Evidence for chemicals sensitizing discharge from skeletal muscle afferents supporting cardiorespiratory reflexes during simulated exercise

Gary A. Iwamoto

Departments of Veterinary Biosciences and Molecular and Integrative Physiology and the Neuroscience Program, University of Illinois at Urbana-Champaign, Urbana, Illinois

The chemical metabolites in skeletal muscle that sensitize the activity of small-diameter afferents and support increases in cardiorespiratory function during exercise have been the subject of much investigation with a variety of methods. The chemicals that change within muscle with exercise have become better known, thanks to improved methods, but not all of these chemicals appear to contribute to these responses (9). One type of direct test is whether or not identified single unit afferent discharge is sensitized by these chemicals or diminished through use of appropriate antagonists in conditions simulating exercise. At least some of the adequacy of the evidence rests with strengths and potential weaknesses of how one models exercise while monitoring this activity. Furthermore, there are often additional implications once a substance is identified, in this case (6), through the contribution of cyclooxygenase products.

In this issue of American Journal of Physiology-Heart and Circulatory Physiology, the experiments by Hayes et al. (6) utilized an exercise model that is usually not discussed in detail in the space of a typical research paper. Mesencephalic locomotor region (MLR) stimulation to evoke locomotion in a “normal” manner is worthy of much additional comment. It is an elegant model used by those interested in studying locomotion for its own sake (7). The area stimulated, in all likelihood, represents an actual site utilized by the animal in generating a supraspinale locomotor command signal based on Fos-labeling results (7). This particular stimulus paradigm was studied in detail by Tansey and Botterman (15, 16) and Tansey et al. (17). These investigators used the simultaneous monitoring of motor neuron pairs to establish that in this specific case, the presence of this “size-related” physiological recruitment order is an undeniable fact (15). Although this recruitment order may not be true in all cases involving physical activity, certainly this idea behind the Hayes et al. (6) experiment is valid. Tansey and Botterman also established in two subsequent papers other effects using this stimulus, the motor unit firing rate modulation (16) and force modulation (17). Thus this stimulus paradigm has been well characterized from the standpoint of how motor neurons and, more particularly, motor units behave under these conditions.

There are, however, some caveats to the manner in which the stimulus was applied by Hayes et al. (6). Because this preparation relies heavily on mechanical stability (clamped in place and largely denervated), we cannot know whether feedback in addition to the output from the monitored muscle that one ordinarily gets from the exercising limb contributes significantly to the overall afferent activity. It is well accepted that that model may be used to provide “fictive locomotion” that is independent of feedback, but this feedback must exist in the normal case. Certainly, it is known that feedback from the periphery has a role to play in various types of motor activity/exercise, although the focus has primarily been on effects on motor control. Work by Bouyer and Rossignol clearly suggests that this is true for cutaneous afferents in both the intact (1) and spinal cat (2). It is also known through the work of many investigators that muscle spindle input is responsible during locomotion (12), which can have many consequences if the firing pattern does not duplicate what is seen in the normal case. This limitation of afferent input could be true in the Hayes et al. (6) case because of the fixed and partly denervated limb. Clearly, if motor control is affected, it can have consequences for afferent activity. Lest one take these points as overly negative criticism, it should be pointed out again that these measures contribute to the mechanical stability of the unparalyzed preparation in which any excessive contraction of muscle may cause movement that could compromise the recording.

The other methodological issue concerns the use of the split fiber technique from Hayes et al. (6). Although conceptually quite simple, this is difficult to achieve in practice, with the technique having a very low yield per experiment. This is especially true of the small-diameter fiber populations. A great advantage of this technique is that it is somewhat more resistant to the aforementioned mechanical disturbances of the animal’s induced locomotor activity. The use of a microelectrode requires a much higher level of stability.

