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Neural Control of Force Output During Maximal and Submaximal Exercise

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Abstract

A common belief in exercise physiology is that fatigue during exercise is caused by changes in skeletal muscle metabolism. This 'peripheral' fatigue results either from substrate depletion during submaximal exercise or metabolite accumulation during maximal exercise in the exercising muscles. However, if substrate depletion alone caused fatigue, intracellular ATP levels would decrease and lead to rigor and cellular death. Alternatively, metabolite accumulation would prevent any increase in exercise intensity near the end of exercise. At present, neither of these effects has been shown to occur, which suggests that fatigue may be controlled by changes in efferent neural command, generally described as 'central' fatigue.

In this review, we examine neural efferent command mechanisms involved in fatigue, including the concepts of muscle wisdom during short term maximal activity, and muscle unit rotation and teleoanticipation during submaximal endurance activity. We propose that neural strategies exist to maintain muscle reserve, and inhibit exercise activity before any irreparable damage to muscles and organs occurs. The finding that symptoms of fatigue occur in the nonexercising state in individuals with chronic fatigue syndrome indicates that fatigue is probably not a physiological entity, but rather a sensory manifestation of these neural regulatory mechanisms.

Fatigue is defined as a decrease in force production,[1-3] or an inability to regenerate the original force[4] in the presence of an increased perception of effort.[5] The causes of fatigue have been classified as either 'peripheral' or 'central' in origin. Peripheral fatigue is defined as a decrease in the force generation capacity of the skeletal muscle because of action potential failure, or excitation-contraction coupling failure, or impairment of cross-bridge cycling, in the presence of unchanged or increasing neural drive.[6,7] Central fatigue is defined as a reduction in neural drive or motor command to the muscle resulting in a decline in force production or tension development.[5]

The peripheral model of fatigue in exercise physiology has traditionally examined force output or velocity of contraction during stimulated contractions of skeletal muscle in either whole or skinned form in an *in vivo* medium. This work has highlighted metabolic changes in peripheral skeletal muscle independent of the central nervous system (CNS). These metabolic changes associated with fatigue

include the relative contributions of lactate level increases, pH decrease and associated proton accumulation, ATP and creatine phosphate depletion, ADP, inosine monophosphate and inorganic phosphate accumulation, skeletal muscle Na^+/K^+ ATPase pump changes, and sarcolemmal, T-tubule and sarcoplasmic reticulum functional changes, described as excitation/contraction coupling failure.[8-11] The researchers using this model have generally concluded that fatigue during maximal intensity exercise is caused by substrate depletion or metabolite accumulation from energy utilisation in the peripheral skeletal musculature. They have concluded that fatigue during submaximal exercise is caused by substrate, energy compound depletion or excitation/contraction coupling failure. However, none of these metabolic changes has been shown to directly cause fatigue during dynamic physical activity.[8,12,13]

The aim of this article is to show that the mechanisms of fatigue may also incorporate neural control mechanisms, or 'governor' processes, which regulate muscle contractions to prevent the maximal capacity of any of the peripheral systems from being reached. This neuromuscular regulation protects vital organs from being damaged during exercise.[12,14-16] It must be noted that this article examines the efferent neural commands which cause changes in force output and are evoked by regulatory mechanisms during exercise activity, rather than the anatomical location and either the feedforward or feedback features of these regulatory mechanisms. The word 'governor' is therefore used in the article as a general term describing the regulatory control mechanisms involved in producing these efferent neural commands.

A number of different exercise protocols have been used to elicit fatigue. Enoka and Stuart[5] have previously suggested that fatigue is not a singular entity, but rather that different processes may cause fatigue during different protocols of differing intensity and duration. They described this as task dependency fatigue. Task dependency describes the complex relationship between speed, duration and intensity which occurs in different exercise activities. Using the task dependency model to classify fatigue, we have defined the following exercise protocols to examine neural control mechanisms involved in these different activities:

- during maximal isometric fatigue
- during maximal repetitive sprint activity
- during maximal intensity endurance exercise
- during submaximal exercise of set (closed-loop) duration
- during submaximal exercise of undetermined (open-loop) duration
- in fatigue associated with pathological medical conditions at rest.

1. Neural Control Mechanisms During Maximal Isometric Fatigue

Most research investigating the relative contributions of the central and peripheral components of isometric fatigue have used surface or invasive electromyographic (EMG) techniques, associated with twitch interpolation techniques, during submaximal or maximal actions.[17]

During submaximal isometric activity, the individual is able to increase motor unit recruitment to counteract the reduction of force output which occurs with the development of fatigue. However, during maximal isometric activity, the individual does not have the capacity to increase the motor unit recruitment, and alterations in firing strategy to individual motor units are needed to alter force production.

