [49] and the enzymes (aromatic L-amino acid decarboxylase and dopamine β-hydroxylase) needed to convert L-DOPA to dopamine and noradrenaline is supported by the fact that a population of intrinsic cardiac neurones express catecholaminergic phenotypical aspects [50]. That one population of intrinsic cardiac neurones is capable of synthesizing and degrading catecholamines [51] is in agreement with the fact that adrenergic receptors are involved in neurotransmission within intrinsic cardiac ganglia studied in vitro [52]. The population of intrinsic

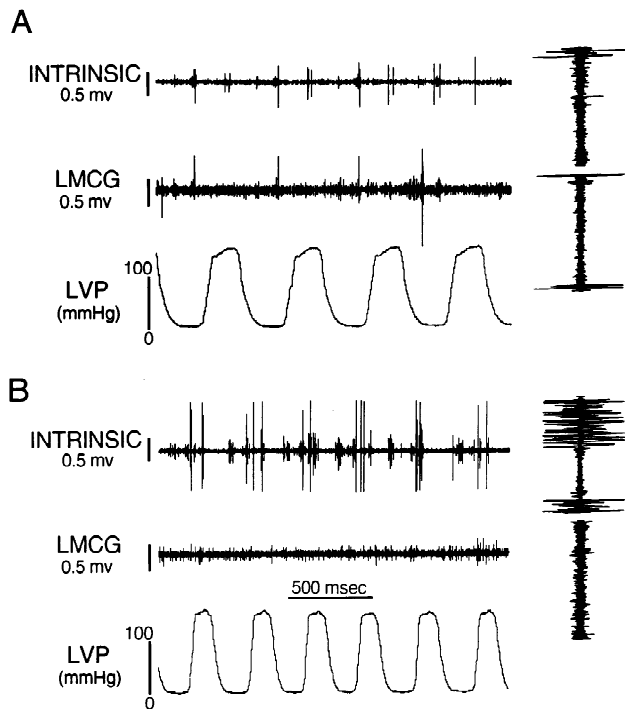


Fig. 3. Activity generated by neurones in intrinsic and extrinsic intrathoracic ganglia recorded concomitantly. (A) During control states, the activity generated by neurones in the ventral intraventricular ganglionated plexus (intrinsic) and the left middle cervical ganglion (LMCG) occurred at specific but differing times in the cardiac cycle (c.f., left ventricular chamber pressure (LVP) trace below). (B) When veratridine (5×10^{-6} g) was applied to the sensory neurites associated with these neurones, the activity generated by the intrinsic cardiac neurones increased while that generated by middle cervical ganglion neurones decreased. The X/Y plots to the right of the neuronal activity traces display activity generated by neurones in intrinsic cardiac (upper right) and middle cervical (lower right) ganglia compared to left ventricular chamber pressure for four consecutive cardiac cycles.

cardiac neurones sensitive to exogenously applied α - or β -adrenoceptor agonists, once activated, increases heart rate and contractile force [53].

Sympathetic efferent postganglionic neurones located in each intrinsic cardiac ganglionated plexus project axons to diverse regions of the dog heart [38,40]. Having said that, adrenergic neurones in atrial ganglia preferentially innervated atrial tissues whereas those in ventricular ganglionated plexuses preferentially innervate ventricular tissue [54]. Intrinsic cardiac neurones are also capable of influencing coronary arterial blood flow [55]. The redundancy of input to each region of the heart from sympathetic efferent neurones located in various intrathoracic ganglia, including those on the heart, ensures adequate cardiac control even when the function of one part of the intrathoracic sympathetic efferent nervous system is compromised [26].

2.2.2. Parasympathetic efferent neurones

The presence of parasympathetic efferent postganglionic neurones on the heart has been appreciated for a long time

