Cardiac neuronal hierarchy in health and disease

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Armour, J. Andrew. Cardiac neuronal hierarchy in health and disease. Am J Physiol Regul Integr Comp Physiol 287: R262–R271, 2004; 10.1152/ajpregu.00183.2004.—The cardiac neuronal hierarchy can be represented as a redundant control system made up of spatially distributed cell stations comprising afferent, efferent, and interconnecting neurons. Its peripheral and central neurons are in constant communication with one another such that, for the most part, it behaves as a stochastic control system. Neurons distributed throughout this hierarchy interconnect via specific linkages such that each neuronal cell station is involved in temporally dependent cardio-cardiac reflexes that control overlapping, spatially organized cardiac regions. Its function depends primarily, but not exclusively, on inputs arising from afferent neurons transducing the cardiovascular milieu to directly or indirectly (via interconnecting neurons) modify cardiac motor neurons coordinating regional cardiac behavior. As the function of the whole is greater than that of its individual parts, stable cardiac control occurs most of the time in the absence of direct cause and effect. During altered cardiac status, its redundancy normally represents a stabilizing feature. However, in the presence of regional myocardial ischemia, components within the intrinsic cardiac nervous system undergo pathological change. That, along with any consequent remodeling of the cardiac neuronal hierarchy, alters its spatially and temporally organized reflexes such that populations of neurons, acting in isolation, may destabilize efferent neuronal control of regional cardiac electrical and/or mechanical events.

adrenergic efferent neurons; afferent neurons; autonomic nervous system; cardiac arrhythmias; cardiac force; cardiac rate; cholinergic efferent neurons; heart failure; intrinsic cardiac ganglia; local circuit neurons; memory; middle cervical ganglion; parasympathetic; sympathetic; stellate ganglion; stochastic behavior

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throughout each cardiac cycle. An important anatomical feature of its intrathoracic component is that its widely distributed neurons form linkages at specific nexus points. The relevance of specific linkages interconnecting spatially distributed populations of neurons lies in the fact that they represent anatomically distinct loci where afferent and efferent neuronal elements functionally interact and, as such, are potential targets for selective therapy (see below).

TRANSDUCTION OF THE CARDIOVASCULAR MILIEU

Overview

The milieu of diverse cardiac regions, the coronary vasculature, as well as major intrathoracic and cervical vessels, is continuously transduced by mechano- and/or chemosensing afferent neurons (2, 3, 7, 9, 29, 44, 45, 53, 92, 97, 110, 131, 140). This information is fed to second-order neurons located in spatially distributed cell stations throughout the cardiac neuronal hierarchy (Fig. 1). It is proposed that the function of efferent neurons coordinating regional cardiodynamics is predicated to a considerable extent on how the cardiovascular milieu is transduced throughout this hierarchy (8). Because the function of the whole network is greater than its individual parts, stable cardiac control generally occurs in the absence of obvious direct cause and effect (Table 1).

Afferent Neuronal Transduction of the Cardiac and Intrathoracic Vascular Milieu

Experimental evidence indicates that limited populations of cardiac afferent neurons transduce purely mechanosensory or Table 1. Summary of major concepts relevant to the hypothesis that the cardiac neuronal hierarchy behaves primarily as a stochastic control system

1. The constitutive parts of this redundant control system can be represented by the following:
   - Basic elements: spatially distributed stations comprising multiple cell lines (neurons).
   - Individual cell stations controlling overlapping, spatially organized cardiac regions.
   - Cell stations distributed throughout this hierarchy interconnect via specific linkages
   - such that each cell station is involved in temporally dependent cardiovascular reflexes.
2. Afferent neurons transduce the CV milieu directly or indirectly (via interconnecting neurons)
3. to cardiac motor neurons that coordinate regional cardiac behavior
4. such that the function of the whole is greater than that of its individual parts.
5. Thus stable cardiac control occurs in the absence of obvious direct cause and effect.
6. Cardiomyocytes require its tonic inputs to sustain adequate cardiac output.
7. During altered cardiac status, its redundancy normally represents a stabilizing feature.
8. It is proposed that during the evolution of cardiac disease,
   - Intrinsic cardiac neurons may undergoing pathological changes.
   - The transduction of altered CV status to the cardiac neuronal hierarchy affects
     - its spatially and temporally organized reflexes such that
     - populations of CV neurons, acting in isolation,
     - destabilize efferent neuronal control of regional cardiac electrical and/or mechanical events.

