The 'sensory tolerance limit':

A hypothetical construct determining exercise performance?

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Abstract

Neuromuscular fatigue compromises exercise performance and is determined by central and peripheral mechanisms. Interactions between the two components of fatigue can occur via neural pathways, including feedback and feedforward processes. This brief review discusses the influence of feedback and feedforward mechanisms on exercise limitation. In terms of feedback mechanisms, particular attention is given to group III/IV sensory neurons which link limb muscle with the central nervous system. Central corollary discharge, a copy of the neural drive from the brain to the working muscles, provides a signal from the motor system to sensory systems and is considered a feedforward mechanism that might influence fatigue and consequently exercise performance. We highlight findings from studies supporting the existence of a 'critical threshold of peripheral fatigue', a previously proposed hypothesis based on the idea that a negative feedback loop operates to protect the exercising limb muscle from severe threats to homeostasis during whole-body exercise. While the threshold theory remains to be disproven within a given task, it is not generalizable across different exercise modalities. The 'sensory tolerance limit', a more theoretical concept, may address this issue and explain exercise tolerance in more global terms and across exercise modalities. The 'sensory tolerance limit' can be viewed as a negative feedback loop which accounts for the sum of all feedback (locomotor muscles, respiratory muscles, organs, muscles not directly involved in exercise) and feedforward signals processed within the central nervous system with the purpose of regulating the intensity of exercise to ensure that voluntary activity remains tolerable.

Introduction

The purpose of this review is to discuss the role of neural feedback and feedforward mechanisms in limiting exercise performance. We focus on two concepts, namely the 'critical threshold of peripheral fatigue' and the 'sensory tolerance limit'. While the former emphasizes the significance of afferent feedback from working limb muscles in limiting muscle fatigue and exercise, the latter considers the influence of both feedback (from various muscles and presumably organs) and feedforward signals in restraining performance. We discuss recent experimental and correlative evidence supporting these two hypothetical constructs from a physiological perspective. Although various psychological and psychophysical factors may also play a role in both models, these influences are not covered in this review - the reader is referred to other articles published in this issue of the journal.

Neuromuscular fatigue develops during strenuous physical activities and causes a temporary reduction in the force or power generating capacity of a muscle or muscle group. This impairment stems from a decrease in neural activation of muscle (i.e., central fatigue) and/or biochemical changes at or distal to the neuromuscular junction that cause an attenuated contractile response to neural input (i.e., peripheral fatigue) (Bigland-Ritchie, Jones, Hosking, & Edwards, 1978). Despite this differentiation, exercise-induced fatigue needs to be viewed as an integrative phenomenon since interactions between central and peripheral fatigue can occur via humoral and non-humoral processes (Taylor, Amann, Duchateau, Meeusen, & Rice, 2016), with the latter including neural feedforward and feedback mechanisms. Although the significance of group III/IV muscle afferents is well described for the circulatory and ventilatory control during exercise, their role in the development of muscle fatigue and the interaction between central and peripheral fatigue is less well-recognized. Specifically, the neural feedforward component, which refers to

corollary discharge (also called “efferent copy”) related to central motor command (Sperry, 1950; Wolpert, Ghahramani, & Jordan, 1995), is a neural signal generated in motor centres of the brain that is not directly involved in the ongoing motor activity (Poulet & Hedwig, 2007). Corollary discharges activate sensory areas within the cortex and thereby influence effort perception and ultimately the development of central fatigue during exercise (Gallagher et al., 2001; Liu et al., 2005). With progressive increases in peripheral fatigue during exercise at a fixed work rate, increases in central motor command are necessary to compensate for fatigued motor units. This increase in central command also increases corollary discharge (Eldridge, Millhorn, & Waldrop, 1981; Williamson et al., 2001) and likely central fatigue (Liu et al., 2005). Therefore, the increase in central command and subsequently central fatigue secondary to the increase in peripheral fatigue highlights the link between the two components of fatigue via a feedforward mechanism. While corollary discharges and associated anatomical structures are difficult to study in humans, related pathways have been identified, to a cellular level, in animals (Poulet & Hedwig, 2006, 2007). The neural feedback component entails afferent feedback (which increases with the development of peripheral fatigue) from contracting muscles to the CNS, the associated activation of sensory areas within the brain, and the subsequent facilitation of effort perception and central fatigue (Amann et al., 2011; Taylor et al., 2016). This interaction highlights the link between peripheral and central fatigue via a feedback mechanism.

The concept of a ‘critical threshold of peripheral fatigue’

Correlative Evidence

Numerous studies have shown that the magnitude of peripheral locomotor muscle fatigue incurred during whole-body exercise typically does not exceed a value specific to the individual and task [e.g., (Amann & Dempsey, 2008; Amann et al., 2006; Gagnon et al., 2009; Hureau, Ducrocq, & Blain, 2016; Hureau, Olivier, Millet, Meste, & Blain, 2014)]. Initial evidence for this phenomenon stemmed from studies that manipulated arterial oxygen content (CaO_2) during simulated 5 km cycling time-trials and constant-load exercise bouts (~7-10 min duration, 80-100% VO_{2max}) (Amann et al., 2006). Compared to control (normoxia, C_aO_2 ~21 ml O_2/dl), decreases in C_aO_2 evoked via breathing a hypoxic gas mixture (inspired oxygen fraction [F_iO_2] 0.15, C_aO_2 ~18 ml O_2/dl) caused a decrease in central motor drive (assessed via quadriceps EMG normalized for changes in M-wave amplitude) and exercise performance. Conversely, increases in C_aO_2 evoked via breathing a hyperoxic gas mixture (F_iO_2 1.0, C_aO_2 ~24 ml O_2/dl) caused an increase in central motor drive and improved exercise performance. Interestingly, however, the level of end-exercise peripheral fatigue (quantified via pre- to post-exercise changes in quadriceps twitch force) was identical across conditions. Accordingly, it was hypothesised that central motor drive and consequently exercise performance are regulated in order not to surpass a certain level of peripheral locomotor muscle fatigue – a degree of fatigue that varies between tasks. Since work rate at the end of each trial increased to the same level as at the start of exercise, classic reflex inhibition can be excluded as the main mechanism regulating muscle activation during exercise. Voluntary alterations in neural drive originating at higher brain areas are more likely to explain the differences in pace and ultimately performance. Regardless, these observations led to the concept of a “critical threshold of peripheral fatigue” (Figure 1A), which was confirmed by subsequent studies using whole-body exercise of various intensities, including all-out repeated sprints where pacing strategy does not play a role [e.g. (Amann & Dempsey, 2008; Gagnon et al.,

