

20 **Abstract**

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

40 **Introduction**

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

51 Neuromuscular fatigue develops during strenuous physical activities and causes a
52 temporary reduction in the force or power generating capacity of a muscle or muscle group. This
53 impairment stems from a decrease in neural activation of muscle (i.e., central fatigue) and/or
54 biochemical changes at or distal to the neuromuscular junction that cause an attenuated contractile
55 response to neural input (i.e., peripheral fatigue) (Bigland-Ritchie, Jones, Hosking, & Edwards,
56 1978). Despite this differentiation, exercise-induced fatigue needs to be viewed as an integrative
57 phenomenon since interactions between central and peripheral fatigue can occur via humoral and
58 non-humoral processes (Taylor, Amann, Duchateau, Meeusen, & Rice, 2016), with the latter
59 including neural feedforward and feedback mechanisms. Although the significance of group III/IV
60 muscle afferents is well described for the circulatory and ventilatory control during exercise, their
61 role in the development of muscle fatigue and the interaction between central and peripheral
62 fatigue is less well-recognized. Specifically, the neural feedforward component, which refers to

63 corollary discharge (also called “efferent copy”) related to central motor command (Sperry, 1950;
64 Wolpert, Ghahramani, & Jordan, 1995), is a neural signal generated in motor centres of the brain
65 that is not directly involved in the ongoing motor activity (Poulet & Hedwig, 2007). Corollary
66 discharges activate sensory areas within the cortex and thereby influence effort perception and
67 ultimately the development of central fatigue during exercise (Gallagher et al., 2001; Liu et al.,
68 2005). With progressive increases in peripheral fatigue during exercise at a fixed work rate,
69 increases in central motor command are necessary to compensate for fatigued motor units. This
70 increase in central command also increases corollary discharge (Eldridge, Millhorn, & Waldrop,
71 1981; Williamson et al., 2001) and likely central fatigue (Liu et al., 2005). Therefore, the increase
72 in central command and subsequently central fatigue secondary to the increase in peripheral fatigue
73 highlights the link between the two components of fatigue via a feedforward mechanism. While
74 corollary discharges and associated anatomical structures are difficult to study in humans, related
75 pathways have been identified, to a cellular level, in animals (Poulet & Hedwig, 2006, 2007). The
76 neural feedback component entails afferent feedback (which increases with the development of
77 peripheral fatigue) from contracting muscles to the CNS, the associated activation of sensory areas
78 within the brain, and the subsequent facilitation of effort perception and central fatigue (Amann et
79 al., 2011; Taylor et al., 2016). This interaction highlights the link between peripheral and central
80 fatigue via a feedback mechanism.

81

82 **The concept of a ‘critical threshold of peripheral fatigue’**

83 *Correlative Evidence*

84 Numerous studies have shown that the magnitude of peripheral locomotor muscle fatigue
85 incurred during whole-body exercise typically does not exceed a value specific to the individual
86 and task [e.g., (Amann & Dempsey, 2008; Amann et al., 2006; Gagnon et al., 2009; Hureau,
87 Ducrocq, & Blain, 2016; Hureau, Olivier, Millet, Meste, & Blain, 2014)]. Initial evidence for this
88 phenomenon stemmed from studies that manipulated arterial oxygen content (C_aO_2) during
89 simulated 5 km cycling time-trials and constant-load exercise bouts (~7-10 min duration, 80-100%
90 VO_{2max}) (Amann et al., 2006). Compared to control (normoxia, C_aO_2 ~21 ml O_2 /dl), decreases in
91 C_aO_2 evoked via breathing a hypoxic gas mixture (inspired oxygen fraction [F_{iO_2}] 0.15, C_aO_2 ~18
92 ml O_2 /dl) caused a decrease in central motor drive (assessed via quadriceps EMG normalized for
93 changes in M-wave amplitude) and exercise performance. Conversely, increases in C_aO_2 evoked
94 via breathing a hyperoxic gas mixture (F_{iO_2} 1.0, C_aO_2 ~24 ml O_2 /dl) caused an increase in central
95 motor drive and improved exercise performance. Interestingly, however, the level of end-exercise
96 peripheral fatigue (quantified via pre- to post-exercise changes in quadriceps twitch force) was
97 identical across conditions. Accordingly, it was hypothesised that central motor drive and
98 consequently exercise performance are regulated in order not to surpass a certain level of
99 peripheral locomotor muscle fatigue – a degree of fatigue that varies between tasks. Since work
100 rate at the end of each trial increased to the same level as at the start of exercise, classic reflex
101 inhibition can be excluded as the main mechanism regulating muscle activation during exercise.
102 Voluntary alterations in neural drive originating at higher brain areas are more likely to explain
103 the differences in pace and ultimately performance. Regardless, these observations led to the
104 concept of a “critical threshold of peripheral fatigue” (Figure 1A), which was confirmed by
105 subsequent studies using whole-body exercise of various intensities, including all-out repeated
106 sprints where pacing strategy does not play a role [e.g. (Amann & Dempsey, 2008; Gagnon et al.,