The first mechanism by which this may be performed has been described as 'muscle wisdom.'[16,18] Previous work on muscle wisdom demonstrated that the decline in force during a 60-second maximal voluntary contraction (MVC) of adductor pollicis could be mimicked by a decrease in stimulation frequency from 60 to 20Hz used for electrical stimulated force generation (fig. 1). When stimulus frequency was held constant, force declined more rapidly.[5,20-22] Later studies showed that during maximal voluntary isometric contraction, human motor units reduce their firing rates from a high to a low value.[16,23] As suggested by Windhorst and Boorman,[16] this decrease in firing rate would be counter-intuitive, as during steady-state force frequency activity, fir-

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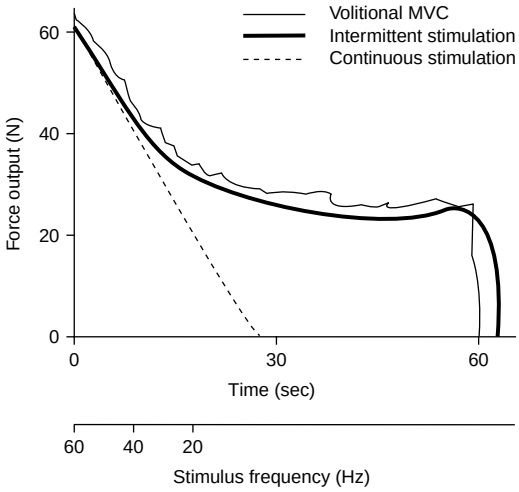

Fig. 1. Previous work on muscle wisdom changes of Jones[19] demonstrated that the decline in force during a 60-second MVC of the abductor pollicis muscle could be mimicked by a decrease in stimulation frequency from 60 to 20Hz used for electrical stimulated force generation (adapted from Enoka and Stuart,[5] with permission). **MVC** = maximal voluntary contraction.

ing rate would be expected to increase. De Luca and Erim[24] postulated that the neuromuscular system was designed to optimise some combination of force and the duration the force was sustained by decreasing the firing rate to the muscle fibres recruited later. In this scheme, feedback via group III and IV afferents depresses the excitability and discharge rate of motor neurons to match the prolonged relaxation of twitch responses found during fatigue in electrically stimulated muscle.

Enoka and Stuart[5] suggested that the functional significance of muscle wisdom was optimisation of force output and economical activation of fatiguing by the CNS. Gandevia et al.[1] suggested that the concept of muscle wisdom was a misnomer, and that the regulation occurs proximal to the muscle itself, in the brain or neural control pathways. The decrease in firing frequency may therefore be a centrally controlled mechanism to maintain force output while protecting fatiguing fibres from damage incurred by ongoing muscle contraction and ATP and phosphocreatine depletion. Further work is need to confirm this hypothesis. Nevertheless, decreases in force output during a maximal voluntary isometric contraction may be due to this mechanism, rather than due to maximal substrate depletion or metabolite accumulation.

During maximal voluntary isometric contractions, a number of studies using surface EMG techniques have shown that the frequency spectrum of the EMG signal decreases.[2,25-27] This decrease in frequency content occurs during both volitional and electrically stimulated conditions. This spectral compression has been shown to be caused largely by decreases in neuromuscular conduction velocity,[28] and is generally found to be correlated with the percentage of type II muscle fibres.

Enoka and Stuart[5] suggested that the final discharge of the action potential is more synchronised among motor units with smaller and slower twitches, and thus the decrease in frequency content during fatigue profiles indicates selective recruitment of type I fibres later in the MVC. Type I fibres would be selectively recruited during fatiguing contractions, because of their higher resistance to fatigue.[29,30] Kupa et al.[27] suggested that the reason for the correlation with type II fibres and frequency content in their study was the different metabolic activity and membrane potentials in type II fibres. The type II fibres have a greater potential for intramuscular pH to decrease during a contraction, and this change in pH may lead to a decrease in conduction velocity and frequency content of the EMG signal, because of type II fibres either being derecruited early on during the MVC, or not being recruited later in the contraction. An afferent reflex originating in type II fibres may thus either initiate the changes in frequency content or alter its pattern of action.

However, work in our laboratory has shown that these decrements in frequency occurred within the first few seconds of beginning a maximal isometric contraction, and are related ($r = 0.93$; $p < 0.05$) to skeletal muscle fibre composition (fig. 2) [unpublished data]. This indicates the possibility of a preprogrammed centrally driven command process which is initiated immediately as a contraction be-

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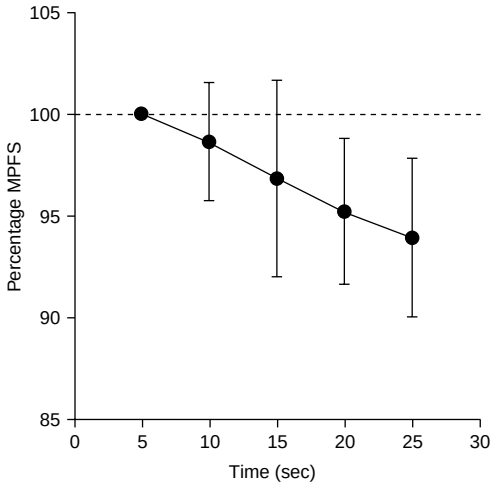

Fig. 2. Early frequency compression changes [mean percentile frequency shift (MPFS)] during short term maximal voluntary contractions. Each time point is normalised to the first time point, which is described as 100% MPFS (unpublished data).

gins and occurs relative to an individual's different muscle phenotype. Indeed, Belhaj-Sahif et al.[31] recorded discharge patterns from cortical cells in the brain of monkeys as they exerted repetitive isometric activity. Cortical activity was shown to either decrease, increase or remain constant in the same way as the EMG power spectrum changed. They concluded that the motor neurone discharges may be modulated by descending signals from these motor cortical areas.

