Are type III–IV muscle afferents required for a normal steady-state exercise hyperpnoea in humans?

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Abstract  When tested in isolation, stimuli associated with respiratory CO₂ exchange, feedforward central command and type III–IV muscle afferent feedback have each been shown to be capable of eliciting exercise-like cardio-ventilatory responses, but their relative contributions in a setting of physiological exercise remains controversial. We reasoned that in order to determine whether any of these regulators are obligatory to the exercise hyperpnoea each needs to be removed or significantly diminished in a setting of physiological steady-state exercise, during which all recognized stimuli (and other potential modulators) are normally operative. In the past few years we and others have used intrathecal fentanyl, a μ-opiate receptor agonist, in humans to reduce the input from type III–IV opiate-sensitive muscle afferents. During various types of intensities and durations of exercise a sustained hypoventilation, as well as reduced systemic pressure and cardioacceleration, were consistently observed with this blockade. These data provide the basis for the hypothesis that type III–IV muscle afferents are obligatory to the hyperpnoea of mild to moderate intensity rhythmic, large muscle, steady-state exercise. We discuss the limitations of these studies, the reasons for their disagreement with previous negative findings, the nature of the muscle afferent feedback stimulus and the need for future investigations.

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Introduction

The ventilatory response to rhythmic exercise is an exquisite example of a highly efficient homeostatic response. Not only does alveolar ventilation rise in precise proportion to respiratory CO₂ exchange, but the nature of each hyperpnoeic breath is also tightly controlled in terms of increasing frequency vs. tidal volume, breath duty cycle and recruitment of inspiratory and expiratory musculature of the chest and abdominal walls as well as the upper airway dilator musculature. These responses are dedicated to both regulate the arterial blood gases and acid–base status as well as to minimize the work, and the metabolic and circulatory costs, required to

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produce up to 10- to 20-fold increases in ventilation. Furthermore, as eloquently espoused by the late Brian Whipp (1937–2011), in health with increasing exercise intensity, anatomical (airway) dead space volume (\(V_d\)) increases as a linear function of increasing tidal volume (\(V_T\)) and \(V_d/V_T\) falls as a hyperbolic function of increasing \(V_T\). Thus, overall expiratory minute ventilation (\(V_E\))/rate of CO\(_2\) production (\(V_{CO2}\)) is reduced proportionately with increasing exercise intensities so as to maintain constant the ratio of alveolar ventilation to CO\(_2\) production (\(V_A/V_{CO2}\)) and thus maintain normocapnia over the range of mild to moderate intensity exercise in the steady state (Whipp, 2008):

\[
P_{aCO2} = \frac{863}{\left(\frac{V_E}{V_{CO2}} \times \left(1 - \frac{V_d}{V_T}\right)\right)}
\]

where \(P_{aCO2}\) is the arterial partial pressure of CO\(_2\).

Of relevance to this mysterious capability of the control system to somehow ‘know’ to increase total ventilation only to levels commensurate with the demands for pulmonary CO\(_2\) exchange, is the observation that with healthy ageing, reduced lung elastic recoil increases \(V_d/V_T\) at rest and during exercise. Despite this age-dependent disruption to gas exchange efficiency, \(V_A/V_{CO2}\) and normocapnia are maintained during exercise in the elderly, similarly to that in the young adult, as \(V_E/V_{CO2}\) is adjusted further upward in the elderly to accommodate their higher \(V_d/V_T\) (Johnson et al. 1991; Forster et al. 2012).

In our brief review we first outline what we and others consider to be three key mechanisms which probably contribute significantly to the exercise hyperpnoea and then focus specifically on recent evidence in humans supporting an essential role for type III–IV muscle afferents to the steady-state hyperpnoea.

Three key mechanisms underlie exercise hyperpnoea

A century plus long debate has centred upon the tight link of \(V_A\) to \(V_{CO2}\), i.e. what is the nature of the mechanism(s) underlying this link? Three candidates have proven worthy based on their capability to drive ventilation – at least when studied in isolation – namely CO\(_2\) exchange at the lung, central command in proportion to locomotor muscle recruitment (feed-forward) and muscle afferent feedback.

