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Acute and chronic hypoxia: implications for cerebral function and exercise tolerance

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Abstract

Purpose—To outline how hypoxia profoundly affects neuronal functionality and thus compromise exercise-performance.

Methods—Investigations using electroencephalography (EEG) and transcranial magnetic stimulation (TMS) detecting neuronal changes at rest and those studying fatiguing effects on whole-body exercise performance in acute (AH) and chronic hypoxia (CH) were evaluated.

Results—At rest during very early hypoxia (<1-h), slowing of cerebral neuronal activity is evident despite no change in corticospinal excitability. As time in hypoxia progresses (3-h), increased corticospinal excitability becomes evident; however, changes in neuronal activity are unknown. Prolonged exposure (3–5 d) causes a respiratory alkalosis which modulates Na⁺ channels, potentially explaining reduced neuronal excitability. Locomotor exercise in AH exacerbates the development of peripheral-fatigue; as the severity of hypoxia increases, mechanisms of peripheral-fatigue become less dominant and CNS hypoxia becomes the predominant factor. The greatest central-fatigue in AH occurs when S_aO₂ is ~75%, a level that coincides with increasing impairments in neuronal activity. CH does not improve the level of peripheral-fatigue observed in AH; however, it attenuates the development of central-fatigue paralleling increases in cerebral O₂ availability and corticospinal excitability.

Conclusions—The attenuated development of central-fatigue in CH might explain, the improvements in locomotor exercise-performance commonly observed after acclimatisation to high altitude.

Keywords

brain; exercise; hypoxia; muscle; oxygen

Introduction

Humans can only survive for a few minutes in the absence of oxygen (O₂) and the brain's susceptibility to hypoxia depicts the key factor determining this critical dependency (1). Cerebral oxygenation is reduced at rest in hypoxia and neuronal damage can occur in the face of a prolonged mismatch between O₂ supply and demand (1). At sea-level (SL), cerebral oxygenation is known to increase during low to moderate intensity, but decrease during maximal intensity whole body exercise at SL (2). Furthermore, at SL, exercise-induced reductions in arterial O₂ saturation (S_aO₂; 3) reduce homeostasis and the associated hyperventilation-induced lowering of arterial carbon dioxide reduces cerebral blood flow (4), consequently reducing cerebral O₂ supply (cerebral blood flow × arterial O₂ content [C_aO₂]) and neuronal activity (5). Moreover, the exaggerated reduction of S_aO₂ and increased ventilatory demand during exercise in acute hypoxia (AH; 6) poses an overwhelming threat to cerebral function.

Exercise-induced fatigue can be defined as a reversible decrease in maximal voluntary force or power produced by a muscle (7). The production of voluntary muscle force/power is the consequence of a number of processes within the central nervous system (CNS). After input from higher brain areas, descending drive from the primary motor cortex activates spinal motoneurons and the peripheral motor nerve which in turn activates muscle fibres in the target muscle to contract and produce force (8). During repetitive or sustained muscle action, processes that contribute to fatigue can arise within any region of this motor pathway. Fatigue itself is determined by a central and a peripheral component (8, 9). Peripheral fatigue can be defined as a reduction in force or power output secondary to changes occurring at or distal to the neuromuscular junction. Specifically, force output of a muscle is compromised in response to a given neural input. Central fatigue can be defined as a reduction in central motor drive (central motor drive; i.e. neural activation of the muscle) resulting in a decrease in voluntary muscle activation during exercise (8). The decrease in central motor drive has been documented to occur mainly, but not exclusively, 'upstream' from the motor cortex (10, 11).

AH has a profound impact on the development of both of these determinants of fatigue during exercise (6, 12–18). Recent studies at severe altitude (5,260 m) documented that a chronic exposure to hypoxia (CH), which is associated with a substantial recovery of arterial O₂ saturation and content, can attenuate the development of central fatigue, but does not recover the exacerbated rate of development of peripheral fatigue observed during exercise in AH (19, 20). Based on the attenuated rate of central fatigue development in CH (vs. AH), which is mediated by the CNS benefiting from improved oxygenation (21), the aim of this review is to briefly discuss the impact of low O₂ availability on the functionality of CNS neuronal structures and to relate this relationship to hypoxia-related changes in whole body endurance capacity/performance. The review is split into two distinct sections detailing the resting responses in AH and CH, prior to the exercise-induced effects on the mechanisms of fatigue and CNS function.

Methods of investigation

The Medline database, via PubMed, was utilised to firstly identify investigations studying neuronal changes at rest in hypoxia; specific details of the neuroscientific methods are outlined below. Secondly, PubMed was used to obtain investigations concerned with the fatiguing response to whole-body exercise in AH and CH. Accordingly, the article is split into two distinct sections detailing the resting responses in AH and CH, prior to the exercise-induced effects on the mechanisms of fatigue and CNS function.

