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Muscle afferents and cardiorespiratory control: the Birmingham connection

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New findings

• What is the topic of this review?
  This brief review describes the work of Professor John Coote and colleagues at the University of Birmingham, which has contributed to understanding of the role of muscle afferent involvement in cardiorespiratory control in exercise.

• What advances does it highlight?
  The seminal findings of John Coote’s early work are highlighted, as well as more recent developments in the field, especially the role of muscle afferents in the control of human ventilation during exercise.

Through the work of John Coote, research into the role of muscle afferent involvement in cardiorespiratory control has had strong links with Birmingham since the late 1960s. This brief review gives an historical background to John’s early work and how his research and mentorship of colleagues continues to have a profound influence on the field today.

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The idea that neural feedback from working muscle plays an important role in the control of cardiovascular and respiratory responses to exercise can be traced back to the late 19th century. When combined with feedforward signals, initiated by the intention to perform exercise, this creates a powerful control circuit, which is essential to prevent catastrophic failure of the systems during exercise. Initially, the feedforward signal was thought of as a form of efference copy, then later it was termed cortical irradiation (Krogh & Lindhard, 1917), and it is now generally referred to as central command (Williamson et al. 2006).

Early experimental evidence that suggested a role for feedback from exercising muscle in the control of the cardiovascular and respiratory systems was based on a number of different approaches. Perhaps the simplest involved passive movement of animal limbs. As there is no intention to exercise, this technique avoids the generation of central command, and some muscle afferent activation is likely. However, joint receptors are unavoidably activated too and may be responsible for some of the cardiorespiratory responses observed (Barron & Coote, 1973). Electrical stimulation to evoke isometric muscle contraction is a more promising technique. This still avoids the generation of central command, whilst increasing mechanical force and metabolic activity within the muscle. Isometric contraction minimizes the involvement of joint receptors. In Krogh and Lindhard’s laboratory in the early 1900s, intermittent tetanic stimuli were produced by the fearsome-sounding Bergonie apparatus. Stimulation was applied through plate electrodes to activate large muscle masses in the legs and abdomen of their subjects. Heroic stuff! They showed that cardiovascular and respiratory responses could be generated during involuntary exercise, suggesting the involvement of signals arising within the exercising muscle (Krogh & Lindhard, 1917).

In their seminal paper, Alam & Smirk (1937) used simple experiments to produce compelling evidence that
reflex feedback from exercising human muscle could evoke strong cardiovascular responses. They showed that rhythmic exercise of forearm or calf muscles caused blood pressure to rise, but when the same exercise was performed with local circulatory occlusion, blood pressure rose substantially higher. Continuing the occlusion after exercise had ceased sustained most of the blood pressure rise until restoration of circulation after cuff deflation. During this postexercise circulatory occlusion (PECO) period, the muscle was relaxed so there could be no central command or mechanically stimulated reflex activity from the muscle. In a model discussion, employing deductive reasoning, Alam and Smirk concluded that circulatory occlusion trapped metabolites in the previously active muscle and this activated a reflex generating the pressor response observed.

Direct proof of the existence of this reflex pathway did not come until the late 1960s and early 1970s. The problem was the lack of a good animal preparation that allowed direct electrical stimulation of motor outflow to cause muscle contraction, without inadvertent electrical stimulation of afferent nerves. When he arrived at the University of Birmingham in 1967, John Coote became aware that a colleague in the Department of Physiology, the late Peter Rack, was using a cat preparation for his work on muscle contractile properties and the stretch reflex. This preparation allowed discrete stimulation of ventral roots and recording from dorsal roots. John quickly realized that it had great potential for cardiovascular and respiratory control work. Looking back at a Physiological Society communication John made at that time (Coote & Perez-Gonzalez, 1968; Coote et al. 1968), it is easy to see the rapid progression of understanding about the role of muscle afferents, as opposed to other somatic afferent feedback on cardiovascular responses mediated by the sympathetic nervous system. These experiments initially reported depressor as well as pressor responses to activation of somatic afferents. Nevertheless, a clear link was shown between muscle afferent feedback in response to evoked muscle contraction and activation of the sympathetic nervous system. In addition, he was able to use anodal block to identify the involvement of smaller muscle afferents in generating a pressor response to electrically evoked exercise of the cat hindlimb. He was also able to conclude that an intact medulla–cord connection was essential for the facilitatory and inhibitory influence of the somatic afferents on the sympathetic outflow.