Pulmonary CO\(_2\) exchange. If arterial \(P_{CO2}\) is indeed a key regulated variable then ‘CO\(_2\)’ should have a major voice in its own regulation. In addition to the apparently inevitable proportional link of \(V_A\) to \(V_{CO2}\), outlined above there is ample experimental evidence to prove cause (\(V_{CO2}\)) and effect (\(V_A\)) (Whipp, 2008): (a) increasing or decreasing CO\(_2\) flow to the lung, by itself, using extracorporeal circulation in a resting animal elicits a near isocapnic hyperpnoea or hypopnoea – at least over relatively small changes in \(V_{CO2}\) near eupnoea (Yamamoto & Edwards, 1960; Phillipson et al. 1981a,b; Green & Sheldon, 1983); (b) increasing \(V_{CO2}\) by increasing the respiratory quotient via carbohydrate ingestion elicits an isocapnic hyperpnoea in humans at rest (Douglas & Priestley, 1924; Whipp, 2008); (c) with sinusoidal variation in work rate over different durations, the ventilatory response varies more closely with \(V_{CO2}\) rather than work rate (Casaburi et al. 1978); and (d) electrical stimulation of limb muscle contractions to induce increases in \(V_{CO2}\) elicits an isocapnic hyperpnoea and this persists following spinal cord lesioning (in most studies) in humans and animals – again over a limited range of \(\Delta V_{CO2}\) (Green & Sheldon, 1983; Adams et al. 1984). Further, it follows that this \(V_A/V_{CO2}\) link probably also underlies the near-identical resting \(P_{aCO2}\) commonly observed among humans who vary in body mass by as much as 150 kg with a threefold variation in \(V_{CO2}\) (Dempsey et al. 1966).

Despite these compelling arguments it is still not entirely clear how and where a signal that is proportional to pulmonary CO\(_2\) exchange is sensed. The carotid chemoreceptors provide an important tonic contribution to the eupnoic drive to breathe at rest (Blain et al. 2009), but based on chemo-denervation effects on ventilation and \(P_{aCO2}\) which were similar at rest and during steady-state exercise (Wasserman et al. 1975; Forster et al. 2000, 2012), the magnitude of further increases in steady-state ventilation induced by exercise does not appear to be dependent upon intact chemoreceptors. There are other promising possibilities. First, the well-controlled experiments of Green et al. (Green & Sheldon, 1983) in anaesthetized animals identified pulmonary C-fibres or J receptors in the lung interstitial fluid as a potential site for sensing changes in pulmonary blood flow, with vagally mediated input to the medullary respiratory controller. More recently, Luijendijk (2012) theorized that both pulmonary J receptors and the aortic bodies sensed changes in the osmotic state of plasma, the magnitude of which is determined by pulmonary capillary pressure and plasma osmotic pressure, both of which are indirectly influenced by pulmonary blood flow and excess plasma HCO\(_3^-\), and therefore linked to \(V_{CO2}\). This concept of linking changes in respiratory CO\(_2\) exchange to J receptor and aortic body stimulation via changes in plasma osmolality is a promising new twist deserving further study, after all it may provide insight into the mysterious CO\(_2\) exchange:ventilatory control link which has long been sought.

Is the stimulus driven solely by respiratory CO\(_2\) exchange obligatory to a normal exercise hyperpnoea or even the major controller of the hyperpnoea? Experimentally this question was addressed by reducing the normal CO\(_2\) flow to the lung (via an extracorporeal circuit used to scrub the CO\(_2\) in the venous return) in exercising sheep and dogs (Phillipson et al. 1981a; Bennett

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et al. 1984). While $V_E$ was reduced coincident with a reduced CO$_2$ flow, it was controversial among studies to what extent coincident small changes in P$_{aCO_2}$ could have accounted for the changes in ventilation.

A fundamental problem with these extremely difficult to conduct studies in awake, exercising animals is that the $\Delta V_{CO_2}$ achievable via the extracorporeal circuit was small, thus the accompanying $\Delta V_E$ values were in the range that might be explained by small deviations in P$_{aCO_2}$ alone (Bennett et al. 1984; Dempsey et al. 1985). We believe the evidence to date is consistent with the concept that CO$_2$ exchange at the lung provides the underpinning for the control of breathing, especially on either side of eupnoea at or near a resting $V_{CO_2}$ (Menna & Mortola, 2002). However, we know of no evidence that would support a major role for this CO$_2$-linked stimulus as the dominant mediator of up to five- to tenfold increases in $V_E$ experienced during mild and moderate exercise intensities.

