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The little brain on the heart

The function of the cardiovascular neuronal hierarchy is ultimately to match cardiac output to regional body blood flow demands. To comprehend how the varied elements of this hierarchy interact to accomplish this task, we must determine how its peripheral (intrathoracic and cervical ganglion) and central neurons communicate on an ongoing basis in the coordination of regional cardiac indices.[1]

The cardiac neuronal hierarchy can be represented as a massively parallel and, for the most part, stochastic control system such that stable cardiac control generally occurs in the absence of obvious cause and effect **(see sidebar below)**. Its peripheral neuronal interactions display emergent properties, functioning as they normally do in a highly optimized fashion to tolerate normal cardiac perturbations.

From a clinical perspective, excessive activation of select elements within the cardiac neuronal hierarchy has been thought to result in the genesis of atrial[2] or ventricular[3] arrhythmias. Indeed, the functional interconnectivity of the various neurons in the hierarchy is so organized that the whole can be catastrophically disabled by cascading failures initiated by relatively minor abnormal inputs. Defining the function of each of its populations may be required to understand how, for instance, excessive activation of select elements initiates cardiac arrhythmias. Such an understanding is required if one is to manage this state from a neurocardiological perspective.

This brief review presents the anatomy and function of this hierarchy's afferent and efferent neurons and discusses the putative interactions that occur among its neuronal populations.

The cardiac neuronal hierarchy

The cardiac neuronal hierarchy can be represented as a massively parallel and, for the most part, stochastic control system such that stable cardiac control occurs in the absence of obvious cause and effect (ie, it displays emergent properties).

This hierarchy displays robust external behavior while matching cardiac output to whole-body blood flow demands.

Its target organ component, the "little brain on the heart," transduces centripetal and centrifugal inputs in the coordination of regional cardiac electrical and mechanical indices.

Although optimized to tolerate *normal* perturbations, the system can be catastrophically disabled by cascading failures initiated by relatively minor input changes.

What it cannot tolerate, as these are not design features, are:

- Rearrangement of its interconnecting parts
- Excessive activation of select components that engender cardiac pathology (cf, arrhythmias).

Therapeutic targeting of select components of the hierarchy should take into consideration the emergent properties of the whole.

ANATOMY

Cardiac afferent neurons

Pain associated with myocardial ischemia is frequently referred to a patient's left upper limb and/or anterior thoracic wall.[4] As a result, the somata of cardiac afferent neurons are assumed to be located primarily in left-sided, cranial thoracic dorsal root ganglia. Anatomic evidence indicates that cardiac afferent neurons are distributed relatively evenly throughout the nodose ganglia and the C7 to T4 dorsal root ganglia bilaterally.[5] They are also located in intrathoracic ganglia, including those intrinsic to the heart.[1,6]

Cardiac efferent neurons

Cholinergic neurons. The somata of parasympathetic efferent preganglionic neurons that synapse with cholinergic efferent postganglionic neurons on the heart are located primarily in the ventral lateral region of the nucleus ambiguous of the medulla;[7] fewer are found in its dorsal motor nucleus and the zone intermediate between these two medullary nuclei.[8] Cardiac preganglionic motor neurons in individual medullary loci project axons to parasympathetic efferent postganglionic neurons distributed throughout each major atrial and ventricular ganglionated plexus.[9]

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Adrenergic neurons. Cardiac sympathetic efferent preganglionic neurons in the spinal cord project axons via the T1 to T5 rami[10] to synapse with cardiac sympathetic efferent postganglionic neurons located in the cranial poles of the stellate ganglia, throughout the right and left middle and superior cervical ganglia and mediastinal ganglia adjacent to the heart.[1] They also project to adrenergic neurons in each intrinsic cardiac ganglionated plexus.

Local circuit neurons

Yet another neuronal population within the intrathoracic nervous system lies interposed between cardiac afferent and efferent neurons. These neurons can project axons to neurons not only within their individual ganglia but also to neurons distributed in other intrathoracic ganglia. Thus, they appear to function as local circuit neurons.[1] Some of these relatively large-diameter neurons (ie, up to ~30 µm) form rosettes within intrathoracic ganglia, including those on the heart, frequently arranged in the periphery of intrinsic cardiac ganglia. Their centrally projecting dendrites synapse with one another within that rosette, and thus may represent an anatomical substrate for local information processing within such ganglia. Intrathoracic neurons display immunoreactivity to various peptides and other chemical markers.[11–13] These anatomical findings indicate that intrathoracic neurons may be involved in a multiplicity of interactions in the coordination of regional cardiac motor outputs.