Therefore, it may be suggested that motor efferent recruitment patterns are altered in fatigue processes to prevent the extreme metabolic derangements from damaging muscle fibres during fatiguing contractions. These control mechanisms are altered early on during the fatigue process, terminating exercise with muscle reserve capacity, possibly as a protective governor reflex.

2. Neural Control Mechanisms During Maximal Repetitive Sprint Activity

During maximal repetitive sprint activity, studies have shown that power output decreases immediately after the first sprint activity. The previous work examining fatigue during either individual or repetitive sprint activity have examined metabolic causes and considered both substrate utilisation and metabolic accumulation as being the cause of decrements in force output during this type of activity. Particularly, changes in the glycolytic and creatine phosphate pathways have been described as the cause of fatigue in this intermittent sprint model.[9,32,33] However, studies have shown that the decrements in force are not tightly correlated with these metabolic derangements, suggesting that other factors such as neural control mechanisms may be important determinants of the fatigue that develops in this form of physical activity.[34]

Gaitanos et al.[35] and research conducted in our laboratory (fig. 3), have shown that during consecutive sprint activity, the greatest decrement in sprinting performance occurred in the first sprints. The decrement in sprinting speed was attenuated in the next sprints (fig. 3). This work showed that the rate of decline in performance was curvilinear rather than linear. Furthermore, performance was essentially stable without any further decrements after ≈50% of the sprints had been completed.

Gaitanos et al.[35] assumed that the decreases in sprinting speed were caused by substrate unavailability or metabolite accumulation. However, in their trial, neither creatine phosphate, muscle glycogen or ATP level decreased sufficiently to be regarded as limiting for muscle contraction. It is important to note that the speed decrements were curvilinear and not linear. It is logical to assume that if metabolite accumulation or substrate depletion was the cause of these speed decrements, that the effect would be cumulative, and speed decrements would decrease linearly to zero through the course of the sprint trial as the participants eventually became completely exhausted.

It may be hypothesised that during these intermittent sprint activities, the first sprint is performed maximally to the limits of volitional control by the individual. The afferent input signals to the cortex or brainstem would indicate that this level of intensity repeated again would damage the muscle tissue

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leading to cellular damage. Therefore, in accordance with this theory, the efferent neural command and power output may be down-regulated in successive sprints. It is not clear whether the 'governor' in this model would be a central feedforward command or response to afferent input from the peripheral muscles. The adjusted power output would reduce the metabolic requirements needed to perform these sprints so as not to cause cellular damage with the repetitive activity. Ulmer[36] has defined this 'resetting' of the power output as teleoanticipation. Eventually, a speed is reached that can be sustained essentially indefinitely, without risk of organ damage.

It is not clear what inhibitory processes may be occurring even during the first maximal sprint activity. As shown in the data on isometric activity, it is likely that regulatory governor alteration in conduction velocity leading to power output inhibition may occur early on during the first sprint activity. Thus maximal power output occurs only in the first second or two of the maximal activity, with inhibition occurring as the first sprint continues. Indeed, work performed in our laboratory (unpublished observations) on neural changes during Wingate testing, which would represent maximal sprint activity, has shown that as power output decreased, although integrated EMG (IEMG) activity was maintained, the frequency spectrum was decreased in a manner similar to that described previously. Thus, some form of central control may occur even during this first sprint.

Secondly, theoretically, during even the first maximal sprint in all these studies there may be a degree of subconscious inhibition, for the motor cortex programming could take into account any prior experiences of maximal exercise. No human being can have gone through their life up to the point of maximal sprint activity without having performed prior maximal activity. Inhibitory sequences are almost certainly programmed into the pre-motor or motor cortex from prior activities of daily living which induce fatigue, or due to prior athletic performance from the time of infancy, and these would regulate even an initial ballistic sprint activity. Therefore, in the study of Gaitanos et al.[35] and work in other laboratories, where we assume that the first sprint represents maximal volitional activity, this assumption is perhaps incorrect and during this maximal volitional activity, a muscle reserve may be present. One must speculate that this muscle reserve is maintained by either learned responses from prior experience or due to innate intrinsic efferent inhibitory pathways.