**The ‘work’ factor(s): feedforward and feedback.** Erling Asmussen and Marius Nielsen coined this term long ago to suggest that the stimulus to hyperpnoea required a non-humoral component specific to exercise or locomotion per se (Asmussen et al. 1943). Two sources have been identified.

First, the ‘central command’ stimulus whereby parallel recruitment occurs of both locomotor muscles and the cardiorespiratory response has been shown to be capable – by itself – of driving the exercise hyperpnoea. Eldridge et al. (1981) showed that electrical or pharmacological stimulation of hypothalamic locomotor areas elicited a progressive, robust cardioventilatory response in the decorticate cat, even in the presence of limb musculature under neuromuscular blockade, i.e. ‘fictive locomotion’. Further, in hypnotized humans, at rest, the ‘suggestion’ of increasing exercise intensity prompted immediate hyperventilatory and cardioaccelerator responses and coincident brain-imaging measures showed an increased blood flow to motor control regions of the cortex and cerebellum (Thornton et al. 2001; Williamson et al. 2002). Direct recordings from electrodes implanted in humans have shown increased neuronal activity in the periaqueductal grey region to accompany the cardiorespiratory response to low level exercise (Green et al. 2007). Finally, locomotor muscle weakness achieved via partial curarization elicited hyperventilatory and cardioaccelerator responses to exercise which exceeded those in the intact control subject, presumably via heightened central command mechanisms which are called into play to recruit more motor units and maintain work rate in the face of weakened locomotor muscles (Asmussen et al. 1965; Galbo et al. 1987). A significant role for central command mechanisms in the normal, intact exercising animal or human has been inferred from studies of this mechanism in isolation. Whether this mechanism is obligatory to the hyperpnoea has not been tested by removing or diminishing this feedforward input during physiological exercise when other potential inputs were operative (also see section below on ‘Exercise hyperpnoea as a learned phenomenon’).

Research on the peripheral ‘feedback’ component of the ‘work’ or locomotor-linked factor in exercise hyperpnoea has provided mixed but mostly negative findings, especially in humans. On the positive side, using anaesthetized canines with cross-circulation preparations, Kao demonstrated a near-normal hyperpnoeic response to limb muscle electrical stimulation, even in the absence of increased CO$_2$ flow back to the lung and this ‘neural’ drive effect on $V_E$ was blocked by denervation of the dorsal spinal columns (Kao, 1963). This mechanism was later shown to be mediated via group III–IV muscle afferents (Coote et al. 1971; McCloskey & Mitchell, 1972). Type III–IV muscle afferents were also shown to increase their activity even during low intensity rhythmic contractions (Adreani et al. 1997). These afferents project via the dorsal horn of the spinal cord to the nucleus of the solitary tract and the medullary cardiorespiratory controller neurons. Recent evidence in the isolated brain stem–spinal cord rodent preparation confirmed that lumbar locomotor networks can rhythmically entrain medullary respiratory neurons (Morin & Viala, 2002). On the other hand, negative evidence includes the finding of a normal ventilatory response to limb muscle stimulation with increased $V_{CO_2}$ in quadriplegic patients (Adams et al. 1984), and spinal cord-transected anaesthetized animals (Weissman et al. 1980). In healthy humans, total vascular occlusion of the limbs accelerated the return of ventilation to resting levels during the recovery period following exercise, thereby suggesting that metabolite accumulation in the occluded muscle was not an important contributor to ventilatory drive (Rowell et al. 1976; Innes et al. 1989; Haouzi et al. 1993). Several studies have also used epidural lidocaine (lignocaine) in humans to block afferent feedback from the legs during rhythmic exercise (Hornbein et al. 1969; Strange et al. 1993; Smith et al. 2003; Amann et al. 2008; Forster et al. 2012). This anaesthetic-induced blockade caused a significant reduction in MAP but either no effect or even increases in heart rate or $V_E$ during cycling exercise, suggesting that the muscle afferents were not obligatory to exercise-induced hyperpnoea or cardioacceleration (also see Fig. 6).