[7,24,37]. Although there is varied opinion expressed concerning the locations of parasympathetic efferent pre-ganglionic neurones which project axons to cardiac parasympathetic postganglionic neurones, a consensus of opinion is developing that they are located for the most part in the nucleus ambiguus of the medulla in most mammalian species [56,57]. Lesser numbers are located in the dorsal motor nucleus and the regions in between these two medullary nuclei. There is no consensus of opinion with regard to whether parasympathetic pre-ganglionic neurones in one region of the medulla project axons to parasympathetic postganglionic neurones in one intrinsic cardiac ganglionated plexus. Results vary depending on the species studied. Data obtained from the feline model indicate that there is a cardiotoxic organization of medullary parasympathetic pre-ganglionic neurones [58,59], whereas no such organization has been identified in canines [57]. Parasympathetic efferent postganglionic neurones, when activated either chemically or electrically, suppress atrial rate and force [37,38], atrio-ventricular nodal conduction [60] and ventricular contractile force [61]. Parasympathetic postganglionic neurones in each intrinsic cardiac ganglionated plexus innervate tissues throughout the heart [38], such neurones in atrial ganglia preferentially innervating atrial tissues while those in ventricular ganglia preferentially innervating ventricular tissues [54].

2.3. Local circuit neurones

Populations of neurones in different intrathoracic ganglia communicate with one another [14]. Much of the processing which occurs within the intrathoracic nervous system apparently involves local circuit neurones, neurones that interconnect neurones within one ganglion as well as neurones in different intrathoracic ganglia. For instance, intrinsic cardiac ganglia contain not only small diameter cells (10–20 μ M), some of which are SIF cells [23,46], but relatively large diameter neurones (20–40 μ M). These latter neurones possess multiple nucleoli [22,25,35]. Rosettes of these relatively large diameter neurones (i.e., about 30 μ M) are found in intrinsic cardiac ganglia, most of the neurones therein projecting their relatively short axons to the axons of other neurones within that rosette. The intrinsic cardiac nervous system also possesses neurones that project axons to neurones in other intrinsic cardiac ganglia [6,14]. Similar rosettes of relatively large diameter neurones are found in intrathoracic extracardiac ganglia too. Some of these neurones display immunoreactivity to specific peptides such as neuropeptide Y or vasoactive intestinal peptide [62]. These neurones may account in part for the complex information processing that occurs within the intrathoracic nervous system [6,54].

Burnstock and his associates have identified unique electrophysiological properties associated with three different populations of cultured intrinsic cardiac neurones [63]. One population exhibits pronounced after-hyperpolariza-

tions and thus generally generate single action potentials when relatively-long-duration currents are injected intracellularly. This type of neurone (the AHs-type) may account for the fact that multiple stimuli delivered to axons connecting to intrinsic cardiac ganglia induce some neurones to generate single rather than multiple action potentials in situ [33–35]. The second type of intrinsic cardiac neurone (the AHm-type) displays pronounced after-hyperpolarizations. This type of neurone is capable of generating brief bursts of action potentials in response to prolonged intracellular current injection. The third type of neurone (the M-type) does not display prolonged after-hyperpolarizations, discharging tonically in response to relatively prolonged current injection. The varied anatomical [13,23] and physiological [45,52,63] properties displayed by cultured intrinsic cardiac neurones are similar to those found in situ, supporting the thesis that different neuronal types which are located in the peripheral cardiac nervous system normally interact in the maintenance of cardiac function [14].

2.4. Peripheral autonomic neuronal interactions

Intrathoracic ganglia have long been considered to act as monosynaptic relay stations distributing efferent sympathetic (extracardiac ganglia) or parasympathetic (intrinsic cardiac ganglia) centrifugal information to the heart [64]. Recent evidence indicates that they also process centripetal information [14,65–67]. The complex functional hierarchy represented by neurones within the various intrathoracic ganglia utilizes excitatory and inhibitory synapses [68,69]. Afferent neurones in the intrathoracic nervous system receive inputs from sensory neurites located not only on the heart, but major thoracic vessels or pulmonary tissues [6,14,26]. They also receive inputs from spinal cord neurones which are indirectly influenced by afferent neurones with sensory neurites located elsewhere in the body [6], including mechanosensory neurites on carotid arteries [26]. While data remain incomplete, a tentative organization of the intrathoracic cardiac nervous system has been proposed in which cardiac afferent neurones influence local circuit neurones which, in turn, modify autonomic efferent postganglionic neurones via multiple feedback loops [6,26,54,70]. These varied intrathoracic reflexes regulate cardiodynamics on a beat-to-beat basis, even when the intrathoracic nervous system is disconnected from more centrally located neurones [12]. A number of chemicals modify neurones in canine intrathoracic extracardiac and intrinsic cardiac ganglia. These chemicals include α - and β -adrenoceptor agonists, acetylcholine, muscarinic agonists, nitric oxide donors, excitatory and inhibitory amino acids, peptides, purinergic agents [14] and hydroxyl radicals [71]. Inhibitory synapses within the intrathoracic cardiac nervous system suppress intrathoracic reflexes, as can some inputs from central neurones [6]. Inhibitory synapses become particularly

important during prolonged activation of the cardiac sympathetic efferent nervous system [72], such as occurs when intracranial pressure is raised [73].