3. Neural Control Mechanisms During Maximal Intensity Endurance Exercise

The cause of fatigue during maximal endurance activity has perhaps received the most attention in the field of exercise physiology in the last few decades. Research has traditionally focused on the role of maximal aerobic capacity (maximal oxygen uptake: $\dot{V}O_{2max}$) in causing fatigue during maximal high intensity endurance exercise. These exercise protocols usually involve incrementally increasing exercise intensity usually during horizontal or incline treadmill running or during cycle ergometry. During this exercise testing, oxygen uptake ($\dot{V}O_2$) is recorded during the activity, and when a plateau

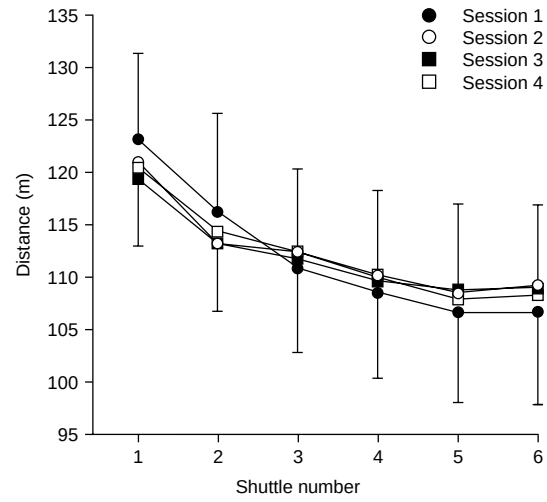

Fig. 3. Power decrements during intermittent maximal sprint activity. Distance covered during the 6 repetitive maximal running shuttle bouts decreased similarly in 4 separate exercise sessions performed on different days.

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is reached in $\dot{V}O_2$, or when the athlete terminates the test in the absence of a plateau, the $\dot{V}O_2$ value attained is termed the $\dot{V}O_{2max}$. It has been previously concluded that this inability to consume any more oxygen and the resultant skeletal muscle anaerobiosis is the reason for fatigue in these exercise protocols.[37-39]

However, Noakes[40] described the problems inherent in the assumption that $\dot{V}O_{2max}$ and aerobic capacity were the important determinants of maximal exercise determination and fatigue. He suggested that a plateau in $\dot{V}O_2$ may not always exist, but rather occurs as an artefact of testing. This is supported by work in our[41] and other laboratories,[42,43] which has shown that 50% or more of trained individuals do not experience a plateau during $\dot{V}O_{2max}$ testing. These individuals terminate exercise with $\dot{V}O_2$ values still increasing (fig. 4).

Further studies have shown that the muscle does not become anaerobic in the human model when fatigue occurs volitionally. Hochachka[44] described that peripheral skeletal muscle never becomes more than ≈70% deoxygenated and even at these relatively aerobically maintained levels, myoglobin acts as a buffer to oxygen insufficiency, shifting the O_2 dissociation curve and moving O_2 to the areas where O_2 is required (such as the mitochondrial membrane) as an active process during maximal endurance activity. Therefore, as first described by Noakes,[40] maximal aerobic capacity does not directly regulate fatigue and exercise termination during maximal endurance activity.

Noakes,[12,45,46] as a consequence of this earlier work, recently proposed that as the skeletal muscle does not become anaerobic and that maximal aerobic capacity is not the major determinant of fatigue, the receptors for the 'governor' regulating fatigue in maximal endurance may be located in the cardiac muscle, and the reason for termination of exercise during maximal capacity is to protect the heart muscle from damage during maximal endurance exercise intensity. The hypothesis assumes that a receptor located in the myocardium sends afferent inhibitory signals centrally before the maximal capacity of the heart is reached, and that this inhibitory level is more sensitive than that in the peripheral skeletal muscle, leaving a large reserve in peripheral skeletal muscle capacity during fatigue in this endurance model.

The hypothesis is enticing because the heart is reliant on generating its own blood supply, and if pump capacity was ever exceeded during maximal endurance exercise intensity, the blood delivery of oxygen to the myocardium would be impaired which would lead to decreased pump capacity and cause the heart to fail. During exercise, healthy individuals do not experience angina, the symptom of cardiac ischaemia. Therefore, exercise in healthy individuals must be terminated before the maximal capacity of the heart is reached, and ischaemia occurs, by an inhibitory governor, as described by Noakes.[45,46] In this model, skeletal muscle anaerobiosis is obviously not possible, and exercise is terminated by efferent inhibitory command before the maximal capacity of either the heart or the exercising skeletal muscle is reached.

The importance of this hypothesis was not only for describing the possible presence of a governor of fatigue during maximal endurance exercise, but that it moves the control of fatigue during maximal endurance exercise upstream from the peripheral skeletal muscle. For this governor to work, afferent signals must arise from type III and IV chemoreceptors situated in the myocardium, and generate inhibitory efferent commands to the peripheral skeletal muscle. In this model, the function of these efferent neural commands is not to protect the peripheral skeletal muscle from fatigue, but to reduce force generation and speed of locomotion to reduce the metabolic requirements upstream from the peripheral musculature.