**Use of \(\mu\)-opioid agonists suggests an obligatory contribution of III–IV muscle afferents to steady-state exercise hyperpnoea**

Following serendipitous observations from a study concerned with inhibitory feedback effects from fatiguing limb muscles on motor output (Amann et al. 2009)
we asked if III–IV muscle afferents were required for a normal cardioventilatory response to rhythmic steady-state exercise in humans. Based on previous demonstrations in anaesthetized animals that \( \mu \)-opioid agonists blocked much of the cardioventilatory response to static muscle contraction (Hill & Kaufman, 1990) we used lumbar level intrathecal injection of fentanyl (50 \( \mu \)g) in humans to partially block afferent feedback.

**Figure 1**

A, group mean effects of blockade of type III–IV opiate-sensitive limb muscle afferents on cardioacceleration and mean arterial blood pressure (MAP) at rest and during the transient and steady-state phases of voluntary rhythmic cycling exercise in healthy humans. Data obtained from Amann et al. (2010).

B, reduced steady-state ventilation (\( V_{E}/V_{CO_2} \)) and breathing frequency (\( f_R \)), and the resultant CO\(_2\) retention, resulting from type III–IV muscle afferent blockade via intrathecal fentanyl in healthy humans at mild to heavy exercise intensities. Fentanyl had no effect on mean \( S_aO_2 \) except at the 327 W work rate where \( S_aO_2 \) was 97.7% in placebo and 95% with fentanyl. Note the persistence of the hypoventilatory response in the presence of type III–IV afferent blockade – especially during mild and moderate intensity exercise – despite the presence of increased CO\(_2\)-induced chemoreceptor stimulation. Plasma lactate levels were within 0.5 mmol l\(^{-1}\) of resting values (0.9 ± 0.1 mmol l\(^{-1}\)) during 50–150 W exercise and rose to 7-fold > rest during exercise at 325 W in both the placebo and fentanyl trials. Data from Amann et al. (2010).
mediated by $\mu$-opioid-sensitive receptors in the dorsal horn. We and others documented with plasma assays, and with ventilatory responses to inhaled $\text{CO}_2$ and to arm exercise that the fentanyl probably did not spread above the thoracic level or reach the systemic circulation (Amann et al. 2010, 2011 b; Gagnon et al. 2012).

The premise of these studies was to determine the effects of blocking only the type III–IV limb muscle afferent influences during steady-state exercise, i.e. under conditions where all other proposed major stimuli to hyperpnoea (including $\text{CO}_2$ exchange and central command) would continue unaffected from their normal levels. Based on the time course of changes shown in Fig. 1A and B it was clear that the heart rate, $V_E/V_{\text{CO}_2}$, the end-tidal partial pressure of $\text{CO}_2$ ($P_{\text{ETCO}_2}$), and $V_{\text{CO}_2}$ (not shown) achieved a steady state by the final minute of each 3 min session at mild to moderate work intensities, implying that all of the potential stimuli to hyperpnoea were probably operative under these conditions.

As shown in Fig. 1A and B there were no effects of the fentanyl observed at rest but throughout each of the three mild to moderate intensity cycling exercise levels, mean arterial blood pressure (MAP), heart rate, breathing frequency ($f_R$) and $V_E/V_{\text{CO}_2}$ were significantly reduced below placebo levels and $P_{\text{ETCO}_2}$, substantially elevated. This sustained hypoventilation and the $\text{CO}_2$ retention resulting from type III–IV afferent blockade with fentanyl were also obtained during the first half of a 5 km time trial cycling exercise (Amann et al. 2009; see Fig. 2) and over most of the duration of constant load heavy intensity cycling exercise (see Fig. 3; Amann et al. 2011 a). Similarly, use of the intrathecal fentanyl block in chronic obstructive pulmonary disease (COPD) patients caused $f_R$, $V_E$, heart rate and MAP to be substantially reduced throughout the entire duration of a constant-load high intensity cycling exercise (see Fig. 4). In these patients $V_d/V_T$ during exercise with the fentanyl block was also reduced, thus only minimal $\text{CO}_2$ retention occurred during exercise with afferent blockade (Gagnon et al. 2012).