That the different populations of intrathoracic neurones respond differently when similar stimuli are applied to cardiac sensory neurones implies that the heart's reliance on any one population of peripheral autonomic neurones is minimal. How a given population of intrathoracic neurones influences cardiodynamics depends on the nature and content of their sensory neuronal inputs. Preliminary evidence indicates that the intrathoracic nervous system, acting as a distributive processor with multiple nested feedback control loops, modulates cardiac function throughout each cardiac cycle in concert with central neuronal reflexes (Fig. 1). The reflexes within this intrathoracic neuronal hierarchy can exert considerable influence on cardiac rate and force [67].

2.5. Central autonomic neuronal integration

Electrical excitation of a significant population of cardiopulmonary afferent inputs to medullary neurones can induce sustained elevations in systemic arterial pressure [74]. In contrast, stimulation of the sensory neurites of one population of nodose ganglion cardiac afferent neurones induces bradycardia [75]. In agreement with that, bradycardia is initiated following activation of cardiac afferent neurones in nodose ganglia by exposing their cardiac sensory fields to purinergic agents [76]. When cardiovascular afferent axons in sympathetic nerves are activated, systemic vascular pressure increases [19,77]. Thus, concomitant activation of the cardiac afferent neurones in nodose and dorsal root ganglia initiates a variety of cardiovascular reflex responses, dependent upon the population of afferent neurones activated and the stimulus applied. Given the variety of intrathoracic and central reflexes induced by altered cardiac states and the relative paucity of information concerning interactions among central and peripheral neuronal reflexes, it is premature to ascribe specific roles to each of the reflex responses induced by a cardiac perturbation.

3. Influence of myocardial ischaemia on the cardiac nervous system

How autonomic neurones involved in cardiac regulation respond to myocardial ischaemia depends on their location as well as the location and response characteristics of their sensory inputs. The response characteristics of the intrathoracic cardiac neurones to myocardial ischaemia will be discussed first, followed by a discussion on the involvement of central neurones in that state. Because much of what follows is inferential, the concepts presented about how ventricular ischaemia affects the cardiac nervous system are tentative. They are presented with the aim of

stimulating interest in the fact that the complex cardiac nervous system may be amenable to manipulation when ventricular ischaemia occurs in order to influence the outcome of that state.

3.1. Modification of intrathoracic neurones by myocardial ischaemia

Intrinsic cardiac neurones are modified by myocardial ischaemia in two fashions: one direct and the other indirect. Transient occlusion of the coronary arterial blood supply to a population of intrinsic cardiac neurones directly affects the function of their somata and/or dendrites [78]. Presumably, a lack of energy substrates normally available to them via their local arterial blood supply accounts in part for their altered behavior, as well as the fact that they are bathed by local products of ischaemia such as oxygen-free radicals [71] and purinergic agents [79]. Each major intrinsic cardiac ganglionated plexus on human or dog hearts is perfused by two or more arterial branches arising from different major coronary arteries [78]. Intrinsic cardiac neurones and cardiomyocytes are affected by hypoxia. Myocardial ischaemia of 5–10 min duration affects cardiac myocyte function, including that of their β -adrenoceptors [80]. It also reduces the capacity of intrinsic cardiac neurones to respond to sensory inputs [34]. Metabolites accumulating locally when the regional coronary arterial blood supply of intrinsic cardiac neurones is compromised influences the somata and dendrites of such neurones in a direct manner.

