A “love triangle” elicited by electrochemistry: complex interactions among cardiac sympathetic afferent, chemore-, 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 reflexes (i.e., a depression in 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-excitative 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 whereafferent 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
stimulation of CSAR inhibits baroreceptor reflex in normal rats, whereas epicardial application of local anesthetic lidocaine reverse the blunt 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 chemoreceptor reflex in CHF. For instance, AT1-receptor blockade has been shown to rescue arterial baroreflex function, normalize CSAR function in CHF. For instance, AT1-receptor antagonist losartan into NTS abolished both capsaicin-induced activation of peripheral chemoreflex in response to nicotine and electrical stimulation of CSAR. This 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

A. F. Chen’s laboratory is supported by National Institutes of Health R01 GM-077352 and American Heart Association (AHA) Grant-in-Aid 0655642Z. Y.-H. Du is the receipt of AHA Midwest Postdoctoral Fellowship 062571OZ.

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