107 2009; Hureau et al., 2016; Hureau et al., 2014)]. To explain this regulatory loop, it was
108 hypothesized that central motor drive during whole-body exercise is carefully controlled in order
109 to limit metabolic perturbation within locomotor muscle and, therefore, the development of
110 peripheral fatigue. In this context, it is important to note that changes in intramuscular metabolites
111 and peripheral fatigue are tightly correlated (Figure 2) (Blain et al., 2016).

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

124 The aforementioned studies support the idea that exercise performance is tightly regulated
125 to ensure that the metabolic milieu, and therefore peripheral fatigue, does not exceed a certain level
126 that varies between tasks. But, what links peripheral fatigue and intramuscular perturbation with
127 the CNS to allow for the precise regulation of spinal motoneuronal output (the ultimate
128 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).

152 Although these functional differences have been observed in both animals and humans, the
153 specific phenotypic distinction of metaboreceptors vs metabo-nociceptors remains elusive. It is
154 recognized, however, that molecular differences between the two subtypes include the differential
155 expression of purinergic receptors (P2X_{2,3,4}), transient receptor potential vanilloid type 1 and/or
156 2 (TRPV1/2), and acid-sensing ion current 1, 2, and 3 (ASIC 1-3) (Birdsong et al., 2010; Jankowski
157 et al., 2013; Light et al., 2008). Although the two different subtypes of group III/IV muscle
158 afferents project to the same location in the superficial dorsal horn (Jankowski et al., 2013), it is
159 currently unknown to what extent each subtype is anatomically linked to lamina I neurons which
160 have direct projections to various supraspinal sites.

161

162 *Experimental Evidence*

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

174 (Amann et al., 2011; Amann et al., 2009; Blain et al., 2016; Gagnon et al., 2012; Sidhu et al.,
175 2014).

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

182

183 *Considerations, Limitations, and Future Directions*

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

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

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

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

219 additional questions concerning the mechanisms limiting endurance exercise of different
220 durations. Regardless, these and other recent findings suggest that the magnitude of end-exercise
221 peripheral fatigue is highly specific and varies between tasks (Amann, Pegelow, Jacques, &
222 Dempsey, 2007; Goodall, Gonzalez-Alonso, Ali, Ross, & Romer, 2012; Goodall, Ross, & Romer,
223 2010; Johnson et al., 2015; Rossman, Garten, Venturelli, Amann, & Richardson, 2014; Thomas,
224 Elmeua, Howatson, & Goodall, 2016; Thomas et al., 2015). Therefore, although the critical
225 threshold model remains a valid concept, comparisons of end-exercise fatigue across different
226 exercise modalities, tasks (i.e., intensity and duration), and/or drastically different environmental
227 conditions may not be appropriate as the absolute threshold appears to be condition specific.

228

229 **The concept of a ‘sensory tolerance limit’**

230 *General Idea*

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

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

246 The sensory tolerance limit may be described as a global (i.e., not limited to a single muscle
247 / muscle group) negative feedback loop leading to task failure when a finite level of stimulation is
248 reached from sensory afferents originating in muscles that are directly (e.g., leg muscles during
249 cycling) or indirectly (e.g., respiratory muscles during cycling) involved in the exercise, and from
250 corollary discharge associated with central motor command (Figure 1B). The Borg scale (Borg,
251 1970), a tool frequently used to rate the intensity of perceived exertion (RPE), might offer a
252 suitable means to quantify an individual’s relative ‘proximity’ to the sensory tolerance limit.
253 Importantly, both muscle afferent feedback and central motor command have been shown to
254 influence RPE (Amann et al., 2010; Amann et al., 2008; Galbo, Kjaer, & Secher, 1987;
255 Winchester, Williamson, & Mitchell, 2000) and might be considered as key determinants of the
256 sensory tolerance limit. However, the validity and relevance of the sensory tolerance limit is
257 difficult to prove. The following sections highlight some observations which could be interpreted
258 as support for the concept and its potential role in limiting exercise. It needs to be emphasized,
259 however, that the studies discussed below were originally *not* designed to address questions
260 concerning the sensory tolerance limit.

