Point:Counterpoint: Supraspinal locomotor centers do/do not contribute significantly to the hyperpnea of dynamic exercise

PURPOSE AND SCOPE OF THE POINT: COUNTERPOINT DEBATES

This series of debates was initiated for the Journal of Applied Physiology because we believe an important means of searching for truth is through debate where contradictory viewpoints are put forward. This dialectic process whereby a thesis is advanced, then opposed by an antithesis, with a synthesis subsequently arrived at, is a powerful and often entertaining method for gaining knowledge and for understanding the source of a controversy.

Before reading these Point:Counterpoint manuscripts or preparing a brief commentary on their content (see below for instructions), the reader should understand that authors on each side of the debate are expected to advance a polarized viewpoint and to select the most convincing data to support their position. This approach differs markedly from the review article where the reader expects the author to present balanced coverage of the topic. Each of the authors has been strictly limited in the lengths of both the manuscript (1200 words) and the rebuttal (400). The number of references to publications is also limited to 30, and citation of unpublished findings is prohibited.

POINT

Breathing and cardiovascular function during exercise are well known to be tightly correlated with the intensity of exercise (9, 13, 24). This association is absolutely required to provide an increased uptake and delivery of oxygen to active muscles and for removal of metabolites produced during exercise. It is clear that the mechanism(s) responsible for the exquisite control of breathing during exercise involves signals and/or drive indicative of the level of muscular activation.

Two major mechanisms have been proposed for regulation of breathing and cardiovascular function during exercise (13, 24). A first mechanism consists of feedback to respiratory centers that is triggered by stimuli associated with the physical activity. Possible triggers for this mechanism include changes in muscle tension, pH, lactate, or potassium ions (13). Recently, it is been proposed that the stimulus could be “plethysmometric” in nature associated with the volume of blood in vascular spaces in active skeletal muscles (10). A second type of control mechanism consists of a central feedforward mechanism (central command), which simultaneously provides drive to locomotor circuits as well as appropriate input to cardiorespiratory centers (24). This coactivation results in adjustments in breathing and cardiovascular activity related to the intensity of the motor activity.

Strong support exists for both mechanisms and it is likely that both are engaged during normal exercise. However, central command appears to be the more dominant mechanism based on both direct and indirect evidence. Both animal and human studies have clearly shown that descending drive from supraspinal areas can elicit increases in cardiorespiratory function correlated with the intensity of exercise (24).

Attention has been focused on identifying regions that appear to provide drive to both spinal locomotor circuits and to cardiorespiratory control areas in the brain stem. The best characterized locomotor areas that provide descending drive to spinal locomotor circuits are located in the hypothalamus and in the mesencephalon (21, 24). Early work demonstrated that activation of these brain sites elicits coordinated locomotion in lightly anesthetized and in decorticate animals (21). A number of laboratories have explored the possibility that these well-known supraspinal locomotor centers also provide parallel drive to respiratory and cardiovascular control regions. Electrical stimulation of this region produces locomotion, which is accompanied by increases in breathing, blood pressure, heart rate, and a redistribution of organ blood flows consistent with...
exercise (9, 24, 25). Cardiovascular and respiratory (phrenic nerve activity) responses persist after paralysis, demonstrating that feedback from contracting muscles is not the cause (9). Additional studies have shown that activation of cell bodies alone in the hypothalamic locomotor region is sufficient for this cardiorespiratory and locomotor activation (23).

Connections between these locomotor regions and areas in the midbrain and brain stem known to be involved in cardiorespiratory and locomotor regulation have been elucidated. In the case of locomotor control, there are extensive interconnections of these areas (3). The hypothalamic locomotor region receives input from many regions, including areas of the cortex and the cerebellum (5, 24). In addition, there are extensive projections from this region to cardiorespiratory control regions in the midbrain and medulla (1, 20). In a double-virus tracing study, single neurons have been identified that have polysynaptic projections to areas involved in central motor control and to areas affecting sympathetic outflow to the heart (15). Such neurons were located in an area of the hypothalamus consistent with the hypothalamic locomotor region. Thus clear evidence exists for the appropriate neuronal connections needed for the hypothalamic locomotor region to be involved in both locomotor and cardiorespiratory regulation.

