THE CONTROL OF THE EXERCISE HYPERPNOEA: CONTRIBUTIONS FROM THIN FIBRE SKELETAL MUSCLE AFFERENTS

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Running title: Group III/IV muscle afferent control of the exercise hyperpnoea

Keywords: Exercise, Muscle afferent feedback, Respiratory control

Word count: 7560
NEW FINDINGS

1. What is the topic of this review?

This review examines the evidence for control mechanisms underlying the exercise hyperpnoea, with particular attention placed on the feedback from thin fibre skeletal muscle afferents, and highlights the often conflicting findings and difficulties encountered by researchers using a variety of experimental models.

2. What advances does it highlight?

There has been a recent resurgence of interest in the role of skeletal muscle afferent involvement, not only as a mechanism of the healthy exercise hyperpnoea but also for its involvement in the manifestation of breathlessness and exercise intolerance in chronic disease.

ABSTRACT

The ventilatory response to dynamic submaximal exercise is immediate and proportional to metabolic rate, which maintains isocapnia. How these respiratory responses are controlled remains poorly understood given that the most tightly controlled variable (\(\text{PaCO}_2/\text{H}^+\)) provides no error signal for arterial chemoreceptors to trigger reflex increases in ventilation. This review discusses evidence for different postulated control mechanisms with a focus on the feedback from group III/IV skeletal muscle mechanosensitive and metabosensitive afferents. This concept is attractive as the stimulation of muscle mechanoreceptors may account for the immediate increase in ventilation exercise onset, and signals from metaboreceptors may be proportional to metabolic rate. A variety of experimental models have been used to establish the contribution of thin fibre muscle afferents in exercise ventilatory control with equivocal results. Inhibiting afferent feedback via the application of lumbar intrathecal fentanyl during exercise supresses ventilation, which provides the most compelling supportive evidence to date. However, stimulating afferent feedback at rest has no consistent effect on respiratory output. However, evidence is emerging for synergistic interactions between muscle afferent feedback and other stimulatory inputs to the central respiratory neuronal pool. These seemingly hyperadditive effects might explain the conflicting findings encountered when using different experimental models. The review also discusses the increasing evidence that patients with certain chronic diseases exhibit exaggerated muscle afferent activation during exercise resulting in enhanced cardiorespiratory responses. This may provide a neural link between the well-established limb muscle dysfunction and associated exercise intolerance and exertional dyspnoea, and hence offer therapeutic targets for these patients.
INTRODUCTION

Muscular exercise imparts a considerable and complex set of physiological stresses on the human body, which must be rapidly responded to if homeostasis is to be maintained. The immediate increases in muscular carbon dioxide production \((\text{VCO}_2)\) and oxygen consumption \((\text{VO}_2)\) at the onset of exercise must be met by proportionate increases in pulmonary ventilation \((\text{V}_\text{E})\) and gas exchange to ensure the maintenance of arterial partial pressures of carbon dioxide \((\text{PaCO}_2)\), oxygen \((\text{PaO}_2)\), and pH. However, despite significant attention from physiologists for well over a century, the mechanism(s) by which ventilation matches metabolic rate during exercise remains very poorly understood – or “ultrasecret” (Grodins, 1981).

Haldane & Priestley (1905) were among the first to establish the importance of \(\text{PaO}_2\) and \(\text{PaCO}_2\) in the regulation of ventilation, and they hypothesised that hyperpnoea during muscular work might simply be a consequence of increased metabolic \(\text{CO}_2\) production. However, as first observed by Douglas and Haldane (1909), \(\text{PaCO}_2\) does not significantly change from resting levels during mild/moderate exercise, and so provides an inadequate stimulus to drive breathing increases. In general, a small transient hypocapnia is often observed at the onset of exercise, and during steady state mild/moderate exercise \(\text{PaCO}_2\) only changes by ≈1-3 mmHg from resting levels in humans (Barr et al., 1964; Forster et al., 1986). This prevention of hypercapnia, despite the large increase in \(\text{VCO}_2\), characteristic of exercise, is an impressive accomplishment of the respiratory system given that its most tightly controlled variable \((\text{PaCO}_2/\text{H}^+\); (Kumar & Prabhakar, 2012)) does not provide an error signal for central and/or peripheral chemoreceptors to trigger reflex increases in ventilation.

How an isocapnic exercise hyperpnoea is achieved remains largely elusive, but there is evidence to suggest that both neural and humoral mechanisms may contribute. In this review, we will briefly describe the characteristics of the normal respiratory responses to dynamic exercise, and evaluate the potential mechanisms involved in the control of the steady-state hyperpnoea. This review will pay particular attention to the contributions of thin-fibre skeletal muscle afferents which has seen a resurgence of interest over the previous decade, not only as a mechanism of the healthy exercise hyperpnoea but also for its involvement in the manifestation of breathlessness and exercise intolerance in chronic disease (Casaburi, 2012). It will discuss the impact of local muscle training interventions on muscle afferent feedback and cardiorespiratory control. Furthermore, the review will also reflect on the numerous difficulties encountered by researchers aiming to reveal the control mechanisms of the exercise hyperpnoea, and how these may inform us about the underlying physiology as well as guiding future lines of inquiry.

THE RESPIRATORY RESPONSES TO EXERCISE

The increases in \(\text{V}_\text{E}\) and gas exchange which occur during constant-load submaximal exercise (i.e. below ‘anaerobic threshold’; Figure 1B) are classically divided into three characteristic phases (Figure 1A; Bennett et al., 1981; Whipp et al., 1982; Casaburi et al., 1989). Phase I: a rapid increase in ventilation within the first breath of exercise onset, with a time constant of only a few seconds. Phase II: a slow exponential rise in ventilation, with a time constant dependent on workload and training status, but typically ≈ 1 minute. Phase III: a steady state in ventilation is achieved. However,
during “heavy” exercise intensities (i.e. above ‘anaerobic threshold’; Figure 1B), steady state ventilation is not achieved, and will continue to drift upwards until exercise cessation.

The important feature of the steady-state hyperpnoea to submaximal exercise, is that its magnitude is proportional to the increase in metabolic rate (\(\dot{V}CO_2\) and \(\dot{V}O_2\)). This is most clearly observed by examining the ventilatory responses to incremental exercise (Figure 1B). Ventilation increases linearly with \(\dot{V}CO_2\) and mixed venous \(PCO_2\) (\(P_{VCO_2}\)), and hence \(\dot{V}CO_2\) remains similar to resting levels. During heavy exercise however, ventilation increases at a proportionately greater rate than \(\dot{V}CO_2\), and \(\dot{V}CO_2\) consequently declines. This hyperventilation is traditionally explained by the simultaneous metabolic acidosis (elevated plasma lactate/\(H^+\), produced from working muscles) stimulating peripheral chemoreceptors; and the augmented ventilation partially compensates for the reduction in arterial pH(Rausch et al., 1991). However, it is likely that other mechanisms are also able to significantly contribute to this phenomenon (for review see Forster et al., 2012). During maximal exercise, minute ventilation can rise beyond 150 l.min\(^{-1}\) in healthy adults, and it has been recorded >200 l.min\(^{-1}\) in elite endurance athletes – although these can only be maintained for brief periods(Lumb, 2017).

