Sensory transduction of the ischemic myocardium

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REFLEX CONTROL OF cardiac function is dependent on the transduction of the sensory milieu in cardiac tissues and within major intrathoracic and cervical blood vessels. Transduction can involve mechanosensitive and/or chemosensitive inputs. Reflexes for the control of autonomic efferent outflows to the heart so engendered include the peripheral and central aspects of the cardiac nervous system. It is the interdependent reflex processing of that sensory information at the various levels of the hierarchy for cardiac control that ultimately determines the effenter outflows that modulate regional cardiac function (1).

In this issue of the American Journal of Physiology-Heart and Circulatory Physiology, the article by Fu and Longhurst (6) is a continuation of a line of investigation into the differential sensory transduction capabilities of ventricular sensory neurites whose cell bodies are contained within the dorsal root ganglia. Many of these afferents are multimodal, responding to chemical and mechanical stimulation, generating relatively low levels of activity under basal conditions (10, 11). When they are exposed to appropriate stressors, their activity is modified with induced changes in the pattern and level of activity (10, 11). This article focuses on the differential responses of ischemic-sensitive versus ischemic-insensitive sympathetic afferent neurons. The underlying hypothesis is that different mediators may affect cardiac afferent activity during ischemia-reperfusion in an interactive and multifactorial manner. Previous work from this laboratory and others has established potential roles for mediators such as bradykinin, histamine, endothelin, thromboxane A2, 5-hydroxytryptamine, reactive oxygen species, substance P, and adenosine, among others in transducing the ischemic event (3, 10–12). Importantly, specific antagonists to each of these potential mediators blunt, but may not extinguish, the myocardial ischemia-induced increase in afferent activity (4, 7, 8). Moreover, experiments using multiple chemically induced changes in sympathetic afferent neuronal activity have identified augmentative or occlusive interactions between several of these mediators (5, 7). As such, further investigations are required to unravel the activity profiles that differ ent afferent neurons generate when transducing myocardial ischemia-reperfusion.

The present article tested the hypothesis that endogenous ATP excites ventricular sympathetic afferents during ischemia via the activation of P2 receptors. The data presented support the concept that two different subtypes of P2 receptors coexist on ventricular sensory neurites, these being the P2X and P2Y subtypes. For ischemia-sensitive afferents, whereas P2 blockade abolished the response to exogenous ATP challenge, it attenuated the response of these afferents to the transient ischemia-reperfusion. For nonischemic-sensitive afferents, exogenous ATP was ineffective in modifying activity, yet exogenous bradykinin readily activated this neuronal population. Ischemic-sensitive dorsal root ganglion afferent neurons likely subserve the perception of angina in addition to their reflex effects on cardiovascular function (1, 3, 12). It is unclear as to the function of the nonischemic-sensitive afferents. These data point to the heterogeneity of afferent transduction of the ventricular milieu, even within a single population of cardiac sensory neurons in dorsal root ganglia. This diversity of transduction capability is even more pronounced when one includes the differential static and dynamic transduction characteristics of nodose and intrathoracic (extracardiac and intrinsic cardiac) afferent neurons (1, 2). Future studies should consider how second-order neurons within the central and peripheral aspects of the cardiac nervous system process this time-varying afferent neuronal input that ultimately modulates effenter autonomic activity. Similarly, future studies should consider whether the dynamic characteristics of sensory transduction of an ischemic event impacts the perception of that event (c.f., angina vs. silent ischemia).

Afferent neuronal transduction of myocardial ischemia exhibits both phasic and lower-level static activity components. Antagonists to various potential mediators discussed above preferentially influence different aspects of this time-varying afferent signal. In this article, preemptive P2 blockade attenuates the phasic component at occlusion onset, with minimal effects on the steady-state response during the later stages of the 5-min occlusion. These data indicate that ATP may preferentially affect the early phasic response. In contrast, histamine likely exerts preferential effects on afferent neuronal activity in the later stages of myocardial ischemia, while endothelin similarly affects early and late-phase afferent responses (4, 8). Such data point to the time-varying components of the afferent neuronal signals provided to processing centers within the cardiac neuronal hierarchy.

Furthermore, differential reflex responses are evoked by afferent neurons transducing events within the anterior versus posterior parts of the left ventricle. Within this study, exogenous ATP induced pressor responses in 50% of animals and depressor responses in the remaining 50%. Future studies should consider what contribution differential afferent transduction plays in these opposing hemodynamic responses. Correspondingly, the neurochemical diversity exists among cardiac afferent neurons that transduce signals from the ventricular myocardium, with horseradish peroxidase-identified ventricular neurons in T3 dorsal root ganglion staining for substance P, calcitonin gene-related peptide, or neuronal nitric oxide synthase, either alone or with two markers colocalized (9). These data indicate that cardiac sympathetic afferent neurons transduce a variety of neurochemicals. In addition, the activity profile of each affected afferent neuron during the course of myocardial ischemia-reperfusion is likely reflected in the combination of neurotransmitters released at second-order neurons.

In conclusion, the study by Lu and Longhurst (6) supports the underlying hypothesis that different mediators can affect...
cardiac afferent neuronal activity during ischemia-reperfusion in an interactive and multifactorial manner. Future studies to elucidate these interactions at the level of sensory neurites, the information content provided to second order neurons, and in the integrated reflex responses to such inputs should provide critical data for understanding not only cardiovascular control but also the perception of pain.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES