Control of breathing during dynamic exercise by thin fiber muscle afferents

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THE VENTILATORY as well as the cardiovascular responses to exercise are widely believed to be evoked by two neural mechanisms. The first is a feedforward mechanism, called central command (3), which may originate in or involve the posterior hypothalamus and midbrain (4). The second is a feedback mechanism that arises from contracting muscles and has been termed the exercise pressor reflex (10). Thin fiber afferents (i.e., group III and IV) comprise the afferent limb of the exercise pressor reflex arc; these afferents are believed to respond to both mechanical and metabolic stimuli arising from the exercising muscles (7, 9). The roles played by the two neural mechanisms in causing the ventilatory and cardiovascular responses to exercise have been controversial and the subject of much debate. The general consensus appears to be that central command is primarily responsible for the ventilatory and the cardioaccelerator responses to exercise, whereas the exercise pressor reflex is primarily responsible for the sympathetically induced vasoconstrictor responses to exercise.

The concept that the ventilatory increase in response to exercise is primarily determined by central command (14) is challenged in a paper by Amman et al. (2) that appears in this issue of the Journal of Applied Physiology. Using a novel approach, Amman et al. blocked thin fiber afferent input to the spinal cord of healthy humans with intrathecal injection of fentanyl, a μ-opioid receptor agonist. Previously, thin fiber muscle afferent input to the spinal cord had been blocked by epidural injections of lidocaine, an agent that not only attenuated or abolished sensory impulse activity in the dorsal roots but also attenuated motor impulse activity in the ventral roots. The result of using lidocaine to block sensory input to the cord was that after blockade central command had to be increased to obtain the same level of muscle contraction as that before blockade; this increase in central command may have masked the effect of any lidocaine-induced attenuation of the exercise pressor reflex.

Amann et al. found that fentanyl injected intrathecally into the L3–L4 space had no effect on the ventilatory response to breathing carbon dioxide at rest. Likewise, Amann et al. found that intrathecal fentanyl injection had no significant effect either on the ventilatory and cardiovascular responses to upper body (i.e., cycling) exercise or on the levels of this synthetic opioid in the venous blood. Both findings were interpreted to mean that fentanyl did not migrate to either the medulla or the cervical spinal cord to exert its effect. In contrast, the authors found that fentanyl injection substantially attenuated the ventilatory, cardioaccelerator, and pressor responses to lower body exercise performed on a bicycle. The most interesting finding was that fentanyl substantially attenuated the ventilatory, pressor, and cardioaccelerator response to bicycle (lower body) exercise at a workload of 100 W in trained male cyclists.

Moreover, fentanyl significantly attenuated the pressor response to bicycle exercise even at 50 W. These workloads for trained cyclists placed minimal metabolic stress on the exercising muscles.

The importance of the findings by Amann et al. is that they alter our thinking about four important issues concerning the neural control of ventilatory and cardiovascular function during exercise. The first and most obvious issue is that the exercise pressor reflex plays an important role in stimulating breathing during dynamic exercise, a function previously assigned to central command (14). The second issue concerns the relatively low level of exercise needed to evoke the reflex-induced increase in ventilation, heart rate, and arterial pressure. It is difficult to conceive of these increases as being evoked by a metabolite produced by a mismatch between blood/oxygen supply and demand in working muscles. Traditionally this mismatch has been thought to trigger the exercise pressor reflex. If a muscle metabolite produced by a mismatch is not the sole trigger, then what other stimuli fulfill this purpose? One possibility is that the afferents are stimulated by mechanical distortion of their receptive fields, which is caused by the shortening and lengthening of the dynamically contracting muscle (1, 7, 11, 12). Another possibility is that the afferents are stimulated by vascular distension produced, in turn, by an increase in arterial blood flow to the exercising muscles (5, 6). A final possibility is that the afferents are responding to a contraction-induced metabolite that is not generated by a mismatch between blood/oxygen supply and demand (8).

The third issue concerns redundant control mechanisms. Sometimes removing or decreasing the strength of one neural mechanism has been reported to have no effect on the output being measured. This lack of effect has been attributed to redundancy in the system that compensates for the removal of one mechanism by increasing the impact of another. The findings of Amann et al. do not support the concept of redundancy with regard to the control of ventilatory and cardiovascular function during dynamic exercise, and instead point to the important contribution of thin fiber muscle afferents to these responses.

A fourth and final issue needs to be considered. Traditionally, the exercise pressor reflex and central command have been considered separate mechanisms that do not interact with each other within the brain stem. Suppose that this is not the case. Instead, suppose that thin fiber muscle afferents input onto posterior hypothalamic and midbrain neurons evoking the central command for autonomic and ventilatory output. If this was found to be true, and there is evidence in support of this concept (13), then blocking thin fiber afferent input with fentanyl might also reduce both the central command for autonomic and ventilatory output as well as the reflex. Consequently, the possibility exists that thin fiber muscle afferent input during exercise amplifies the central command controlling autonomic and ventilatory function, and that the removal of this afferent input, such as that done by Amann et al., decreases both neural mechanisms.
Conventional wisdom stated that the thin fiber afferents’ only function was to signal the spinal cord and brain stem that perfusion of exercising muscle was not adequate to meet its metabolic needs. Conventional wisdom further stated that the exercise pressor reflex played a major role in the control of the sympathetic outflow to the vasculature but played little, if any, role in the control of ventilation. The impact of the findings presented by Amann et al. is that they cause us to reconsider the role played by thin fiber muscle afferents in evoking the ventilatory and cardiovascular responses to exercise. Although there is no doubt that thin fiber afferents provide an error signal about muscle perfusion to the spinal cord and brain stem, the evidence presented by Amann et al. indicates that these afferents may also play an important role in increasing ventilation, heart rate, and arterial blood pressure at low levels of dynamic exercise when the metabolic demand of the working muscles is not large. More investigation is needed about the nature of the stimuli discharging group III and IV muscle afferents during low levels of exercise when there is no mismatch between blood/oxygen supply and demand in the working muscles.

DISCLOSURES

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

REFERENCES