Turning the PAG on central control of the exercise pressor reflex in humans

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EXPERIMENTS IN BIOLOGICAL SCIENCE are often envisioned as ultimately providing rational approaches to problems confronting human health. Additionally, pragmatic solutions evoked by clinical problems often provoke new questions in basic science. Deep brain stimulation therapy in human patients with implanted electrodes (2, 4, 5) has provided an opportunity for evaluation of basic science predictions about the functional relevance of the periaqueductal gray (PAG) to the central circuits participating in the exercise pressor reflex.

The Exercise Pressor Reflex

Even modest increases in physical activity evoke coordinated cardiopulmonary responses that match oxygen and nutrient delivery to the demands of the body. In response to physical exercise or even electrical stimulation of muscle, increases occur in heart rate, blood pressure, and ventilation. These adaptations are attributed in part to groups III and IV afferents within the exercising muscles (1) that respond to either mechanical distortion (mechanoreceptor) or the presence of chemical signals related to the metabolism of the muscle (metaboreceptor). An additive contribution to the muscle driven reflex arises from the “central command” that initiates muscle contraction but also provides parallel activation of the cardiopulmonary system, even in anticipation of muscle contraction. The exercise pressor reflex is of substantial clinical relevance insofar as pathological changes in skeletal muscle metabolism and metaboreceptor responses result in exaggerated cardiopulmonary responses during exercise in patients recovering from heart failure (11) as well as following experimental myocardial infarction (MI) in animals. A variety of studies have implicated the PAG and a number of proximal regions as likely participants in the exercise pressor reflex. The PAG in particular demonstrates neural activity correlated with muscle afferent activation during the exercise pressor reflex (14).

The PAG and Antinociception

The PAG, however, is far from a monolithic structure. It is organized into at least four longitudinal columns serving roles in diverse behaviors. These include pain and analgesia, fear and anxiety, lordosis and vocalization, as well as the mediation of cardiopulmonary responses participating in exercise homeostasis or in the orienting response of the autonomic nervous system to novel stimuli (3). The early observation that electrical stimulation in the rat PAG elicits a profound analgesia (13) has been extended by maps of multiple brain regions where electrical or chemical stimulation produces antinociception. However, antinociception seldom occurs in the PAG in the absence of other behaviors and it appears improbable that a subportion of the PAG functions strictly within the context of antinociception. It has alternatively been argued that the phenomenon of antinociception is rather a permissive component of some of the diverse behaviors in which the PAG participates (9). Despite the as yet uncertain nature of PAG overall function, it remains one of the best documented and most reliable regions for stimulation-induced analgesia. As a result, intracranial stimulation of the PAG has become a significant human therapeutic alternative for patients suffering pharmacologically unresponsive intractable pain (4).

In the context of therapeutic stimulation of the PAG for antinociception (2, 5), physiological characterization of electrode placements in the PAG is a necessity, and the measurement of neuronal activity related to the exercise pressor response appears to be a particularly fruitful addition to the simple evaluation of antinociception consequent to electrical stimulation. While the PAG appears to be readily activated by muscle afferent activity evoked by exercise, one should be mindful that it is located amidst other regions that have also been experimentally related to central circuits relevant to movement and its attendant cardiopulmonary activation. Particularly relevant is the mesencephalic locomotor area, which has been loosely identified with the region of the cuneiform nucleus (laterally adjacent to the PAG) as well as cholinergic cells comprising the pedunculopontine tegmental nucleus (PPT) and neurons in the posterior hypothalamic area (6, 7, 10).

In examining local evoked potentials within the human PAG, Basnayake et al. (2) particularly focused on the exercise pressor reflex and documented correlated activation of the PAG. In an earlier report, these authors (5) also linked the PAG to the central command component of the cardiovascular response to rhythmic exercise in observing that exercise, or just the anticipation of exercise, increased heart rate, blood pressure, and ventilation in parallel with increases in PAG evoked electrical activity. Changes in the PAG were generally greater than those seen in other brain regions.

Basnayake et al. (2) have now revisited this paradigm. They again examined changes in PAG evoked electrical activity during exercise but also documented maintained activity in the PAG in the postexercise epoch when blood flow was occluded by inflation of a pressure cuff on the exercised right arm. This precludes escape of chemical signals from the muscle while maintaining activation of muscle metaboreceptors in the absence of mechanoreceptor activation. Under these conditions, increases in blood pressure were maintained as were increases in PAG evoked electrical activity. These data taken together with the previous report from the same group and the aggregate data from decades of animal experiments reinforce the importance of the PAG as part of the effector circuits mediating autonomic changes adapted to ongoing behaviors and particu-
larly in the exercise pressor reflex. It is particularly notable in the Basnayake et al. (2) report that none of the other forebrain hypothalamic, extrapyramidal, or cortical regions that they were able to monitor in patients with deep brain electrodes, evinced sustained activity correlated with the exercise-related cardiopulmonary activation that is dependent on muscle afferents.

While the coincidence of evoked activity in the PAG with the exercise pressor reflex is striking, at least some caution is in order. As the authors acknowledge, the recording sites in the human PAG were limited a priori to the electrode recording node at which antinociception was evoked. This does not preclude that periexercise or postexercise evoked activity might not be as great or greater at another nearby site. Such alternate targets, however, appear unlikely to be represented by the other regions that were measured in their alternate patients with deep brain electrodes, i.e., in subthalamic nucleus, globus pallidus, hypothalamus, and cingulate cortex.

Another caveat is the possibility that Basnayake et al. (2) underestimated the magnitude of PAG activation in some of their subjects. One might predict that the greatest activation of the PAG should occur on the side of the PAG contralateral to a unilaterally activated muscle (14). In the report by Basnayake et al. (2) the muscle task appeared to always involve activation of the right biceps while the side of the implanted electrodes in their patients varied from left to right.

The varied roles of the PAG are far from fully characterized. For example, the PAG may function both as part of an ascending sensory system relaying viscerosensory and somatosensory spinal afferents to posterior thalamus as well as acting as a descending effector system providing homeostatic feedback to cardiorespiratory systems while modulating somatosensory and pain pathways within the brain stem and spinal cord (9). As suggested above, it is likely that activities of the PAG act in parallel with the other forebrain and brain stem systems. A relevant example is the PPT, which is activated during exercise and has direct descending influences on neurons in the region of the rostral ventrolateral medulla that are potentially involved in cardiorespiratory output (10). Interestingly, nonspecific blockade of rostral PPT neurons attenuates the ventilatory responses to exercise without altering exercised-induced cardiovascular changes (12).

Over the long view, the report by Basnayake et al. (2) attests to the reproducibility and validity of the basic research examining the exercise pressor reflex and antinociception in animal experiments. It also highlights the significance of translating this basic research into applications aimed at improving the quality of life for our fellow humans afflicted with intractable pain. An alternative perspective is that understanding of human brain mechanisms participating in the cardiopulmonary systems activated by the exercise pressor reflex will pay substantial dividends in its own right. As mentioned above, exaggerated pressor reflexes compromise recovery in heart failure patients and introducing therapeutic measures to remediate these dysfunctional homeostatic responses is an ongoing area of clinical research. Moreover, it has also been reported that exaggerated exercise pressor reflexes may characterize animals with experimental hypertension (8). Insofar as hypertension is a risk factor for myocardial infarction, dysregulation of the exercise pressor reflex might be viewed as both a contributing cause and an exacerbating consequence of failure of the heart.

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