The ‘relative’ influence of type III–IV muscle afferent feedback with changing exercise intensities/durations/muscle mass

During mild to moderate exercise intensities with type III–IV afferent blockade we observed a 3–10 l min$^{-1}$ reduction in $V_E$ and 3–8 mmHg increases in $P_{\text{ETCO}_2}$ (vs. placebo), as well as significant reductions in heart rate and the prevention of any increase in MAP above resting levels. These effects were present within the initial 15 s of each work rate and persisted throughout the ensuing 3 min of each load and for a cumulative 12–15 min of exercise over several loads (see Fig. 1A and B). The sustained hypoventilation and accompanying hypercapnia (and reduced}

Figure 2. Power output and physiological responses to three 5 km cycling time trials with control, placebo and intrathecal fentanyl

Note the reproducibility in the responses of force output and $V_E/V_{\text{CO}_2}$ between control and placebo in these trained cyclists throughout the trial. This contrasts with the marked increase in power output (and quadriceps EMG, not shown) ‘chosen’ by the subject over the initial 1–2 km when somatosensory neural feedback was blocked. Thereafter, power output fell as limb fatigue progressed. $V_E/V_{\text{CO}_2}$ was reduced and $P_{\text{ETCO}_2}$ increased throughout the initial 2.5 km in the fentanyl trial vs. placebo, but this relative hypoventilation did not persist throughout the trial as plasma lactate rose over the final 2.5 km. $S_{\text{O}_2}$ averaged 90–93% over the final 2.5 km vs. 95–96% in placebo (data not shown). Data from Amann et al. (2009).
arterial oxygen saturation, $S_{aO_2}$) with type III–IV afferent blockade does not mean that chemoreceptors remained non-responsive to this substantial systemic (and brain) acidity. Rather, even greater reductions in $\dot{V}_E$ and heart rate with type III–IV afferent blockade were probably masked by several secondary factors, including: (a) the concomitant and substantial chemostimulation secondary to increasing $P_{aCO_2}$ (and reduced arterial $O_2$ saturation), which undoubtedly prevented $\dot{V}_E$ from falling further secondary to the fentanyl blockade (Bennett & Fordyce, 1988); and (b) a lower MAP and therefore unloading of the carotid sinus and aortic baroreceptors which via feedback effects will increase both heart rate and the drive to breathe (Ohtake & Jennings, 1992).

In Fig. 5 we calculate the relative contributions of type III–IV muscle afferents to the total hyperpnoea by including estimates of the ‘masking’ effect of one of these feedback influences, i.e. the coincident hypercapnia, on the hyperpnoeic response. For this estimate we used the group mean ventilatory response to inhaled CO$_2$ measured at rest ($\Delta \dot{V}_E/\Delta P_{ETCO_2}$; Amann et al. 2010). Note that an average of 38–47% of the total steady-state ventilatory response to mild to moderate intensity cycling exercise was attributed to the type III–IV muscle afferent input. Given that we only accounted for one of the secondary feedback effects (i.e. hypercapnia) and that we have only blocked the $\mu$-opiate-sensitive afferents, this estimate probably represents a minimum effect of muscle afferent feedback effects on the hyperpnoea.

As exercise intensity increased and/or exercise duration at high intensity was prolonged, the relative effects
of afferent blockade on the hyperventilatory, cardioaccelerator and MAP responses were clearly diminished. We attribute this apparent reduction in the contribution of III–IV afferents to two factors. First, these reduced effects of opiate agonists on \( V_E \) with increasing exercise intensities/durations did not mean that type III–IV muscle afferents were decreasing their absolute activity. On the contrary, just the opposite effect would be expected with accumulation of muscle metabolites. Thus, it is more likely that our partial blockade of opiate-sensitive type III–IV afferents became progressively more incapable of suppressing hyperventilation in the face of rising muscle metaboreceptor stimuli. Secondly, based on the observed increase in plasma lactate (see Figs 1B, 2 and 3) we speculate that this reduced relative influence on \( V_E \) from III–IV afferents was due in part to the addition of two types of overriding influences, namely: (a) increased chemoreceptor stimuli such as circulating \( \text{H}^+ \), \( \text{K}^+ \) and noradrenaline (Paterson et al. 1990; Forster et al. 2012); and (b) the augmented central command influences which would have accompanied attempts to maintain force output as muscle fatigue progressed. Given these additional causes of hyperventilation during heavier intensity exercise and the increasing uncertainty of the relative adequacy of our type III–IV muscle afferent blockade in the face of rising muscle metaboreceptor stimuli, we are unable to attribute the calculated \( \Delta V_E \) in Fig. 5 at the heaviest intensity solely to the effects of muscle afferent feedback and its sequelae.