261

262

263 *Support for the Sensory Tolerance Limit Concept*

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

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

286 quadriceps fatigue compared to the same task performed with prior contralateral quadriceps fatigue
287 (~5 min). Moreover, quadriceps fatigue was substantially greater following the exercise performed
288 without prior contralateral leg fatigue compared to the bout performed with prior contralateral leg
289 fatigue (Amann et al., 2013). Since the exercise performed with prior fatigue in the contralateral
290 leg was associated with afferent feedback arising from both the active and likely also the
291 recovering quadriceps, it was concluded that, given these two sources of sensory feedback, the
292 compromised endurance time and the lower end-exercise fatigue may be explained by a more rapid
293 attainment of the sensory tolerance limit (Figure 3). This interpretation may also apply to the
294 Johnson study (discussed above) documenting reduced cycling endurance and end-exercise
295 peripheral fatigue when intense leg cycling exercise to exhaustion was preceded by fatiguing arm
296 cranking as compared to intense leg cycling exercise alone (Johnson et al., 2015).

297 Metabo-nociceptors, in addition to metabosensitive muscle afferent feedback, also limit
298 exercise performance, perhaps by contributing to the sensory tolerance limit. This idea is reflected
299 in a study during which muscle pain was induced by hypertonic saline injection into the *vastus*
300 *lateralis* of one leg. The performance during a subsequent maximal single-leg hop task executed
301 with the infused (i.e., painful) leg was compromised compared to the same task performed without
302 pain (Deschamps et al., 2014). Interestingly, however, hopping performance of the contralateral
303 (i.e., non-painful) leg was also compromised following hypertonic saline infusion in the other leg
304 (Deschamps et al., 2014). Further studies triggered metabo-nociceptors by occluding blood supply
305 to the fatigued elbow extensors at the end of exercise (tourniquet placed proximally to fatigued
306 muscle) to investigate the impact of ischaemic muscle pain on performance and voluntary muscle
307 activation. Similarly, muscle pain decreased maximal voluntary activation and performance of the
308 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

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

337 The second sensory aspect related to the respiratory system is the subjective experience of
338 breathing discomfort, or ‘dyspnoea’, during exercise. A schematic illustration of mechanisms
339 determining exertional dyspnoea and its potential contribution to the sensory tolerance limit via
340 the somatosensory cortex is provided in Figure 4. The perception of respiratory work and effort,
341 which arises from a combination of respiratory muscle afferent feedback and corollary discharge
342 (related to central command associated with breathing) to sensory areas, has been identified as a
343 key component of exertional dyspnoea (Laviolette & Laveneziana, 2014). Indeed, reducing the
344 work of breathing by up to 80% using a mechanical ventilator during intense cycling exercise
345 (80% W_{peak} for ~10 min) attenuated the rate of increase in overall effort perception compared to
346 control exercise, but also significantly reduced the rate of dyspnoea and improved endurance
347 performance (Amann et al., 2007; Harms, Wetter, St Croix, Pegelow, & Dempsey, 2000; Romer
348 et al., 2006). In contrast, increasing respiratory muscle work through inspiratory loading during
349 heavy cycling exercise caused a faster rate of both overall effort perception and dyspnoea and
350 reduced endurance performance by 15-20% (Harms et al., 2000). It was suggested that part of the
351 limitation to exercise might have been accounted for by the increased rate of dyspnoea (Harms et
352 al., 2000; Romer et al., 2006). The above studies focusing on limb and respiratory muscle suggest
353 that muscle afferent feedback, regardless of its origin, exerts an inhibitory effect on motoneuronal

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

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

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

377 1984; Park et al., 2016) and thereby decreases the stimulation of group III/IV muscle afferent
378 feedback during exercise at a given workload. This training-induced reduction in intramuscular
379 metabolic perturbation at a given workload would be expected to decrease peripheral fatigue and
380 therefore require less neural drive / central command which, in turn, would decrease corollary
381 discharge. Although currently not supported by well controlled studies, exercise training might
382 also attenuate the sensitivity or density of receptors linked with sensory neurons. As a
383 consequence, a given level of afferent stimulation may result in a reduced discharge and therefore
384 attenuated central projection of group III/IV muscle afferents. Alternatively, exercise training may
385 alter the central representation and/or processing of neural feedback. Interesting in the context of
386 these potential effects is a recent study which showed that an improvement in exercise performance
387 following eight weeks of endurance training was associated with greater end-exercise peripheral
388 fatigue, but similar central fatigue (Zghal et al., 2015). Given the tight relationship between
389 intramuscular metabolites and peripheral fatigue (Figure 2) (Blain et al., 2016), the greater
390 tolerance for peripheral fatigue might indirectly support a training-induced decrease of the
391 sensitivity, or altered central processing, of group III/IV muscle afferents.

