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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 recent findings from studies focusing on fatigue-related feedback and feedforward mechanisms and discuss their relevance for the previously proposed hypotheses that a 'critical threshold of peripheral fatigue' and/or a 'sensory tolerance limit' may regulate neuromuscular fatigue and ultimately exercise performance. The concept of a 'critical threshold of peripheral fatigue' is based on the idea that a negative feedback loop operates to protect the exercising limb muscle from severe threats to muscle homeostasis during whole-body exercise. The concept of a 'sensory tolerance limit' can be viewed as a more global negative feedback loop suggesting that the sum of all feedback and feedforward signals is processed within the central nervous system which ultimately regulates the intensity of exercise to ensure that voluntary activity remains tolerable.

Keywords

central command; exercise limitation; fatigue; muscle afferent feedback; performance

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

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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; (Gandevia, 2001)) 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 (J. L. Taylor, Amann, Duchateau, Meeusen, & Rice, 2016), with the latter including neural feedforward and feedback mechanisms. Although the significance of these neural mechanisms 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 determinants is less well-recognized. Specifically, the neural feedforward component, which refers to corollary discharge (also called “efferent copy”) related to central motor command, activates sensory areas within the cortex and thereby influences 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 and central fatigue and therefore highlights the link between the two components of fatigue via a feedforward mechanism. 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; J. L. 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 5 km cycling time-trials and constant-load exercise bouts and quantified exercise-induced quadriceps fatigue after each trial (~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 CaO_2 evoked via breathing a hypoxic gas mixture (inspired oxygen fraction (F_iO_2): 0.15, CaO_2 ~18 ml O_2/dl) caused a decrease in central motor drive (assessed via quadriceps EMG) and exercise performance. Conversely, increases in CaO_2 evoked via breathing a hyperoxic gas mixture (F_iO_2 1.0, CaO_2 ~24 ml O_2/dl) increased central motor drive and improved exercise performance. Interestingly, however, the level of end-exercise peripheral fatigue 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 which varies between tasks. Importantly, since work rate at the end of each trial increased to the same level as at the start of exercise, classic reflex inhibition might 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 hypothesised 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 which 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 considered to play a key role in this regulatory mechanism.

Muscle Afferent Feedback

While group Ia and Ib and group II spindle afferents may, with a few exemptions (Enoka et al., 2011), play a negligible role in muscle fatigue (McNeil, Giesebrecht, Khan, Gandevia, & Taylor, 2011), group III and IV afferents significantly influence the development of peripheral and central fatigue during both single-joint and whole-body exercise (J. L. Taylor et al., 2016). Most of the thinly myelinated group III afferents are mechanically sensitive and respond to muscle contraction and/or stretch. Group IV muscle afferents and associated receptors (see below) are sensitive to various intramuscular metabolites and metabolic changes within the contracting muscle as well as to noxious levels of mechanical strain. Recent findings in animals (Birdsong et al., 2010; Jankowski, Rau, Ekmann, Anderson, & Koerber, 2013; Light et al., 2008) and humans (Pollak et al., 2014) indicate the existence of two subgroups of metabosensitive group III/IV muscle afferents characterized by anatomical and functional differences (Amann & Light, 2015). One subtype, the so-called metabo- or ergoreceptors, respond to innocuous levels of intramuscular metabolites (e.g., lactate, ATP, protons) associated with ‘normal’ (i.e., freely perfused and predominantly aerobic) exercise up to strenuous intensities (Bangsbo, Johansen, Graham, & Saltin, 1993; Li, King, & Sinoway, 2003). In contrast, the other subtype, the so-called metabo-nociceptors, only respond to high (noxious) levels of metabolites present in muscle during ischaemic contractions or following hypertonic saline infusions – but not to non-noxious metabolite concentrations associated with normal exercise (Jankowski et al., 2013; Light et al., 2008; Pollak et al., 2014). The specific phenotypic distinction of metaboreceptors vs metabo-nociceptors remains elusive. It is, however, recognized 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 during high intensity whole-body exercise (Amann et al., 2011; Amann, Proctor, Sebranek, Pegelow, & Dempsey, 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 Direction

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 (M. A. 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 designed to cause subjects to voluntarily surpass the threshold (namely fatigue more) during a specific task is required, since a consistent exceedance of the threshold is requisite to challenge this concept. 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).