![Fig. 1. Hypothetical model of the cardiac neuronal hierarchy, with emphasis being placed on its peripheral neuronal components.](https://example.com/cardiological-diagram.png)
chemosensory signals. Mechanosensory afferent neurons are defined as those that demonstrate the capacity to transduce mechanical deformation in the region of their sensory neurites. Chemosensory afferent neurons transduce alterations in the chemical milieu surrounding their sensory neurites. Most cardiac afferents transduce multimodal stimuli in as much as they can simultaneously sense local mechanical and chemical alterations (17, 74, 97, 140). Anatomical and functional data indicate that cardiovascular afferent neuronal somata are distributed throughout the nodose ganglia (69, 139), as well as caudal cervical and cranial thoracic dorsal root ganglia bilaterally (69, 144). They are also present in intrathoracic ganglia (10, 31, 72), including those intrinsic to the heart (6, 28, 41). Their sensory neurites lie concentrated at the origins of the superior and inferior vena cava and in the sinoatrial (SA) node, the dorsal atria, the outflow tracts of both ventricles (epicardial, midwall, and endocardial locations) and the inner arch of the aorta (7, 44, 45, 92, 110, 140).

Cardiac Mechanosensory Transduction

A relatively limited population of cardiac afferent neurons solely transduces the phasic mechanical changes that their sensory neurites undergo during each cardiac cycle (7, 39, 92, 110). In physiological states their phasic activity relates to where their associated sensory neurites are located in the heart (9, 24, 39, 44, 45, 53, 92, 97, 110, 131, 140) reflective of local muscle deformation during each normal cardiac cycle (7, 45, 97, 110, 131). An example of their unique transduction capabilities is represented by mechanosensory neurites located in the ventral right ventricular papillary muscle that transduce local muscle fascicle deformation in a nearly linear fashion (7, 9). Because of the fact that this papillary muscle stretches when increasing loads are placed on its cordae tendinea, this muscle segment undergoes a reduction in length change when right ventricular chamber systolic pressure increases (23) to initiate a reduction in their activity (9). When right ventricular systolic pressure falls as less blood enters that chamber from the right atrium, the right ventricular papillary muscle readily overcomes the consequent lesser tension placed on its corda tendinea to generate greater length change (23); in that state their activity increases (9).

Right and left ventricular outflow tract mechanosensory neurons transduce local deformation in a positive, exponential fashion, their behavior peaking during maximum chamber pressure development (7). Left ventricular mechanosensory neurons display 1) increasing, 2) decreasing, or 3) complex activity patterns in response to increasing left ventricular systolic pressure (74). Thus ventricular mechanosensory neurons do not necessarily transduce ventricular dynamics in an algebraic fashion with respect to peak chamber pressure development. That other ventricular mechanosensory neurons transduce diastole (9, 140) indicates that collectively mechanosensory neurons sense a wide range of ventricular dynamics.

Intrathoracic Vascular Mechanosensory Transduction

Significant populations of afferent neurons in nodose, dorsal root, and especially intrathoracic, extracardiac ganglia have sensory neurites in the adventitia of major intrathoracic vessels, particularly along the inner arch of the thoracic aorta and at the bases of both vena cavae (7, 9, 10). They transduce with considerable precision phasic mechanical changes that the underlying vascular wall undergoes during each cardiac cycle (7). For instance, the activity generated by aortic ones reflects not only systolic pressure, but also the diastolic events (10).