A further interesting hypothesis is that the $\dot{V}O_{2max}$ plateau may actually be an artefact of the inhibition of muscle recruitment in response to the cardiac governor. Individuals who show no plateau may have a tightly controlled efferent inhibitory response to the cardiac signal, while individuals who show a plateau may have a longer period of down-regulation of afferent signal before the final efferent inhibitory signal is induced. Thus, individ-

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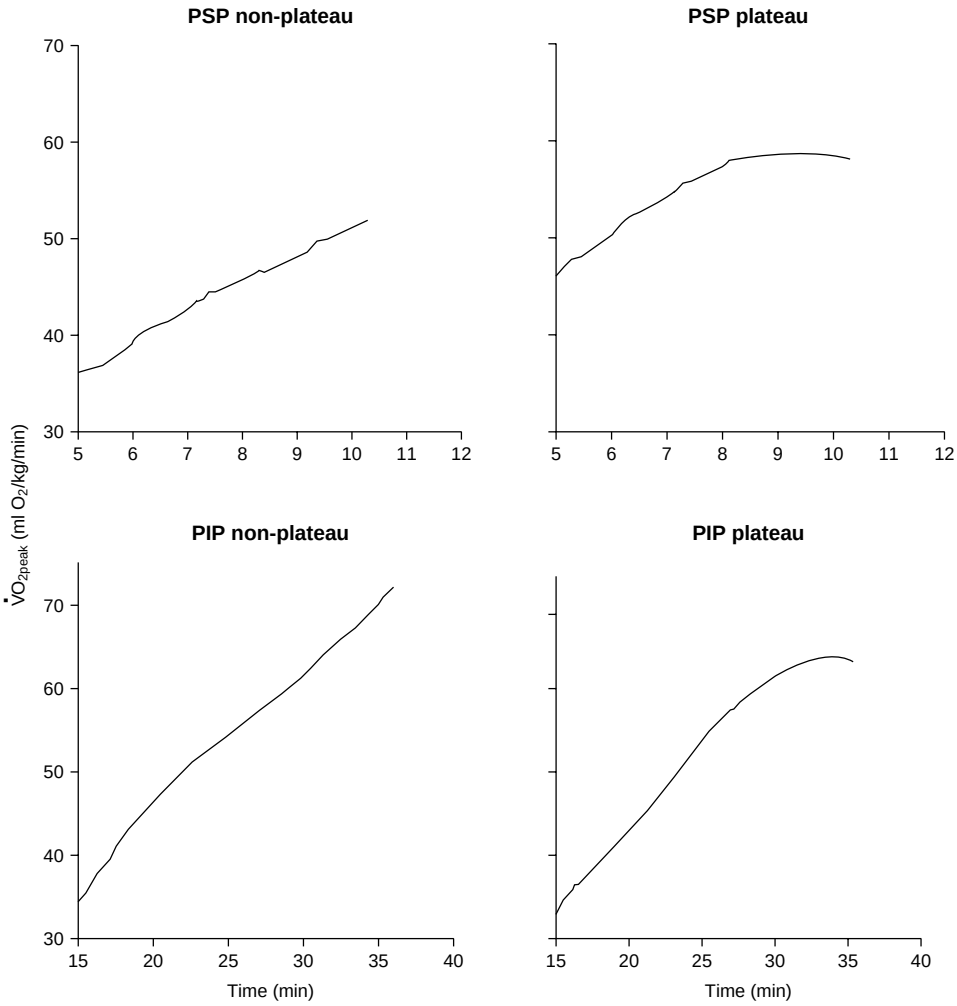

Fig. 4. Individual maximal aerobic capacity during different protocols of incremental tests to exhaustion. **PIP** = modified Balke incline treadmill protocol; **PSP** = Noakes horizontal treadmill protocol; $\dot{V}\mathbf{O_{2peak}}$ = peak oxygen uptake.

uals may have either differences in the conduction velocities of their afferent and efferent nerves, or the afferent chemoreceptors in the myocardium may have a longer reaction time in individuals who exhibit the plateau phenomenon or allow a greater percentage change in metabolic profile before becoming completely inhibitory. Therefore, the existence of the plateau may be merely an artefact of the reaction time of cardiac chemoreceptors or afferent nerve signal processing. Further research is needed to assess these hypotheses.

Evidence for Noakes' hypothesis has been shown both directly during maximal endurance testing and indirectly from exercise at altitude. A recent study examined the percentage of muscle recruitment activity of the lower limb during maximal incremental endurance testing using magnetic resonance imaging analysis of metabolic changes in the lower

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limb musculature.[47] The protocol involved both horizontal and uphill treadmill running until maximal exhaustion. Although different muscle groups were used to different degrees during horizontal and uphill running, the lower limb musculature was only used to ≈40 to 80 % of maximal capacity during either testing procedure. These findings supported the idea of Noakes[45,46] that governor-induced cessation of activity would occur before peripheral skeletal muscle was completely activated.