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

398 Psychological, psychophysical, and other endogenous reference signals – for example,
399 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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641

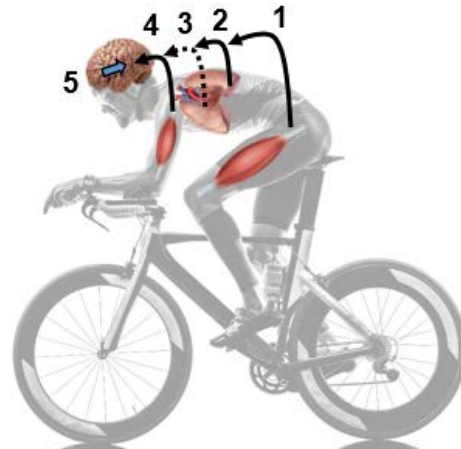
642 **Figures**

643

A **Muscle afferent feedback**



B **Corollary discharges + Σ muscle afferent feedback**

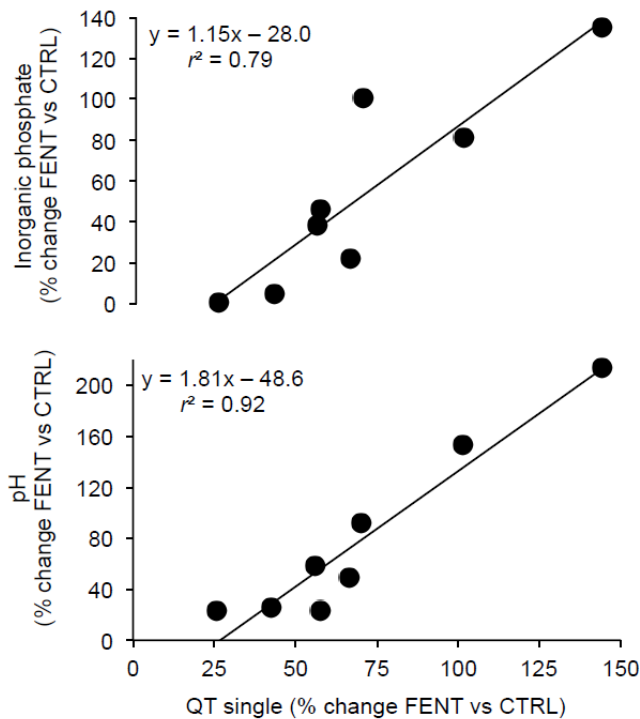


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645

646 **Figure 1. Simplified schematic illustration of the ‘critical threshold of peripheral fatigue’ (A)**
647 **and the ‘sensory tolerance limit’ (B).**

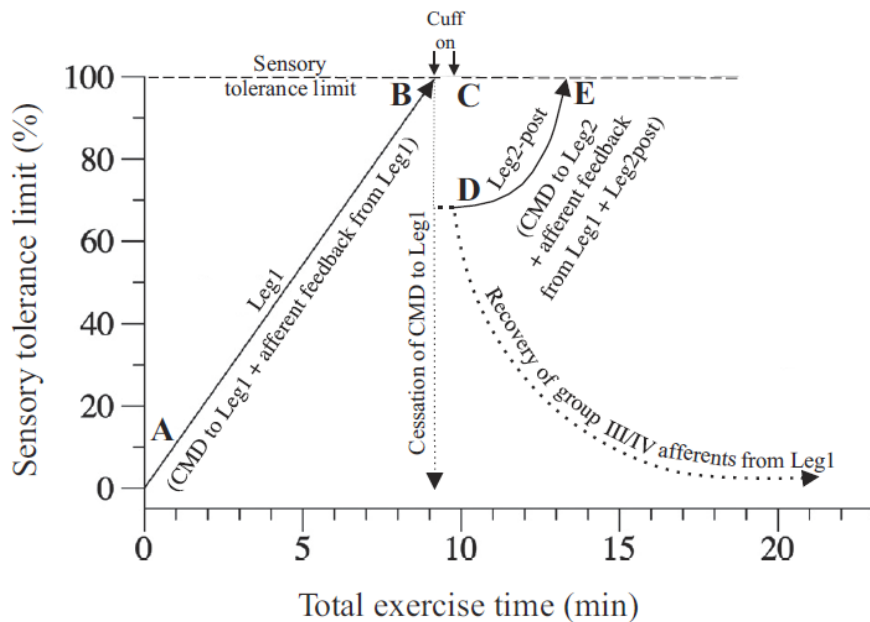
648 The critical threshold model proposes a large influence of muscle afferent feedback from
649 locomotor muscles in regulating the degree of exercise-induced neuromuscular fatigue and
650 exercise performance (panel A). The sensory tolerance limit is less specific and suggests that
651 neural feedback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