The chemical milieu of the sensory neurites associated with intrinsic cardiac afferent neurones may also change when the blood flow in a coronary artery is compromised. Locally liberated adenosine, ATP, oxygen-free radicals and peptides can affect the sensory neurites associated with afferent neuronal somata in nodose, dorsal root or intrathoracic ganglia [16,18,20,21,79]. Oxygen-free radicals also affect the functional integrity of ventricular nerves [81]. The quantities of purinergic agents liberated into the local blood stream [82] and pericardial fluid (Kollain, M., Budapest, Hungary, personal communication, 1997) increases during ventricular ischaemia, as may those of peptides or hydrogen peroxide [20]. Thus, myocardial ischaemia can affect the activity generated by intrathoracic and central cardiac afferent neurones in an indirect fashion as chemicals accumulated in myocardial tissues and pericardial fluid modify their sensory neurites. When coronary arterial blood flow is restored, during the reperfusion phase various metabolites which had accumulated upstream can influence intrinsic cardiac neurones and their sensory neurites supplied by that blood even more [78].

An issue that has been raised concerns ischaemia-induced effects on nerves which course over a transmural infarction. It has been proposed that a transmural ventricular infarction impairs the function of nerves coursing over that infarction because the nutrient blood supply to such

axons would be compromised [83]. If that were so, cardiac regulatory processes could be altered considerably. However, cardiac nerves possess their own rich blood supply, much of which arises from extracardiac arteries [84]. For that reason, the blood supply of nerves coursing over a ventricular infarction is not affected when underlying myocardial tissue becomes ischemic. In accordance with that, nerves coursing over a transmural ventricular infarction of the canine heart *in situ* retain their capacity to conduct action potentials [84].

3.2. Ischaemia-sensitive cardiac afferent neurones which interact with central neurones

As mentioned above, a number of the ventricular sensory neurites of nodose ganglion cardiac afferent neurones and most of those associated with dorsal root ganglion afferent neurones (Fig. 4) are sensitive to local ischaemia [16,17]. It has been proposed that angina of cardiac origin in man is dependent to a large extent on the capacity of local ischaemia to modify ventricular sensory neurite P1-purinoceptors [85]. Peptides such as substance P apparently play a supportive role in the genesis of such cardiac symptoms [86]. That many ventricular sensory neurites associated with dorsal root ganglion afferent neurones of anesthetized dogs no longer respond to local ischaemia when their adenosine receptors are blocked *in situ* [79] supports the contention that adenosine-sensitive cardiac afferent neurones play an important role in the transduction of afferent information to central neurones during myocardial ischaemia.

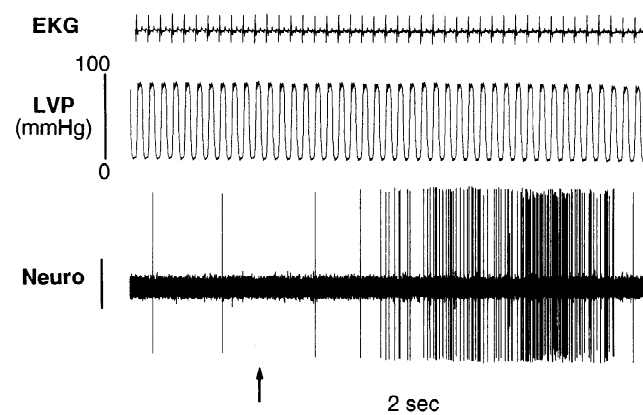


Fig. 4. Ischaemia-sensitive neurone in a left T_2 dorsal root ganglion that was associated with mechanosensory neurites located on the ventral surface of the left ventricle. This neurone generated sporadic activity during control periods. When the major coronary artery which supplied blood to its sensory field (the left anterior descending coronary artery) was occluded (arrow below), activity increased even though heart rate and left ventricular systolic and diastolic pressures remained unchanged. EKG=electrocardiogram; LVP=left ventricular chamber pressure; Neuro=afferent neuronal activity. Vertical calibration bar to the left of the neurogram=0.1 mV.

3.2.1. Nodose ganglion cardiac afferent neurones

Local ischaemia increases the activity generated by chemosensitive ventricular neurites of about 20% of nodose ganglion cardiac afferent neurones (0.26 ± 0.12 – 1.66 ± 0.61 impulses per second) [16]. The suggestion that most ischaemia-sensitive neurites associated with nodose ganglion afferent neurones are located in the dorsum of the left ventricle is not borne out by data from animal experiments [16]. The sensory neurites of most ischaemia-sensitive nodose ganglion cardiac afferent neurones are responsive to chemical as opposed to mechanical stimuli *in situ* [16]. Furthermore, the peak activity levels achieved by mechanosensory nodose ganglion cardiac afferent neurones are less than those achieved by chemosensory neurones. Thus it is unlikely that alterations in the mechanical milieu predominate in this population of neurones during myocardial ischaemia. That these neurones may generate even more activity (2.51 ± 0.47 impulses per second) when their arterial blood supply is restored (during reperfusion) indicates that nodose ganglion cardiac afferent neurones may participate in reperfusion events.