In July 1971, after a rather uncharacteristically long gestation period for John (due in part it seems to the competing distraction of working with the great Sidney Hilton, on the defence reaction) he, Hilton and Perez-Gonzalez (Coote et al. 1971) produced a now classic paper on the topic. Electrical stimulation of the hindlimb of the decerebrate cat produced a pressor response, a rise in heart rate and an increase in ventilation. These responses were abolished if the muscle was pharmacologically prevented from contracting, so could not be due to inadvertent electrical stimulation of any afferent pathway. Sequential sectioning of the dorsal roots carrying sensory information from the hindlimb progressively reduced and eventually abolished the responses to the evoked exercise.

In July 1972, McCloskey and Mitchell published another now classic paper, which used a similar cat preparation and anodal block and local anaesthetic application at the dorsal root to block afferent feedback differentially from larger (group I and II) and smaller (group III and IV) muscle afferent fibres, respectively. Only blockade of the smaller fibres was effective in abolishing the cardiovascular response to electrically evoked exercise, indicating beyond doubt that they were responsible for the responses that resulted from this evoked exercise.

These two papers are universally recognized as having established the existence of a reflex pathway capable of signalling to the central nervous system information about metabolic conditions and mechanical activity in the exercising muscle, i.e. the reflex causing heart rate, blood pressure and ventilation to increase during exercise.

Not surprisingly, the physiological properties and central projections of these thin fibre muscle afferents (group III and IV) then became a field of intense and careful study (Kaufman et al. 1983). This work is ongoing in the light of increasing knowledge about the behaviour and plasticity of receptor subtypes located on the afferents. Broadly, afferents discharging in response to metabolites accumulated within the muscle interstitium generate the ‘muscle metaboreflex’ and those responding primarily to mechanical stimuli the ‘muscle mechanoreflex’. However, this is an oversimplification because a number of afferent fibres are known to be activated by both mechanical and chemical stimuli so are in fact classified as polymodal afferents. Some fibres may respond better to mechanical stretch than to active muscle force and some may become sensitized to mechanical stimuli by the presence of metabolites produced and accumulated during exercise (for review, see Kaufman, 2012). It is also apparent that sensitivity to different stimuli can change and adapt with disuse and training (Sinoway et al. 1989) or in disease states through modification to receptor subtypes (Sinoway & Li, 2005).

At the segmental level, muscle afferents are able to modulate α-motoneurone excitability through activation of interneurones. In this way, they play a role in recruitment of motor units and coding of firing rate (Gandevia, 2001), a factor increasingly appreciated in voluntary muscle fatigue and the perception of effort in exercise (Amann et al. 2009). The further upward projections of the muscle afferents arrive at important control areas at many levels of the brain. Those reaching the medulla (Iwamoto & Kaufman, 1987), specifically the nucleus tractus solitarii, cause ventilation, heart rate and
blood pressure to rise in exercise. Actions on vagal and sympathetic control of the heart and blood vessels as well as the baroreflex explain, in part, how the regulated variable in the cardiovascular system, blood pressure, is allowed to rise in exercise (McWilliam & Yang, 1991; Potts, 2006).