Chemosensory Transduction

Most nodose and many dorsal root ganglion cardiac afferent neurons transduce the cardiac chemical milieu (33). Their activity is aperiodic in nature (0.1–1 Hz), reflective of a relatively slowly varying cardiac chemical milieu (7), thus normally bearing little relationship to regional cardiac mechanics (17, 138). In the presence of hypoxemia, their activity increases (9). Individual cardiac chemosensory neurons are capable of transducing a host of chemicals (74, 76, 78, 97, 138, 139, 142, 143). When their sensory neurites are exposed to multiple chemicals, their activity may reflect the relative concentration of each chemical that they are capable of transducing (138). Thus one afferent neuron can generate activity patterns in different frequency domains of their power spectra when its sensory neurites are exposed to increasing quantities of different chemicals. This suggests that one afferent neuron can simultaneously transduce to second-order neurons unique information regarding multiple chemicals (74). These include chemicals known to be liberated in increasing quantities by the ischemic myocardium (17, 29, 36, 65, 123, 153). That individual cardiac afferent neurons respond to multiple chemicals presumably increases the efficiency of information transduced to second-order neurons by such a limited population.

LOCAL CIRCUIT NEURONS IN CARDIAC CONTROL

Hamos et al. (63) applied the term local circuit neurons to neurons in the hippocampus that project to others in divergent regions of that structure. Intrathoracic ganglia also possess local circuit neurons that project to adjacent neurons or neurons in other intrathoracic ganglia, thereby accounting for the varied functional interconnectivity present within the intrathoracic nervous system (16, 116). The multiple linkages within this nervous system render the sum greater than its individual parts such that ultimately its capacity to influence cardiodynamics must be studied in situ. This is relevant when attempting to unravel the role of intrathoracic local circuit neurons in cardiac control (18).

Intrathoracic ganglia contain unipolar (afferent), bipolar, and multipolar neurons that form multiple synaptic contacts (20, 28, 47, 66, 73, 86, 113, 128, 147, 148) to process centripetal and centrifugal information (5, 12, 120). Many ganglia contain large diameter (25–40 μm) neurons organized as rosettes with central axo-dendritic and axo-somatic synapses, as well as dendritic membrane specializations (20, 28, 47, 111, 113, 148). These features may represent the anatomical substrate for two-way information processing within intrathoracic ganglia (8, 10, 12, 31, 72, 117, 137). Although many short-loop intrathoracic cardio-cardiac reflexes apparently involve direct afferent and efferent neuronal interactions (8), most of the cardiac sensory information transduced to cardiac motor neurons within the intrathoracic nervous system occurs via interposed local circuit neurons (18). Such transduction involves a host of neurochemicals so that the removal of one may result in insignificant loss in their overall function (12). That some intrinsic cardiac neurons project axons to not
only neurons in the same ganglionated plexus (129) but also those in other ganglionated plexuses (61) presumably accounts for the ability of neurons in one intrathoracic locus to exert control over widely divergent atrial (109) and ventricular (149) regions (Fig. 2).

**MOTOR CONTROL OF CARDIAC FUNCTION**

Intrathoracic cardiac neurons that express catecholaminergic phenotypic properties (55, 66, 72), when excited, increase heart rate, dromotropism, and force of contraction. That occurs when populations of intrinsic cardiac neurons are exposed to locally applied adrenergic agonists or nicotine (12). Intrinsic cardiac neurons that express acetylcholinesterase- or butyrylcholinesterase-like activities, when activated, reduce these cardiac indexes (46). It has been assumed by some authors that neurons in one intrinsic cardiac ganglionated plexus exert control solely over adjacent cardiac regions. In such a scenario, neurons in the right atrial ganglionated plexus solely regulate adjacent SA nodal tissue, whereas those in the inferior vena cava-inferior atrial ganglionated plexus control the atrioventricular (AV) node (58, 114, 115). Neurons in the ventral cava-inferior ganglionated plexus affect the adjacent AV node (58) as well as the SA node, left atrial tissue, and both ventricles (149); so do ventricular cholinergic neurons (48). Adrenergic neurons in each major ganglionated plexus do likewise (34, 149).

It is known that respiratory mechanics reflexly affect normal sinus rhythm (87, 130). One tool used to characterize cardiac autonomic efferent control in the clinical setting is the determination of heart rate variability, an index that when altered is considered to represent an early sign of cardiac dysfunction (87, 98, 108). As cardiac motor control is not represented by a simplistic reciprocal balance of adrenergic/cholinergic motor function (105) and because many neurons responsible for heart rate variability reside outside the pericardiac sac (103), it may be difficult to attribute alterations in that index to malfunction of a specific neuronal population (104).