3.2.2. Dorsal root ganglion neurones

Most of the ischaemia-sensitive ventricular sensory neurites of canine dorsal root ganglion afferent neurones respond to local application of peptides and/or purinergic compounds (and other chemicals), as well as mechanical stimuli *in situ* (Fig. 2). Although bradykinin and substance P are involved in the genesis of pain arising from other body organs [87], these peptides apparently act only to exacerbate cardiac symptoms [88]. Purinergic compounds have been implicated in the genesis of referred pain secondary to ventricular ischaemia in man [85]. Individual afferent neurones are capable of transferring information to central neurones simultaneously in multiple domains, each reflecting the relative mechanical and chemical inputs to its sensory neurites at any time. In addition, the power modality of the frequency generated by these afferent neurones depends on the amount and type of mechanical and chemical stimuli their sensory neurites receive at any time (Fig. 2D), as well as the transduction characteristics of their sensory neurites [18]. The fact that the sensory neurites of dorsal root ganglion cardiac afferent neurones respond to multiple stimuli may account for the fact that a greater population of these afferent neurones are sensitive to transient myocardial ischaemia (~80%) than nodose ganglion cardiac afferent neurones (~20%). That ischaemia-induced enhancement of activity generated by ventricular sensory neurites associated with dorsal root ganglion afferent neurones is greater (2.2 ± 1.6 – 8.0 ± 2.8 Hz; maximum activity of 205 Hz) than ischaemia-induced enhancement of nodose ganglion afferent neurone ventricular sensory neurite activity (0.26 ± 0.12 – 1.66 ± 0.61 Hz; maximum activity of 27 Hz) may also account, in part, for the manifestation of cardiac symptomatology in the sensorium. Symptomatology may also relate the fact that

some dorsal root ganglion afferent neurones associated with cardiac sensory neurites project axons to ipsilateral skin tissues [89].

3.2.3. Central neuronal reflexes induced by myocardial ischaemia

A variety of cardiovascular reflexes occur when the ventricular sensory neurites of cardiac afferent neurones located in nodose and dorsal root ganglia are exposed to local ischaemia in anesthetized animals [90,91]. Activation of dorsal root ganglion cardiac neurones by exposing their associated sensory neurites to ischaemia results in the modification of sympathetic efferent postganglionic neurones which innervate widely diverse regions of the body [78], including the heart [91]. The relatively localized nature of ischaemia-induced cardio-cardiac reflexes is exemplified by the finding that regional ventricular ischaemia activates sympathetic efferent neurones which innervate the non-ischemic myocardium, while reducing sympathetic efferent neuronal input to the ischemic zone [91]. Reflex activation of cardiac parasympathetic and sympathetic cardiac efferent neurones can occur concomitantly when a sufficient population of ischaemia-sensitive cardiovascular afferent neurones in nodose and dorsal root ganglia become excited [31]. The central and intrathoracic reflex interactions involved in regulating the ischemic myocardium have yet to be fully elucidated.

4. Neurocardiological sequelae of myocardial ischaemia

Cardiac ischaemia-induced cardiovascular reflexes must be understood in the context that arterial baroreflexes can become blunted in heart disease [92]. Furthermore, ischaemia-induced local liberation of chemicals such as adenosine and hydroxyl radicals results in suppression ventricular myocyte behavior [93]. As mentioned above, locally released adenosine [94] or hydroxyl radicals [71] can influence the cardiac nervous system. Thus when devising therapy to modify the outcome of myocardial ischaemia one must consider not only altered cardiac myocyte behavior, but neuronal alterations. Modification of the cardiac nervous system may be important when permanent cardiomyocyte damage occurs since significant restoration of cardiomyocyte function in such a state may be difficult to achieve. A brief summary of some of the issues concerning autonomic neuronal responses to myocardial ischaemia are presented below, including that of neuronal responses to ischaemia-induced cardiac failure.