Furthermore, task specificity is a key factor in terms of the validity of the critical threshold concept. Specifically, it was recently reported that the degree of end-exercise peripheral fatigue was dependent on the duration, and therefore intensity, of the task. Specifically, following completion of a longer 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. 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; M. A. Johnson et al., 2015; Rossman, Garten, Venturelli, Amann, & Richardson, 2014; Thomas, Elmeua, Howatson, & Goodall, 2016; Thomas et al., 2015). The critical threshold model may therefore not be applicable when comparisons of end-exercise fatigue are made across different exercise modalities, tasks (i.e., intensity and duration), and/or drastically different environmental conditions.

Finally, the exact relationship between neuromuscular fatigue and exercise duration/intensity remains unknown. In fact, the recent finding that, 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) further

complicates the situation and raises additional questions concerning the mechanisms limiting endurance exercise of different durations.

The concept of a ‘sensory tolerance limit’

General Idea

In addition to inhibitory neural feedback from working muscles, exercise performance may be limited by fatigue and neural feedback from remote muscles previously or simultaneously exercising (Amann et al., 2013; M. A. 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; B. J. 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 these 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 and the exercising human either terminates the task or, if possible, reduces the exercise intensity to ensure the continuation is tolerable.

The sensory tolerance limit might 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 scientifically difficult to prove. The following sections highlight some observations which could be interpreted as support for this idea 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 (from both legs) to the CNS. In addition, overall central command and corollary discharge was 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).

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

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

In addition to the traditional respiratory system limitations described elsewhere [e.g., (Dempsey, Amann, Romer, & Miller, 2008)], the sensory aspect related to breathing has also been suggested to limit exercise (Sheel, Foster, & Romer, 2011) and is therefore potentially relevant for the sensory tolerance limit theory. This section describes two of these sensory aspects. First, the ventilatory demand associated with sustained vigorous exercise causes significant respiratory muscle fatigue (B. D. Johnson, Babcock, Suman, & Dempsey, 1993; B. J. Taylor, How, & Romer, 2006), which increases neural feedback from these muscles (Hill, 2000) and triggers a sympathetically-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 during intense cycling exercise (80% W_{peak} for ~10 min) by up to 80% using a mechanical ventilator 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 by 3–7 cmH_2O/l s during heavy cycling exercise caused a faster rate of both overall effort perception and dyspnoea and compromised 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). Together, 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 supports 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) might 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 might 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 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 during 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 be expected to 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, 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 also alter the sensory tolerance limit and therefore affect exercise performance (Lambert, St Clair Gibson, & Noakes, 2005). The influence of these factors on effort perception and exercise performance are discussed elsewhere in this review series.

Summary

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

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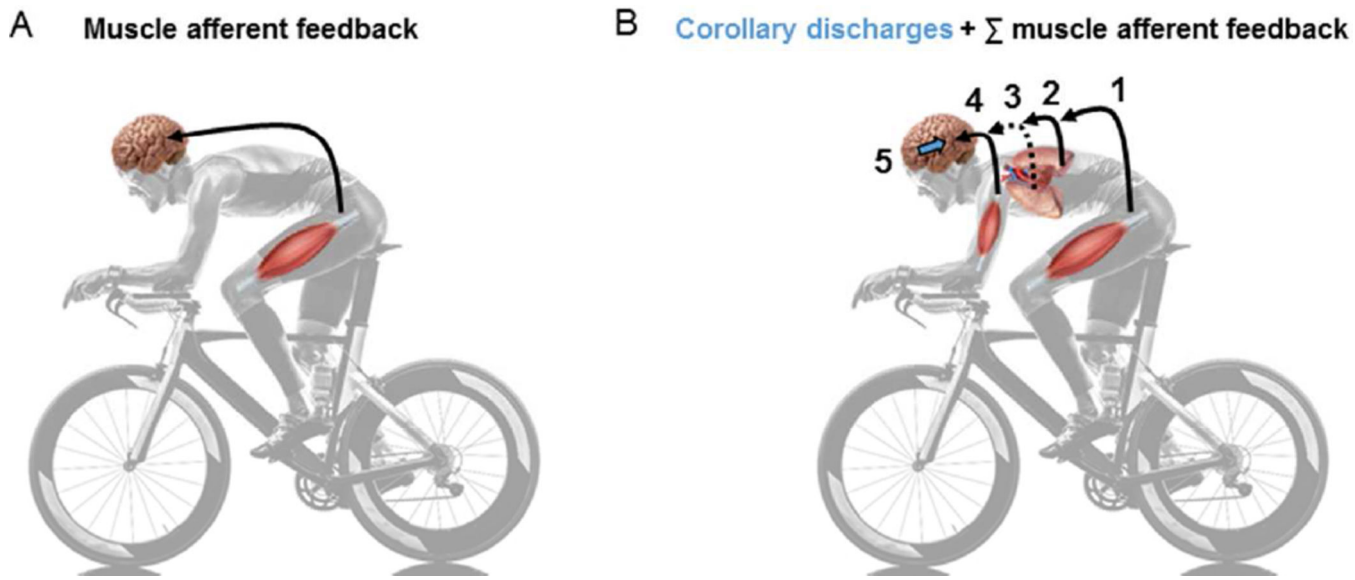