Interactions exist between descending central drive provoked by activation of supraspinal locomotor regions and peripheral feedback elicited by contraction of skeletal muscles during exercise. For example, neurons in the hypothalamic locomotor region increase their discharge rate when muscular contraction is elicited (27). Moreover, a presumed neural occlusion occurs when activation of locomotor centers and feedback from contracting muscles are evoked simultaneously (26). It is likely that this results from an inhibition of neurons in the ventrolateral medulla or in the dorsal horn of the spinal cord by descending central command from locomotor centers (8, 18).

Additional support for the involvement of locomotor regions in regulation of the cardiorespiratory systems during exercise is provided by the effects of locomotor stimulation on baroreceptor-evoked responses. Exercise is well known to induce a resetting of the baroreceptor reflex. Activation of locomotor regions has been shown to alter both the respiratory and cardiovascular responses to baroreceptor stimulation, an effect that is likely due to an activation of neurons in the nucleus of the solitary tract (2, 7, 16).

Available evidence suggests that operationally defined locomotor areas play a role in actual exercise. Numerous studies have demonstrated that blood flow to brain areas involved in motor activation is enhanced during exercise (6, 24, 29). Our laboratory has used c-fos labeling as an indication of brain activation in conscious rats running on a treadmill (12). In addition to known cardiorespiratory control areas in the medulla, increased activity was observed in both the hypothalamic and mesencephalic locomotor regions. In a subsequent study, it was shown that there is a reduced activation of these areas in trained rats (11). This finding is consistent with a reduction in effort required after training to perform the same work load. A recent study from our group provided evidence that training evokes an attenuation of dendritic arborizations in the hypothalamic locomotor region and other areas associated with cardiovascular and locomotor control (17). This training-induced effect may also relate to the reduction in arterial pressure and the decreased discharge rate of posterior hypothalamic neurons that occurs in hypertensive rats after exercise training (4, 14).

A limitation of both the animal and human studies described above is that activation of motor areas in the brain during the exercise could have been due to either central drive or peripheral feedback from the muscles active during exercise. However, this central activation has been shown to not be dependent on feedback from contracting muscles. For example, Nowak et al. (19) used positron emission tomography and oxygen-15-labeled water to examine brain activation patterns during handgrip exercise and in attempted handgrip exercise after regional anesthesia in humans. Several brain areas associated with motor activity displayed increased activation during both rhythmic handgrip exercise and after attempted handgrip following axillary blockade. Thornton et al. (22) used positive emission tomography to examine brain areas activated during imagined exercise under hypnosis. When the hypnotized subjects were asked to imagine themselves exercising on a bicycle, hyperventilation and increases in heart rate were observed. In addition, several motor areas of the brain were activated. It has also been demonstrated that blood flow increases to cortical areas, and heart rate and blood pressure increase in hypnotized human subjects who are instructed to imagine performance of static handgrip exercise (28). This imagined handgrip activity was not accompanied by force production.

The ultimate control of breathing and autonomic function during exercise must involve a variety of drives including both central command and feedback related to the intensity of exercise. Although arguments can be made as to the primary drive during exercise, it is very difficult to design an experiment that would definitively settle this question. Yamamoto (30) in 1977 very articulately described this situation by stating that “you may have sufficient mechanisms, each of which in a given, isolated circumstance explains the whole phenomenon. When they act simultaneously, they mask each other.” We would be wise to heed this advice today.