CONTROL MECHANISMS OF THE EXERCISE HYPERPNOEA

It is important to consider the characteristics of the normal ventilatory responses to exercise as any control mechanism, or combination of mechanisms, must account for the entirety of the response. Perhaps the most significant characteristics are:

- The immediate increase in ventilation at the onset of exercise
- The close matching of ventilation with metabolic rate during submaximal exercise
- The large magnitude of the ventilatory response

Consequently, the mechanism responsible must be able to generate all these features. This has led to speculation that no single mechanism can possibly account for all the characteristic responses, and multi-mechanistic or ‘neurohumoral theories’ have been developed(Dejours, 1964). Dejours was amongst the first to reason that because ventilation increases within the first breath at exercise onset, it is unlikely to be mediated by a ‘slow’ humoral mechanism, but instead implicates a ‘fast’ neural mechanism. Furthermore, the achievement of steady state ventilation which closely matches metabolic rate was regarded to be more consistent with a humoral mechanism fine tuning the ventilatory response. Whether or not different mechanisms contribute to certain aspects of the hyperpnoea’s temporal pattern is unclear, but there certainly is evidence that multiple mechanism can drive, in part at least, exercise ventilatory responses. Figure 2 shows a schematic diagram of several structures hypothesised to contribute to the control of the exercise hyperpnoea.

HUMORAL MECHANISMS – CENTRAL AND PERIPHERAL CHEMORECEPTION

Several intracranial chemoreceptive sites have been identified; localised in regions including the brainstem, cerebellum and hypothalamus(Nattie & Li, 2012). One important group of brainstem neurones is the retrotrapezoid nucleus (RTN), which is thought to contribute to the generation of
the respiratory rhythm and chemoreception (Nattie & Li, 2002; Guyenet, 2014). Central chemoreceptors are sensitive to [H+] within the brain's extra cellular fluid, supplied by freely diffusing CO₂ across the blood brain barrier. Peripheral sites capable of chemoreception include the carotid body (CB) and the aortic body, with the former considered most important (Prabhakar & Peng, 2004). Their glomus type 1 cells are sensitive to a variety of chemical signals; e.g. PO₂, PCO₂, pH, K⁺, catecholamines; and are innervated by the carotid sinus branch of the glossoaryngeal nerve relaying signals to the nucleus tractus solitarii (NTS; Kumar & Prabhakar, 2012) which further projects to RTN (Guyenet et al., 2018). Although chemoreceptors are stimulated by both hypercapnia and hypoxaemia they are significantly more sensitive to the former, with the V̇e-PaCO₂ slope being much steeper around its respective sea-level operating point (Lumb, 2017).

As stated above however, PaCO₂/H⁺ (and PaO₂) changes little during exercise; and while PaCO₂ increases proportionately with workload (Figure 1B), there is currently no strong anatomical or functional evidence supporting the existence of chemoreceptors in the venous circulation that can drive the exercise hyperpnoea (although their existence is still be possible; for review see Parkes, 2017). Despite this, other mechanisms have been hypothesised which may permit arterial chemoreceptors to contribute to the exercise ventilatory response, such as an increased chemosensitivity to PaCO₂. This hypothesis has been tested repeatedly but with contrasting outcomes, where sensitivity to CO₂ inhalation during exercise has been shown to increase (Weil et al., 1972; Cummin et al., 1986), or undergo no change (Asmussen & Nielsen, 1957; Duffin et al., 1980). The cause of this disparity is unclear, although training status might affect the change in CO₂ sensitivity from rest to exercise (McConnell & Semple, 1996). However, as PaCO₂ changes very little during exercise, and because the threshold of central and peripheral chemoreceptor responsiveness to CO₂/H⁺ also remains unchanged (Casey et al., 1987; Duffin & McAvoy, 1988), any increase in chemosensitivity would likely only account for a small fraction of the normal exercise ventilatory response. Despite these findings, there is evidence that RTN serotonergic neurons are activated during dynamic exercise in animals (Veasey et al., 1995; Barna et al., 2012), suggesting that central chemoreceptors may regulate the exercise hyperpnea by mechanisms independent of PaCO₂/H⁺ (Guyenet & Bayliss, 2015). Indeed there is emerging evidence that RTN neurones may be activated by feedback from skeletal muscle afferent fibres (Kanbar et al., 2016).

Studies have also examined the specific contribution of the CB and there is evidence of increased CB sensitivity to hypoxia in exercise (Asmussen & Nielsen, 1957). Further proposed CB stimuli during exercise include: increases in the amplitude and/or slope of the breath-to-breath oscillations in arterial pH (Band et al., 1980; Cross et al., 1982); and workload dependent increases in circulating catecholamines or K⁺ (Paton, 1992). For example, the infusion of K⁺ (Paterson et al., 1992) and noradrenaline (Heistad et al., 1972) to levels observed in heavy exercise results in small increases in resting ventilation (≈40% and ≈25% increases respectively) which were abolished with the application of hyperoxia, demonstrating the CBs as the likely site of action. Again however, these responses driven by the CB seem only able to account for a very small fraction of the normal exercise ventilatory response. Furthermore, although human carotid body denervation seems to slow ventilatory kinetics during constant load exercise (i.e. the phase II time constant), it does not prevent phase I or the eventual achievement of isocapnic steady state ventilation (phase III; Wasserman et al., 1975). This seems consistent with the notion that CBs may be important in
‘fine-tuning’ the ventilatory response to exercise, but may not be necessary for the rapid increase at exercise onset, nor the gross matching of steady-state ventilation with metabolic rate (Parkes, 2013).

NEURAL MECHANISMS – CENTRAL COMMAND

Within the concept of ‘central command’ it is generally viewed that descending neural signals from suprapontine sites, that excite spinal locomotor neurones during exercise, concurrently converge onto cardiovascular and respiratory control areas of the brainstem (Williamson, 2010; Paterson, 2014). Central command therefore operates as a ‘feedforward’ control system where there is parallel activation of locomotor and cardiorespiratory neurones at exercise onset. While there is strong indirect evidence that descending signals from higher brain centres can alter cardiorespiratory responses it has been a continual challenge for physiologists to definitively examine the concept.