Sensitivity of cerebral neurons to acute hypoxia

The brain is plastic in nature (22) and can adapt to a hypoxic stimulus in a matter of seconds (23, 24), but a brief lack of O₂ can cause an instantaneous loss of consciousness in healthy humans (25). However, the peripheral nervous system and lower regions of the CNS (spinal cord and parts of the brainstem) are less sensitive to hypoxia (26). Every neuron in the brain has the capacity to sense and, crucially, modify its activity in response to hypoxia. Most neurons respond to hypoxia by decreasing metabolic demand and thus the need for aerobic energy (27). The predominant metabolic demand of a neuron is the maintenance of ion gradients, a cost that is directly related to level of neuronal activity (27). Consequently, most neurons reduce their metabolic requirement via reducing their activity in hypoxia due to the limited provision for anaerobic metabolism. Indeed, it is not viable for all neurons in the brain to reduce their activity during hypoxia and there are populations of neurons located within the caudal hypothalamus and rostral ventrolateral medulla which are directly excited by hypoxia. Such neurons, during both *in-vitro* and *in-vivo* investigations, have been shown to increase sympathetic and respiratory activity, blood pressure and heart rate to compensate for the negative effect of hypoxia on physiological function (28–31). It is vital for such hypoxia-tolerant neurons to remain ‘vigilant’ and ready to respond in a co-ordinated manner as their response is especially important for the initiation of activity in short and long-term periods of hypoxia (32).

The duration and severity of energy substrate (O₂ and glucose) deprivation experienced in hypoxia dictates a sequence of alterations in trans-membrane electrochemical gradients (33). In normoxic/normobaric conditions, O₂ and glucose are the prime substrates for oxidative metabolism. However, in hypoxic/hypobaric conditions, a deficit of O₂ for glucose metabolism results in a faster depletion of ATP due to the greater reliance on anaerobic metabolism (34, 35). As the hypoxic stimulus is sustained and O₂ deficiency continues, ATP supply declines to a level insufficient to maintain activity of ion pumps (K⁺, Ca²⁺ and Na⁺ channels, see 27, 33) leading to a rapid and widespread depolarisation. Such occurrence of a widespread cell membrane depolarisation, leads to an extensive depression of synaptic transmission and the electrophysiological isolation of neurons (35).

Although *in vitro* methods have improved our understanding of neuronal function during hypoxia, studies investigating neuronal changes in the *intact* human nervous system are crucial. Neurophysiological cognition involves rapid co-ordination of processes widely distributed across cortical and sub-cortical regions. No one brain imaging technique can provide the measurement of electrical signals that accompany higher cognitive functions which are subtle, spatially complex and change rapidly in response to environmental

demand (36). High-resolution electroencephalography (EEG) is well suited to monitoring rapidly changing regional patterns of neuronal activation and has previously been used in hypoxia (36). Briefly, EEG is a compound extracellular measure that quantifies electrical fluctuations arising from the ionic flow of current within cerebral brain (37). Recorded using a configuration of multiple electrodes placed over the scalp, the EEG is typically described in terms of rhythmic activity which can be divided into 'bands' based on the frequency of the signal. The exquisite sensitivity of EEG to changes in mental activity was first recognised in 1929 when Berger (38) reported a decrease in the amplitude of the alpha rhythm during mental arithmetic. Moreover, in addition to the tonic alterations observed by Berger (38), EEG measurements of phasic stimulus-related brain activity (i.e., evoked potentials) are well suited for measuring processes related to sensory, motor and cognitive components (36).

EEG recordings of cerebral hypoxia have been studied since the 1930s (39, 40) and it is well understood that neuronal activity is sensitive to changes in cerebral O₂ supply (41–43). In awake, resting, healthy humans, a slowing of EEG activity is generally observed in investigations under the condition of acute normobaric (44–46) and hypobaric hypoxia (47–49). Due to the differences in the severity and time of hypoxic exposure or methods utilised, direct comparisons between previous investigations are difficult to make. However, it does seem that the greatest change in EEG occurs at a similar S_pO₂ or oxygen tension (PO₂) (75% or 40 mmHg; 35, 44, 48, 50). Nevertheless, such slowing of the EEG signal might reflect the previously discussed widespread depolarisation of cerebral neurons known to occur in AH. To overcome some of the methodological limitations that are apparent in the early investigations studying the EEG response to hypoxia, Papadelis et al. (35) used a complex analysis of the dynamic EEG signal in an attempt to further understand the effect of hypoxia on electrical activity within the brain. These authors exposed 10 participants to three levels of hypobaric hypoxia at simulated altitudes of 25,000, 20,000 and 15,000 ft. The hypobaric chamber was decompressed to the lowest pressure and the environment was held constant for 9 min; during minutes 0–3 participants breathed 100% O₂, between minutes 3–6 participants experienced hypobaric hypoxia (min 6 PO₂ = 30 mmHg) and between minutes 6–9 100% O₂ was again administered. This procedure was repeated at all three altitudes whilst multichannel EEG recordings were taken. In line with the aforementioned investigations, Papadelis et al. (35) reported an increased slowing of the EEG signal in hypoxia representative of a reduced neuronal activity. Figure 1 shows the frequency spectra of EEG segments (5 s duration) measured during simulated altitude (25,000 ft; 282 mmHg); the first panel are measurements taken whilst breathing 100% O₂, hypobaric hypoxia is experienced in panel 2 prior to the recovery session which involved breathing 100% O₂ (35). F_z, C₃ and C_z demonstrate 3 of 19 positions where EEG measures were taken from, determined by the International 10–20 system (51). Further analysis of the EEG signal allowed Papadelis et al. (35) to report a progressive reduction in approximate entropy, which is thought to reflect the degree of isolation of the system from its surroundings (52), with further increases in the severity of hypoxia. Specifically, hypoxia results in a depression of synaptic transmission, presumably in those neurons that are not hypoxia resistant, which leads to neurons' electrophysiological isolation from those neurons that are hypoxia resistant (i.e., no change in activity). Conversely, a brain rich in O₂ supply has strong lines of

communication allowing for coherent synaptic transmission between all neurons (53). These data provide a plausible mechanism for the commonly reported slowing of the EEG signal and widespread neuronal depolarisation in AH.