2009; Hureau et al., 2016; Hureau et al., 2014)]. To explain this regulatory loop, it was hypothesized that central motor drive during whole-body exercise is carefully controlled in order to limit metabolic perturbation within locomotor muscle and, therefore, the development of peripheral fatigue. In this context, it is important to note that changes in intramuscular metabolites and peripheral fatigue are tightly correlated (Figure 2) (Blain et al., 2016).

The critical threshold concept is reinforced by MRI studies based on exercise involving a relativity small muscle mass (Burnley, Vanhatalo, Fulford, & Jones, 2010; Chidnok et al., 2013; Hogan, Richardson, & Haseler, 1999; Vanhatalo, Fulford, DiMenna, & Jones, 2010). For example, Hogan *et al*. (1999) showed that the accumulation of inorganic phosphates (P_i) and hydrogen ions (H^+) was faster during incremental plantar flexion exercise to exhaustion in hypoxia (F_iO_2 0.10) compared to normoxia (FiO_2 0.21). Conversely, P_i and H^+ accumulation was slower when the exercise was repeated in hyperoxia (F_iO_2 1.0). Despite these differences in the rate of metabolic perturbation, end-exercise P_i and H^+ concentrations, two determinants of peripheral fatigue (Allen, Lamb, & Westerblad, 2008), were identical in all conditions. The observation of an invariable intramuscular level of metabolites at exhaustion was confirmed by other studies using different methodologies, such as varied exercise intensities (maximal *vs* submaximal contractions) (Burnley et al., 2010) or varied exercise/rest ratios during repeated contractions (Chidnok et al., 2013).

The aforementioned studies support the idea that exercise performance is tightly regulated to ensure that the metabolic milieu, and therefore peripheral fatigue, does not exceed a certain level that varies between tasks. But, what links peripheral fatigue and intramuscular perturbation with the CNS to allow for the precise regulation of spinal motoneuronal output (the ultimate determinant of muscle activation and therefore exercise performance)? Sensory neurons were

129 considered to play a key role in this regulatory mechanism (Amann et al., 2011; Amann, Proctor,
130 Sebranek, Pegelow, & Dempsey, 2009; Blain et al., 2016; Gagnon et al., 2012; Sidhu et al., 2014).

131

132 *Muscle Afferent Feedback*

133 While group Ia and Ib and group II spindle afferents may, with a few exemptions (Enoka
134 et al., 2011), play a negligible role in muscle fatigue (McNeil, Giesebrecht, Khan, Gandevia, &
135 Taylor, 2011), group III and IV afferents significantly influence the development of peripheral and
136 central fatigue during both single-joint and whole-body exercise (Taylor et al., 2016). Most of the
137 thinly myelinated group III afferents are mechanically sensitive and respond to muscle contraction
138 and/or stretch. Group IV muscle afferents and associated receptors (see below) are sensitive to
139 various intramuscular metabolites and metabolic changes within the contracting muscle as well as
140 to noxious levels of mechanical strain. Recent findings in animals (Birdsong et al., 2010;
141 Jankowski, Rau, Ekmann, Anderson, & Koerber, 2013; Light et al., 2008) and humans (Pollak et
142 al., 2014) indicate the existence of two subgroups of metabosensitive group III/IV muscle afferents
143 characterized by anatomical and functional differences (Amann & Light, 2015). One subtype, the
144 so-called metabo- or ergoreceptors, respond to innocuous levels of intramuscular metabolites (e.g.,
145 lactate, ATP, protons) (Jankowski et al., 2013; Light et al., 2008; Pollak et al., 2014) associated
146 with 'normal' (i.e., freely perfused and predominantly aerobic) exercise up to strenuous intensities
147 (Bangsbo, Johansen, Graham, & Saltin, 1993; Li, King, & Sinoway, 2003). In contrast, the other
148 subtype, the so-called metabo-nociceptors, only respond to high (noxious) levels of metabolites
149 present in muscle during ischaemic contractions or following hypertonic saline infusions – but not
150 to non-noxious metabolite concentrations associated with normal exercise (Jankowski et al., 2013;
151 Light et al., 2008; Pollak et al., 2014).

Although these functional differences have been observed in both animals and humans, the specific phenotypic distinction of metaboreceptors vs metabo-nociceptors remains elusive. It is recognized, however, that molecular differences between the two subtypes include the differential expression of purinergic receptors (P2X2,3,4), transient receptor potential vanilloid type 1 and/or 2 (TRPV1/2), and acid-sensing ion current 1, 2, and 3 (ASIC 1-3) (Birdsong et al., 2010; Jankowski et al., 2013; Light et al., 2008). Although the two different subtypes of group III/IV muscle afferents project to the same location in the superficial dorsal horn (Jankowski et al., 2013), it is currently unknown to what extent each subtype is anatomically linked to lamina I neurons which have direct projections to various supraspinal sites.