**INTERACTIVE HIERARCHICAL CONTROL**

Sensory data arising from the heart (7, 9) and major vessels (84, 141) initiate central (2, 52, 145) and peripheral (11) reflexes controlling cardiac motor neurons (48, 133). Such control can be resolved into two basic issues: 1) how afferent neurons transduce the cardiovascular milieu directly or indirectly to cardiac motor neurons and 2) the type and time scale (latency of reflexes) of information transmitted to such neurons.

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**Fig. 2.** Atrial and ventricular electrical events affected by neurons within a locus in the right atrial ganglionated plexus (RAGP). When nicotine (100 μM, 0.1 ml) was applied locally to neurons in the caudal portion of the RAGP of an anesthetized open-chest dog, changes were identified in some of the 127 epicardial unipolar electrograms recorded from the atria (top panel) and in the 127 electrograms recorded simultaneously from the ventricular epicardium (bottom panel) showing alterations in repolarization intervals from control states. Initial phase (phase 1) was dominated by electrical alterations adjacent to the sinoatrial node, in the interatrial septum and the cranial left atrium, as well as in the left ventricular apical region. During the subsequent tachycardia phase, whereas limited atrial areas were modified, most of the ventricular epicardium underwent electrical change. This representative figure is illustrative of the fact that right atrial neurons influence adjacent atrial tissues as well as distant atrial and ventricular regions. Ventricular surfaces are depicted according to a polar representation in which the outer circumference represents the ventricular base and the apex is at the center. lad, Left anterior descending; pda, posterior descending coronary artery. This research was performed in collaboration with René Cardinal and Michel Vermeulen.
As some intrathoracic neurons are sensitive to excitatory or inhibitory amino acids (75), these reflexes involve excitatory and inhibitory synapses (12). Their varied latencies depend on the distance of afferent somata from the target organ (distance of the control center from the heart) and the number of synapses they use. Direct transduction of cardiac mechanical events to cardiac motor neurons may represent an unstable control state (82). The relatively slow transduction of the cardiac chemical milieu via local circuit neurons to cardiac motor neurons over many cardiac cycles imparts longer-term, stable control.

Mechanosensory-Based Cardio-Cardiac Reflexes

The short-term scaling properties of fast-responding cardiac mechanosensory neurons generate short-latency reflexes that exert rapid control over select populations of cardiac motor neurons. Their relatively short distance to first synapse permits differential activation of cardiac motor neurons during specific phases of the cardiac cycle (8) to exert beat-to-beat coordination of heart rate and regional contractility (22). These short-loop mechanosensory-based reflexes are under central neuronal control (12).

Mechanosensory-Based Vascular-Cardiac Reflexes

Arterial-cardiac reflexes are initiated by mechanosensory neurites in the carotid arteries and intrathoracic aorta. Mechanosensory neurites associated with individual afferent neurons are concentrated in the adventitia of the carotid bulbs as well as the inner arch of the thoracic aorta (9). They transduce deformation of the arterial wall in which they are located with considerable fidelity (2, 7) via their nodose ganglion somata to neurons in the nucleus of solitary tract, initiating short-latency medulla-based activation of cardiac parasympathetic efferent preganglionic neurons (2). They presumably account for the fact that many cardiac vagal efferent neurons display working memory reflective of events in the immediate past (8, 85), thereby influencing parasympathetic effector control of the SA node differentially throughout each cardiac cycle (90) to initiate short-term heart rate variability (87). Some intrathoracic sympathetic efferent neurons also display phase-related activity reflective of reflexes initiated by carotid artery, aortic, or cardiac mechanosensory neurons (10, 16). Vena cava mechanosensory afferent neurons also mediate cardiac efferent neurons via intrathoracic reflexes (16).