Work from Johansson (1893) and Krogh & Lindhard (1913) first established the central command hypothesis. Krogh & Lindhard’s experiments were the first performed on humans and proposed that “cortical irradiation” (central command) caused the immediate ventilatory and heart rate increases observed at the beginning of exercise, and were responsible for the altered cardiorespiratory responses to changes in perceived load of a cycling exercise. Over the following century, a wide variety of ingenious experimental designs have been used to examine the role of central command in ventilatory and cardiovascular control.

Uncoupling motor drive and exercise workload

Several techniques have been used to manipulate the level of central motor drive (central command) during the performance of a given exercise workload in humans. These include using partial neuromuscular blockade (NMB) via intravenous application of tubocurarine in humans (Asmussen et al., 1965; Galbo et al., 1987), and tendon vibration to elicit tension in the muscle via activation of spindle afferents and the local ‘stretch’ reflex pathway (Goodwin et al., 1972). During NMB, the augmented ventilatory, heart rate and blood pressure responses to cycling exercise likely reflect greater central command activation needed to maintain the constant workload in the ‘weakened’ muscles. In addition, diminished cardiorespiratory response during vibration of the exercising muscles tendon likely reflect the reduced central command required to generate a given tension. Collectively, these results provide evidence, albeit indirectly, for the concept of a central command mechanism as they demonstrate that the magnitude of the central motor drive affects cardio-respiratory responses to a given exercise task.

Identifying the neurocircuitry of central command

Several investigations have attempted to identify areas of the brain capable of driving parallel locomotor and cardiorespiratory responses. Early animal studies have shown that electrical and pharmacological stimulation of the subthalamic locomotor region in unanaesthetised decorticate cats induces locomotion and results in respiratory and blood pressure responses similar to that of spontaneous exercise (Eldridge et al., 1981; Eldridge et al., 1985; Waldrop et al., 1988). Importantly, respiratory responses were also observed in paralysed cats suggesting that neural
feedback from the exercising muscles was not driving the effect. Further decorticate animal studies have also demonstrated that other regions, including the thalamus, hypothalamus, basal ganglia and mesencephalic locomotor region, can generate locomotion in parallel with cardiorespiratory responses (Smith et al., 1960; DiMarco et al., 1983; Ordway et al., 1989; Bedford et al., 1992). Together, these findings are consistent with the concept of a central command control system and suggests these subcortical structures could be involved in its neurocircuitry. They also imply that feedback control mechanisms are unessential for normal exercise ventilatory responses. However, as hypothalamic lesioning has no effect on the cardiorespiratory responses to exercise in the awake animal (Waldrop et al., 1986; Ordway et al., 1989), an element of redundancy in the control system is likely.

Since these early studies, the functional neurosurgery of patients with movement disorders or chronic pain has made it possible for deep brain stimulating electrodes to be implanted stereotaxically into the midbrain of humans. It has been experimentally demonstrated that stimulation of the subthalamic nucleus, thalamus, substantia nigra and dorsal periventricular/periaqueductal grey matter can all result in significant increases in mean arterial pressure and heart rate (Thornton et al., 2002; Green et al., 2005). However, caution is still necessary as “their role has to be viewed in context with the higher centres that are responsible for initiating exercise” (Thornton et al., 2002). So, although the isolated stimulation of these regions can induce cardiorespiratory responses, it is impossible to establish whether this is comparable to the activation of these pathways during normal human exercise.

Therefore, several techniques have been used to establish regions of the brain that are active during human exercise (Paterson, 2014). Using positron emission tomography, Thornton et al. (2001) demonstrated that imagined exercise under hypnosis increased ventilation and heart rate, and activates several motor areas of the brain (e.g. dorsolateral prefrontal cortex, the primary and supplementary motor areas, cerebellum), as they are in voluntary exercise (Fink et al., 1995). As these areas are known to be involved with motor control including the volitional control of respiratory muscles (Colebatch et al., 1991; Ramsay et al., 1993) these structures might conceivably form part of a central command system. Interestingly, the findings also imply that the cardiorespiratory responses to central command activation may not require the parallel increase in central motor drive, and that perhaps it’s the perception of work/effort that drives the response.

More recently Green et al. (2007) examined the neural activity of midbrain regions during mild pedalling exercise (15W) by recording local field potentials with deep brain stimulating electrodes. As predicted from previous work (Thornton et al., 2002), exercise resulted in increased activity of the subthalamic nucleus. Furthermore, both the anticipation to exercise and its performance increased the activity of periaqueductal grey (PAG) neurones. It was concluded that the PAG is likely an important site for cardiorespiratory control in exercise, perhaps acting as a relay centre for descending signals from higher brain centres to cardiorespiratory neurones in the medulla, although there is no evidence that it has a role in the control of locomotion (Green et al., 2007). Furthermore the activity of the PAG increases during skeletal muscle afferent activation (via post exercise circulatory occlusion, (Basnayake et al., 2011)) signifying that this site may be also be important in integrating the cardiorespiratory responses to muscle afferent activation and central command.

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In conclusion, despite the limitations of imagined exercise, using very low exercise intensities, and testing patients with movement disorders, the human studies described above provide indirect evidence for the central command hypothesis and offer possible cortical and subcortical areas that could be involved in its neurocircuitry. Animal studies provide more direct evidence (e.g. Eldridge et al., 1981) but it is impossible to determine whether the findings from experimental conditions are comparable to voluntary exercise. Nevertheless, despite incomplete understanding of the neurocircuitry, it is likely that descending motor signals from higher brain areas are able to drive ventilatory and cardiovascular responses in exercise.

NEURAL MECHANISMS – SKELETAL MUSCLE AFFERENT FEEDBACK

The cell bodies of skeletal muscle afferent nerves are located in the spinal dorsal root ganglion, and are classically categorised into 4 groups by their physiological characteristics (Lloyd, 1943). Group I (subdivided as Ia and Ib) and II afferent fibres are thickly myelinated and conduct impulses between 72-120 m/s and 31-71 m/s respectively. Group Ia and II afferents innervate muscle spindles and group Ib innervate Golgi tendon organs. Group III (Aδ) and group IV (C-fibres) muscle afferents are thinly myelinated and unmyelinated respectively. Group III fibres conduct impulses between 2.5-30 m/s and group IV afferents are slower still at <2.5 m/s. The free nerve endings of group III muscle skeletal muscle afferent fibres are commonly located within the myotendinous junction, and group IV fibres within the vascular network (Stacey, 1969); likely reflecting their physiological characteristics (see below). These thin fibre afferents synapse at the laminae of the dorsal horn and project to several regions of the brainstem including the NTS – a key integrating site for afferent inputs integral in cardio-respiratory regulation (Kalia et al., 1981; Kaufman & Forster, 1996; Potts, 2001).