Kayser et al.[48] examined changes in muscle recruitment in the lower and upper limbs during exhaustive exercise at low and high altitude. At low altitude, as the exercise intensity increased, lower limb IEMG activity increased linearly in both arms and legs. At high altitude, where oxygen partial pressure and concentration was lower, while the upper limb IEMG activity increased with increased work output, the IEMG activity in the lower limb did not increase at all, and power output in the lower limbs was significantly diminished (fig. 5). When oxygen was given to individuals at high altitude, the power output and IEMG activity increased, but not to the level achieved at low altitude. The conclusion from this study was that these changes were a protective reflex to prevent skeletal muscle damage occurring from excessive activity, and inhibitory efferent output to the lower limbs rather than the upper limbs occurred because of the large muscle mass in the lower limb compared with that in the upper limb. The finding that oxygen supplementation partially increased lower limb activity indicated that these changes involved oxygen metabolism.

This study[48] supports Noakes' theory of cardiac governor control during maximal endurance exercise. Again, both at altitude and during treadmill running at sea level, skeletal muscle reserve is maintained during maximal volitional activity. Interestingly, during studies of brain function at high altitude, Hochachka et al.[49] showed that with long term acclimatisation, different areas of the brain either down- or up-regulate metabolism. The frontal and occipital cortex regions, and thalamus section of the midbrain, showed decreased activity while activity in the cerebellum was increased. One may postulate that these changes play a role in the generation of inhibitory efferent neural activity, along with the cardiac governor-induced inhibitory processes, or that these two processes are linked.

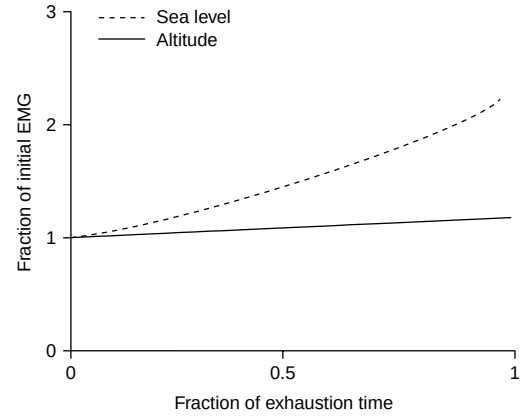

Fig. 5. Integrated electromyogram (IEMG) activity patterns during maximal exercise at sea level and high altitude in quadriceps femorus muscle. IEMG values are described as a fraction of their initial starting values.

4. Neural Control Mechanisms During Prolonged Submaximal Exercise of Set (Closed-Loop) Duration

Most research on fatigue during submaximal exercise have used closed-loop models to examine the metabolic determinants of fatigue. This research has centred on the effect of carbohydrate or fat ingestion in attenuating fatigue, or on muscle glycogen and other substrate availability during performance trials. Researchers have concluded that lack of availability of these substrates are the determinants of fatigue during prolonged submaximal exercise.[50-52]

However, recent studies in this laboratory[53] have shown that with adequate placebo control, and with a closed-loop design which incorporates stochastic high intensity activity similar to that occurring in the field, the supposedly positive effect of carbohydrate ingestion on fatigue attenuation dur-

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ing exercise is minimised. Fitts[8] suggested that it is unlikely that muscle glycogen depletion, low blood glucose or decline in carbohydrate oxidation were exclusive factors causing fatigue, as participants still fatigue and halt exercise activity with normal carbohydrate oxidation rate and when receiving adequate carbohydrate ingestion in control groups in carbohydrate supplementation trials (fig. 6).

In the close-loop study design, individuals are aware of the nature and length of the trial and the time and number of sprints which are to be performed. Ulmer[36] suggested that efferent command signals to skeletal muscles regulate not only the spatial and temporal pattern of motion, but also the control of metabolic rate by adjustment of power output. He suggested that a central 'programmer' would take into consideration the length of time necessary to complete the sprints and endurance activity. This adjustment would enable the individual to complete the activity without damaging cellular structures. This teleoanticipation system may be responsible for decreasing power output during a time trial or exercise bout despite seemingly adequate reserves of metabolic fuel, as part of a subconscious mental calculation, with the feeling of fatigue being the outward manifestation of the efferent inhibitory command processes derived from this mental calculation.

Recent work from our laboratory supports this theory (unpublished data). In this trial, individuals performed a 100km time trial interspersed with high intensity bouts during which EMG activity was recorded. During the trial, despite participants being instructed and encouraged to perform at maximal intensity, power output decreased incrementally and significantly during the high intensity workbouts of the trial. IEMG activity declined in parallel with these decreases in power output, and these changes occurred despite only ≈20% or less of possible fibres being recruited during the time trial as compared with that recruited during a MVC (fig. 7). These findings indicated that the CNS down-regulates power output by decreasing motor command to the peripheral musculature during this stochastic exercise activity, despite all conscious attempts by the participants to maintain power output. Because this efferent motor command down-regulation occurred from early on in the trial, and with most muscle fibres not recruited at any stage during the exercise activity, one may speculate that this efferent inhibition is a protective response performed by the CNS to prevent muscle damage caused by the ongoing high intensity activity, which would occur if the efferent signal was excitatory rather than inhibitory.

Our further studies[54] have shown that in stochastic exercise of short duration (1 hour), power output and IEMG activity decreased during the first sprints similar to the finding in the above study. However, in contrast to these findings, in that study[54] both power output and IEMG activity increased in the final sprint, indicating that IEMG activity was tracking power output changes and that decrements in IEMG during the first few sprints could not be explained solely by temperature, conductivity or electrode placement changes during the trial. Hence, the decrements in EMG activity and low percentage of muscle recruitment throughout this trial are not an artefact of the testing method used.

