A “love triangle” elicited by electrochemistry: complex interactions among cardiac sympathetic afferent, chemo-, and baroreflexes

There are three major cardiovascular reflexes: the baroreflex, chemoreflex, and cardiac sympathetic afferent reflex (CSAR). This commentary provides a brief overview of these three reflexes and also discusses the interplay among them. In addition, it outlines the potential centrally integrative mechanisms of the input signaling from these reflexes, especially involving the regulation of sympathetic outflow in congestive heart failure (CHF) state.

CHF is a syndrome that is usually initiated by a reduction in pump function of the heart and characterized by increased sympathetic outflow, which can be measured by both plasma norepinephrine levels and direct sympathetic nerve activity recordings (20). Cardiovascular reflexes play important roles in the control of the circulation, and the three major cardiovascular reflexes include baroreflex, chemoreflex, and CSAR.

The baroreceptor reflex is a sympathoinhibitory reflex located in the aortic arch and carotid sinus. It is the primary peripheral regulator of sympathetic outflow, and inasmuch a depressed arterial baroreflex leads to an increase in sympathetic outflow. Consistent with this notion, it is now well established that the arterial baroreflex is depressed in experimental and clinical CHF (20). However, recent studies have revealed that a reduction in baroreceptor sensitivity is the consequence, but not the cause, of a reflex sympathetic excitation, because the extent of elevated plasma norepinephrine is influenced neither by arterial baroreceptor denervation nor by total cardiac denervation in dogs with pacing-induced heart failure (1, 7). The latter findings suggest that one mechanism of sympathetic overactivity in the CHF state could be attributed, at least in part, to the activation of excitatory reflexes, rather than the loss of inhibitory baroreflex only.

Accumulating evidence has shown that augmented excitatory reflexes in CHF may contribute to activation of sympathetic outflow. The chemoreflex, composed of chemoreceptors and located in the internal carotid and aortic bodies as well as the brain stem, is sympathetic-excitatory in nature. As such, it exerts powerful influences not only on breathing but also on the regulation of cardiovascular functions. The peripheral chemoreceptors respond primarily to hypoxic stimulation, whereas the central chemoreceptors are highly responsive to hypercapnia. Chemoreflex activation results in increased sympathetic activity, heart rate, blood pressure, and minute ventilation (11). However, these cardiovascular effects can be subsequently attenuated by the chemoreflex response-induced hyperventilation and increased baroreceptor input as a result of increased blood pressure (16, 17). Indeed, a majority of studies has demonstrated an enhanced sensitivity of peripheral and central chemoreflex activity in both animal models and patients with CHF, especially in the late and severe stages (4, 12). In addition, spontaneously hypertensive rats and human subjects with sleep apnea exhibit an increased chemoreflex drive, even under normoxic conditions (13, 15).

A second sympathoexcitatory reflex is the so-called CSAR, which consists of sympathetic sensory endings in the cardiac chambers and thoracic aorta. It is sensitive to both mechanical and chemical stimuli, and it is also implicated in the pathogenesis of sympathetic activation in CHF (3, 9). The activation of CSAR results in an increase in arterial pressure, heart rate, and myocardial contraction with positive-feedback characteristics. The sympathetic nerve afferent activity is markedly increased in myocardial ischemia (2). In CHF, increased oxygen consumption contributes to myocardial ischemia, which, in turn, stimulates cardiac sympathetic afferents to increase sympathetic outflow. Consistently, recent studies have shown that CSAR activity is augmented in rats and dogs with CHF (21, 22).