Muscle afferent feedback is important in controlling autonomic output and the cardiovascular system in human exercise (Kaufman & Hayes, 2002; Fisher et al., 2015). Alam & Smirk (1937) were first to demonstrate that after cessation of exercise the occlusion of blood flow to the previously exercised muscle resulted in a maintained elevation of blood pressure above resting levels. Post exercise circulation occlusion (PECO) traps metabolic by-products of muscle contraction and this blood pressure response, or ‘pressor reflex’, continues until perfusion is restored. PECO generates a sustained sympathoexcitation (Seals et al., 1988), and one commonly used explanation for its function is to assist in the adequate perfusion of muscles generating low contractile force, removing the metabolic error signal by clearing metabolites, and potentially delaying muscle fatigue (Luu & Fitzpatrick, 2013). Though occluding pressures can be a very low percentage of maximal force in human muscle (e.g. 20% in calf and quadriceps [Barcroft & Millen, 1939; Edwards et al., 1972]) making this unlikely as a universal explanation.

The reflex component of this pressor response was examined further in animals. Electrically evoked hindlimb muscle contraction results in cardiovascular responses in isolation of central command activation (Coote et al., 1971). These responses could then be abolished by sectioning the dorsal roots (L6-S1), thus clearly demonstrating the reflex nature of the response. As electrical stimulation of group III and IV afferents increased sympathetic nerve output (Coote & Perez-Gonzalez, 1970), it was likely that the pressor reflex is triggered by the stimulation of these afferent...
fibres. This was subsequently confirmed by McCloskey & Mitchell (1972), as only the selective blockade of group III and IV afferent fibres (but not I and II) abolished the cardiovascular response to hindlimb contraction. The discharge properties of group III and IV muscle afferents suggest they tend to respond to different stimuli (Kaufman et al., 1983; Kaufman et al., 1984a). Group III afferents primarily fire rapidly after contraction, in synchrony with rhythmic contractions, and are also activated by mechanical non-noxious stimuli such as stretching and compression (Kaufman et al., 1983; Mense & Stahnke, 1983; Kaufman & Rybicki, 1987). As such, group III muscle afferents are viewed as more mechanosensitive or ‘mechanoreceptors’. During muscle contraction, group IV afferent discharge increases with a latency consistent with the build-up of metabolites, and concurrent circulatory occlusion results in a greater discharge frequency of group IV afferents compared with group III (Kaufman et al., 1984b). As such, group IV muscle afferents are viewed as more metabosensitive or ‘metaboreceptors’. Metabolites able to stimulate skeletal muscle afferent fibres include lactic acid/H\(^+\), ATP, bradykinin, and prostaglandins (Kaufman et al., 1983; Rotto & Kaufman, 1988; Hanna & Kaufman, 2004). However, group III and IV afferents also display a degree of polymodality as, for example, metabolite accumulation can increase the discharge firing frequency of populations of group III afferents and increase their sensitivity to mechanical stimuli (Kaufman et al., 1984b; Hayes et al., 2006).

Skeletal muscle afferent feedback and ventilatory control

Limbs afferent feedback is important in the phenomenon of locomotor-respiratory coupling, where the discharge rhythm of sensory inputs can entrain central respiratory pattern generation (Potts et al., 2005; Shevtsova et al., 2019). This current review however will focus on whether thin fibre muscle afferents (group III/IV) can drive hyperpnoea in exercise. Due to the well-established importance of muscle afferent feedback on cardiovascular control in exercise (Smith et al., 2006; Fisher et al., 2015) it is logical to hypothesise that it could also elicit ventilatory responses. Indeed, this hypothesis is very attractive as neural projections from mechanosensitive afferents may be able to account for the rapid increase in ventilation at the onset of exercise, and signals from metaboreceptive afferents may be in proportion to metabolic rate – and hence drive two key characteristics of the exercise hyperpnoea (see section: Control Mechanisms of the Exercise Hyperpnoea). The following section reviews the evidence from studies utilising different experimental techniques.

Electrically induced muscle contractions

Electrically induced muscle contractions allow the assessment of muscle afferent contributions to cardiorespiratory control in isolation from central command. Early studies using anesthetised animals have demonstrated reflex ventilatory responses which can be abolished by spinal cord transection (Comroe & Schmidt, 1943; Coote et al., 1971) or the specific blockade of group III and IV muscle afferent fibres (McCloskey & Mitchell, 1972; Tibes, 1977). However, the removal of humoral stimuli downstream of the exercising muscle by use of a cross-circulation model does not affect the ventilatory (Kao, 1963). These initial findings support the concept that nervous signals projecting from the working muscle can mediate the exercise hyperpnoea, without the need for humoral stimuli. It is likely that both metabolic (Tallarida et al., 1979; Rotto et al., 1989; Hanna et al., 2002) and mechanical stimuli (Wilson et al., 1994; Hayes & Kaufman, 2001) drive this reflex response.
However, these findings are not universally demonstrated. Several other investigations which similarly used electrically induced hind-limb muscle contractions of anesthetised animals have shown ventilation increasing proportionately to metabolic rate despite spinal cord transection (Lamb, 1968; Levine, 1979; Weissman et al., 1980). Further inconsistencies are shown in human experiments. Electrically induced muscle contractions of both awake healthy humans and paraplegic patients with complete spinal cord transection result in hyperpnoea proportional to metabolic rate (Adams et al., 1984a; Adams et al., 1984b; Brice et al., 1988a; Brice et al., 1988b). It was argued that the apparently normal ventilatory response in the paraplegic patients was likely driven by a humoral mechanism. Indeed, when venous outflow from the contracting muscle of paraplegic patients was abolished by the inflation of a cuff a decrease in the ventilatory response was observed (Brown et al., 1990). However, this decrease was only several seconds after (and in proportion to) a decrease in \( P_{\text{ETCO}} \), and could be predicted by normal \( CO_2 \) responsiveness. This implies that reductions in \( PaCO_2 \) likely supressed ventilation in this instance, which therefore does not support the concept of a humoral exercise control mechanism, as \( PaCO_2 \) remains stable in ‘normal’ mild-moderate exercise. Interestingly, closer examination of the data reveals that \( \approx 50\% \) of the exercise ventilatory response was maintained during occlusion (Brown et al., 1990). As contractions were applied in the apparent absence of a central command, muscle afferent and humoral stimulus, the mechanism of the response is unclear. As such, electrically induced muscle contractions may be an unreliable or invalid approach to examine the contributions of muscle afferent feedback in ventilatory control; other methods are clearly needed.