Figure 1. Simplified schematic illustration of the 'critical threshold of peripheral fatigue' (A) and the 'sensory tolerance limit' (B)

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.

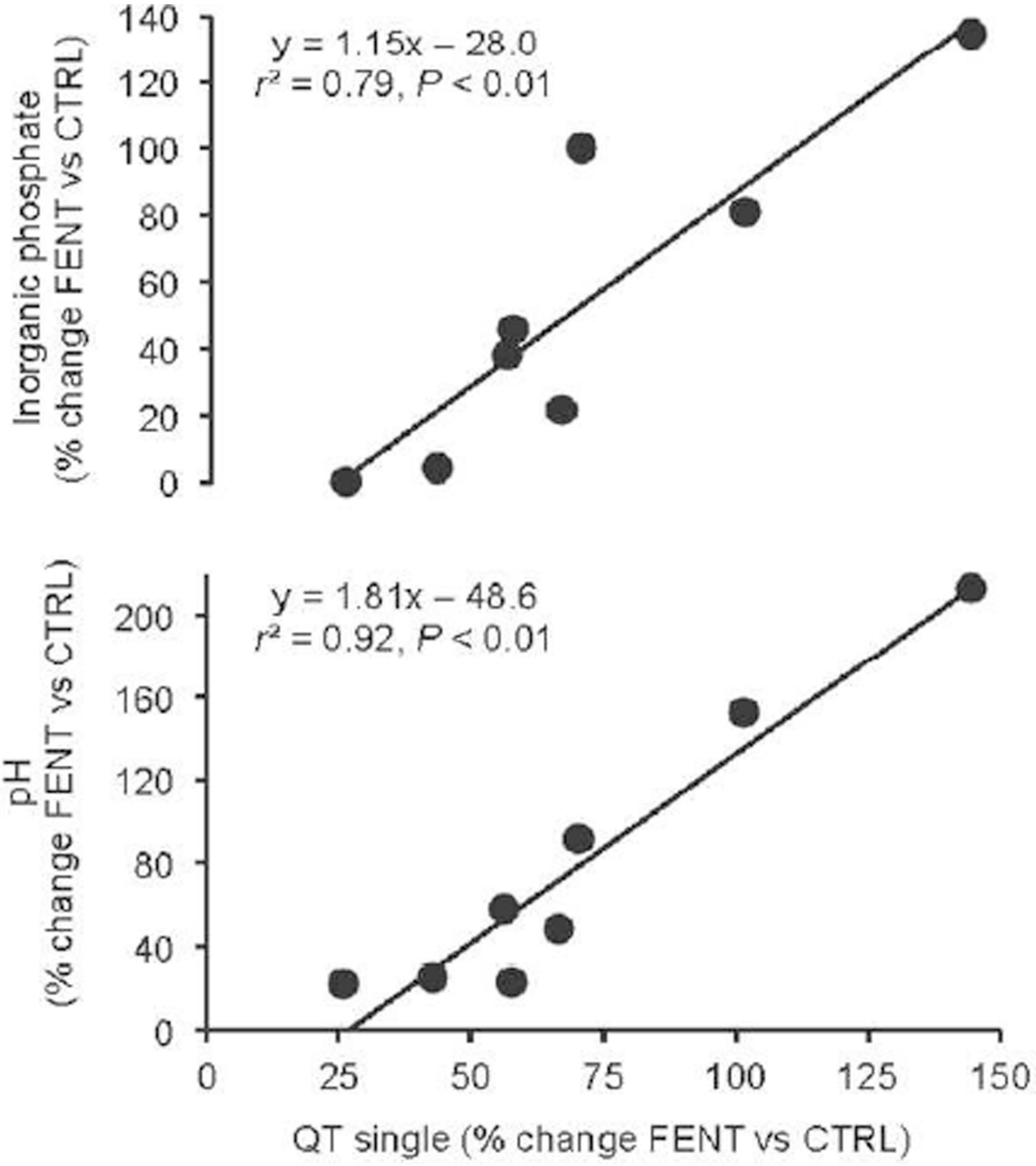

Figure 2. Relationship between peripheral muscle fatigue and intramuscular metabolites