Given this background, it is understandable that much effort has been expended in attempting to define the role of muscle afferent feedback in human cardiovascular and respiratory control in health and disease states. As described earlier, a long standing but nevertheless very useful method to investigate their influence, in the absence of central command, is the use of electrically evoked muscle contraction. It is perhaps appropriate here to expand on the influence that John Coote had on a career (mine) and the development of the field. In 1989, the late A. R. ‘Sandy’ Lind came to Birmingham on sabbatical leave from St Louis (MO, USA). He was old friends with John and my then Head of Department, C. T. M. Davies. They introduced me to Sandy, and when he found out that I had a considerable amount of experience of electrically evoking strong isometric muscle contractions in human volunteers, he immediately suggested a study. This was essentially an extension of the Alam and Smirk model of exercise followed by PECO. However, the muscles would be made to contract using electrical stimulation, thereby removing central command. In the original study by Alam & Smirk (1937), blood pressure fell slightly on cessation of exercise but was then sustained at this new level by the PECO. The fall could have been due to the loss of central command at the end of the exercise or it could have been due to the loss of mechanoreflex stimulation, or both. Using electrically evoked exercise followed by PECO would resolve this issue, at least in respect of muscle mechanoreflex involvement. We found that during isometric calf muscle exercise, blood pressure and heart rate rose by the same amount in both electrically evoked and voluntary exercise (Fig. 1A and B). During PECO, blood pressure fell to similar levels in both tests and was then sustained at the given level by PECO (Fig. 1A). However, heart rate fell to baseline during PECO in both tests (Fig. 1B). Our conclusion was that central command was not essential for the production of the heart rate and blood pressure changes we saw during the voluntary test and that the falls in heart rate and blood pressure seen at the end of evoked exercise could only be explained by the loss of mechanosensitive afferent activity. I wrote up the study, and it was published in The Journal of Physiology (Bull et al. 1989). John’s sage advice to cut short my discussion by two pages was, I am sure, instrumental in the paper being accepted without revision. Sadly, Sandy died before the study was fully completed, so it was a posthumous publication for him. However, his ideas were vindicated, as the sketches he made when we first discussed the study were near identical to the figures we produced in the paper. (I so wish that I had kept that beer mat!)

My laboratory continued to use the model of electrically evoked calf exercise to study the effect of muscle afferent activation in the absence of the effect of central command. In a series of studies on man, we were able to show that muscle fibre type was an important factor in influencing the magnitude of the cardiovascular response to evoked exercise. Those with a slower contracting calf muscle produced a smaller exercise pressor reflex than those with a faster contracting muscle during a standardized period of exercise. Muscle biopsy samples confirmed that the contractile speed of the muscle was dependent on the predominance of slow and fast isoforms of myosin in the gastrocnemius and soleus muscles (Carrington et al. 1995).

Interestingly, the decline in fast-twitch muscle content with old age appears to be more marked in the leg muscles than in the arms (McDonagh et al. 1984). In line with this, we found smaller pressor responses to evoked exercise of the legs than the arms of older men. The arm responses were similar to those of younger men. These findings concur with data from animal work showing that fast fibre involvement is required to generate appreciable exercise pressor responses (Petrofsky & Lind, 1980) and fibre type changes in muscles after cross-innervation can correspondingly alter the exercise pressor response (Wilson et al. 1995).

One exception to this positive relationship between fast fibre content and the pressor response to a standardized evoked exercise protocol was revealed by a study of sprint-trained athletes (Carrington et al. 1999). Whilst undeniably having a very high proportion of fast-twitch fibres in their calf muscles, some sprint athletes (those specializing in 200–400 m events) produced unexpectedly low pressor responses. We could not say from these data whether these athletes had a genetic predisposition to produce low exercise pressor responses, possessed different muscles which had become insensitive to anaerobic conditions or simply produced lower levels of metabolite due to their training.

This prompted a study designed to examine whether the human exercise pressor response could be altered by 6 weeks of intense training (Fisher & White, 1999). Subjects trained one calf muscle, whilst the contralateral limb acted as an untrained control. Cardiovascular responses to voluntary and electrically evoked exercise and PECO were examined in both legs. Training caused an impressive decrease of 30% in the exercise pressor response to the standard evoked exercise in the trained leg. This decrease was also seen during PECO, indicating a reduced muscle metaboreflex after training. Not surprisingly, the voluntary exercise response was also reduced by 30%, as was the PECO response, confirming a reduced metaboreflex (Fig. 2). The decrease in the pressor response was also correlated with a change in the fatigue resistance of the trained muscle, assessed by an electrically evoked
protocol. This part of the study showed that the exercise pressor reflex could be adapted by training. Reassuringly, the control limb produced the same exercise pressor responses during evoked exercise and PECO after training as it had before. However, the surprising result was that voluntary exercise of the untrained limb produced an exercise pressor response that was reduced by 30%, exactly as in the trained limb. The PECO response was unchanged from pretraining values (Fig. 2). This reduced response to exercise could therefore be explained only by altered central command and would appear to be a ‘crossover’ effect from the trained limb, with the most likely explanation being a reduced effort required to activate the muscles of the untrained limb after training of the contralateral limb. Whether this is a local spinal effect or a higher central command effect remains to be determined.