4.1. Symptomatology

The somata of isolated afferent neurones are sensitive to adenosine [95]. ATP and, to a lesser extent, adenosine influence the skin sensory neurites of dorsal root ganglion

neurons [96]. The importance of adenosine in the genesis of cardiac pain became evident when Christer Sylvén and his colleagues administered adenosine into the blood stream of patients' diseased coronary arteries [85]. The symptoms induced in these patients mimicked those which they experienced during effort [85,86,88]. These data are in accord with the finding that purine-sensitive afferent neurons in dorsal root ganglia play an important role in the genesis of limb pain [96] and that the ventricular sensory neurites of dorsal root ganglion neurons can become non-responsive to ischaemia in the presence of adenosine receptor blockade [79].

4.2. Cardiovascular reflexes secondary to myocardial ischaemia

Alterations in heart rate secondary to ventricular ischaemia can be due, in part, to altered neural control of cardiac pacemaker cells. Myocardial ischaemia can be attended not only by tachycardia, but by bradycardia. Many ventricular sensory neurites associated with nodose ganglion cardiac afferent neurons are sensitive to purinergic agents [16]. Activation of a sufficient population of nodose ganglion afferent neurons by exposing their sensory neurites to purinergic agents can result in the induction of bradycardia via medullary reflexes [76]. Bradycardia can also be elicited when a sufficient population of intrinsic cardiac neurons projecting axons to medullary neurons is activated by purinergic agents [94]. In contrast, excitation of the cardiac sensory neurites of dorsal root ganglion neurons by chemicals such as adenosine results in the reflex excitation of sympathetic efferent neurons which innervate the systemic vasculature [19,77] and the heart [31].

These so-called sympathetic reflexes may be either regionally specific [90,91] or global in nature [74,78]. The details of the various reflex responses induced when specific populations of cardiac afferent neurons in nodose as opposed to dorsal root ganglia are modified by local ischaemia remain to be fully elucidated. Coordination of autonomic outflows to the heart depends to a large extent upon the sharing of inputs from higher centers concomitant with interactions among neurons in various intrathoracic ganglia. That sharing of cardiac afferent information occurs within the intrathoracic and brainstem/spinal cord feedback loops depicted above allows for overall coordination of neuroeffector control of the heart.

4.3. Cardiac arrhythmias

Another sequel of myocardial ischaemia is the development of cardiac arrhythmias. As neurons from the level of the insular cortex [97] to the intrinsic cardiac nervous system [98,99] can be involved in the genesis of cardiac arrhythmias (Fig. 5), it is important to recognize that such neurons can induce untoward cardiac electrical events in

the presence of myocardial ischaemia. For instance, activation of a relatively minor population of intrinsic cardiac neurons in anesthetized canine preparations by exogenous application of an α - or β -adrenoceptor agonist [100], endothelin I [101] or angiotensin II [100,102] can induce ventricular dysrhythmias or even fibrillation. Whatever modulator role the cardiac nervous system plays during the development of cardiac arrhythmias, it resides not only in its capacity to release catecholamines during preconditioning [103] but in alterations in its nested feedback regulatory system.

4.4. Heart failure

Disordered function of autonomic efferent neurons can result in coronary vascular malfunction [3,4,104]. Ischaemia may result in a loss of ventricular cardiomyocyte contractile function secondary to such malfunction, a pathological state that can lead to heart failure [105]. Little is known about the capacity of the cardiac nervous system to support myocyte function in the presence of heart failure. Alterations in cardiomyocyte adenosine receptors [106], ion channels [107], second messengers [107] and β -adrenoceptors [108] occur in heart failure. The sympathetic efferent nervous system involved in cardiac regulation also changes during the development of heart failure. The generalized activation of this nervous system which occurs in heart failure has been thought to include its cardiac component [105,109]. That has been one explanation for the fact that tachycardia occurs in this syndrome [109]. There is also a concomitant reduction in the content of noradrenaline in the failing myocardium [110]. Little information exists concerning how the cardiac nervous system responds to the development of this syndrome.