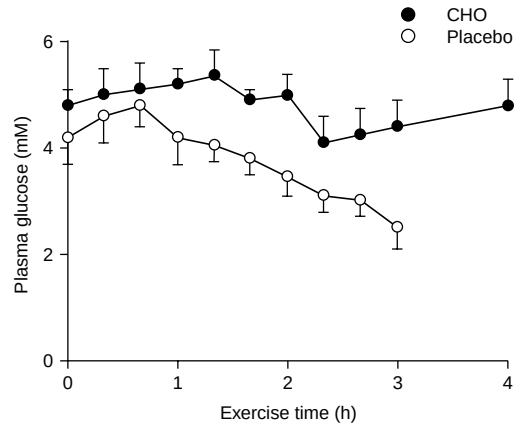

Fig. 6. Blood glucose levels during endurance cycling activity in carbohydrate supplemented volunteers (CHO) and controls (placebo) [from Fitts,[8] with permission].

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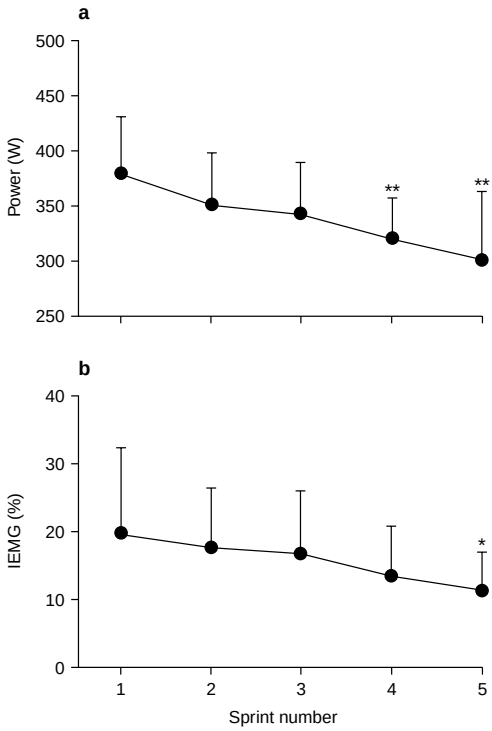

Fig. 7. Integrated electromyogram (IEMG) and power output changes during five 1km sprint bouts during a 100km cycling time trial. * indicates $p < 0.05$; and ** indicates $p < 0.01$.

Other studies have similarly speculated that during fatiguing exercise, inhibitory signals may decrease power output as a protective response. Nicol et al.[55] found that MVC and IEMG decreased by ≈30% after a marathon, and speculated that their findings were caused either by insufficient motivation or altered central recruitment strategies. Sacco et al.[56] found that during a fatiguing protocol of the lower limb, efferent output to the fatiguing muscle decreased. The efferent output to the synergistic muscles, which were not involved in the fatiguing process, were also inhibited or derecruited during and after the fatiguing contractions.

It has previously been suggested that changes in excitation/contraction coupling[8,19] may be responsible for the decrements in power output during this cycling activity. Although no obvious cycling EMG patterns occurred during the high intensity episodes, excitation/contraction coupling may also be a cause of the reduced neuromuscular activity and force decrements.

It was not clear from our study (unpublished observations) if these inhibitory changes were caused by fatigue in the central cortical tissue, or by planned decreased efferent output from nonfatigued cortical structures. As discussed previously, earlier studies which examined cortical and efferent output changes during fatiguing contractions[1] found that fatigue in the motor cortex was not responsible for decreased efferent command. Rather, the changes in motor command were regulated by changes 'upstream' from the motor cortex, either excitatory or inhibitory changes in other brain structures or as a result of failure to drive corticospinal neurons with normal excitability because of decreased afferent input from group III and IV afferents in the peripheral musculature. However, these authors found that the motor cortex itself was responsive to artificial perturbations during these fatiguing protocols, and thus fatigue of this brain region was not responsible for the decreased efferent motor drive. These findings indicated that changes in efferent command in our study (unpublished data) were probably caused by teloanticipation changes in the higher cortical structures and/or responses to afferent input from metabolic changes in peripheral organs.

An important finding in our study (unpublished observations) was that during the closed-loop cycle ride, ≈20% of maximal muscle capacity was utilised at any stage during the ride. Previous studies have shown similar low levels of recruitment during cycling activity.[57] However, at the end of the trial, muscle biopsies showed that muscle glycogen levels had decreased to levels far lower than would be expected if only 20% of muscle fibre glycogen stores had been utilised. This finding indicates that decreased efferent motor changes were part of a strategy in which the recruitment patterns of the entire limb were altered during the fatiguing process. An alternative explanation is that different muscle fibres within the same rectus femoris muscle were

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recruited at different times during the testing period, with fatiguing fibres being replaced by previously inactive fibres at the same time that central command was decreasing.