Experimental Evidence

More recent studies have focused on the specific role of group III/IV muscle afferents in limiting the development of peripheral fatigue, as quantified via pre- to post-exercise changes in quadriceps twitch force, during high intensity whole-body exercise (Amann et al., 2011; Amann et al., 2009). To address this issue, group III/IV afferent feedback from the legs was pharmacologically blocked (via lumbar epidural lidocaine or intrathecal fentanyl) during 5 km cycling time-trials (Amann et al., 2008; Amann et al., 2009). The temporary reduction in neural feedback resulted in a higher motoneuronal output during the time-trial and greater peripheral fatigue and metabolic disturbances within locomotor muscle compared to the same exercise performed with intact afferent feedback (Amann et al., 2009; Blain et al., 2016). Later studies confirmed this finding and, combined, suggest that participants surpass the critical threshold of peripheral fatigue when group III/IV muscle afferent feedback is pharmacologically attenuated

(Amann et al., 2011; Amann et al., 2009; Blain et al., 2016; Gagnon et al., 2012; Sidhu et al., 2014).

The findings from these neural blockade studies suggest that in order to prevent abnormal deviations from locomotor muscle homeostasis and therefore severe fatigue during a given task, the CNS continuously monitors the intramuscular environment of locomotor muscle via group III/IV afferents. Elevated feedback from these sensory neurons to the CNS causes a centrally-mediated restriction of motoneuronal output and muscle activation which, in turn, closes the regulatory loop.

Considerations, Limitations, and Future Directions

Recent correlative findings have been interpreted to question the validity of the critical threshold theory. For example, Johnson et al. noted that cycling endurance time was significantly reduced and, consequently, end-exercise peripheral locomotor muscle fatigue significantly lower, when intense leg cycling exercise to exhaustion was preceded by fatiguing arm cranking as compared to intense leg cycling exercise alone (Johnson, Sharpe, Williams, & Hannah, 2015). This finding was viewed as evidence disproving the existence of a critical threshold of peripheral fatigue. To disprove the threshold concept, however, an experimental intervention that causes subjects to voluntarily surpass the threshold (i.e., fatigue more) during a specific task is required. Clearly, not reaching the degree of peripheral locomotor fatigue associated with the task-specific threshold is a limitation in this context and does not actually challenge the validity of the concept (Broxterman, Richardson, & Amann, 2015).

Interestingly, Nordsborg et al. found higher levels of extracellular K^+ (*vastus lateralis*)

during dynamic single-leg knee-extension exercise preceded by fatiguing arm cranking compared to knee-extension exercise alone (i.e., without prior arm exercise) (Nordsborg et al., 2003). While knee-extension exercise time to exhaustion was, similar to the Johnson study discussed above, shorter when the leg exercise was preceded by arm exercise, end-exercise quadriceps fatigue was not quantified. Important in this context is the fact that interstitial K^+ is known to stimulate metabosensitive muscle afferents (Kaufman & Rybicki, 1987), which influence central fatigue and therefore likely contributed to the shorter time to exhaustion during the leg exercise preceded by arm cranking (i.e. higher extracellular K^+). However, the contribution of *extracellular* potassium to peripheral fatigue is likely smaller compared to intracellular metabolites. Regardless, the higher levels of *vastus lateralis* interstitial K^+ following arm and leg exercise compared to leg exercise alone challenges the idea of a tightly regulated intramuscular metabolic milieu during exercise.

A key factor in terms of the validity of the critical threshold concept is task specificity. The degree of end-exercise peripheral fatigue is dependent on the duration, and therefore intensity, of the task. Specifically, following completion of a long cycling time-trial (20 km, relatively low intensity), peripheral fatigue was attenuated and central fatigue accentuated compared to a shorter time-trial (4 km, relatively high intensity) (Thomas et al., 2015). This observation might reflect other (aside from group III/IV afferent feedback from locomotor muscle) inhibitory influences, such as fluid balance or body/brain temperature (Nybo & Secher, 2004), on the CNS-mediated regulation of muscle activation which could prevent peripheral fatigue from reaching a greater degree. However, the exact relationship between neuromuscular fatigue and exercise duration / intensity remains unknown. In fact, in contrast to the difference in fatigue following 4 km and 20 km cycling time-trials, similar end-exercise peripheral and central fatigue is present after 20 km and 40 km time-trials (Thomas et al., 2015). This further complicates the situation and raises

additional questions concerning the mechanisms limiting endurance exercise of different durations. Regardless, these and other recent findings suggest that the magnitude of end-exercise peripheral fatigue is highly specific and varies between tasks (Amann, Pegelow, Jacques, & Dempsey, 2007; Goodall, Gonzalez-Alonso, Ali, Ross, & Romer, 2012; Goodall, Ross, & Romer, 2010; Johnson et al., 2015; Rossman, Garten, Venturelli, Amann, & Richardson, 2014; Thomas, Elmeua, Howatson, & Goodall, 2016; Thomas et al., 2015). Therefore, although the critical threshold model remains a valid concept, comparisons of end-exercise fatigue across different exercise modalities, tasks (i.e., intensity and duration), and/or drastically different environmental conditions may not be appropriate as the absolute threshold appears to be condition specific.