Chemosensory-Based Cardio-Cardiac Reflexes

Populations of afferent neurons transduce the cardiac and arterial blood chemical milieu to intrathoracic and higher center neurons, doing so over longer timescales reflective of a normally slowly changing local chemical milieu (81). The effects of exposing the sensory neuritis of individual cardiac chemosensory neurons to increased amounts of a chemical can reset their activity for a considerable period of time after removal of that chemical stimulus (138), presumably indicative of memory (81). Because of their relative numbers, chemosensory-based reflexes can influence large numbers of cardiac motor neurons over multiple cardiac cycles (12). For these reasons it appears that intrathoracic sympathetically efferent postganglionic neurons display either phase-related or stochastic behavior predicated primarily on whether they transduce mechanosensory- vs. chemosensory-based inputs, respectively.

Neuronal Memory

In the context of this review, memory can be defined as a faculty displayed by populations of interactive neurons in various animal species such that past events affect their current status (60). It has been hypothesized that the interposition of a class of neurons that collectively display memory assures stable control over cardiac motor neuronal function in the presence of altered cardiac status (82). Precise coordination of heart rate and regional dynamics apparently depends to a considerable extent on mechanosensory transduction that requires little memory, being essentially short-latency reflex based (8). As mentioned above, cardiac chemosensory neurons display working memory reflective in part of a changing local cardiac chemical milieu (81) such that, once the stimulus is removed, behavioral modification frequently persists (138). Such thresholded adaptation reflective of events in the immediate past may assure “smoothing” of information transduced to second-order neurons throughout the neuroaxis (81). The cardiac milieu transduced during one cardiac cycle can be stored among populations of intrathoracic local circuit neurons via their interactive linkages to exert control over cardiac motor neurons during subsequent cardiac cycles (10). That short-term retention of information occurs among intrathoracic neurons chronically disconnected from central ones (10) indicates that this capacity can reside solely within the intrathoracic neuronal hierarchy.

Remodeling of the Cardiac Neuronal Hierarchy in Cardiac Disease

It is now recognized that remodeling of the cardiac neuronal hierarchy may either initiate or exacerbate cardiac disease. Selected intrinsic cardiac neuronal components remodel during the evolution of heart failure (36, 136) or after long-term removal of their central neuronal inputs (104, 132). This is in agreement with the fact that arterial baroreceptor transduction resets during the evolution of hypertension (3) or heart failure (152). The overbuilt cardiac nervous system apparently can withstand some linkage malfunction such as occurs when the arterial blood supply to some of its neurons becomes compromised. This may be because the filtering capacity of its relatively large intrathoracic local circuit neuronal population acts to stabilize cardiac efferent neuronal function in the presence of excessive sensory inputs arising from an ischemic myocardium (19, 54). In contrast to irreversible cardiomyocyte (122) or intrinsic cardiac neuronal (70) damage secondary to any reduction in their arterial blood supply, remodeling of this nervous system occurs in the absence of cellular damage and, as such, represents state change that can be subsequently retrieved.

Regional Myocardial Ischemia

When myocardial ischemia is transduced to second-order neurons throughout the cardiac neuronal hierarchy (33, 97, 101, 121), some neurons can become sufficiently activated to influence suprabulbar neurons (e.g., the limbic system, hypothalamus, insular cortex, etc.) and initiate symptoms (135).
Central neuron-derived myocardial ischemia reflexes. Cardiac parasympathetic and sympathetic efferent preganglionic neurons become activated when sufficient populations of centrally projecting cardiac afferent neurons transduce myocardial ischemia to central neurons (101). Myocardial ischemia initiates cardiac depressor or augmentor reflexes, depending on how alterations in the local cardiac milieu are transduced throughout the neuroaxis (106).

Ischemia in either the anterior or posterior wall of the left ventricle is transduced by both dorsal root and nodose ganglion afferent neurons (17, 74, 76, 138). Bradycardia occurs when sufficient populations of nodose ganglion cardiac afferent neurons transducing such an event activate parasympathetic motor neurons (2, 80). Ischemia-induced excitation of dorsal root ganglion afferent reflexes rapidly activates sympathetic efferent neurons innervating the heart and systemic vasculature (8, 97) to initiate arterial hypertension (133). Regional myocardial ischemia can also influence ascending spinal cord pathways to affect medullary cardiomotor neurons (2), yet another cardiocardiac reflex. Given the multiplicity of these reflexes, it is difficult to sustain the thesis that select heart rate changes can be ascribed to reflexes initiated from a specific left ventricular region. Rather, anatomical (69) and functional (17, 74, 138) data indicate that central reflexes initiated by regional ventricular ischemia induce regionally specific or global (cardiac and systemic vasculature) effects depending on how that event is transduced throughout the entire cardiac neuroaxis (21, 106). How these reflexes act to stabilize or destabilize cardiac control in the presence of altered baroreceptor sensitivity (152) remains unknown.