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.

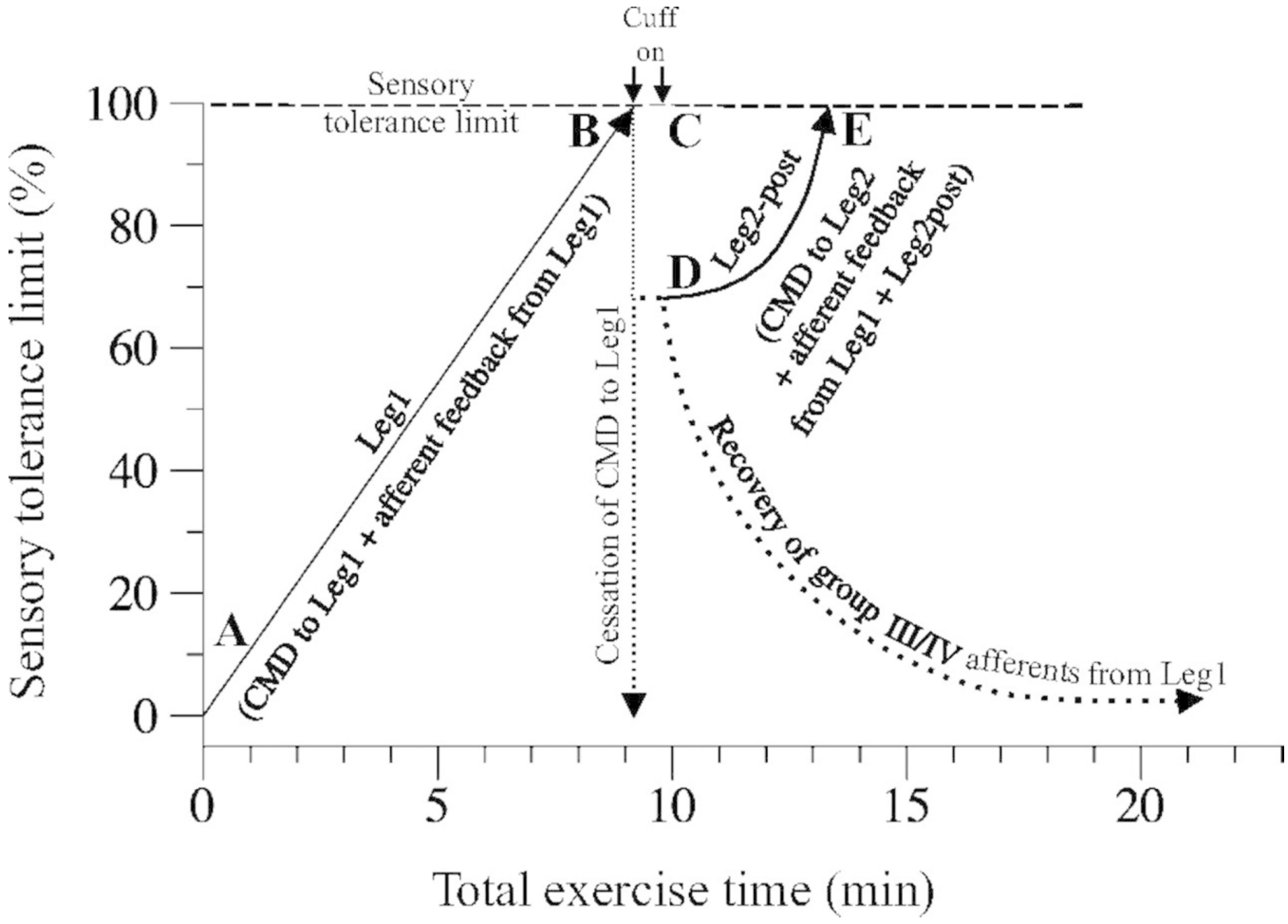

Figure 3. Schematic illustration reflecting potential sensory alterations during the consecutive single-leg knee extensor performance tests