The concept of a 'sensory tolerance limit'

General Idea

In addition to inhibitory neural feedback from working muscles, exercise performance may be limited by neural feedback from remote muscles previously or simultaneously exercising (Amann et al., 2013; Johnson et al., 2015; Matkowski, Place, Martin, & Lepers, 2011; Rossman et al., 2014; Sidhu et al., 2014), respiratory muscle work/fatigue (Amann et al., 2007; Romer, Lovering, Haverkamp, Pegelow, & Dempsey, 2006; Taylor & Romer, 2008; Wuthrich, Notter, & Spengler, 2013), frank pain in exercising and non-exercising muscles (Deschamps, Hug, Hodges, & Tucker, 2014; Foster, Taylor, Chrismas, Watkins, & Mauger, 2014; Graven-Nielsen, Lund, Arendt-Nielsen, Danneskiold-Samsoe, & Bliddal, 2002), and corollary discharge associated with central motor command (Gallagher et al., 2001). Observations from the abovementioned studies suggest that the sum of all neural feedback and feedforward signals and associated sensations

might be important in terms of limiting exercise performance. Indeed, Gandevia (2001) suggested the existence of a 'sensory tolerance limit' - a hypothetical 'threshold' whereby the consequences of continuing the task become sufficiently unattractive such that the exercising human either terminates the task or, if possible, reduces the exercise intensity to ensure the continuation is tolerable.

The sensory tolerance limit may be described as a global (i.e., not limited to a single muscle / muscle group) negative feedback loop leading to task failure when a finite level of stimulation is reached from sensory afferents originating in muscles that are directly (e.g., leg muscles during cycling) or indirectly (e.g., respiratory muscles during cycling) involved in the exercise, and from corollary discharge associated with central motor command (Figure 1B). The Borg scale (Borg, 1970), a tool frequently used to rate the intensity of perceived exertion (RPE), might offer a suitable means to quantify an individual's relative 'proximity' to the sensory tolerance limit. Importantly, both muscle afferent feedback and central motor command have been shown to influence RPE (Amann et al., 2010; Amann et al., 2008; Galbo, Kjaer, & Secher, 1987; Winchester, Williamson, & Mitchell, 2000) and might be considered as key determinants of the sensory tolerance limit. However, the validity and relevance of the sensory tolerance limit is difficult to prove. The following sections highlight some observations which could be interpreted as support for the concept and its potential role in limiting exercise. It needs to be emphasized, however, that the studies discussed below were originally *not* designed to address questions concerning the sensory tolerance limit.

Support for the Sensory Tolerance Limit Concept

Recent studies comparing muscle fatigue at the end of exercise suggest that, independent of the origin of the sensory signals, exercising humans reduce the intensity of exercise, or voluntarily terminate the task, once they attain the sensory tolerance limit. For example, following rhythmic right-leg knee extension exercise to task failure at 85% of W_{peak} (~8 min, ~2.5 kg of active muscle mass), end-exercise peripheral quadriceps fatigue was significantly greater compared to the same exercise performed with both legs (85% of two-leg W_{peak}, ~10 min, ~5 kg of active muscle mass) (Rossman et al., 2014). Given the tight relationships between intramuscular metabolic perturbation and peripheral fatigue (Allen et al., 2008; Blain et al., 2016) (Figure 2) and between the magnitude of ensemble group III/IV muscle afferent feedback and exercising muscle mass (Freund, Hobbs, & Rowell, 1978), it could be argued that, compared to single-leg exercise, the sensory tolerance limit during the two-leg exercise was reached with less metabolic disturbance in the right quadriceps, but a similar overall level of sensory feedback to the CNS. In addition, overall central command / corollary discharge and neural feedback related to the cardiovascular and ventilatory response during exercise were likely greater during the two-leg vs the one-leg exercise. As a consequence, right quadriceps fatigue at task failure was about 50% lower following the two-leg vs. the one-leg exercise (Rossman et al., 2014).

The idea of a sensory tolerance limit determining exercise performance is also supported by findings from a study which compared time-to-task-failure during rhythmic one leg knee-extension exercise (85% W_{peak}) performed with or without prior fatigue of the contralateral quadriceps (Amann et al., 2013). Quadriceps fatigue in the contralateral leg was induced by dynamic knee-extension exercise (85% W_{peak}) to task failure (~9 min). Interestingly, endurance time (~9 min) was significantly longer in the exercise trial performed without prior contralateral

quadriceps fatigue compared to the same task performed with prior contralateral quadriceps fatigue (~5 min). Moreover, quadriceps fatigue was substantially greater following the exercise performed without prior contralateral leg fatigue compared to the bout performed with prior contralateral leg fatigue (Amann et al., 2013). Since the exercise performed with prior fatigue in the contralateral leg was associated with afferent feedback arising from both the active and likely also the recovering quadriceps, it was concluded that, given these two sources of sensory feedback, the compromised endurance time and the lower end-exercise fatigue may be explained by a more rapid attainment of the sensory tolerance limit (Figure 3). This interpretation may also apply to the Johnson study (discussed above) documenting reduced cycling endurance and end-exercise peripheral fatigue when intense leg cycling exercise to exhaustion was preceded by fatiguing arm cranking as compared to intense leg cycling exercise alone (Johnson et al., 2015).