Finally, we note that fentanyl blockade during exercise using a single leg kick (Amann et al. 2011b) elicited a significant although relatively small hypoventilatory effect, perhaps revealing the important influence of muscle mass on the role of muscle afferents in hyperventilation (Rowell & O’Leary, 1990). These data, as well as those obtained during high intensity prolonged exercise (Amann et al. 2011b), also revealed a relatively greater effect of III–IV afferent blockade on reducing the arterial pressure response to exercise (probably via a reduced sympathetic vasoconstrictor response) than on reducing the exercise hyperventilation.

Why do the fentanyl effects on hyperventilation differ from previous negative findings concerning contributions from muscle afferents to exercise hyperventilation?

We propose that the recent fentanyl blockade findings in health and COPD reveal an obligatory role in steady-state exercise hyperventilation for group III–IV muscle afferent feedback. These data and interpretations differ from previous negative findings (see ‘The work factor’ section above) for the following reasons. First, epidural anaesthetics (see Fig. 6) block efferent (ventral horn) as well as afferent (dorsal horn) neurons resulting in a 20–40% decrement in strength of the lower limbs. Accordingly (as with the effect of curare (Asmussen et al. 1965; Galbo et al. 1987), to maintain a given power output, central command is

![Figure 5. Relative contributions of muscle afferents to hyperventilation during mild to maximum intensity exercise](image-url)
augmented in order to recruit more motor units. The associated parallel increases in respiratory motor output (i.e. corollary discharge) would result in no (net) effect of afferent blockade or even a greater hyperventilatory and/or heart rate response (see Fig. 6; Smith et al. 2003; Amann et al. 2008). On the other hand intrathecal fentanyl blocks only muscle afferents and leaves leg strength unaffected (Amann et al. 2009, 2010, 2011a; Hilty et al. 2011). Presumably then, this μ-opiate receptor agonist partially blocks afferents from a contracting muscle while leaving the remaining primary feedforward stimuli to hyperpnoea unchanged.

Secondly, reports of an accelerated decline of ventilation during recovery from exercise in the face of total vascular occlusion may be explained by two limitations of experimental design. First, there are important interactive effects between mechano- and metabosensitive afferents in a contracting muscle (Hayes et al. 2006), which would not be present in a muscle at rest, i.e. during recovery from exercise. Secondly, the use of total vascular occlusion may have actually reduced (rather than augmented) type III–IV afferent activity in contracting limb muscles as demonstrated by the reduction in $V_E$ accompanying arterial occlusion alone vs. the hyperpnoea which accompanied venous occlusion alone (Haouzi et al. 1993, 2004a) (also see ‘Mechanisms underlying afferent contributions’ section below regarding the effects of venous distension).

It is encouraging that significant effects of intrathecal fentanyl on the cardiorespiratory response occurred with different types of whole body exercise in health (see Figs 1–3) and even in disease states such as COPD (Fig. 4). On the other hand many unknowns remain. Importantly, we do not know to what degree the total III–IV afferent feedback was blocked in any of these experiments – presumably only those, or a portion of those, sensitive to μ-opioid agonists (Hill & Kaufman, 1990). Nor do we know whether the substantial cardiorespiratory effects we have observed are secondary to blockade of the supraspinal pathway from the dorsal horn to the nucleus of the solitary tract and medullary rhythm-generating neurons and/or whether we have interfered with the interactive effects of ascending afferents on descending ‘central command’ influences at the level of the brain stem or spinal motor neurons (Garland & Kaufman, 1995; Dempsey, 2012).

We recognize that there is currently only a very limited amount of data testing the role of group III–IV afferents in cardiorespiratory control in the exercising human using methods which avoid secondary effects on central command mechanisms. Further studies need to consider drug dosages, alternative methods of blockade, means of assessing the degree of total (afferent) blockade and the use of exercise of varying durations, intensities and muscle mass. Also, given the substantial effects of type III–IV muscle afferent blockade in COPD patients on the cardioventilatory response as well as on central locomotor output during exercise (Gagnon et al. 2012; see Fig. 4), similar protocols need to be applied in other chronic diseases such as congestive heart failure (CHF). In animal models of CHF, an enhanced sensitivity of muscle mechanoreceptors to muscle contraction has been reported and implicated.