REFERENCES


term potentiation (STP) (25), applies to physiological conditions in mammals, and more importantly in humans, the amplitude of the ventilatory response to exercise should be proportional to the magnitude of the motor or locomotor response. This is in total contradiction with so many examples, because the original publications of Dejours, Kao, or Grodins (7, 15, 17, 18), which have shown that the ventilatory response to a constant work rate exercise is fundamentally dissociated from any central mechanisms controlling the motor component of a dynamic exercise, but appears to be coupled to the level of metabolic rate (2, 3, 5, 8, 28). One of the most “spectacular” illustrations of this idea has been obtained by showing that the motor control of the respiratory muscles can be separated from the control of skeletal muscles during actual exercise. Indeed, the amplitude of the $V_e$ response of subjects exercising on a cycloergometer with sinusoidal changes in work rate (WR) (4) decreases dramatically when the WR oscillation periods decrease, following the expected dynamics of the gas exchange.
response, despite a constant WR amplitude. Similar results have been found in walking sheep (16): when the speed of a treadmill is oscillated with a sinusoidal pattern, the frequency and amplitude of limb movements remains constant, reflecting the constancy of the amplitude of the output signal controlling locomotion, whatever the period of oscillations (at least for period between 10 and 1 min). In contrast, the ventilatory response decreases by >70% when the oscillation period is reduced to 1 min (Fig. 1), the response being almost out of phase. Such a dynamic response is in total disagreement with the very fast kinetics of the phrenic response to SLC stimulation (even associated to a putative STP) (12), as illustrated by most of the original phrenic nerve recordings (10). These results show that the motor acts of walking and breathing cannot be activated in a “parallel or proportional manner during exercise” because for the same activation of locomotion, the level of ventilation can change by a factor of four being predominantly dictated by a (still debated) mechanism proportional to the gas exchange rate (28).

The concept of central command relies on an assumption based on conclusions obtained in decoricate animals during SLC stimulation. Here are two series of examples showing that crucial pieces of information are cruelly missing before being able to apply this idea to the ventilatory response to muscular exercise.

First, is a key role for subthalamic (vs. spinal or bulbar) structures as a controller of “physiological” walking really established? The answer is no (see Refs. 1, 6, 13, 14, 19 for discussion). In contrast to results obtained in anesthetized preparations, the destruction of the hypothalamic locomotor regions in freely moving animals does not support the idea that these supraspinal sites are essential in the responses to walking, as locomotion is not affected (21). This has been interpreted as being due to other structures that compensate for the loss of hypothalamic structures. Another logical explanation for this could be the lack of essential contribution of these structures during spontaneous walking! Why reject such an interpretation?

In human locomotion, the contribution of the subthalamic locomotor centers as the primary controller of locomotion is not guaranteed (9, 13, 14, 20). Finally, what evidence is there to show that the SLC are involved in other types of muscular exercise than locomotion?

Second, the response triggered by SLC stimulation is not specific. In many animal preparations, the increase of breathing during locomotion appears to be independent of the site of stimulation-induced locomotion (22, 24). Thus what is really the function of the SLC during a motor activity?

In conclusion, the available data do not support the contention that the response to hypothalamic or mesencephalic locomotor center stimulation in cats resembles the ventilatory response to dynamic exercise in humans; fundamental differences exist. The inference of the response obtained in cats to exercise in “corticale” humans remains to be demonstrated. Many attempts to prove such a role in walking mammals are inconclusive or at odds with the hypothesis. The idea that “the hypothalamic locomotor region is the primary source of respiration” during exercise has never been demonstrated. So far, there is no reason to consider the subthalamic locomotor region as a significant site controlling exercise hyperpnea, and this should be considered as good news because the search for the primary mechanisms regulating breathing in exercise has to go on.

REFERENCES

27. Whipp B and Ward S. Coupling of ventilation to pulmonary gas exchange during exercise. In: Exercise Pulmonary Physiology and Patho-
An examination of the counterpoint arguments reveals no strong argument against supraspinal locomotor areas being involved in exercise regulation. First, it is claimed that the respiratory response to activation of locomotor centers is different than what is observed during spontaneous exercise. A careful examination of the original papers by Eldridge et al.(1) shows that the respiratory response evoked by stimulation of locomotor regions does appear exceedingly similar to what is observed in a spontaneous burst of locomotor activity in the cat (compare Figs. 6 and 7 in Ref. 1).