Metabo-nociceptors, in addition to metabosensitive muscle afferent feedback, also limit exercise performance, perhaps by contributing to the sensory tolerance limit. This idea is reflected in a study during which muscle pain was induced by hypertonic saline injection into the *vastus lateralis* of one leg. The performance during a subsequent maximal single-leg hop task executed with the infused (i.e., painful) leg was compromised compared to the same task performed without pain (Deschamps et al., 2014). Interestingly, however, hopping performance of the contralateral (i.e., non-painful) leg was also compromised following hypertonic saline infusion in the other leg (Deschamps et al., 2014). Further studies triggered metabo-nociceptors by occluding blood supply to the fatigued elbow extensors at the end of exercise (tourniquet placed proximally to fatigued muscle) to investigate the impact of ischaemic muscle pain on performance and voluntary muscle activation. Similarly, muscle pain decreased maximal voluntary activation and performance of the fatigued elbow extensors, but also that of the elbow-flexors (Kennedy, McNeil, Gandevia, &

309 Taylor, 2013). These investigators later documented that post-exercise ischaemic muscle pain and
310 related metabo-nociceptive feedback to the CNS not only decreases voluntary activation of the
311 fatigued and painful muscle (adductor pollicis), but also that of an unfatigued proximal muscle
312 within the same limb (elbow flexor) (Kennedy, McNeil, Gandevia, & Taylor, 2014).

313 Instead of *triggering* sensory feedback from a muscle by evoking an intramuscular stimulus
314 for metabo-nociceptors, Sidhu and colleagues pharmacologically *attenuated* sensory feedback
315 from the lower limbs during fatiguing leg exercise and evaluated the consequences on voluntary
316 activation and torque of an uninvolved (and unfatigued) remote muscle. Specifically, during
317 constant-load cycling exercise to exhaustion at 80% W_{peak} (~9 min), subjects were asked to
318 perform brief elbow flexor MVCs every minute and at task failure. While both MVC torque and
319 motoneuronal output / voluntary activation of the elbow flexor decreased from the start of cycling
320 exercise to task failure under control conditions, these impairments were abolished when the same
321 exercise was repeated with pharmacologically blocked afferent feedback from the lower limbs
322 (Sidhu et al., 2014). These observations confirm the global inhibitory effect of muscle afferents
323 noted in the various pain studies discussed above.

324 In addition to the traditional respiratory system limitations described elsewhere [e.g.,
325 (Dempsey, Amann, Romer, & Miller, 2008)], the sensory aspect related to breathing has also been
326 suggested to limit exercise (Sheel, Foster, & Romer, 2011) and is therefore potentially relevant for
327 the sensory tolerance limit theory. This section describes two of these sensory aspects. First, the
328 ventilatory demand associated with sustained vigorous exercise causes significant respiratory
329 muscle fatigue (Johnson, Babcock, Suman, & Dempsey, 1993; Taylor, How, & Romer, 2006),
330 which increases neural feedback from these muscles (Hill, 2000) and triggers a sympathetically-
331 mediated restriction of locomotor muscle blood flow (Harms et al., 1997). As a consequence of

the compromised leg perfusion, the development of locomotor muscle fatigue is accelerated (Romer et al., 2006) and afferent feedback from these muscles increased. Breathing during strenuous exercise may therefore accelerate the attainment of the sensory tolerance limit by evoking a) sensory feedback from the fatiguing respiratory muscles, and b) additional sensory feedback from locomotor muscles.

The second sensory aspect related to the respiratory system is the subjective experience of breathing discomfort, or 'dyspnoea', during exercise. A schematic illustration of mechanisms determining exertional dyspnoea and its potential contribution to the sensory tolerance limit via the somatosensory cortex is provided in Figure 4. The perception of respiratory work and effort, which arises from a combination of respiratory muscle afferent feedback and corollary discharge (related to central command associated with breathing) to sensory areas, has been identified as a key component of exertional dyspnoea (Laviolette & Laveneziana, 2014). Indeed, reducing the work of breathing by up to 80% using a mechanical ventilator during intense cycling exercise (80% W_{peak} for ~10 min) attenuated the rate of increase in overall effort perception compared to control exercise, but also significantly reduced the rate of dyspnoea and improved endurance performance (Amann et al., 2007; Harms, Wetter, St Croix, Pegelow, & Dempsey, 2000; Romer et al., 2006). In contrast, increasing respiratory muscle work through inspiratory loading during heavy cycling exercise caused a faster rate of both overall effort perception and dyspnoea and reduced endurance performance by 15-20% (Harms et al., 2000). It was suggested that part of the limitation to exercise might have been accounted for by the increased rate of dyspnoea (Harms et al., 2000; Romer et al., 2006). The above studies focusing on limb and respiratory muscle suggest that muscle afferent feedback, regardless of its origin, exerts an inhibitory effect on motoneuronal

output, not only to the working and fatiguing limb but also to unfatigued limb muscles, and support the idea that the sensory tolerance of an individual could modulate exercise performance.

The sensory aspect related to central command and corollary discharge (McCloskey, 1978) may also be involved in limiting exercise performance. However, this hypothesis is only supported by indirect evidence from studies using neuromuscular blocking agents (i.e., curare or analogue drugs) during exercise. These agents partially block neuromuscular transmission at the neuromuscular junction, thereby necessitating an increase in central motor drive to perform exercise at a fixed power output. As a consequence of this blockade and associated increase in central motor drive, the rate of effort perception is increased compared to control exercise performed without the blocking agent (Gallagher et al., 2001). Based on the observation that the rate of increase of RPE predicts the duration of exercise to exhaustion during constant-load exercise (Crewe, Tucker, & Noakes, 2008; Garcin & Billat, 2001), this indirectly suggests that central command and associated corollary discharge may contribute to a centrally-mediated limitation of exercise performance. However, more direct evidence is needed to confirm this hypothesis.

