I’d like it to be true, but do group III and IV muscle afferents really contribute to the ventilatory response to exercise?

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TO THE EDITOR: The recent study of Amann et al. (1) adds further to the debate over the roles of central command, also known as feed forward, and activation of thin-fiber muscle afferents, or feedback, in controlling human ventilation during dynamic exercise. They report that following intrathecal fentanyl infusion into the lumbar spine a reduction in the ventilatory response to leg cycle exercise is seen at intensities ranging from low (50 W) to almost maximal in well-trained cyclists. In a carefully designed series of experiments they further show that the reduction in ventilation is not due to translocation of the drug within the spinal cord to the brain, where it could directly influence ventilatory control, so its effects must be mediated at the local segmental level. Crucially, they argue that as the level of integrated electromyogram (IEMG) activity recorded during cycling at all intensities of exercise was unaffected by fentanyl, the level of central command required to perform each exercise bout would also be the same with or without the drug. If this point is accepted, then the logical conclusion is that fentanyl infusion has reduced feedback from the active muscles and that this deficit in afferent feedback to the brain stem causes the reduction in the ventilatory response that is seen.

However, much as I would like to believe that muscle afferent feedback influences the ventilatory response to exercise, and there is some evidence to support this contention (5), I do not believe that the evidence provided by the experiments of Amman and coworkers should be interpreted as is.

As I understand it, fentanyl, a μ-opiate agonist, modulates neurotransmission in the dorsal horn of the spinal cord (see 6 for review), attenuating the effects of muscle afferent activation, and hence reducing feedback to control centers in the brain. I have no problems with this argument as the evidence for it is very strong. My concern is with the effect that this fentanyl-induced modulation of neurotransmission may also have on thin-fiber muscle afferent modulation of the excitability of the alpha motoneuron. This neuron can be visualized as an integrator of many excitatory and inhibitory inputs. At the segmental level there is good evidence that activation of small-diameter muscle afferents reflexly inhibits the motoneuron (see 3 for review). Indeed, this was proposed as the mechanism underpinning the “muscular wisdom” hypothesis relating to central fatigue, advanced by Bigland-Ritchie and colleagues (2, 7) and Garland et al. (4) in the 1980s. Therefore, measuring IEMG as the net output of the motor system during exercise does not provide a reliable estimate of the level of excitatory input, i.e., central command, that was required to generate this output. If fentanyl reduces the influence of inhibitory interneurons on the alpha motoneuron, then the level of descending drive required to recruit this motor unit will be correspondingly reduced. This would of course have no effect on the maximal force-generating capacity of the motor unit when fully activated. Assuming full recruitment of the motor unit pool and full activation by adequate rate coding under control conditions (easily verified by twitch or tetanus interpolation), then fentanyl could not be expected to alter maximal voluntary force-generating capacity of the muscle. This was reported to be the case in the study of Amann et al. (1). However, the removal of the inhibitory influence of thin-fiber afferents, especially those that are mechanoreceptive, could reduce the “bias” that their activation normally exerts on motor unit recruitment even at low levels of exercise. In short, central command would be less at all levels of exercise. Indeed, the subject’s perception that exercise was easier following fentanyl infusion could be taken to support this view. Therefore, applying Occam’s Razor, “the simplest explanation is more likely the correct one,” a reduced ventilatory response to exercise after drug infusion might, after all, be because central command is reduced, albeit in an effect mediated through activation of thin-fiber muscle afferents.

DISCLOSURES

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

REFERENCES