Fluctuations in a recorded EEG signal can reflect the on-going maintenance of a functional state within the brain. Rozhkov and colleagues (50) investigated changes in the balance of brain regulatory structures and rearrangement of the multi-channel EEG signal at rest during a period of AH. Normobaric hypoxia was administered in the form of a lowered fraction of inspired O₂ (F_IO₂ = 0.08) to participants for 15–25 min (S_pO₂ 75%). In line with the EEG-hypoxia literature, it was found that the acute exposure to hypoxia was accompanied by slowing and synchronisation of the EEG signals (50). Such a reduction and synchronisation of the EEG signal was said to characterise a functional brain state that was relatively lower compared to baseline (i.e. normoxia); a state that is presumably unfavourable for activity and cognitive function. This is, however, a functionally necessary state for the brain to adopt as transferring from a high level of function to a lower level state, would lead to a reduction in neuronal energy cost providing the essential reserves for survival in hypoxia (27, 50). Moreover, in addition to changes in characteristics of the EEG signal, the authors report rearrangements in temporospatial relationships between oscillations of cortical potentials, demonstrating reorganisation of the inter-centre interactions within the CNS (50). Specifically, acute hypoxia led to a rearrangement of electrical activity in a lateral direction which may have reflected involvement of structures within the medial and basal area of temporal lobes (Figure 2). Such an increase in the electrical activity in these regions of the brain is thought to reflect activation of the limbic system (hippocampus, dentate nucleus and amygdaloid complex; 50). The limbic system plays a central role in integrating the emotional-motivational and autonomic-visceral components of the body's activity under different conditions (54); thus, the limbic system occupies an important position to initiate the body's adaptation when in an oxygen deprived environment. This transition in hypoxia appears to be associated with the special role of the limbic system (the 'visceral brain') in controlling autonomic function during the process of survival (50, 55). Thus, the brain naturally adapts a protective strategy, channelling neuronal activity in an appropriate way for survival in hypoxia.

Despite the abundance of literature pertaining to changes in cerebral function recorded with EEG, the technique is not without limitation. Most pertinent is the poor level of spatial resolution and the fact that EEG is most sensitive to particular sets of post-synaptic potentials generated on superficial layers of the cortex, thus deep structures within the brain are insignificant to the basic EEG signal (56). Transcranial magnetic stimulation (TMS) is an alternative, non-invasive method used to stimulate the motor cortex and investigate the excitability, not activity, of the brain-to-muscle pathway (57). TMS over the motor cortex preferentially activates corticospinal neurons trans-synaptically via excitatory interneurons and corticocortical axons (58). The response to TMS critically depends on membrane excitability of motor cortical neurons and ion-channel function (59, 60). The aforementioned reductions in ion channel function known to occur in hypoxia likely contribute to some observed TMS-specific changes reported in AH. Responses to TMS are recorded using electromyography (EMG) from the muscle of interest and, typically, changes in the motor evoked potentials (MEPs) are studied. TMS-induced MEPs can be elicited in a target muscle

only above a given stimulation intensity, a 'threshold'. Such a threshold can be determined in a relaxed (resting motor threshold) or active (active motor threshold) muscle with the goal of eliciting MEPs. The change in threshold and characteristics of an MEP (amplitude and area) can be monitored to reveal changes in corticospinal excitability (61).

Whereas a slowing of the EEG response has been seen at rest in AH (S_pO_2 75% or PO_2 40 mmHg; 35, 44, 48, 49, 50), unchanged corticospinal excitability as reflected in an unaltered MEP and maximally evoked peripheral M-wave (MEP/ M_{max} ratio), is a consistent finding within the TMS literature that has used varying severities of hypoxia ($F_I O_2$ = 0.14-0.10; $S_a O_2$ = 93-74%) for as little as 10 min to 1 h (62–64). In contrast to the majority of papers reporting a lack of change in resting MEP (i.e., no prior exercise) in moderate to severe AH, Szubski et al. (65) reported increased corticospinal excitability, expressed as a reduced motor threshold (but no alteration in MEP/ M_{max} ratio), after ~30 min of breathing hypoxic air ($F_I O_2$ = 0.12; resting $S_p O_2$ = 75%). Rupp et al. (64) found a time dependent effect of AH ($F_I O_2$ = 0.12; $S_p O_2$ = 86%) on corticospinal excitability; after 3 h of AH, the MEP amplitude had increased by approximately 10% during isometric knee extensor contractions of 50, 75 and 100% maximal voluntary contraction. These changes were independent of any change in the responsiveness of the peripheral motor nerve (i.e., hypoxia had no effect on M-waves) suggesting the observed increase in MEP were the consequence of adaptive mechanisms at spinal or supraspinal sites (64). It must be noted, however, that EEG measurements reflect neuronal *activity* in higher brain areas whereas TMS measurements reflect neuronal *responsiveness* of a different portion of the CNS (motor cortex & spine), specifically related to motor function. Based on this, the two methods focus on somewhat different brain areas/function so it is difficult to directly compare results. Moreover, we are unaware of any EEG related experiments that have recorded responses after 3 hours of exposure or after exercise in AH. Further research using EEG following a prolonged exposure to hypoxia and bouts of exercise is warranted.