Is it possible to alter the sensory tolerance limit? Exercise training might potentially 'raise' the sensory tolerance limit by decreasing the magnitude of both feedback and feedforward mechanisms during a given task. As an overall consequence of these training-induced changes, the attainment of the sensory tolerance limit might be delayed to a higher workload and/or a later point in time and therefore improve exercise performance. Specifically, endurance training has been shown to improve the metabolism within working muscle (e.g., by improving mitochondrial respiratory capacity and/or slowing the utilization of muscle glycogen at a given workload) which, in turn, results in less intramuscular metabolic disturbances (Green et al., 1992; Holloszy & Coyle,

1984; Park et al., 2016) and thereby decreases the stimulation of group III/IV muscle afferent feedback during exercise at a given workload. This training-induced reduction in intramuscular metabolic perturbation at a given workload would be expected to decrease peripheral fatigue and therefore require less neural drive / central command which, in turn, would decrease corollary discharge. Although currently not supported by well controlled studies, exercise training might also attenuate the sensitivity or density of receptors linked with sensory neurons. As a consequence, a given level of afferent stimulation may result in a reduced discharge and therefore attenuated central projection of group III/IV muscle afferents. Alternatively, exercise training may alter the central representation and/or processing of neural feedback. Interesting in the context of these potential effects is a recent study which showed that an improvement in exercise performance following eight weeks of endurance training was associated with greater end-exercise peripheral fatigue, but similar central fatigue (Zghal et al., 2015). Given the tight relationship between intramuscular metabolites and peripheral fatigue (Figure 2) (Blain et al., 2016), the greater tolerance for peripheral fatigue might indirectly support a training-induced decrease of the sensitivity, or altered central processing, of group III/IV muscle afferents.

In contrast, given the muscular changes associated with deconditioning (i.e., greater metabolic disturbance at a given workload), prolonged inactivity or detraining might lower the sensory tolerance limit. In addition, disease-related alterations in intrinsic muscle characteristics and/or afferent feedback mechanisms might also lower the sensory tolerance limit and thereby account, at least in part, for the exercise intolerance characterizing various disease populations such as heart failure or COPD.

Psychological, psychophysical, and other endogenous reference signals – for example, motivation, anxiety, mental stress, bodily discomfort, hunger/thirst, prior experience, etc. – may

400 also alter the sensory tolerance limit and therefore affect exercise performance (Lambert, St Clair
401 Gibson, & Noakes, 2005). The influence of these factors on effort perception and exercise
402 performance are discussed elsewhere in this review series.

403

404 **Summary**

405 The concept of a 'critical threshold of peripheral fatigue' is based on the idea that a negative
406 feedback loop operates to protect the exercising limb muscle from severe threats to muscle
407 homeostasis, and therefore neuromuscular function, during whole-body exercise. Existing
408 evidence for this control theory suggests that the CNS continuously 'monitors' the intramuscular
409 environment of the exercising limb muscle via group III/IV muscle afferents and restricts
410 motoneuronal output and therefore muscle activation in proportion to the magnitude of the
411 feedback from these sensory neurons. Importantly, the degree of end-exercise peripheral fatigue
412 varies between individuals and tasks. The concept of a 'sensory tolerance limit' extends this idea
413 and suggests that the sum of all feedback and feedforward signals is processed within the CNS and
414 ultimately regulates the intensity of exercise to ensure that voluntary activity remains tolerable. As
415 such, the sensory tolerance limit might be viewed as a more global (i.e., not limited to a single
416 muscle / muscle group) negative feedback loop.

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Figures

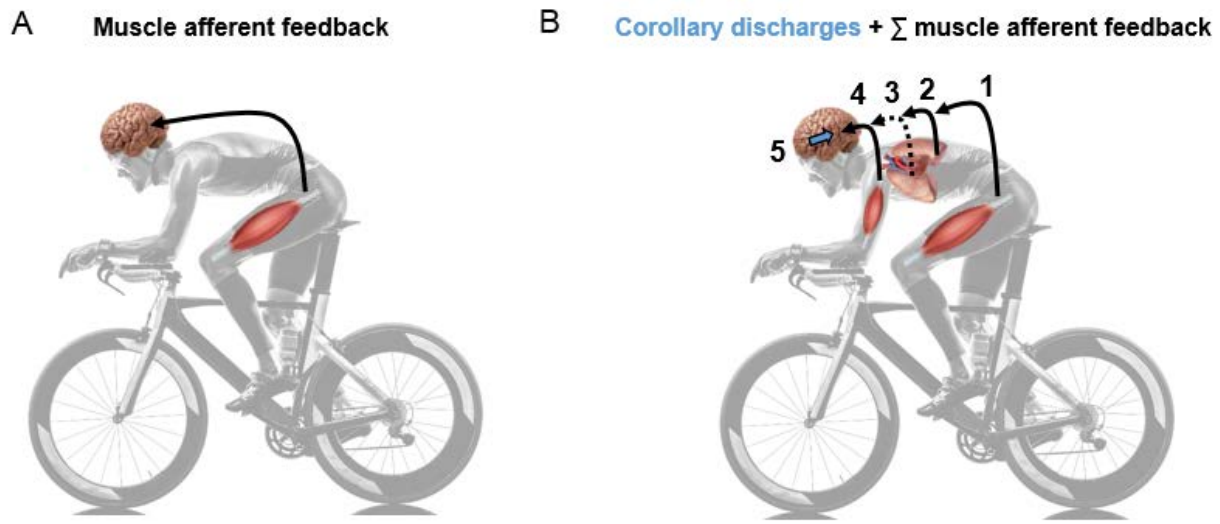


Figure 1. Simplified schematic illustration of the 'critical threshold of peripheral fatigue' (A) and the 'sensory tolerance limit' (B).