The idea that cyclooxygenase products of arachidonic acid may have something to do with “normal” cardiorespiratory responses in exercise is an issue deserving closer examination. While it is true that the earlier papers on this subject that have come from the Kaufman group using static contraction (13, 14) have been highly suggestive, as pointed out by Hayes et al. (6), there are at least three reasons that the use of static muscle contraction from ventral root stimulation is not completely adequate. First, as mentioned above, the recruitment pattern is clearly not the same. Second, the discharge of the motor units in normal exercise is asynchronous, whereas electrical stimulation is not. Third, with MLR stimulation, it is thought that the problem of nociception due to tetany entering into the responses is minimized. The last, the issue of nociception entering into the stimulus under the conditions of the present experiment, is not completely obviated because the monitored limb is essentially static. Because the force levels generated with the MLR stimulus are comparatively low, this does not rise to the level of an electrically induced, sustained tetanic contraction. However, there still may be a nociceptive contribution here. Despite this, it seems undeniable that the products of cyclooxygenase are likely to have a role in circulatory

Address for reprint requests and other correspondence: G. A. Iwamoto, Dept. of Veterinary Biosciences, Univ. of Illinois at Urbana-Champaign, Urbana, IL 61802 (e-mail: iwamoto@uiuc.edu).
control in normal exercising humans. The more indirect approaches used in exercising humans by Middlekauf and Chiu (11) and Fontana et al. (5) have shown data consistent with the present result. However, until the Hayes et al. (6) study, we did not have a good idea of the behavior of actual single afferents under conditions that closely approach the situation of normal exercise.

Finally, these results (6) further raise the issue that elements of nociception may be involved with normal exercise, even though the actual sensation may not be perceived as pain. Certainly, even the most general clinical texts on the use of nonsteroidal anti-inflammatory agents (NSAIDs), of which the indomethacin used by Hayes et al. (6) remains a standard, mention their effectiveness on muscle pain (4). Unfortunately, as was duly noted by Kehl et al. (8), although the vast majority of our information about pain is from cutaneous sensation, “comparatively little is known about activation of visceral, joint and perhaps least of all musculoskeletal nociceptors although clinically-treated pain originates principally in these structures.” Although much important work on muscle nociceptors has been carried out, there is still a relative paucity of information in situations such as the muscle contraction associated with actual exercise. Not surprisingly, the dividing lines between nociception and pain remain unclear in conditions such as those in allodynia [in which a normally nonnoxious stimulus is perceived as painful (10)] and the afferent activity evoked by normal exercise. Certainly they share a common basis in the products of cyclooxygenase. Does this mean that nociception or pain based on these products enters into normal exercise as a natural occurrence? One must be careful to define nociception and pain. The modern accepted definition of nociceptor remains the one recognized by Sherrington (18) as sensory receptors that respond to stimuli that threaten to or actually damage tissue. However, pain is not a simple matter of nociception but rather (in one of the better definitions from Ref. 10) “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.” In addition, it is an experience highly dependent on a complex array of additional factors (10).

Some highly dependent experiments by Kaufman and colleagues (3) have shown that the activity of dorsal horn cells stimulated by muscular contraction is suppressed by MLR stimulation. If current thought is correct and the MLR is active during actual exercise (7), MLR may suppress signals from the dorsal cells that are signaling group III and IV nociception to the extent that the sensory and emotional experience of pain never develops. Thus exercise may be a context in which muscle pain is less likely to occur even though cyclooxygenase products are present.

Thus, although these experiments may not precisely model exercise, they are certainly representative of the state of the art given current methods of directly monitoring afferent activity and stimulus paradigms that model exercise. Until better techniques are devised, they will be the best evidence for participation of cyclooxygenase products and other chemicals in sensitizing identified afferents in skeletal muscle during exercise. These experiments will also continue to raise additional questions about the role of cyclooxygenase products and other sensitizing chemicals, (e.g., bradykinin) in cardiovascular control accompanying normal exercise and the nature of nociception and pain.

REFERENCES