A loss of total ventricular β -adrenoceptors occurs in animal heart failure models induced by rapid cardiac pacing [107,111] or aortic banding [112]. On the other hand, the density and affinity of cell surface β -adrenoceptors associated with ventricular cardiomyocyte obtained from genetic [113] or tachycardia derived (unpublished results) models of heart failure are similar to those found in the non-failing ventricle. Thus results obtained concerning the function of β -adrenoceptors associated with cardiomyocytes derived from failing heart models differ depending on whether total or cell surface cardiomyocyte β -adrenoceptors are quantified. There is agreement on the fact that cardiomyocytes obtained from failing hearts retain their response characteristics to calcium [114], while expressing decreased adenylate cyclase reactivity [107]. Given all of the above, the blunting of cardiomyocyte responsiveness to catecholamine challenge in heart failure may be due in large part to decreased reactivity of cardiomyocyte adenylate cyclase [107].

Pharmacological agents which block β -adrenoceptors [6,9,52] or angiotensin II receptors [101] affect not only cardiomyocyte function but the intrathoracic cardiac ner-

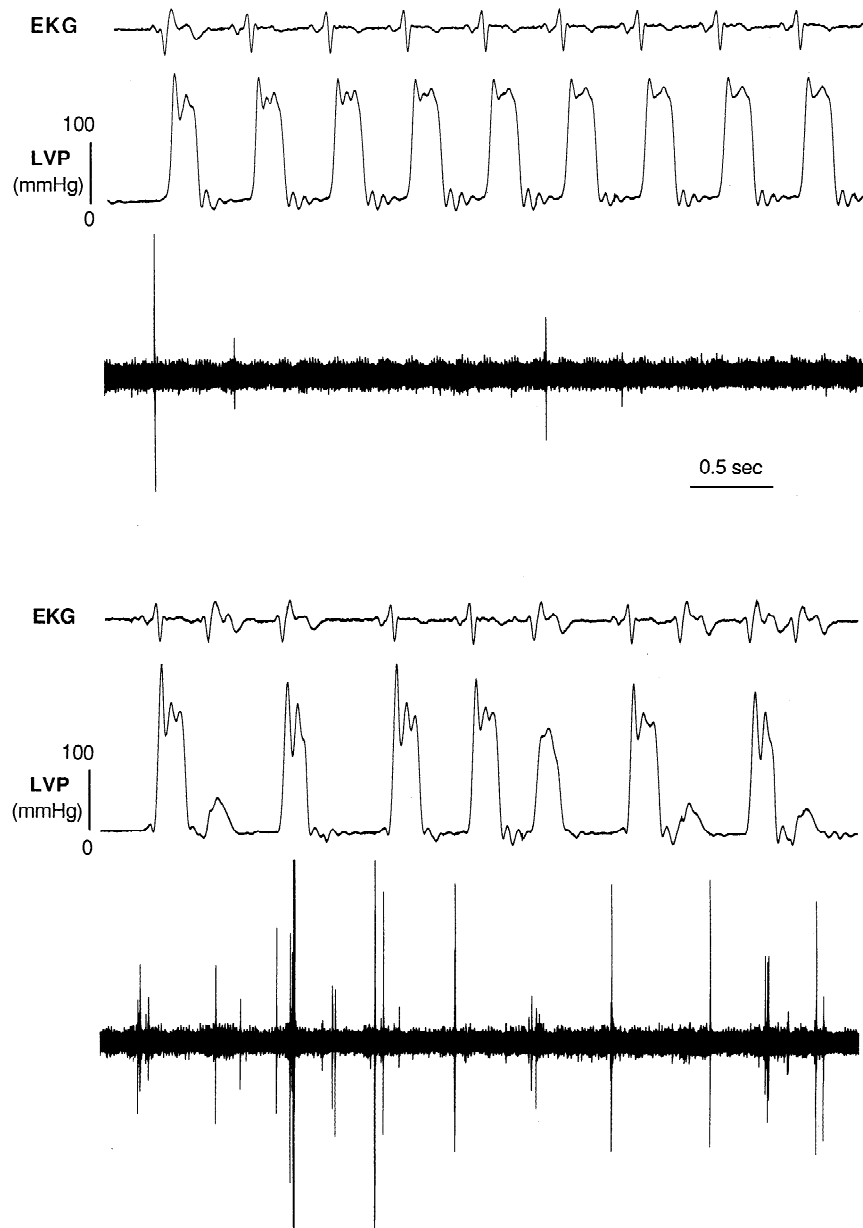


Fig. 5. The activity generated by right atrial neurones increased when angiotensin II (0.1 ml of a 10 μ M solution) was administered to them via their local arterial blood supply in situ (between panels A and B). Concomitant increases in left ventricular systolic pressure occurred along with the generation of ventricular premature beats. Traces are, from top down, a lead II EKG, left ventricular chamber pressure (LVP) and a neurogram (vertical bar=1 mV).