Ischemia-induced intrathoracic reflexes. Compromised regional coronary arterial blood flow can affect intrinsic cardiac neuronal function and initiate intrathoracic reflexes.

DIRECT ISCHEMIA EFFECTS. Somata of intrinsic cardiac neurons perfused by a coronary artery that is involved in an obstructive process may undergo pathological change over time (70) such that their function becomes compromised (15). Regional ventricular ischemia can also induce regional nerve terminal sprouting (40) or pathology (38), the latter resulting in loss of local sensory (102) and motor (64, 100) neurite function. On the other hand, the viability of nerves coursing over a transmural ventricular infarction remains unimpaired by that state as major intrinsic cardiac nerves are accompanied by their own rich blood supply arising from extracardiac sources (79).

INDIRECT ISCHEMIA EFFECTS. Chemicals such as purinergic agents (123), peptides (65), and hydroxyl radicals (78, 142, 143) liberated in increasing quantities from the ischemic myocardium modify local cardiac sensory neurite function (17, 29, 78, 97, 140). Many cardiac afferent neurons are further affected on restoration of the arterial blood supply to their sensory neurites during early reperfusion (19, 25, 54). Presumably that is when the greatest concentration of locally accumulated metabolites becomes available to affect their sensory neurites. The various ischemia-induced reflexes so initiated modulate not only cardionamics (15), but also regional coronary arterial blood flow (83, 141).

Symptomatology. Regional ventricular ischemia excites many cardiac afferent neurons maximally (17, 33, 74, 78, 121, 140). Current information indicates that symptoms associated with myocardial ischemia depend to a considerable extent on the capacity of afferent neuron P1-purinoceptors to transduce such an event (135). That their capacity to transduce myocardial ischemia becomes blunted in the presence of adenosine receptor blockade (76, 139) lends support to that contention. Peptides liberated from the ischemic myocardium reportedly play a supportive role in the genesis of such symptoms (57).

Cardiac failure. Central (51, 152) and peripheral (26, 136) processing of cardiovascular sensory inputs undergo remodeling during the evolution of heart failure (126). Arterial baroreflexes become blunted (152). Heart failure is associated with increased circulating levels of catecholamines due to global enhancement of sympathetic efferent neuronal tone (43). It has been reported that chronic activation of adrenergic efferent neurons attending heart failure downregulates cardiac myocyte β-adrenoceptor function such that their responsiveness to adrenergic agonist becomes obtunded (32). Thus far heart failure therapy involving adrenergic receptor blockade has been considered in terms of cardiomyocyte β-adrenoceptor modulation (32) and afterload reduction (49).

It is now evident that β-adrenergic or angiotensin receptor blockade also target select populations of intrathoracic cardiac neurons (12, 50, 136). Despite a reduction of ventricular norepinephrine content in canine models of heart failure, adrenergic efferent neurons when activated liberate sufficient amounts of catecholamines into the myocardial interstitium (136) to enhance ventricular contractility (36). That is due, in part, to retention of cardiomyocyte cell surface β-adrenoceptor function in such a state (89). Not only do cardiomyocytes possess β-adrenoceptors (32), so do intrathoracic neurons (12). The latter are also sensitive to angiotensin II (71). That β-adrenoceptor or angiotensin II receptor blockade affects neurons within the intrathoracic nervous system indicates that these therapies share a common target (12, 71). For instance, angio-
tensin II receptor blockade reduces sympathetic efferent neuronal inputs to the SA node and ventricles (71), accounting in part for the concomitant fall in heart rate and blood pressure attending such therapy. These therapies minimize remodeling that the cardiac neuronal hierarchy undergoes during the evolution of heart failure as well (136).

