Invited Editorial on “Femoral arterial injection of adenosine in humans elevates MSNA via central but not peripheral mechanisms”

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THE EXERCISE PRESSOR REFLEX (8) is widely believed to make an important contribution to the cardiovascular and respiratory responses evoked by exercise. Much is known about this reflex. For example, its afferent limb is composed of group III afferents, the axons of which are thinly myelinated, as well as of group IV afferents, the axons of which are unmyelinated (6). Moreover, the axons of these thin-fiber muscle afferents terminate in laminae I and V of the dorsal horn of the spinal cord, a site where they project to several brain stem neural pools, the activation or inhibition of which increases sympathetic tone, decreases parasympathetic tone, increases breathing, and relaxes airway smooth muscle (4).

Despite this knowledge, little information is available concerning the stimuli initiating and maintaining the exercise pressor reflex. Many investigators believe that these stimuli are metabolic in nature, because the afferent limb of the exercise pressor reflex arc signals the spinal cord and brain stem that blood and/or oxygen supply is not meeting the metabolic demands of the exercising muscles. The consequence of this mismatch between blood supply and demand in the working muscle is thought to be the generation and accumulation of some “ischemic metabolite” capable of increasing the discharge of thin fiber (i.e., group III and IV) muscle afferents. The responses arising from the stimulation of these afferents have been called “the muscle chemoreflex” (10).

Many different substances, including bradykinin, potassium, lactic acid, and prostaglandins, have been proposed to be the ischemic metabolite. One which has generated controversy has been adenosine. This substance is produced when skeletal muscle is ischemic (1) and has been shown to stimulate both peripheral chemoreceptors (7) and, possibly, sympathetic cardiac afferents (3). Part of the usual approach to test the hypothesis that a particular substance functions as an ischemic metabolite is to inject it into the arterial supply of the limb skeletal muscles while one measures arterial blood pressure, ventilation, and/or sympathetic nerve discharge. It is reasonable to expect that if the substance under scrutiny is an ischemic metabolite then its injection into the vasculature of muscle would evoke a pattern of responses similar, if not identical, to those evoked by the muscle chemoreflex (10).

This approach has been taken for adenosine and, as stated above, has generated considerable controversy. For example, in anesthetized animals, injection of adenosine into the arterial supply of hindlimb skeletal muscle neither evoked a pressor reflex (12) nor stimulated to any great extent group III and IV afferents (9). In conscious humans, however, injection of adenosine into the brachial artery increased heart rate, muscle sympathetic nerve activity (MSNA), and arterial pressure. In these human experiments, the venous outflow from the arm was thought to be occluded, thereby preventing the injectate from circulating to other vascular beds. The increases in mean arterial pressure, heart rate, and MSNA evoked by adenosine in these experiments were attributed to the muscle chemoreflex (2).

After reviewing these findings, MacLean et al. (5) had two concerns. First, the onset of the autonomic responses to intra-arterial injection of adenosine seemed too long (i.e., ~15–20 s) to be attributable to the stimulation of group III and IV muscle afferents. Second, the role of baroreceptor unloading in causing the responses to adenosine injection was uncertain. In their paper in this month's issue of the Journal of Applied Physiology, MacLean et al. offer an alternative explanation for the hypothesis that adenosine evokes the muscle chemoreflex. This explanation is based on their findings that intravenous phenylephrine infusion attenuated by one-half the autonomic responses to femoral arterial injection of adenosine and that inflation of a leg cuff to 220 mmHg abolished the responses to adenosine injection. The former maneuver was found to prevent baroreceptor unloading, and the latter prevented circulation of adenosine, which was injected distal to the leg cuff, to other vascular beds, such as those perfusing the arterial chemoreceptors.

Two possible concerns about the finding by MacLean et al. (5) come to mind. First, during circulatory arrest, which MacLean et al. achieved by inflating a cuff placed around the leg to 220 mmHg, perhaps the adenosine, injected into the femoral artery, never reached the endings of the thin fiber muscle afferents. This possibility appears unlikely because intra-arterial injections through a syringe are done under high pressure. The second concern involves the authors' use of phenylephrine infusion to prevent baroreceptor unloading, which, in turn, was caused by an adenosine-induced drop in...
diastolic blood pressure. Was it possible that phenylephrine, an \(\alpha\)-adrenergic agonist, prevented group III and IV afferents from responding to adenosine? Presently, there is no evidence to support this possibility. The only known chemical effect of phenylephrine on sensory nerves is to inhibit arterial chemoreceptor discharge (11). This effect might have combined with the maintenance of diastolic pressure by phenylephrine to counter the circulating effects of adenosine.

The findings by MacLean et al. (5) are striking and cast doubt that adenosine is capable of evoking a muscle chemoreflex. If a substance is an ischemic metabolite capable of signaling the spinal cord that blood supply and demand in exercising muscle are mismatched, then exogenous injection of this substance should be able to evoke the muscle chemoreflex. This does not appear to be the case for adenosine but certainly is the case for substances such as bradykinin, lactic acid, and potassium (4). On the other hand, the finding by Costa and Biaggioni (2) that blockade of adenosine receptors with theophylline attenuated the cardiovascular and sympathetic responses to static handgrip points to a role for adenosine in evoking the muscle chemoreflex. Consequently, the present findings about the role played by adenosine in the generation of the muscle chemoreflex are conflicting. The resolution of this controversy lies in the confirmation and extension of the findings by MacLean et al. (5) and Costa and Biaggioni (2) by future investigations.

REFERENCES