The critical threshold model proposes a large influence of muscle afferent feedback from locomotor muscles in regulating the degree of exercise-induced neuromuscular fatigue and exercise performance (panel A). The sensory tolerance limit is less specific and suggests that neural feedback from locomotor muscles (1), respiratory muscles (2), possibly organs (3), remote muscles not directly involved in the exercise (4), and the corollary discharges associated with central command (5, blue arrow) are integrated within the brain and ultimately determine the magnitude of central motor drive.

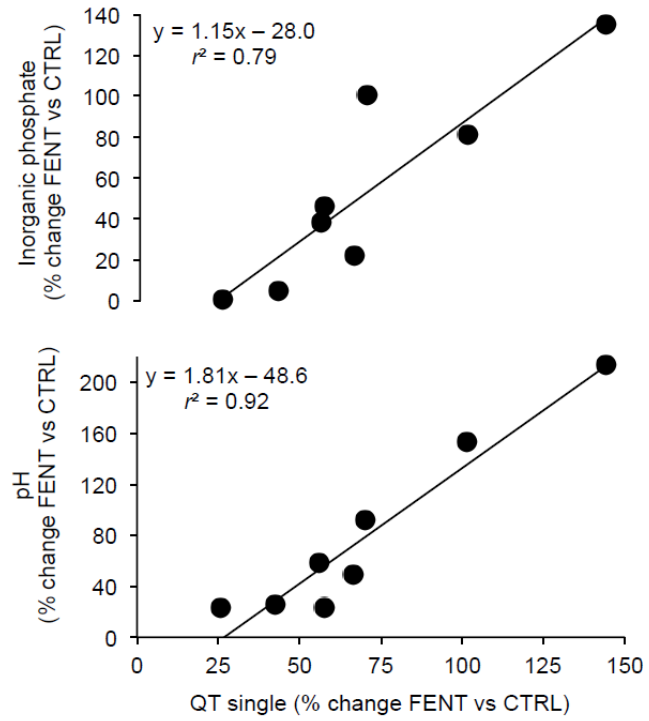
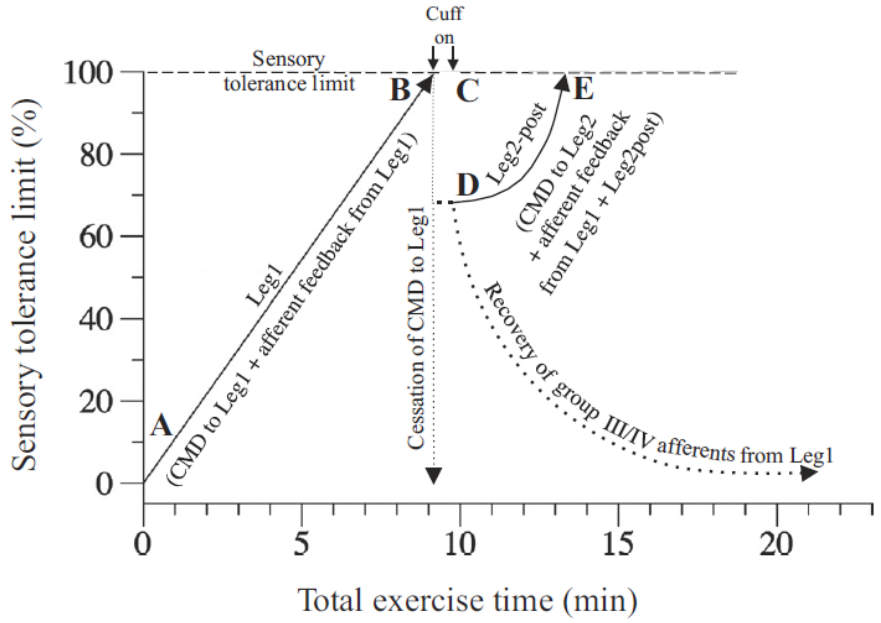


Figure 2. Relationship between peripheral muscle fatigue and intramuscular metabolites.

Subjects performed 5 km cycling time trials with intact (CTRL) and blocked group III/IV muscle afferent feedback. Vastus lateralis muscle biopsies were taken before and immediately after completion of each trial. Exercise-induced changes in intramuscular metabolites, for example inorganic phosphates (panel A) and hydrogen ions (panel B), were determined using liquid and gas chromatography-mass spectrometry. Peripheral fatigue was quantified by pre- to post-exercise changes in potentiated quadriceps twitch torque (QT_{single}) evoked by electrical femoral nerve stimulation. QT_{single} was reduced by ~31% and ~52% following CTRL and FENT, respectively. Data are expressed as percent difference between the FENT and CTRL for both intramuscular metabolites and QT_{single}. Solid lines represent best-fit linear regression. Figure reproduced from Blain et al. (2016), with permission.



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668 **Figure 3. Schematic illustration reflecting potential sensory alterations during the**
669 **consecutive single-leg knee extensor performance tests.**

670 With the onset of exercise of the first leg (Leg1), both muscle afferent feedback and central motor
671 drive (CMD) started to progressively rise (points A and B) until the sensory tolerance limit (dashed
672 line) was reached at exhaustion (point B). With the end of Leg1 exercise, CMD to this leg ceased
673 entirely (thin dotted line), whereas group III/IV afferent firing continued due to the cuff inflation
674 at a high level. Within 10 s, the cuff was released (point C), afferent firing from Leg1 began to
675 decline (dotted line), and afferent feedback and CMD related to the now exercising second leg
676 (Leg2-post) started to increase. In addition, afferent feedback from Leg1 (although recovering)
677 likely remained fairly high, adding to the continuously increasing afferent feedback and CMD
678 associated with the exercise of the second leg (Leg2-post) (points D and E). Consequently, the
679 tolerance limit for this Leg2-post trial was reached relatively quickly, as indicated by the short
680 time to exhaustion (point E). Figure reproduced from Amann et al. (2013), with permission.