When such hypoxic stress is experienced for >24 h, it is common for unacclimatised, healthy humans to experience symptoms of acute mountain sickness (AMS; 66). A severe headache, loss of appetite, dizziness and fatigue are just some symptoms that usually develop within 6–24 h after exposure (67, 68). Miscio et al. (69) investigated the effect of AMS on TMS related parameters 3–5 days after ascending to high altitude (4,554 m). They found a significant decrease in the excitability of both excitatory and inhibitory cortical circuits. The cortical changes observed correlated with the level of AMS and the authors suggested this was linked to the respiratory alkalosis which develops 3–5 d after being exposed to hypoxia (70, 71). A modified bicarbonate ion concentration is a result of respiratory alkalosis and this may subsequently change the properties of neuronal membranes and several characteristics of Na^+ channels, with the net effect being a reduced neuronal excitability (72, 73). However, due to the correlative nature of these findings, interventional studies are now required to evaluate a potential link/cause-and-effect relationship between respiratory alkalosis accompanying AMS and corticospinal tract responsiveness.

In summary, during very early hypoxia (<1 h), a slowing and reorganisation of the EEG signal is evident despite no discernible change in TMS-evoked parameters suggesting

altered neuronal activity with unchanged corticospinal responsiveness. As the time in hypoxia progresses (3 h), an increased corticospinal excitability becomes evident which may reflect a mechanism attempting to restore/protect neuronal homeostasis – EEG responses at this time are unknown. Moreover, following the initial period of AH, a prolonged period of time (3–5 days) causes a respiratory alkalosis which modulates Na^+ channels and might potentially explain the reduced corticospinal responsiveness apparent at this time.

The development of fatigue during exercise in AH

Manipulations in systemic O_2 transport affect muscular performance and the rate of development of both peripheral and central fatigue. Specifically, reduced muscle O_2 delivery accelerates the development of fatigue, whereas an enhanced O_2 delivery attenuates the rate of development (for review see 21). The relative contributions of central and peripheral fatigue owing to voluntary termination of locomotor exercise, or the magnitude of decrease in central motor drive, depend on the severity of hypoxia (74, 75). Although it is well known that hypoxia is associated with an impaired locomotor exercise capacity (12, 76, 77), the mechanisms of limitation have only recently become better understood.

Alterations in O_2 transport to exercising locomotor muscles in healthy humans are the result of changes in arterial O_2 content (C_aO_2) and/or limb blood flow (Q_L). Reductions in C_aO_2 can result from decreases in S_aO_2 and/or decreases in haemoglobin concentration. Reductions in Q_L can be secondary to the hyperventilatory response and associated respiratory muscle metaboreflex during heavy sustained exercise (for review see 78). Specifically, the accumulation of metabolites in respiratory muscles activates unmyelinated group IV phrenic afferents, which reflexly increases sympathetic vasoconstrictor activity in the working limb. The result is a work of breathing-induced reduction in Q_L and a corresponding reduction in O_2 delivery to the working muscles (with a presumable increase in blood flow to the respiratory muscles) (79). The ventilatory response during locomotor exercise is exacerbated at any given intensity in both AH and CH causing, compared to SL, a substantial increase in respiratory muscle work (6, 19, 80). The isolated effects of inspiratory muscle work (W_{insp}) (and associated decreases in Q_L and limb O_2 delivery) vs. hypoxia-induced decreases in C_aO_2 on the development of peripheral locomotor muscle fatigue in AH have recently been quantified. Amann et al. (6) isolated the independent effects of W_{insp} (and Q_L) vs. C_aO_2 during high intensity cycling exercise on locomotor muscle fatigue in AH. SL vs. AH C_aO_2 ($\text{F}_I\text{O}_2/\text{C}_a\text{O}_2 = 0.21/20 \text{ ml O}_2/\text{dl}$ vs. $0.15/18 \text{ ml O}_2/\text{dl}$, respectively) were compared during identical bouts of exercise with similar levels of ventilatory work (via the use of a mechanical ventilator) in both conditions. The authors reported that low C_aO_2 alone, independent of any influence of W_{insp} , exacerbated quadriceps muscle fatigue by about 50% (6). Furthermore, the isolated effect of W_{insp} (and associated decreases in Q_L) vs. hypoxia related decreases in C_aO_2 on the development of peripheral locomotor muscle fatigue in AH was quantified by means of two high-intensity bouts of cycling exercise characterised by identical C_aO_2 ($\text{F}_I\text{O}_2/\text{C}_a\text{O}_2 = 0.15/17 \text{ ml O}_2/\text{dl}$), but different levels of W_{insp} (6). When the exercise trial was performed using a mechanical ventilator capable of unloading the inspiratory muscles by up to 70%, Q_L was increased by 5% and leg O_2 uptake by 3% compared with control conditions without ventilatory assistance (79). As a consequence, exercise-induced quadriceps fatigue was reduced by over

35%, emphasising the substantial effects of W_{insp} alone (independent of C_aO_2) on the development of peripheral locomotor muscle fatigue during exercise in AH (6). Taken together these findings suggest that both, decreases in C_aO_2 and respiratory muscle work associated with hypoxia can independently impair the development of fatigue during exercise at altitude.