Figure 6. Effects of epidural lidocaine on power output, quadriceps EMG (marker of central motor output) and hyperpnoea during a 5 km time trial
With epidural lidocaine, prior to cycle exercise, maximum voluntary contraction (MVC) force output was reduced 22% and percentage voluntary activation reduced from 97 to 81%. Throughout the time trial with epidural lidocaine, power output was reduced but quadriceps EMG (%EMG) and $V_E/V_{CO_2}$ were elevated, as was heart rate at any given $V_{O_2}$ (not shown). Data from Amann et al. (2008).
in their sensitized sympathetic response to exercise (Wang et al. 2010).

Mechanisms underlying muscle afferent contributions to the cardiorespiratory response to rhythmic exercise

The cardiorespiratory effects of fentanyl blockade occurred during rhythmic exercise with normal muscle blood flow under steady-state exercise conditions. These findings, though, provide significant anticipatory feed-forward forms of cardioventilatory responses and limb fatigue development in conditions approximating physiological exercise.

Exercise hyperpnoea as a ‘learned’ phenomenon?

The afferent blockade findings have a bearing on the concept of central command as a 'learned' phenomenon pertaining to both the drive to locomotor muscles and to breathing. This idea has emerged, at least in part, because of the failure to demonstrate 'obligatory' reflex contributions to the exercise hyperpnoea (Yamamoto, 1977). For example, Somjen (1992) reasoned that the medullary respiratory neurons are incapable of solving the complex differential equations associated with simultaneous input from multiple peripheral reflexes; thus the higher CNS must rely on stored information learned from past experiences and mistakes to anticipate present and future needs. Thornton et al. also suggested, from their identification in humans of cortical areas involved in central command (see above), that an 'error free' ventilatory response to exercise must be accompanied by 'adaptive feedforward control' (Thornton et al. 2001). Further, Poon et al. postulated an 'emergent controller signal encoding the projected metabolic requirement', which incorporates an 'internal model, self-tuning adaptive control paradigm' (Poon et al. 2007).

Hypothesis

Although several mechanisms which are present during exercise have been shown to drive ventilation when each is studied in isolation, they have not shown an obligatory contribution to the normal hyperpnoea when manipulated in the presence of other 'competing' stimuli during physiological exercise (Yamamoto, 1977). In order to determine whether type III–IV muscle afferents were obligatory to steady-state exercise hyperpnoea we proposed that this proof required: (a) a setting of physiological steady-state exercise, i.e. during which all...
potential stimuli are operative; and (b) a reduction in the hyperpnoea response upon removal/reduction of the stimulus in question without significant alteration of coexisting inputs. We believe the findings employing an intrathecal opiate agonist in several different types of exercise and subjects to date support the hypothesis of an essential contribution of type III–IV muscle afferents to the normal hyperpnoea experienced during mild to moderate rhythmic, large muscle exercise in the human. These findings do not rule out major contributions to the hyperpnoea from other proposed stimuli. Indeed when studied in isolation, CO₂ respiratory exchange and central command elicit significant, precise influences on ventilatory control (see section ‘Three key mechanisms’ above). It remains to be determined what role respiratory CO₂ exchange-related stimuli and/or central command might play as modulators and/or primary drivers of the hyperpnoea when they coexist with each other and with muscle afferent influences during physiological exercise. In anticipation, we would predict a significant interactive effect on the cardioventilatory response to occur between muscle afferent feedback and feedforward central command, with a strong secondary modulatory ‘fine-tuning’ effect of a mechanism specific to CO₂ exchange sensed at the lung. As judged by the substantial ‘feedback’ we have received from many investigators since our first opiate agonist findings were published, it is abundantly clear that many fundamental questions remain. Our hope is that innovative research at the molecular to integrative levels will experience a much needed rejuvenation on this hyperpnoea problem that is so very fundamental to the field of cardiorespiratory control.

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**Additional information**

**Competing interests**

None.

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