Local muscle training certainly appears capable of altering muscle afferent feedback and the cardiovascular

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**Figure 1.** Blood pressure and heart rate responses to voluntary and electrically evoked calf exercise in man

*A*, data from Bull *et al.* (1989) showing equal blood pressure rises during voluntary and electrically evoked isometric calf muscle exercise at 30% of maximal voluntary contractile (MVC) strength. Circulatory occlusion following both forms of exercise sustained part of the blood pressure rise due to continued activation of the muscle metaboreflex. The blood pressure fall after evoked exercise cannot be due to cessation of central command, because it is not present in this mode of exercise. Only the loss of muscle mechanoreflex activity can explain it. *B*, heart rate data from the same study showing that increases in heart rate during both forms of exercise are not maintained by continued muscle metaboreflex activation after exercise. Muscle mechanoreflex activation appears to explain the heart rate rise during evoked exercise, and its cessation explains the fall during postexercise circulatory occlusion. *Significant difference from baseline (P < 0.05). †Significant difference between electrically evoked and voluntary contraction (P < 0.05).*
response that it generates. This is important because there are a number of conditions where abnormal afferent feedback is proposed as a mechanism explaining effort intolerance. In conditions such as chronic heart failure, it is implicated in abnormal cardiac sympathovagal balance, as well as vasoconstriction of active muscle and other organs in exercise (Coats et al. 1994; Carrington et al. 2001, 2004; Sinoway & Li, 2005). Local muscle exercise training may facilitate normalization of afferent feedback without requiring whole body or large muscle mass exercise that simply cannot be tolerated by patients.

A major factor in effort intolerance in disease states such as chronic heart failure and chronic obstructive pulmonary disease is dyspnoea. Although animal studies have shown that activation of muscle afferents causes a ventilatory response (Coote et al. 1971; Hayes & Kaufman, 2001), the role of muscle afferents in the human ventilatory response to exercise has long been disputed. The classical observation that increased ventilation caused by exercise cannot be prevented from falling back to resting levels by PECO appears to be damming evidence against involvement of the muscle metaboreflex, at least. However, we demonstrated recently that activation of muscle afferents by means of PECO and controlled passive muscle stretch can sustain an exercise-induced ventilatory response or indeed cause an increase in ventilation from rest if the afferent activation is combined with a modest level of hypercapnia (Bruce & White, 2012). This is not due to a local muscle effect or a peripheral chemoreflex effect of the hypercapnia, suggesting a central synergistic effect of the afferent feedback and the hypercapnia, which combine to cause a ventilatory response. It is possible that in ‘real life’ central command could supply the synergistic input to respiratory neuronal pools which, in combination with muscle afferents feedback, then respond and cause increased ventilation. This evidence fits well with recent observations by Amann et al. (2010) that epidural anaesthesia with fentanyl, which does not affect motor outflow but does attenuate afferent feedback, causes a significant reduction in ventilation during cycling exercise. This reduction is apparent even at low workloads where little muscle metaboreflex would be expected, indicating probable involvement of the muscle mechanoreflex. This finding has now been extended to patients with chronic obstructive pulmonary disease (Gagnon et al. 2012), with significant reductions in ventilation and symptoms of dyspnoea during standardized exercise trails.

Whilst these are impressive findings, it is not yet possible to send patients home with epidural anaesthesia in place, so reductions in afferent feedback will have to be acquired by other means. Pharmacological approaches are undoubtedly to the fore in many minds, but it might now be time to revisit the influence of local muscle training status and muscle fibre type on muscle afferent feedback. Perhaps wider interest in exercise as a therapy will be stimulated?

Figure 2. Changes in the pressor response to isometric exercise following one legged calf raise training
Data from Fisher & White (1999) showing a training-induced change in the magnitude of the pressor response to sustained isometric exercise of the calf muscles. Training lasted for 6 weeks and involved repeated one-legged calf-raise exercise of the dominant leg. The voluntary and evoked test exercise protocols were as developed by Bull and co-workers (see Fig. 1). Similar reductions in the pressor response were seen during both voluntary (hatched bars) and evoked exercise (open bars) in the trained calf. This suggests reduced muscle afferent feedback after training. In the contralateral untrained limb, responses to voluntary exercise were reduced by a similar amount to the trained limb; however, responses to evoked exercise were not different from baseline values. This suggests unchanged afferent feedback in the untrained limb but altered central command.

References


### Additional information

#### Competing interests

None declared.

#### Funding

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