It is then postulated that the “motor control of the respiratory muscles can be separated from the control of the skeletal muscles during actual exercise.” As noted in our “point” statements, one can design experiments that can demonstrate the existence of any mechanism. However, this does not indicate that this “artificial situation” is what is present during actual exercise. In addition, in work from Haouzi’s laboratory, studies were done in sheep, which are not a good model for studying exercise regulation (2). A close reading of this paper indicates that it was necessary to exclude periods of data due to “betching and regurgitation” and that the animals had to be studied under fasting conditions.

Final arguments against a role of locomotor regions in exercise hyperpnea offered by Haouzi involve a study using hypothalamic lesions. Ordway et al. (7) reported that the cardiovascular response to exercise is not altered in beagles after lesions placed in the hypothalamic locomotor region. This does not rule out a role of this region in exercise regulation. As noted, there are several locomotor regions in the brain and loss of one does not mean the overall control would be lost (8). In addition, it is likely the entire hypothalamic locomotor region was not destroyed by the lesions produced. Our most recent studies (4, 5) using Fos labeling indicate that the active areas are more extensive than the areas of the lesions shown by Ordway et al. (7). Finally, studies reported by Hobbs (3) and by Rushmer (6) claim that bilateral hypothalamic lesions prevent the cardiovascular responses to exercise in some primates and dogs.

As noted in our “point” paper, both central command from locomotor regions and feedback associated with local muscular activity provide drive for control of ventilation during exercise. To argue otherwise does not show an understanding of decades of research or fundamentals of the central nervous system.

REFERENCES

REBUTTAL FROM DR. HAOUZI

Waldrop and Iwamoto are providing a great deal of indirect evidence (1, 7) to suggest that the subthalamic locomotor centers (SLC) and discrete cortical area (which incidentally are not locomotor centers) contribute significantly to the ventilatory response to exercise (4, 8). Not only can’t such indirect evidence constitute a demonstration but the direct proofs that refute this conjecture have been disregarded.

How can we account for the observation that the major part of the ventilatory response to sinusoidal exercise in humans (3) or in sheep (5) disappears (for the same amplitude of motor or locomotor activation) by simply decreasing the oscillations in metabolic or gas exchange rate? What about all the literature on ventilatory kinetics that has shown that ventilation closely follows factors related to gas exchange and is not dictated by (and is profoundly dissociated from) motor control during most forms of exercise, including walking, running, and cycling (using constant, ramp, sinusoidal, or impulse exercise) (2, 9). Why ignore the observations that ventilatory phases I and II are virtually abolished in patients with peripheral vascular disease (6) after a blunted gas exchange rise, despite an intact locomotor response?

In these observations, the locomotor and motor control systems are left intact and free to operate, and yet the respiratory control system selects a strategy that constrains ventilation to follow information related to the gas exchange rate (through unclear mechanisms, I must confess) and to “neglect” the others (the ventilatory response is absent despite a normal locomotor response (3, 5))? These data point to PaCO2 homeostasis as the main “goal” of the ventilatory response to exercise, a result impossible to achieve relying on motor or locomotor related information. Again, this does not imply that in specific conditions, which still remain to be determined, SLC cannot affect ventilation (e.g., escaping from danger, deep concentration), but their contribution does not appear to be a general rule at all.

Must we, in keeping with Waldrop and Iwamoto’s conclusion, accept the depressing idea that the contribution of the various ventilatory control systems proposed to account for exercise hyperpnea is by nature impossible to determine because “when they act simultaneously, they mask each other”? This will depend on our ability to design proper experiments to ultimately test, in humans, information obtained from reduced
preparations. More importantly, when data refuting this conception already exist, they should not be ignored.

REFERENCES