**Epidural and intrathecal anaesthesia during human exercise**

The application of local anaesthetics (e.g. lidocaine or bupivacaine) into the lumbar epidural space will inhibit the neurotransmission from group III and IV muscle afferents from exercising lower limbs. Despite the suppression of cardiovascular responses however, the block does not attenuate hyperpnoea during cycling exercise (Hornbein et al., 1969; Fernandes et al., 1990). It could therefore be concluded that muscle afferent feedback is unnecessary for the normal exercise ventilatory response. However, as epidural anaesthesia reduces efferent nerve activity to exercising muscle, the technique will unavoidably enhance the level of central motor drive (and central command) required to achieve the same work load. This increased central command activity may mask the effects of reduced sensory feedback.

More recently, several research groups have inhibited muscle afferent feedback during exercise through the lumbar intrathecal application of the \( \mu \)-opiate agonist fentanyl (e.g. (Amann et al., 2010; Gagnon et al., 2012; Olson et al., 2014). Importantly, this technique seems to not alter the force generating capacity of skeletal muscle (Amann et al., 2009). Amann et al. (2010) demonstrated that both the ventilatory and cardiovascular responses to dynamic cycling exercise are significantly attenuated with the use of fentanyl compared to placebo conditions. No differences were shown during exercise at 50W exercise, but minute ventilation at 100W, 150W and 325W was reduced by \( \approx 8\%-17\% \). However, this is likely an underestimate of the true effect due to the rise in \( PaCO_2 \) that occurred by consequence of the hypoventilation \( P_{\text{ETCO}} \) was elevated above control exercise conditions by \( \approx 4\%-7\text{mmHg} \), and based upon participant \( CO_2 \) sensitivity, it was estimated that the inhibition of afferent input could reduce ventilation by as much as \( 15\%-49\% \). This data provides the most compelling evidence to date that muscle afferent feedback contributes to the generation of the exercise hyperpnoea.
Muscle metabo/mechano receptor stimulation via PECO and passive stretch/movement

PECO and passive muscle stretch/movement allow researchers to isolate the reflex contributions of muscle metaboreceptors and mechanoreceptors. Indeed, these approaches have suggested that the ‘metaboreflex’ and ‘mechano reflex’ differentially regulate autonomic outflow in exercise, with larger contributions to sympathoexcitation and vagal withdrawal respectively (Seals et al., 1988; Gladwell et al., 2005). However, using these approaches to examine ventilatory control have yielded far less consistent results.

Although it is well established that the stimulation of metabolically sensitive afferents via PECO increases sympathetic vasomotor activity, most evidence suggests it is unable to drive increases in ventilation. As classically shown by Rowell et al. (1976), following the cessation of cycling exercises performed at different intensities (50W-250W) PECO maintained blood pressure at the exercising level, but ventilation returned to baseline. In direct contrast to the findings of Amann et al. (2010), Rowell et al. concluded that “respiratory control ‘centres’ appear to receive no significant input from ‘metabolic sensors’ in muscle.” These results have been confirmed in healthy humans by other investigations applying circulatory occlusion following cycling exercise (Innes et al., 1989; Haouzi et al., 1993; Scott et al., 2000; Haouzi et al., 2001; Fukuba et al., 2007; Olson et al., 2010), rhythmic handgrip exercise (Scott et al., 2002; Bruce et al., 2016), and static exercise (Wiley & Lind, 1971; Bruce, 2014).

It is not fully understood why inhibiting afferent feedback during exercise can suppress ventilation but stimulating afferent feedback after exercise has no consistent effect on respiratory output. It is possible that enhanced neural feedback from metabosensitive afferents is unable to drive ventilation alone without the presence of other potentially interactive/synergistic inputs to the central respiratory neuronal pool that are normally active in exercise – such as central command, muscle mechanoreflex, or feedback from central/peripheral chemoreceptors. Indeed, it has been shown that circulatory occlusion following handgrip (Lykidis et al., 2010) and calf plantar flexion exercise (Bruce & White, 2012) can induce ventilatory responses, but only during conditions of concurrent hypercapnia. Indeed, the responses are progressively augmented with increasing P_{ET}CO_2 (Alghaith et al., 2018). These findings could be explained by an augmented muscle acidosis during hypercapnia, but further studies revealed that the interaction occurs centrally (Bruce & White, 2015). Interactions within the CNS are possible as both peripheral chemoreceptor and skeletal muscle afferents project to the NTS (Paton, 1999), which is a possible site of central chemoreception itself (Nattie & Li, 2012). Therefore, the observations may suggest the existence of a central synergistic, or hyperadditive, interactions between feedback from the metaboreflex and ventilatory chemoreflex – where the overall response exceeds the sum of the individual components/mechanisms.

The role of muscle mechanoreceptors in human cardiorespiratory control have been classically examined using passive limb movement or passive sustained stretching of the muscle, which aim to isolate their contribution from central command and a metaboreflex. Dynamic passive movement of both legs using a custom tandem exercise chair apparatus has been shown to drive small ventilatory responses in humans (Bell & Duffin, 2006). However, dynamic movement of a large muscle mass might also lead to the active recruitment of postural muscles, and hence central command activation. Therefore other approaches have been used, but both passive calf muscle

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stretch (Bruce & White, 2012) and passive knee movement (Silva et al., 2018) only result in small insignificant increase in ventilation while breathing room air. However, under both hypercapnic and hypoxic conditions human muscle mechanoreceptor stimulation can generate ventilatory responses (Bruce & White, 2012; Silva et al., 2018) which, similarly to metaboreceptive afferent feedback, suggests the existence of synergistic interactions between the muscle mechanoreflex and ventilatory chemoreflex.

Figure 3 summarises these hyperadditive relationships described above. It also shows that synergistic interactions have not been universally concluded. Circulatory occlusion following static handgrip exercise produces similar responses during normoxia and hypoxia (Edgell & Stickland, 2014). It is not clear why the disparity of findings exist although, interestingly, the ventilatory increase during hypoxic PECO is very similar to that observed during hypercapnia which was raised significantly above steady-state baseline ((Lykidis et al., 2010; Figure 3). Therefore, it is possible that any hyperadditive effect may have been ‘masked’ by the atypical small ventilatory response observed during normoxic PECO ((Edgell & Stickland, 2014)figure 3). Clearly further examination is required.