Recently, Westgaard and De Luca[23] showed that motor unit substitution and rotation occurred during submaximal isometric endurance exercise. They speculated that this substitution phenomenon protected motor units from excessive fatigue when there was a demand for sustained submaximal muscle activity. As the muscle glycogen level in our study reached low levels, with only ≈20% of muscle fibres being recruited at any time during the exercise protocol, it can be speculated that motor unit substitution must have occurred during the fatigue process.

Therefore, during closed-loop type fatigue protocols, different neural inhibitory command processes occur, and recent research has shown that these changes occur irrespective of substrate ingestion or utilisation, although the process may be regulated to a degree by input from these metabolic perturbations. These efferent inhibitory processes occur despite a large peripheral skeletal muscle reserve, when excitatory recruitment patterns would still occur if necessary.

It must be noted that in medical conditions such as heatstroke, certain individuals appear to push themselves to a level of fatigue not reached by normal individuals. One may thus argue that these protective mechanisms are not absolute, and can be manipulated in certain conditions. Interestingly, increased core and peripheral temperature have been shown to increase the conduction velocity of the efferent command processes.[4] Thus, in conditions with significantly raised core temperature, the temperature-related conduction velocity increases may interfere with the inhibitory mechanisms of muscle wisdom, and obscure the time-points of the regulatory inhibitory process and allow the susceptible individual to proceed beyond the point when efferent neural strategy becomes completely inhibitory. This concept requires further research.

5. Neural Control Mechanisms During Submaximal Exercise of Undetermined (Open-Loop) Duration

Fatigue occurring during open-loop submaximal exercise of undetermined duration is interesting, particularly in exercise of low intensity, as individuals terminate their exercise of their own volition with as yet no determined metabolic reason. An example of this is during exercise performed at between 5 to 10% of MVC, where after several hours of repetitive exercise or walking activity, individuals will stop activity stating that they are exhausted or completely fatigued. Excitation/contraction coupling failure has been shown to cause fatigue during low intensity endurance activity.[19] However, this fatigue may also arise 'above the level' of the motor cortex and be related to higher mental functioning such as motivational capacity or ability to concentrate on task activity, which varies in different individuals and causes them to terminate activity after different durations. There may also be a metabolic cost to the act of concentration itself, and the metabolic products of this higher mental functioning, perhaps in the limbic system or reticular formation, may be sufficient to induce the perception of fatigue which causes the individual to terminate the exercise activity.

It can also be assumed that differences in athletic ability between individuals may be related not only to their organic physiological phenotype, but also to their mental capacity to resist the symptoms and physical manifestations of fatigue to a greater degree than those individuals with lesser athletic ability. The origin of these differences in mental ability have as yet not been identified in any structure in the brain. Indeed, the physical process of concentration and mental 'toughness' itself has not been deconstructed to any degree, and research in the future should be concentrated around these concepts, to understand how these higher mental functions influence the individual's physical and physiological capacity.

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6. Neural Control Mechanisms in Fatigue Associated with Pathological Medical Conditions

Finally, the chronic fatigue syndrome also shows how complex the relationship is between fatigue and physiological processes to which it has previously been related. Individuals with chronic fatigue syndrome describe symptoms of extreme fatigue at rest, to a degree that any activity feels difficult to perform, yet when tested for maximal contraction, are able to perform similar levels of maximal force output compared with athletic individuals.[58] Although the pathological cause has not been elicited, Enoka and Stuart[5] suggested that these findings also indicate that fatigue occurs in these individuals 'above the level' of the motor cortex.

These findings show that fatigue is not a physiological process, but rather is a symptom or external signal of underlying central processes occurring either during or even in the absence of exercise performance. The finding that fatigue occurs at rest in individuals with chronic fatigue syndrome indicates that fatigue as an entity or sensory process is loosely related at best with the underlying physiological processes or metabolic perturbations thought previously to lead to fatigue and termination of exercise. That we feel symptoms of fatigue and exhaustion after a long period of mental activity without any physical activity indicates that fatigue as a signal or thought process originates in the regions of the brain involved in higher mental function, perhaps in the limbic system, reticular system or other brain structures involved in setting arousal states in the normally functioning individual.

7. Conclusion

In summary, recent research has questioned the traditional concept of the role of peripheral metabolic changes as the exclusive cause of fatigue. Rather, the brain and efferent neural pathways appear to exquisitely regulate the degree of locomotion to ensure that absolute maximal muscle capacity is never utilised under conditions of volitional rather than artificial control. This control of force output appears to be regulated by governor-induced inhibitory efferent processes. From muscle wisdom during isometric muscle activity, to down-regulation of power output during sprint activity, to cardiac protection in maximal incremental endurance exercise, and power reduction and muscle unit rotation strategies during submaximal activity, the human structure has evolved to maintain muscle reserve and inhibit exercise activity so that no system is stressed beyond its safety capacity. The changes occurring in chronic fatigue syndrome and open-loop exercise activity indicate that fatigue may not be a physiological entity, but rather a sensory manifestation of these neural regulatory processes.

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