**Cardiac Arrhythmias: Rate vs. Rhythm Control**

Neurons from the level of the insular cortex (107) to the intrinsic cardiac nervous system (77) can be involved in the genesis of cardiac arrhythmias (35, 37, 62, 77, 125, 127, 151). Select populations of extracardiac sympathetic and parasympathetic efferent neurons, when maximally activated, initiate atrial (95, 118, 125) or ventricular (35) arrhythmias. In accord with that, ventricular fibrillation can occur when sufficient populations of intrinsic cardiac neurons are activated by, for instance, locally applied neurochemicals such as adrenoceptor agonists, angiotensin II, or endothelin I (13, 14). From a therapeutic standpoint, it may be relevant that the enhancement of intrinsic cardiac neuronal activity secondary to their transduction of an ischemic myocardium can be overcome by increasing their spinal cord neuronal inputs (93). Thus the harmful consequences that activating large populations of intrinsic cardiac neurons consequent to their transducing regional ventricular ischemia may be amenable to therapy.

**Rate control.** Activating select populations of intrinsic cardiac cholinergic efferent neurons that innervate either the SA or AV node can suppress heart rate or AV nodal transmission, respectively. Although it has been reported that neurons in the right atrial ganglionated plexus project solely to the adjacent SA node, whereas those in the inferior vena cava–inferior atrial ganglionated plexus project solely to the adjacent AV node (42, 58, 68, 150), cholinergic efferent neurons that control SA nodal or AV nodal function are located throughout the intrinsic cardiac nervous system (149). Thus AV nodal conduction delay can be induced to stabilize ventricular rate in the presence of atrial tachydysrhythmias by activating not only neurons in right atrial ganglionated plexuses (1, 150), but those in others as well. Focal electrical stimuli delivered to loci within an intrinsic cardiac ganglionated plexus activate adjacent somata as well as afferent and efferent axons of passage (34), whereas locally applied chemicals affect adjacent somata (149). That, along with the fact that local circuit neurons throughout the intrinsic cardiac nervous system are in constant communication (116), presumably accounts for the varied cardiac responses elicited among subjects by such interventions.

**Rhythm control.** Atrial or ventricular arrhythmias can be elicited when select populations of intrinsic cardiac neurons become activated excessively (77); depending on the population of neurons involved, these can degenerate into fibrillation (13, 14). Thus removal of select neuronal elements responsible for such events may be contemplated for rhythm control (37). By ablating somata rather than axons of passage, long-term results can be contemplated as axons rapidly reinnervate distal cardiac tissues after their sectioning (104). The functional interconnectivity displayed among atrial and ventricular neurons makes it likely that ablating or stimulating a locus within one intrinsic cardiac ganglionated plexus or, for that matter, an entire intrinsic cardiac ganglionated plexus, will lead to variable and even unexpected results among individuals (146). In that regard, it should be recalled that activating select intrathoracic neuronal elements can also elicit atrial or ventricular arrhythmias (14, 35, 62, 77, 125). By targeting somata at major centrifugal and centripetal convergence points, nexus points within this hierarchy (Fig. 3), perhaps more predictable and long-term results will accrue (112).

**Perspectives**

The cardiac nervous system is made up of spatially distributed collections of neurons displaying tightly coupled or stochastic behavior that is predicated to a considerable extent on whether they transduce the regional mechanical or chemical milieu. The transduction of alterations in the cardiac chemical milieu throughout the entire cardiac neuronal hierarchy occurs for the most part in a stochastic manner (82). Transduction of regional cardiovascular mechanical events occurs with fidelity by fewer afferent neurons in the genesis of phase-related behavior displayed by some cardiac motor neurons. Given the centrifugal and centripetal transduction of information within its periphery, a far richer picture is emerging concerning the capacity of the cardiac neuronal hierarchy to regulate cardio-dynamics on a beat-to-beat basis than has been considered heretofore. Targeting points of its redundancy rather than its nexus points may exert minor impact on the overall function of this hierarchy or produce unpredicted results. The relevance of understanding its interactive linkages and how they remodel during the evolution of cardiac disease may be key to successfully targeting its select components to retard disease progression.

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