Collectively, these data suggest a possible mechanism responsible for the changes in O₂ and CO₂ sensitivity that have been observed during whole body exercise (e.g. (Weil et al., 1972)). Furthermore, even though these studies are un-physiological, they may indicate that muscle afferent feedback can drive ventilatory responses during the activation of other potentially synergistic inputs that increase central respiratory drive during exercise (e.g. central command, the muscle mechanoreflex etc). Indeed, it is well-established that the circulatory occlusion of exercising limbs results in significant increases in heart rate, blood pressure and ventilation (Asmussen & Nielsen, 1964; Sargeant et al., 1981; Stanley et al., 1985), which may reflect greater metaboreflex activation during exercise. However, it is impossible to distinguish whether these findings are caused by an enhanced muscle metaboreflex or the greater central motor drive (central command) required to compensate for the reduced capacity of the ischemic muscle. A new experimental design aimed to resolve this issue by assessing the cardiorespiratory responses to single legged dynamic exercise during additional isolated muscle metaboreflex activation (of the contralateral leg). Additional metaboreflex activation resulted in a significantly greater steady-state ventilation during exercise, whereas metaboreflex activation at rest had no effect (Lam et al., 2019). These findings clearly demonstrate that muscle metaboreceptive afferents can drive ventilatory responses in exercise, and may help explain why conflicting findings exist between studies which manipulate muscle afferent activity during rest, (e.g. (Rowell et al., 1976); or during exercise (e.g. (Amann et al., 2010) where other potentially synergistic mechanisms are active and the contribution of the metaboreflex on ventilatory control may be revealed.

THE EXERCISE HYPERPNOEA - SYNERGY AND REDUNDANCY

To date, there is no evidence that any one single hypothesised control mechanism can drive the entirety of the human state-state exercise hyperpnoea. Unless another, as yet unknown, mechanism is responsible for the entirety of the response, this may suggest that multiple mechanisms operate collectively. If a linear relationship exists between 1) the number/magnitude of
stimulatory inputs projecting to central respiratory neurons and 2) the resultant ventilatory response (Figure 4A), it should be possible to isolate the contribution of each component to the entire response. However, this concept is not consistent with the literature thus far. But recent evidence that mechanisms might interact synergistically when operating in combination (Lykidis et al., 2010; Bruce & White, 2012; Alghaith et al., 2018; Silva et al., 2018) could have important implications for our understanding of the nature of the control system underlying exercise ventilation. Thus, experimentally stimulating mechanisms alone may result in little or no response, but their combination is hyperadditive so the end response is ‘amplified’. If true, this would explain the difficulty many researchers have encountered when using a variety of experimental models (e.g. PECO, passive movement, IV administration of K⁺ or adrenaline etc.). Furthermore, if multiple mechanisms exist then it is likely that there will be redundancy in the control system(Forster et al., 2012), and hence explain why abolishing/inhibiting control mechanisms (e.g. spinal anaesthesia, carotid body denervation, electrically induced muscle contraction) only has a small effect relative to the size of the total response, or has no effect on ventilation.

This concept of mechanism synergy and redundancy can be illustrated in a theoretical model (Figure 4B). Here the relationship between the input (X axis = number/magnitude of ‘control mechanisms activated’) and output (Y axis = exercise ventilatory response) is described by a sigmoid logistic function. The normal steady-state ventilatory response for a given workload (i.e. Y = 100%) is achieved by the normal activation of multiple control mechanisms (i.e. X = 100%). However, the experimental stimulation of a single control mechanism at rest (e.g. X = 10%), has little effect on ventilation because a theoretical ‘threshold’ has not been reached. Equally, the inhibition of a single mechanism during exercise (e.g. X = 90%) also has little effect due to a ‘saturation’ in the response. This type of relationship might be physiologically advantageous as an abnormality in a control mechanism would have a restricted effect on exercise ventilatory control. Clearly this model is highly speculative, over-simplified, and it does not attempt to explain the more complex question of how steady-state ventilation matches metabolic rate. But it is certainly plausible that ventilatory output will be some complex (i.e. non-linear) function of the neural inputs projecting onto central respiratory control centres, making experimentation difficult. Further work is needed examining animal and human integrative physiology, particularly investigating the existence of synergism in ventilatory control systems.

SKELETAL MUSCLE AFFERENT FEEDBACK AND VENTILATORY CONTROL IN CHRONIC DISEASE STATES

Exertional dyspnoea commonly manifests in several chronic disease states, including chronic obstructive pulmonary disease (COPD) and heart failure (HF). Current opinion considers dyspnoea to be generated in brain networks through dynamic integration of sensory afferent inputs and individual learned experience of dyspnoeic stimuli(Marlow et al., 2019). Sources of respiratory afferent input include peripheral sensory afferents from the pulmonary system and an ascending sensory copy of efferent motor output to the respiratory muscles (neural respiratory drive; NRD(Parshall et al., 2012). The intensity of exertional dyspnoea in chronic respiratory disease patients has been shown to be closely related to increased levels of NRD, reflecting the increased load on, and/or reduced capacity of, the respiratory muscles(Reilly et al., 2011; Faisal et al., 2015; Jolley et al., 2015; Jensen et al., 2016; Jolley & Moxham, 2016). Distinct sensations of dyspnoea,
most importantly “work/effort”, “air hunger” (“unsatisfied inspiration”/”urge to breathe”) and “chest tightness”, are likely to originate from central integration of differing sources of afferent information(Parshall et al., 2012; Laviolette & Laveneziana, 2014; Faisal et al., 2015). Currently, the afferent receptors of the pulmonary system most widely implicated in the neuromodulation of neural respiratory drive and dyspnoea include central and peripheral chemoreceptors, slowly and rapidly adapting stretch receptors, bronchopulmonary C-fibres (including juxtacapillary or j-fibres) and chest wall and respiratory muscle spindles and Golgi tendon organs(Buchanan & Richerson, 2009; Lee, 2009; Widdicombe, 2009; Burki & Lee, 2010).

Sensations of dyspnoea are a major contributor to the reductions in exercise tolerance and quality of life classically observed in chronic conditions such COPD and HF(O’Donnell et al., 2009). However, only weak relationships exist between exercise capacity and ventricular dysfunction in HF(Franciosa et al., 1981; Higginbotham et al., 1983), and flow limitation in COPD(Killian et al., 1992; Gosselink et al., 1996); suggesting that mechanisms other than the ‘primary pathology’ likely contribute. Indeed, there is considerable evidence that exercise capacity is impaired due to limb muscle dysfunction, where there is a reduction in force/power generating capacity and abnormalities in energy metabolism, resulting in weakness and early muscle fatigue(Minotti et al., 1991; Serres et al., 1998; Gosker et al., 2000; Maltais et al., 2014; Keller-Ross et al., 2019). There is substantial overlap in the features of muscle dysfunction between COPD and HF, including: atrophy of muscle fibres and accumulation of fat, slow to fast fibre type transition, increased glycolytic enzyme activity, and decreased mitochondrial density and oxidative capacity(Gosker et al., 2000; Franssen et al., 2002; Gosker et al., 2003).