Intracellular Metabolism—Reductions in convective O_2 transport accelerate, in the exercising muscle, the intracellular accumulation of metabolites which have been identified as major determinants of peripheral fatigue (81). Specifically, contributors to peripheral fatigue at SL (i.e., inorganic phosphate and $[H^+]$ (82–84)) accumulate faster in conditions of reduced muscle O_2 delivery, and slower when O_2 delivery is enhanced (85). A disruption in sarcolemmal reticulum (SR) Ca^{2+} handling has also been suggested as a prominent mechanism of peripheral fatigue (83, 86). Duhamel et al. (87) hypothesised that prolonged low-intensity exercise ($<50\%$ SL $\dot{V}O_{2\text{max}}$) at SL would cause disturbances in SR Ca^{2+} handling; moreover, when the same exercise (identical workloads) protocol was performed in AH ($F_I O_2 = 0.14$) the disturbances in the SR Ca^{2+} -cycling properties would be exaggerated. However, after 90 min of submaximal locomotor exercise, no differences were found between SL and AH for any of the SR properties examined. It was therefore concluded that disturbances in SR Ca^{2+} handling, might not depict a significant determinant of the exaggerated rate of development of peripheral locomotor muscle fatigue in AH. However, the absence of a significant difference in SR Ca^{2+} handling in AH vs. SL in this study might entirely be explained by the low exercise intensity ($<50\%$ SL $\dot{V}O_{2\text{max}}$). At these low intensities, compensatory mechanisms (i.e., increases in heart rate and cardiac output (88) can partially counterbalance the existing hypoxia with the net effect of a similar O_2 delivery in SL and AH (89) with negligible levels of muscle fatigue.

Sandiford et al. (90) hypothesised that exercise in AH might exacerbate the decrease in muscle maximal Na^+K^+ -ATPase activity, a potential determinant of peripheral fatigue (91). However, the authors compared alterations in maximal Na^+K^+ -ATPase activity only at exhaustion in AH vs. SL (i.e., different exercise durations). Based on this limitation, it was, presumably falsely concluded that AH had no impact on the exercise-induced reduction in muscle maximal Na^+K^+ -ATPase activity. However, given the lack of isotime comparisons to date, the potential for hypoxia-related exacerbations in the maximal Na^+K^+ -ATPase activity as a major determinant of the hastened development of peripheral fatigue in AH should not be discarded (92).

Severity of hypoxemia and fatigue—It is evident that only a relatively small arterial desaturation (from 98% S_pO_2 to ~92%) is needed to cause substantial increases in the rate of development of locomotor muscle fatigue during exercise (93). Further reductions in S_pO_2 and C_aO_2 during locomotor exercise serve to accelerate the development of muscle fatigue (14, 16). This has been demonstrated by Amann et al. (94) who reported an exacerbated level of quadriceps muscle fatigue after identical bouts of constant-load cycling exercise (314 ± 14 W) in AH ($F_I O_2/S_a O_2 = 0.15/82\%$), compared to the same exercise at SL and in hyperoxic conditions ($F_I O_2 = 1.00$). Moreover, the same group later manipulated arterial oxygenation over a wide range ($F_I O_2/S_p O_2/C_a O_2 = \text{hypoxia } 0.15/77\%/18 \text{ ml } O_2/\text{dl}; \text{ iso-oxia}$

0.28/98%/23 ml O₂/dl; normoxia 0.21/91%/21 ml O₂/dl; hyperoxia 1.0/100%/24 ml O₂/dl) and examined the effect on time-trial performance and associated consequences for post-exercise fatigue (13). Increasing the C_aO₂ from hypoxia (S_pO₂ 77%) to hyperoxia (S_pO₂ 100%) improved time trial performance (12%), power output during the exercise (30%) and central motor drive (43%). Strikingly, despite significant differences in the time to completion, the end-exercise level of peripheral fatigue did not differ between the four time trials suggestive, of a 'critical threshold' of peripheral fatigue (95). These authors concluded that the arterial oxygenation sensitive development of peripheral fatigue acts as a trigger of 'central fatigue', ultimately reducing exercise performance in order to prevent 'excessive' locomotor muscle fatigue (13).