PHYSIOLOGY

Cardiac afferent neurons

The constantly changing cardiac milieu is transduced to neurons distributed throughout the cardiac neuroaxis via a rich variety of cardiac sensory neurons that are located in nodose, dorsal root, and intrathoracic extracardiac and intrinsic cardiac ganglia. The activity generated by the sensory neurites (nerve endings) of some neurons depends on regional cardiac or major vascular wall mechanics; others transduce the cardiac regional chemical milieu. The vast majority of cardiac afferent neurons transduce regional dynamics and/or the local chemical milieu of their neurites.[14,15] For instance, about 75% of nodose ganglion cardiac afferent neurons transduce chemical stimuli; fewer (about 35%) display mechanosensory capabilities.[14,16]

On the other hand, most dorsal root ganglion cardiac afferent neurons display multimodal (mechanical and chemical) transduction. The varied transduction capabilities displayed by these different cardiac afferent neuronal populations results in a regional specific local dynamic and chemical milieu being transduced to second-order neurons throughout the neuroaxis. The majority of cardiac sensory neurites associated with afferent neuronal somata in intrathoracic extracardiac and intrinsic cardiac ganglia express multimodal properties.[14]

Apparently, the multimodal transduction capacity displayed by individual dorsal root ganglion cardiac afferent neurons permits this relatively limited population of sensory neurons to transduce multiple cardiovascular signals simultaneously to second-order neurons in the central nervous system.[14] Adenosine is released in increasing quantities by the ischemic myocardium.[17] Adenosine activates sensory neurites associated with many ischemia-sensitive cardiac afferent neuronal somata.[14] In fact, it has been proposed that purinergic dorsal root ganglion cardiac afferent neurons are involved in the genesis of ischemic ventricle symptoms.[4]

Mechanosensory neurites associated with a significant population of intrathoracic afferent neuronal somata are also present on major intrathoracic vessels, especially along the inner arch of the aorta. The latter transduce constantly changing aortic wall dynamics that occur throughout each cardiac cycle, as do carotid artery baroceptor neurons that project to nucleus solitarius neurons.[18] These data indicate that multiple populations of intrathoracic and cervical afferent neurons transduce regional vascular dynamics to second-order neurons throughout the neuroaxis, along with the different cardiac afferent neuronal populations described above.

Cardiac motor neurons

Parasympathetic efferent neurons. Medullary (parasympathetic) efferent preganglionic neurons project axons to cholinergic postganglionic neurons distributed throughout the various atrial and ventricular ganglionated plexuses. When activated, cholinergic motor neurons suppress not only atrial rate and force, but also atrioventricular nodal conduction and regional ventricular contractile force. As reflex excitation of these motor neurons involves short-latency medullary reflexes, their activity frequently equates to carotid arterial baroreceptor activity reflective of a constantly changing arterial wall dynamic.[1,18] Indeed, their capacity to influence heart rate depends to a considerable extent on when in the cardiac cycle they become excited.[19]

Sympathetic efferent neurons. Sympathetic efferent postganglionic neurons in each intrathoracic gan-

glion receive inputs from sympathetic efferent preganglionic neurons in the caudal cervical and cranial thoracic spinal cord.[10] Cardiac sympathetic efferent postganglionic neurons are also influenced by cardiac and major intrathoracic vascular sensory neurons.[1] These data indicate that adrenergic motor control of cardiac chronotropism, dromotropism, and regional inotropism ultimately depends on the integration of multiple cardiovascular sensory and central neuronal inputs within the intrathoracic neuroaxis. Intrathoracic local circuit neurons play a key role in such integration.