During exercise, these changes result in an increased reliance on anaerobic metabolism and alterations in muscle metabolite profile during exercise, an early onset lactic acidosis and greater reductions in muscle pH, which in turn is associated with an augmented ventilatory response to a given workload(Massie et al., 1987; Casaburi et al., 1991; Kutsuzawa et al., 1992). Therefore, the manifestation of limb muscle dysfunction may contribute to sensations of exertional dyspnoea. Among other potential factors, such as chronic muscle tissue under-perfusion and hypoxia, it is likely that physical inactivity and disuse significantly contributes to these abnormalities in skeletal muscle function(Serres et al., 1998; Rehn et al., 2012). Indeed, this forms the concept of a ‘dyspnoea spiral’(Cooper, 2001; Polkey & Moxham, 2006; Ramon et al., 2018) where patients avoid physical exertion to prevent the manifestation of dyspnoea, which consequently leads to further skeletal muscle deconditioning and metabolic derangements. In this way, dyspnoea and exercise intolerance can spiral downwards over time (figure 5).

Given the degree of limb muscle dysfunction, evidence of abnormal skeletal muscle afferent feedback during exercise in these chronic disease states is unsurprising. In HF, augmented skeletal muscle afferent feedback is widely regarded as a significant factor to the excessive sympathoexcitation and cardiovascular responses in exercise, as well as the sensations of dyspnoea from excessive ventilatory responses(Sinoway & Li, 2005; Piepoli et al., 2008). Interestingly, it still remains unclear whether this is due to increased feedback from muscle metaboreceptors, greater activation/sensitivity of mechanoreceptors or a combination of both(Middlekauff & Sinoway, 2007; Piepoli & Coats, 2007). Nevertheless, there is substantial evidence that HF patients can exhibit exaggerated muscle metaboreflex activation to PECO, after both handgrip and cycling exercise, resulting in enhanced cardiorespiratory responses(Piepoli et al., 1996; Silber et al., 1998; Scott et al.,

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The increased response, in comparison to that classically shown in health, is likely a reflection of a greater metabolite production/accumulation for a given relative workload, but there is recent evidence of an increased expression of muscle metaboreceptors (P2X3, COX-2, and TRPV1) contributing to the enhanced metaboreflex activity in HF (Smith et al., 2019). There is also emerging evidence in COPD of augmented ventilatory responses to muscle metaboreflex activation (Bruce et al., 2016), and abnormalities in mechanoreflex activation (Aranda et al., 2019) which may contribute to sensations of dyspnoea. More work is needed however to further examine the potential role of exaggerated muscle afferent feedback in COPD pathology.

Further work in chronic disease states has potential to be of great value, as enhanced feedback from group III/IV afferent fibres may provide the ‘neural link’ between skeletal muscle dysfunction and the manifestations of dyspnoea and exercise intolerance (figure 5 in red). If this link exists it could provide a novel therapeutic target as muscle plasticity largely remains intact in these chronic conditions, unlike the often irreversible cardiac and pulmonary changes. The potential for a therapeutic target is enhanced by evidence showing that the experimental inhibition of group III/IV neurotransmission via intrathecal fentanyl administration reduces exercise ventilatory responses, sensations of dyspnoea and improves cycling performance in COPD and HF patients (Gagnon et al., 2012; Olson et al., 2014). Clearly spinal anaesthesia is not a realistic management strategy, but it does suggest that therapies capable of inhibiting muscle metabo/mechanoreceptor activity in exercise has the potential of reducing sensations of dyspnoea and improving functional capacity. In this pursuit, exercise training strategies have been the most widely examined.

MUSCLE AFFERENT FEEDBACK AND EXERCISE TRAINING

Early human cross-sectional studies examining the relationship between whole body, or local muscle, training status and cardiorespiratory and autonomic responses to activation of muscle afferents, produced equivocal results when identifying differences between trained and untrained individuals (Seals, 1991; Saito et al., 1993; Fisher & White, 2004). This may be due, in part, to the confounding influence of central command which is inevitably activated during voluntary exercise. In addition, the influence of differing muscle fibre type distributions on muscle metaboreflex activation was not always appreciated and controlled for. Furthermore, the frequently used standardisation of an exercise task to a given percentage of maximal voluntary force when comparing individuals, may not always adequately control for the variations in intra muscular pressure generated by larger or smaller muscle masses in both trained and untrained participants (Humphreys & Lind, 1963; Edwards et al., 1972). This has implications for occlusion of blood flow, and hence metabolite accumulation, during sustained isometric as well as rhythmic contractions, when a critical closing pressure may be attained at different percentages of maximal muscle force in different participants.

When properly controlled comparisons are made, for example, during measurement of pressor responses during electrically evoked isometric exercise of the calf muscles of athletes and controls, with circulation to the muscle occluded, then clear differences are observed in responses from muscles containing a preponderance of fast or slow twitch myosin isoforms. Muscles expressing more fast myosin and so with a faster twitch time course had larger pressor responses.
than muscles with slower twitches and less fast myosin content (Carrington et al., 1999). This fits well with animal studies reporting the absence of a pressor responses in muscles composed entirely of slow twitch fibres (e.g. cat soleus (Petrofsky & Lind, 1980) and a reduction in the pressor response following fast to slow muscle fibre type conversion via chronic low frequency stimulation (Wilson et al., 1995).

Longitudinal studies involving 4-6 weeks of local muscle training of one limb in humans show very clear reductions in the cardiovascular response to exercise and PECO. The absence of change in the response of the contralateral untrained limb indicates that the adaptation is locally, not centrally, mediated. Sinoway et al. (1989a) reported decreases in the MSNA response to forearm exercise after a period of local muscle training, and since MSNA is little influenced by central command, suggested that this was due to reduced metaboreflex activation. Subsequently, Somers et al. (1992) found attenuated MSNA response during PECO of the forearm, after 6 weeks of unilateral handgrip training, demonstrating that this was indeed due to a decrease in muscle metaboreflex stimulation. Mostoufi-Moab et al. (1998) then showed lower venous lactate and pH levels in response to ischaemic dynamic handgrip exercise performed after 4 weeks of handgrip training, together with an attenuated pressor response to the exercise, supporting a metabolic basis for the adaptation.

Recently, the muscle metaboreflex has been shown to drive ventilatory responses when activated in synergy with a concurrent hypercapnic induced ventilatory chemoreflex (see above). Alghaith and White (2018) used a one legged 6 week calf raise training protocol to reduce muscle metaboreflex activation in the trained limb. This was indicated by a substantial attenuation of the pressor response to a period of PECO in the trained limb but not the untrained contralateral limb. After the training period there was no change in strength of either limb so participants performed exactly the same force x time integral, both before and after the training period. However, hyperpnoea evoked by PECO in the trained leg fell by ~50% from its pretraining value whilst that of the untrained leg did not change from its initial value. This is powerful evidence that exercise training can reduce metaboreflex drive on ventilation.