It appears that peripheral fatigue plays a dominant role in determining central motor drive during 'normal' conditions but might come secondary in severe AH (95). Amann and colleagues (74) tested the hypothesis that in severe AH, there is a hypoxia sensitive source of inhibition to central motor drive which acts independent of peripheral fatigue and the associated feedback at more severe levels of hypoxia, the dominant factor limiting central motor drive during exercise would shift from a peripheral to a central factor, namely brain hypoxia. Participants performed constant-load cycling exercise (81% of SL peak power output) to exhaustion at SL and in two levels of AH (F_IO₂/S_pO₂ = [moderate] 0.15/82%; [severe] 0.10/67%, respectively). At task-failure (cadence <70% of target rpm for more than 10 s) arterial hypoxaemia was surreptitiously reversed via acute O₂ supplementation (F_IO₂ = 0.30) and the participants were encouraged to continue exercising. Hyperoxygenation did not significantly prolong exercise time at task-failure at SL (F_IO₂/S_pO₂=0.21/94%; time to task failure ~656 s) or moderate hypoxia (0.15/82%; time to task failure ~278 s). However, at task failure in severe hypoxia (0.10/67%; time to task failure ~171 s) hyperoxygenation lead to a significant improvement in exercise performance (~171%). Additionally, at task-failure in severe hypoxia, before hyperoxygenation, the level of peripheral fatigue was substantially less than the levels observed at task failure in both SL and moderate hypoxia ($Q_{tw,pot}$ -23% vs. -36% and -37%, respectively; P<0.01). However, following re-oxygenation and subsequent exercise to exhaustion, the level of peripheral fatigue was similar to that experienced in the other conditions ($Q_{tw,pot}$ -36%), supportive of a previously hypothesised 'critical threshold' of end-exercise peripheral muscle fatigue (94). Based on these findings, the authors concluded that the major determinant of central motor drive and exercise performance switches from a predominately peripheral origin of fatigue in normoxia to moderate hypoxia (F_IO₂ 0.21-0.12) to a hypoxia-sensitive central component of fatigue in severe hypoxia (F_IO₂ <0.12) likely involving cerebral hypoxia.

Based on the aforementioned literature it might be concluded that mechanisms of peripheral fatigue contribute to task-failure and primarily limit exercise performance in mild-to-moderate AH (S_pO₂ >75%; altitude <4,000 m). However, as the severity of hypoxia increases (S_pO₂ <75%; altitude >5,000 m), mechanisms of central fatigue prevail (96, 97). Moreover, that the greatest level of central fatigue is observed when S_aO₂ is below 75% is in line with the greatest observed changes in neuronal excitability as measured with EEG (as described above; 35, 44, 48, 50).

Cerebral oxygenation and fatigue—Investigations using near infrared spectroscopy have suggested that a decrease in cerebral oxygenation may play a pivotal role in limiting locomotor exercise performance in AH (2, 98). Subudhi et al. (99) have shown that prefrontal, pre-motor and motor-cortical deoxygenation is accelerated during exercise in AH. This might be reflective of the widespread depolarisation and could manifest as an increased sense of effort throughout the exercise. Moreover, the deoxygenation in premotor and motor-cortices may impair motor neuron excitability leading to the curtailment of exercise and increased levels of central fatigue (99). In line with this postulate, Rasmussen et al. (5) investigated whether reductions in the oxygen-to-carbohydrate-index and the cerebral-mitochondrial-O₂-tension ($P_{\text{mito},\text{O}_2}$) during locomotor cycling exercise in AH ($F_{\text{I}}\text{O}_2/\text{S}_a\text{O}_2 = 0.10/58\%$) would relate to the neuromuscular performance of a remote muscle group (elbow-flexors) not directly involved in the task. On one day, participants performed constant-load cycling exercise at SL and in AH for 20 min (124 ± 21 W, 44% SL peak power). At SL, the low-intensity locomotor exercise did not elicit central fatigue (assessed via TMS) or produce changes in cerebral metabolic status. Conversely, in AH, the same exercise reduced cerebral oxygenation by one quarter (as measured by near infrared spectroscopy) and indices of oxygen-to-carbohydrate-index and $P_{\text{mito},\text{O}_2}$. Moreover, maximal strength and voluntary activation of the elbow-flexors were significantly reduced (6% and 10%, respectively). Unfortunately, methodological shortcomings associated with TMS-related measures in this study limit the interpretation of the findings. Nonetheless, Rasmussen et al. (5) suggest that a reduction in cerebral oxygenation and metabolic status might correlate with the development of central fatigue and hence limit locomotor exercise performance in AH.

The first evidence of a reduced cerebral O₂ availability and the consequential exacerbation of central fatigue in severe AH was demonstrated by Goodall et al. (100). Nine endurance-trained cyclists completed three bouts of locomotor exercise at ~80% of their SL maximum power to task-failure in AH ($F_{\text{I}}\text{O}_2/\text{S}_a\text{O}_2 = 0.13/78\%$); for the same time but at SL (isotime control) and to task-failure at SL. Evoked twitches (electrical femoral nerve stimulation) and responses to TMS were studied from the knee-extensors before and immediately after each exercise to assess neuromuscular and cortical function, respectively. Exercise time was 54% shorter in AH vs. SL (3.6 ± 1.3 vs. 8.1 ± 2.9 min; $P < 0.01$) but post-exercise peripheral fatigue did not differ. Likewise, post-exercise maximal voluntary strength did not differ between AH and SL, but supraspinal mechanisms fatigue contributed more to the force loss during AH compared to SL. Furthermore, throughout the exercise in AH, cerebral oxygenation and cerebral O₂ availability declined, compared to SL, from an initial reduction at baseline; a response that was related to the substantial central fatigue (Figure 3) (100). These findings suggest that increased central fatigue in severe AH occurs in the face of reductions in cerebral O₂ availability and might provide a plausible explanation for the reduced locomotor exercise performance found in these conditions. Moreover, the increased severity of supraspinal fatigue (i.e., suboptimal output from the motor cortex) in AH, might be linked to the widespread neuronal depolarisation that might occur to protect homeostasis.