Local circuit neurons

Interposed between cardiac afferent and efferent neurons are local circuit neurons. Their presence permits information exchange among neurons located not only in one intrathoracic ganglion (including those intrinsic to the heart) but also among neurons in different intrathoracic ganglia.[1]

Neurons of the target organ nervous system are constantly interacting with those in intrathoracic extracardiac ganglia, as well as with central neurons, to influence cardiac motor outputs. Some intrinsic cardiac local circuit neurons even receive inputs from sympathetic and parasympathetic efferent preganglionic neurons, indicating that some neurons process inputs from both efferent limbs of the autonomic nervous system, and not necessarily in a reciprocal fashion.[1]

Intrathoracic local circuit neurons also receive indirect inputs via the spinal cord neurons derived from sensory neurites in extrathoracic tissues.[1] Thus, alterations in the extrathoracic milieu can also influence the intrinsic cardiac nervous system, doing so in an indirect manner. As neurons within the intrathoracic neuronal hierarchy interact via a host of chemicals (including acetylcholine, butyrylcholine, alpha- and beta-adrenoceptor agonists, histamine, nitric oxide donors, peptides, purinergic agents [adenosine and adenosine triphosphate], excitatory and inhibitory amino acids, and serotonin),[1] current cardiac pharmacologic therapy may influence cardiomyocyte behavior directly or indirectly via this nervous system.[1]

Recent data indicate that the target organ nervous system processes centrifugal and centrifugal inputs, doing so via many neurochemical signals. It appears that multiple inputs are required in order that the "little brain on the heart" has sufficient information to coordinate regional cardiac indices on a beat-to-beat basis.[1,20,21] The synapses involved in such cardiac motor neuron control may be targeted therapeutically with agents such as beta-adrenoceptor or angiotensin II receptor blockers. The short-latency reflexes (40 to 100 ms) so engendered apparently influence cardiac motor neurons throughout each phase of the cardiac cycle. On the other hand, the longer latency cardiocardiac reflexes (300 ms to 2 sec) involving intrathoracic extracardiac and central neurons apparently coordinate regional cardiac indices over time scales reflective of multiple cardiac cycles.[1]

POTENTIAL CLINICAL RELEVANCE OF THIS HIERARCHICAL ARRANGEMENT

The cardiac neuroaxis relies to a considerable extent on its capacity to transduce the cardiac mechanical and chemical milieu to cardiac motor neurons on a beat-to-beat basis. Centrally derived parasympathetic efferent neuronal outputs to the heart are dependent to a considerable degree on arterial baroreceptor afferent neuronal function.[18]

Cardiac sympathetic efferent neurons, in contrast, depend to a considerable extent on intrathoracic reflex modulation, thereby placing relatively little demand on central neurons in the routine maintenance of adequate cardiac output.[1,20] The multiple intrathoracic and central reflexes so engendered ultimately assure stable cardiac output during daily activity fluctuations. Understanding the integration of central and peripheral reflexes will require further experimentation.

Interactions so engendered within the peripheral nervous system appear to be optimized to tolerate normal cardiac perturbations. Presumably, the stochastic nature of these interactions results in the fact that cardiac efferent neuronal outputs rarely reflect a simplistic reciprocal (positive and negative) reflex control system **(see sidebar)**.

In contrast, the cardiac neuronal hierarchy appears to be organized in such a manner that the whole can be catastrophically disabled by cascading failures initiated by relatively minor abnormal inputs. Myocardial ischemia modifies the function of many neurons within this hierarchy, doing so in either a direct (local ischemic damage) or an indirect (altered sensory inputs) manner. When sufficient populations of cardiac efferent neurons become excessively activated as a result of such an event, cardiac arrhythmias can be initiated. Concomitant and excessive activation of cholinergic and adrenergic efferent neurons may potentially represent a predisposing factor for the genesis of atrial[2] or ventricular[3] arrhythmias.

Neurons within this hierarchy communicate via numerous receptors, including angiotensin II and beta-adrenergic receptors. Such data indicate that

synapses within this nervous system may be a target for pharmacologic therapies currently used to treat heart disease. In fact, therapy targeting such receptors may influence cardiomyocyte function not only directly, but also indirectly by modifying their autonomic efferent neuronal inputs.[1]

A fuller understanding of how the varied components within the cardiac neuroaxis interact to stabilize cardiac output is required before its individual elements can be targeted therapeutically to improve diseased cardiac status.

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