The cardiovascular neural regulation is likely to result from a complex interaction of central integration and peripheral inhibitory and excitatory reflexes (Fig. 1). Neurophysiological studies have identified areas of the brain stem where afferent inputs from peripheral baroreceptors, chemoreceptors, and cardiac sympathetic nerves converge, including the nucleus tractus solitarius (NTS) (10, 18). It has been reported that there is a central antagonistic interaction between the peripheral chemoreflex and arterial baroreflex under normal and disease states (14, 16). An important example is that a suppression of chemoreflex activity restores the impaired arterial baroreflex function in CHF patients (14). Recently, it has been shown that

Fig. 1. Schematic overview of the interactions among cardiac sympathetic afferent reflex (CSAR), chemoreceptor reflex, and baroreflex. Activation of chemoreceptors in carotid and aortic bodies by changes of PO2 and/or PCO2 produces an increase in sympathetic outflow to peripheral organs. This response is further augmented by mechanical or chemical stimulation of cardiac sympathetic afferents. In addition, activation of the above excitatory cardiovascular reflexes can lead to blunted inhibitory arterial baroreflex as a result of increased blood pressure (BP). Activation of ANG II type 1 (AT1) receptors by ANG II in nucleus tractus solitarius (NTS) and paraventricular nucleus (PVN) may play a major role in these reflex interactions and result in increased sympathetic outflow. In contrast, AT1-receptor blockade by its selective antagonist losartan can restore arterial baroreflex as well as reverse the enhanced peripheral chemoreflex induced by CSAR activation. Nitric oxide (NO) may also act as a central sympathoinhibitory molecule to decrease sympathetic outflow.
stimulation of CSAR inhibits baroreceptor reflex in normal rats, whereas epicardial application of local anesthetic lidocaine reverse the blunted baroreceptor reflex in rats with heart failure (6). Despite the above findings, little information is known regarding the interactions between CSAR and the chemoreflex in either normal or heart failure state.

In this issue of Journal of Applied Physiology, Gao et al. (5) address for the first time the association between CSAR and the peripheral chemoreflex sensitivity in anesthetized normal rats. Activation of carotid chemoreceptors by a bolus injection of potassium cyanide or nicotine into the right internal carotid artery produced a dose-dependent pressor response in mean arterial pressure and an increase in renal sympathetic nerve activity. Importantly, these responses are selectively augmented following epicardial administration of capsaicin that activates CSAR, suggesting that stimulation of CSAR activates the chemoreceptor reflex. This notion is further supported by the similar effects induced by the electrical stimulation of the central end of the left cardiac sympathetic afferents.

To explore the regulatory mechanisms underlying the interaction of the two reflexes, the authors also examined the involvements of NTS, a well-known integrator and mediator from the peripheral to the central site, as well as the AT1 receptors of ANG II. The NTS, a well-known integrator and mediator from the peripheral to the central end of the left cardiac sympathetic afferents.

The important findings here are that microinjection of the selective AT1-receptor antagonist losartan into NTS abolished both capsaicin-induced activation of peripheral chemoreflex in response to nicotine and electrical stimulation of CSAR. These results strongly suggest that ANG II in the NTS plays a critical role for the interaction of CSAR and the peripheral chemoreflex. Together, the study by Gao et al. provides both new evidence and novel insights of the interactions between CSAR and the chemoreflex (Fig. 1).

ANG II has been shown to modulate the central sympathetic function in CHF. For instance, AT1-receptor blockade has been shown to rescue arterial baroreflex function, normalize CSAR sensitivity, and reverse the enhanced peripheral chemoreflex function in animal models of pacing-induced heart failure (6, 8). Future studies on whether similar interactions exist between CSAR and the chemoreflex in CHF are both clearly warranted and of critical importance. In addition, ANG II-induced central mediator effects may not only be limited in NTS. The paraventricular nucleus could also be part of the integration process, where ANG II concentrations and AT1-receptor mRNA and protein levels are known to be increased in heart failure that could account for the enhanced CSAR under the same circumstance (20, 21). Furthermore, it is well established that nitric oxide (NO) acts as a central sympathoinhibitory molecule (23). Because NO bioavailability is decreased under various chronic cardiovascular disease conditions, including CHF, it is also worthy to determine whether reduced NO contributes to the enhanced arterial chemoreflex under such conditions.

GRANTS

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