We have termed the data above pertaining to cerebral O₂ *delivery*, cerebral O₂ *availability* as confusion arises when this parameter is estimated from transcranial Doppler

measurements of velocity, rather than flow. To the best of our knowledge, in all investigations measuring cerebral O₂ delivery (cerebral blood flow $\times$ C_aO₂) a consistent delivery across time at altitude has been reported, not a reduction (101–104). Thus, further work is required to understand the role of ‘true’ cerebral O₂ delivery and its impact on exercise-fatigue in AH.

The effect of acclimatisation on the development of fatigue during exercise

Unlike the abundance of literature pertaining to the mechanisms of fatigue induced by locomotor exercise in AH, data from studies in CH is sparse. There are numerous adaptations that occur during a prolonged (2 weeks) stay at altitude, for example erythropoiesis and an increased ventilatory response to exercise; detailed reviews on these and other hypoxia-related adaptations can be found elsewhere (105–107). Improvements in variables such as [Hb], S_aO₂ and C_aO₂ would intuitively serve to increase O₂ delivery to locomotor muscles in CH. However, despite this improvement in arterial oxygenation and a recovery of C_aO₂ to sea level values known to occur in CH, some investigations have actually reported a failure of muscle O₂ delivery during cycling exercise from AH to CH (108, 109). In contrast, Calbet et al. (110) report an increased O₂ delivery from AH to CH with the net effect of similar O₂ delivery at in CH and SL. Given the critical dependency of muscle O₂ delivery upon the development of peripheral fatigue (93), if muscle O₂ delivery was improved from AH to CH (19), then post-exercise peripheral fatigue would be expected to be attenuated following the same exercise in CH vs. AH. Alternatively, if muscle O₂ delivery does not change from AH to CH (108, 109), similar levels of post-exercise peripheral fatigue would be expected.

Amann et al. (19) recently recruited SL residents to perform identical bouts of locomotor cycling exercise (138 ± 14 W, 11 ± 1 min) at SL (P_IO₂/S_pO₂ = 147 mmHg/94%), in AH (74 mmHg/61%), and in CH (76 mmHg/76%; 14 d at 5,260 m above SL). Exercise-induced peripheral locomotor muscle fatigue was assessed by comparing neuromuscular quadriceps function (electrical femoral nerve stimulation) quantified before and immediately after the exercise in each condition. In line with Calbet et al. (110), the increases in C_aO₂ and S_pO₂ were accompanied by a significant increase in leg O₂ delivery from AH to CH (as suggested by a normalised near infrared response 19). However, despite these beneficial effects, similar significant levels of peripheral fatigue were evident following exercise in AH and CH ($Q_{tw,pot} \sim 20\%$; Figure 4) suggesting a lack of improvement in peripheral locomotor muscle fatigue development with acclimatization. Assuming that the similar level of peripheral fatigue in AH and CH occurred in line with a greater O₂ delivery in CH then other acclimatisation-induced adaptations must have outweighed this benefit (19). For example, a decreased capillary muscle O₂ conductance has been documented to impair skeletal muscle O₂ extraction capacity in CH (111). This influence, despite a greater O₂ delivery in CH vs. AH, might have lowered extracellular PO₂ to, or beyond a previously suggested threshold (~ 30 mmHg), which is known to exacerbate peripheral fatigue (112). Alternatively, the higher O₂ delivery in CH vs. AH (110) in line with the same level of peripheral fatigue, might suggest that C_aO₂ and bulk O₂ delivery, per se, may not be primary determinants of fatigability in hypoxia. Amann et al. (19) emphasise that despite the similar C_aO₂ and O₂ delivery in CH, P_aO₂ only partially recovered over the period of

acclimatisation. Thus, low P_aO_2 might serve to exacerbate the development of peripheral fatigue in CH and future studies should focus on this issue.

Cerebral oxygenation, cortical changes and central fatigue—The aforementioned improvements in arterial oxygenation associated with CH also serve to increase cerebral O_2 delivery (113), reductions in which have been related to a fastened development of central fatigue during locomotor exercise (100). In an attempt to understand the impact of a prolonged stay at altitude on the development of central fatigue during exercise, Goodall et al. (20) investigated corticospinal responses and central fatigue at SL ($P_iO_2/S_pO_2 = 147$ mmHg/93%), in AH (74 mmHg/61%), and in CH (78 mmHg/78%; 14 d at 5,260 m above SL). Sea-level residents performed the identical bouts of locomotor cycling exercise (131 ± 39 W, 10 ± 1 min) in each of the three conditions. The exercise at SL did not induce any change in cerebral oxygenation or indices of fatigue whilst the same exercise in AH reduced cerebral oxygenation and was accompanied by an exacerbated drop in cortical voluntary activation (11%) indicative of central fatigue. When the exercise was performed in CH, cerebral oxygenation was unaffected and the development of central fatigue was attenuated following exercise, reflected in the smaller exercise-induced decrease in voluntary activation (6%). Thus, acclimatisation to high altitude attenuated the development of central fatigue that is evident after an identical exercise bout in AH. Furthermore, the period of CH normalised the pattern of cerebral deoxygenation to that found at SL. In line with this, cerebral O_2 delivery during CH was (based on the assumption that MCA diameter remained unchanged during exercise 114, 115) increased by ~20% in comparison to AH. Similar to above, these data must be taken with caution as there is evidence of MCA dilatation at rest in hypoxia (116, 117), however, there is currently no evidence of MCA dilatation during intense exercise accompanied with substantial exercise-induced hyperventilation and associated hypocapnia. Despite this limitation, periods of CH may elicit increases in cerebral O_2 availability which might contribute to the attenuated level of central fatigue.