655

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

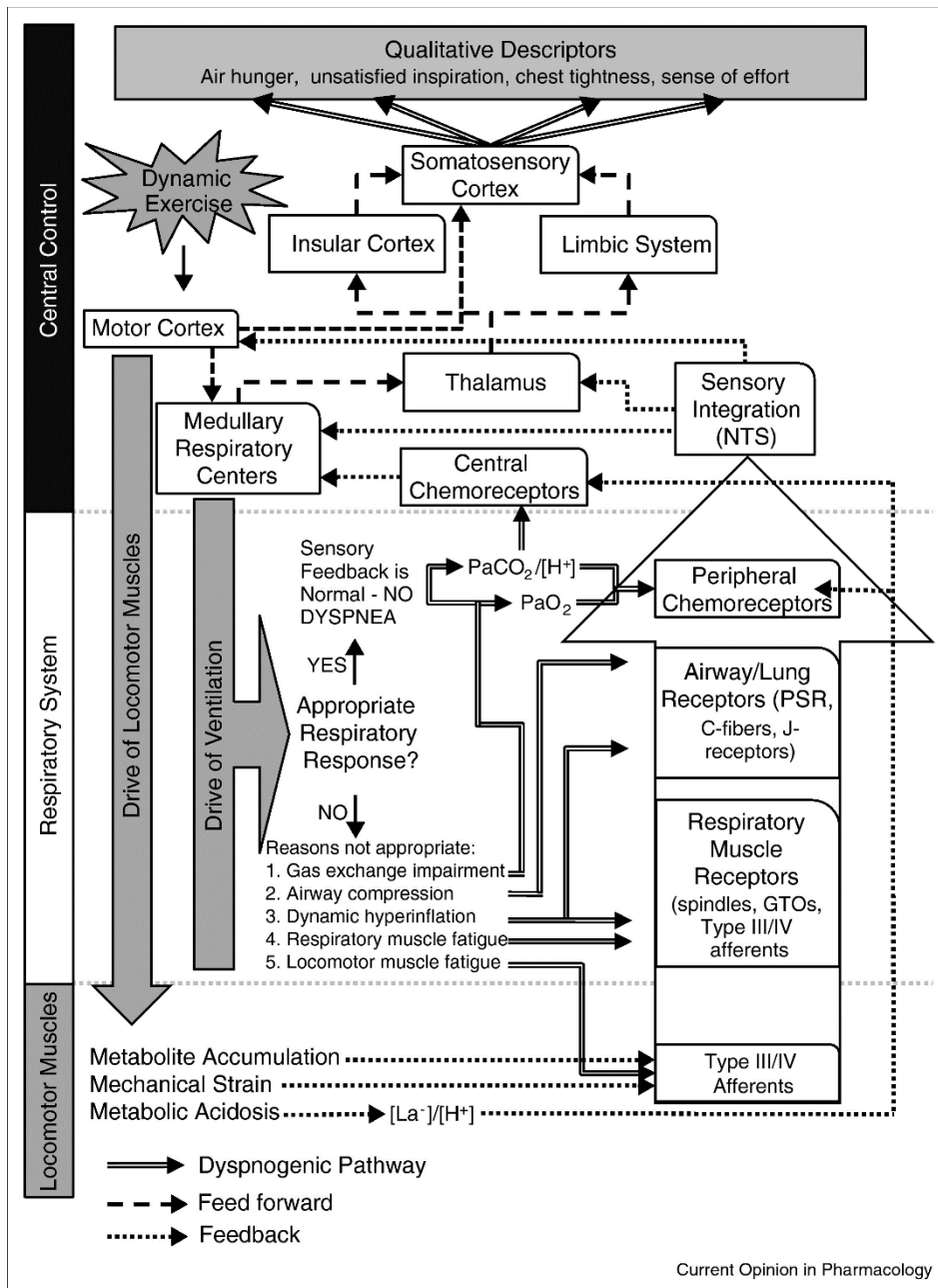
657 Subjects performed 5 km cycling time trials with intact (CTRL) and blocked group III/IV muscle
 658 afferent feedback. Vastus lateralis muscle biopsies were taken before and immediately after
 659 completion of each trial. Exercise-induced changes in intramuscular metabolites, for example
 660 inorganic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



667

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.



681

682 **Figure 4. Mechanisms of exertional dyspnoea.**

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

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

698