vous system. Although ventricular inotropic responses to exogenously applied β -adrenoceptor agonists are reduced in failing as opposed to normal canine hearts, ventricular contractility in the pacing-induced canine model of heart failure can still be enhanced to a considerable degree by such agonists [115]. In contrast, the capacity of cardiac sympathetic efferent postganglionic neurones to release noradrenaline from their efferent nerve terminals becomes compromised in that model of heart failure [115]. That cardiac sympathetic efferent neurones, when maximally activated electrically or chemically, release considerably less noradrenaline in the pacing-induced canine model of heart failure than in normal dogs, despite the fact that

circulating noradrenaline levels are elevated above control values, indicates that blood noradrenaline content may not be an adequate index of the functional status of the cardiac sympathetic efferent nervous system in heart failure. Presumably this is because of the fact that circulating levels of noradrenaline represent noradrenaline liberated by sympathetic efferent neurones throughout the body. A sizable pool of releasable noradrenaline is still present in the cardiac sympathetic efferent postganglionic nerve terminals of failing canine ventricles, as indicated by the fact that tyramine induces considerable augmentation of ventricular contractile force in the pacing-induced canine model of heart failure [115]. Despite that, the failing

canine ventricle is not affected very much when the somata of cardiac sympathetic efferent neurones are activated chemically or electrically [115]. These preliminary data suggest that the function of cardiac sympathetic efferent neuronal somata, as opposed to efferent nerve terminals, is suppressed in heart failure. These animal derived data may help to explain the observed impairment in the capacity of cardiac sympathetic efferent postganglionic neurones to release noradrenaline in heart failure patients [116,117].

In contrast, parasympathetic efferent neurones retain their capacity to influence cardiomyocytes in the tachycardia-induced canine heart failure model. For instance, electrical stimulation of right (117 ± 16 – 18 ± 4 beats per min) or left (119 ± 12 – 35 ± 14 beats per min) vagal efferent preganglionic axons in such a model of heart failure results in a reduction in heart rate that is similar to that elicited in normal dogs [37]. In agreement with these data, canine ventricular cardiomyocyte muscarinic receptors are relatively normal in the canine tachycardia-induced model of heart failure [118] or the failing human heart [119]. These preliminary data indicate that cardiac sympathetic efferent neuronal function, as opposed to cardiac parasympathetic efferent neuronal function, may be impaired during the development of heart failure. Whether alterations in the function of cardiac sympathetic efferent neurones precedes that induced in cardiomyocytes remains to be explored.

5. Implications

The importance of the peripheral cardiac nervous system in the maintenance of normal cardiac output is just beginning to be appreciated. How this nervous system supports cardiac function in the presence of myocardial ischaemia remains unknown. The selective nature of the responses elicited by each component of the intrathoracic neuronal hierarchy to myocardial ischaemia depends on how each population of peripheral autonomic neurones is affected, as well as the nature and content of their sensory inputs. That ischaemia-sensitive cardiac afferent neurones in nodose and dorsal root ganglia influence the behavior of central autonomic neurones which, in turn, modify cardiovascular autonomic efferent preganglionic neurones represents yet another level of this regulatory hierarchy. Understanding how neurones in this regulatory hierarchy interact in diseased states is relevant given the fact that pharmacological agents proven of use in the treatment of heart failure (β -adrenoceptor or angiotensin II receptor blocking agents) affect not only cardiomyocytes but cardiac neurones. Much remains to be known about how central and peripheral cardiac neurones respond to myocardial ischaemia. The challenge remains to understand the response characteristics of each component of the neuronal nested feed-back loops which are involved in cardiac regulation to myocardial ischaemia so that focused neuro-

cardiological strategies can be devised to stabilize cardiac function in such a state.

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