It is well established that exercise training programmes result in skeletal muscle adaptations, improved exercise tolerance and reductions in exertional dyspnoea in patients with chronic diseases such COPD (Maltais et al., 1996; O'Donnell et al., 1998). As muscle afferent mediated mechanisms for these ventilatory adaptations become clearer, they may signpost novel therapeutics to improve exercise tolerance by reducing dyspnoea in disease states.

CONCLUSION

The control mechanisms underlying the isocapnic steady-state exercise hyperpnoea remain poorly understood. Central command, humoral mechanisms and muscle afferent feedback may contribute to the hyperpnoea, but conflicting findings exist, and experimental evidence suggests these mechanisms are only able drive a fraction (at most) of the entire ventilatory response. More recently however evidence has emerged suggesting the presence of synergistic interactions between muscle metabo/mechanoreflex activation and other respiratory control mechanisms such the ventilatory chemoreflex. This hyperadditive effect could have important implications for our understanding of the nature of the control system underlying exercise ventilation, and might explain
the difficulty many researchers have encountered when using a variety of experimental models. Further work is needed to continue the investigation of synergism between ventilatory control systems. Despite this, there is substantial evidence that patients with certain chronic diseases such as HF and COPD exhibit exaggerated muscle metaboreflex activation resulting in enhanced cardiorespiratory responses during exercise. This may provide a neural link between the well-established limb muscle dysfunction and associated exercise intolerance and exertional dyspnoea, and hence also offer therapeutic targets for these patients.
REFERENCES


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Nattie EE & Li A (2002). Substance P-saporin lesion of neurons with NK1 receptors in one chemoreceptor site in rats decreases ventilation and chemosensitivity. The Journal of physiology 544, 603-616.


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AUTHORS CONTRIBUTIONS

R.B. provided the conceptual framework for the review. All authors searched and interpreted the literature. All authors wrote and revised the manuscript. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

Richard Bruce – Biography

Richard Bruce is a lecturer in Human Physiology at Kings College London. He undertook his PhD in Cardio-Respiratory Physiology at the University of Birmingham, and much of his Post-doctoral research was conducted at the University of Oxford. His research interests include examining the neural control of the cardiovascular and respiratory systems during exercise, and how this may be altered by chronic disease and contribute to breathlessness and exercise intolerance. Alongside colleagues at Oxford, he is also interested in the development of new technologies that can non-invasively monitor cardio-respiratory function.
Figure 1. A: The ventilatory response to submaximal constant load exercise (shaded area), beginning at 0 minutes. The response can be categorised into three phases (I, II and III), see text for further explanation. B: Ventilation (solid line), PaCO$_2$ (red dashed line) and mixed venous PCO$_2$ (PvCO$_2$; blue dashed line) during an incremental exercise task from rest to a maximal exercise intensity. Up until a VCO$_2$ of approximately 2.5 l.min$^{-1}$ (i.e. ‘mild/moderate’ submaximal exercise below anaerobic threshold) ventilation increases linearly with VCO$_2$ and PvCO$_2$, and so PaCO$_2$ remains relatively constant. Beyond 2.5 l.min$^{-1}$ (i.e. ‘heavy’ exercise above anaerobic threshold) ventilation increases at a proportionately greater rate than VCO$_2$, and consequently PaCO$_2$ decreases. Figure adapted from Bruce (2017)
Figure 2. Schematic diagram depicting multiple structures which can contribute to the control of ventilation. Respiratory control neurones in the brainstem receive both excitatory and inhibitory inputs from several sources; including skeletal muscle metaboreceptive and mechanoreceptive afferents, central command, and feedback from central and peripheral chemoreceptors, and lung/airway mechanoreceptors – inputs hypothesised to contribute to the normal ventilatory responses to exercise. The existence/involvement of venous chemoreceptors (top left), which would monitor blood within the right heart and/or pulmonary circulation, is still debated (Parkes 2017). Figure adapted from Bruce (2017).
**Figure 3.** Changes in ventilation from steady-state during group III/IV muscle afferent stimulation via post exercise circulatory occlusion (PECO), sustained passive muscle stretch (stretch), or passive knee movement (PKM) – either during 1) control conditions, or 2) during hypoxaemia or hypercapnia. The latter responses have been calculated by subtracting the ‘resting’ ventilatory response to hypoxaemia and hypercapnia from the response to PECO, stretch or PKM. Blue data: Lykidis *et al.* (2010); Red data: Edgell and Stickland (2014); Green data: Bruce and White (2012); Orange data: Silva *et al.* (2018). * = Significant difference between trials (P<0.05).
Figure 4. Two theoretical models presenting the relationship between the input (degree of ‘control mechanism activation’) and output (exercise ventilatory response) as linear (A) or as a sigmoid logistic function (B; see Eq 1.). In both models, the normal steady-state ventilatory response for a given workload (i.e. Y = 100%) is achieved by the normal activation of multiple control mechanisms (i.e. X = 100%). In the linear model (A), the experimental stimulation of a single control mechanism at rest (e.g. X = 10%) or the inhibition of a single mechanism during exercise (e.g. X = 90%) would result in proportionate alterations in ventilation. However, in the non-linear sigmoidal model (B) the experimental stimulation of a single control mechanism at rest (e.g. X = 10%) would have little effect on ventilation (i.e. pre-threshold). Furthermore, the inhibition of a single mechanism during exercise (e.g. X = 90%) would also have little effect on ventilation (i.e. post-saturation). Eq 1: $\dot{V}_E = \frac{\dot{V}_{\text{Emax}} - \dot{V}_{\text{Emin}}}{1+\exp(-n(X-\dot{V}_{\text{EC50}}))} \cdot \dot{V}_{\text{Emin}}$. Where $\dot{V}_{\text{Emin}}$ = Resting ventilation (no exercise ventilatory response), $\dot{V}_{\text{Emax}}$ = Steady-state exercise ventilation (proportional to metabolic rate), $\dot{V}_{\text{EC50}}$ = The control mechanism activation required to achieve 50% of the ventilatory response, X = the degree of control mechanism/s activation, n = slope.
Figure 5. A schematic representation of the mechanisms of breathlessness and a consequential spiral into exercise intolerance and skeletal muscle dysfunction. The blue components form a physiological model of breathlessness modified from Jolley & Moxham (2016) and Jensen et al. (2016), where reduced respiratory capacity, increased mechanical loading and/or ventilatory demand results in an enhanced neural respiratory drive required for ventilation – and ultimately increased breathless intensity. This model has been integrated with the concept of a dyspnoea spiral (in green; Cooper (2001); Polkey & Moxham (2006)), where breathlessness leads to a spiral of physical inactivity, skeletal muscle deconditioning/dysfunction and further breathlessness. The red components illustrate the potential effect of enhanced/sensitised skeletal muscle afferent feedback as a ‘neural link’ between skeletal muscle dysfunction and breathlessness/exercise intolerance.