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

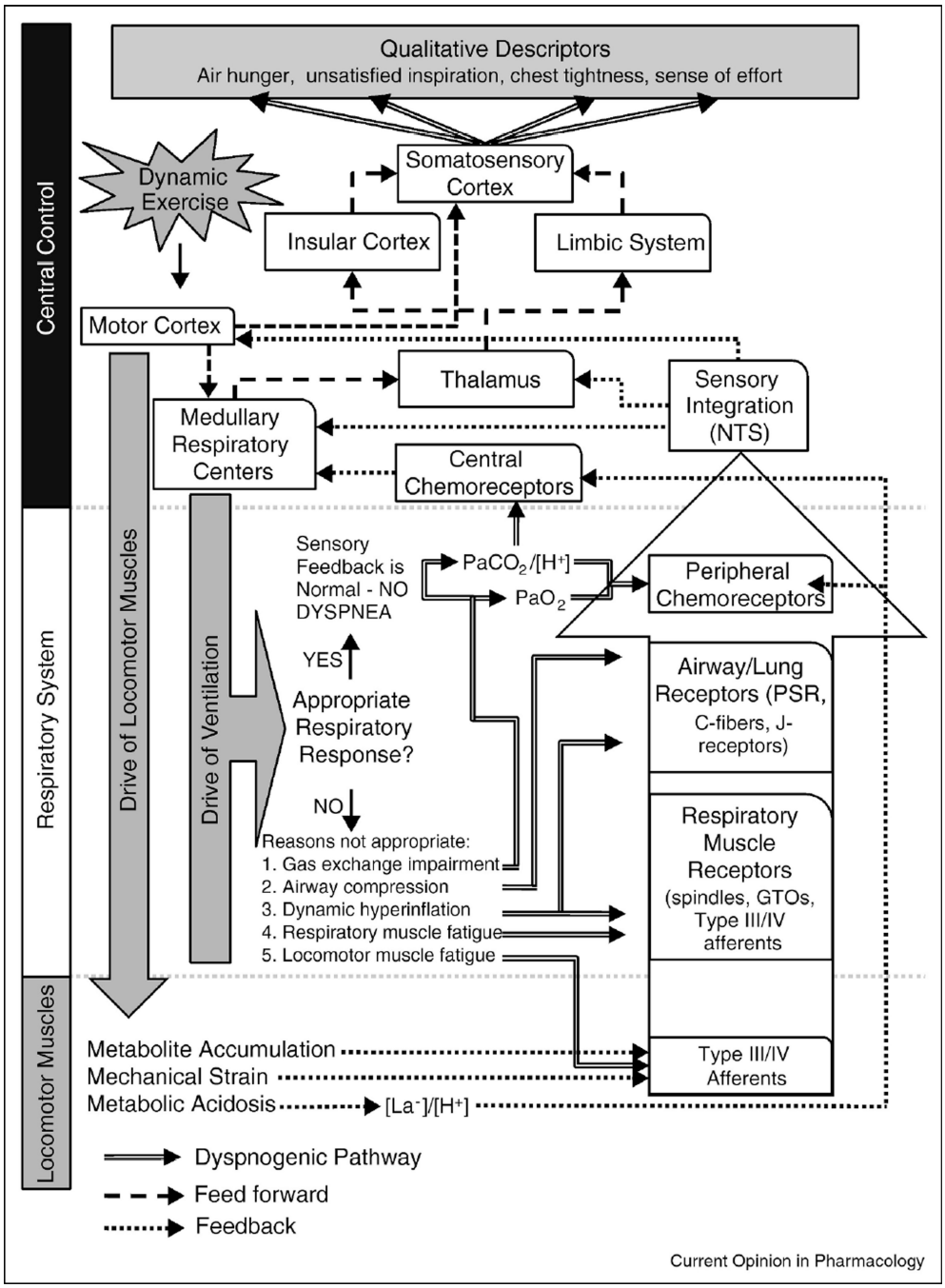

Figure 4. Mechanisms of exertional dyspnoea

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.