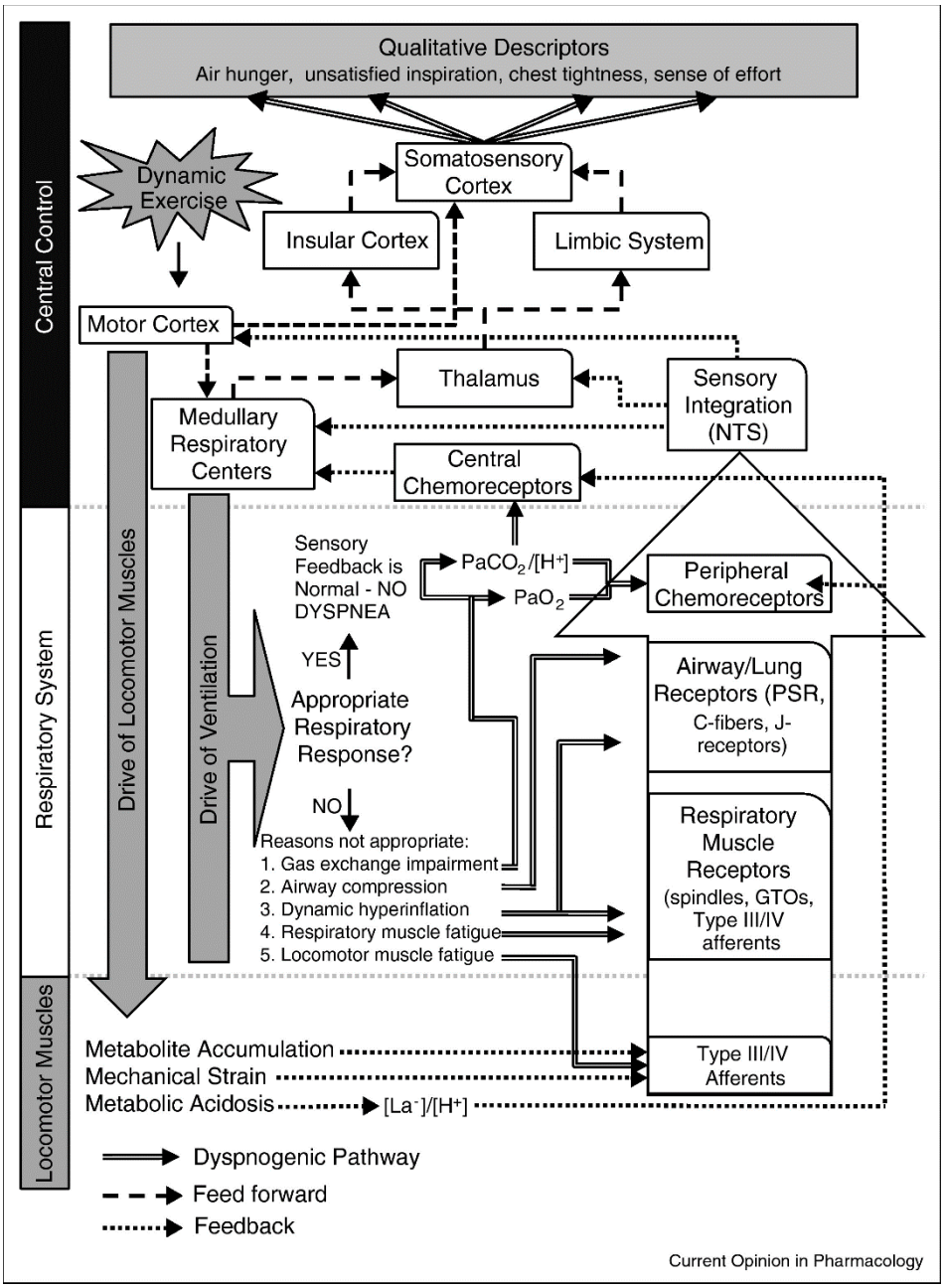

Figure 4. Mechanisms of exertional dyspnoea.

During dynamic exercise the motor cortex prepares the neuromuscular response directed at driving the locomotor muscles. The drive of ventilation is determined by the medullary respiratory centers whose response is governed, partly, by feedforward information received from the motor cortex, and afferent feedback from the locomotor muscles, respiratory muscles, airways/lung, and

chemoreceptors (central and peripheral). The somatosensory cortex continuously compares the afferent information with the efferent information and has 'learned' the correct neuro-mechanical coupling ('Appropriate Respiratory Response'). However, if the respiratory efferent response does not match the afferent feedback then neuro-mechanical uncoupling occurs, leading to dyspnoea. The respiratory response may be considered inappropriate if it leads to gas exchange impairment, airway compression, dynamic hyperinflation, respiratory and/or locomotor muscle fatigue. These factors increase afferent feedback through the highlighted dyspnogenic pathways. The medullary respiratory centers and the NTS project efferent and afferent information via the thalamus to the insular cortex, the limbic system, and the somatosensory cortex where the perception of dyspnoea is felt as a variety of qualitative descriptors. Figure reproduced from Sheel et al. (2011), with permission.