The reduced development of central fatigue in CH occurred in parallel with a two-fold increase in corticospinal excitability (vs. SL and AH) prior to exercise (Figure 5; 20). Although in a non-locomotor muscle group, corticospinal excitability has been suggested to contribute to the development of central fatigue in human muscles (118). Thus, an increased corticospinal excitability might attenuate the development of central fatigue. As discussed in the first section of this review, ion-channel function has been shown, using *in vitro* preparations, to be directly affected by O_2 availability and neuronal hyper-excitability is consequent to hypoxia (119). An elevated neural response is necessary to maintain membrane integrity and ionic homeostasis that is known to occur from a period of insufficient metabolic activity (120). Specifically, evidence suggests that hypo-metabolism is a key mechanism during brain adaptation to CH (121). Additionally, dynamic regulation of metabolic demand is one adaptive mechanism that preserves cognitive development in CH (122). Further investigations are needed to understand the time-dependent changes (20, 64, 69) in corticospinal properties that occur in healthy individuals during acclimatisation to high altitude and whether such modifications remain evident after return to SL.

Conclusion

At rest during very early hypoxia (<1 h), a slowing and reorganisation of the EEG signal is evident despite no discernible change in TMS evoked parameters suggesting altered neuronal activity with unchanged corticospinal responsiveness. As the time in hypoxia progresses (3 h), an increased corticospinal excitability becomes evident which may reflect a mechanism attempting to restore/protect neuronal homeostasis but EEG responses at this time are unknown. Moreover, following the initial period acute hypoxia, a prolonged period of time (3–5 days) causes a respiratory alkalosis which modulates Na⁺ channels and could potentially explain the reduced neuronal excitability apparent at this time.

During locomotor exercise in AH, reductions in O₂ delivery exacerbate the development of peripheral muscle fatigue observed at SL. As the severity of hypoxia increases, mechanisms of peripheral fatigue become less dominant and CNS hypoxia becomes the predominant factor limiting locomotor exercise performance. The greatest level of central fatigue is observed in AH when S_aO₂ is below 75%, a level of saturation that reflects the greatest change in neuronal activity as measured with EEG. Prolonged acclimatisation to hypoxia does not improve the level of peripheral fatigue observed in AH. Mechanisms of central fatigue, however, are attenuated from those found in AH in parallel to an increased cerebral O₂ delivery and corticospinal excitability. The attenuated development of central fatigue in CH might explain, at least in part, the improvements in locomotor exercise performance that are commonly observed after acclimatisation to high altitude.

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Figure 1.

Frequency spectra of segments (5 s duration) derived from three experimental conditions, 100% oxygen, hypobaric hypoxia and recovery (100% oxygen). Note the slowing/reduced activity during the hypoxia session. Reprinted with permission from Papadelis et al. (35).

Figure 2.

Involvement of the temporal lobes (medial and basal areas) and structures of the limbic system in response to cerebral hypoxia (equivalent electrical dipole sources [EEDS] tomography data). *I*) Baseline, *II*) Hypoxia ($F_I O_2 = 0.08$, 15 min), *III*) Recovery back to baseline. Horizontal brain section H7 with outlines of brain structures. EEDS are shown as circles with projections of EEDS electrical axes as straight lines (rays). The level of section H7 is shown on the pictogram in the lower left corner. Note the movement of activity during hypoxia; this transition appears to show an involvement from the limbic system which adapts a protective strategy to channel neuronal activity in an appropriate way for survival. Reprinted with permission from Rozhkov et al. (50).

Figure 3.

Cortical voluntary activation of the knee extensors immediately post-exercise vs. cerebral oxygenation (A and B) and middle cerebral artery O₂ delivery index (C and D) during the final 30 s of exercise. Cerebrovascular responses are shown for the period immediately after (<2.5 min; post-exercise) locomotor cycling exercise when motor cortex stimulation was applied (A and C) and for the final minute of the exercise (B and D; end-exercise). Data are individual (small symbols) and mean (large symbols) for 9 (A and B) and 6 (C and D) participants in acute hypoxia (closed circles), the isotime-control trial (open circles) and

normoxia (open squares). The regression lines are for group mean data. The correlation coefficients (r) and associated P-values are for repeated observations within participants (123). From Goodall et al. (100).

Figure 4.

Individual data illustrating the effects of constant-load cycling exercise (138 ± 14 W; 10.6 ± 0.7 min) on potentiated quadriceps twitch force ($Q_{tw,pot}$) at sea level, in acute hypoxia and chronic hypoxia. Open circles represent individual data whereas the filled circles represent group mean data for each condition. Adapted from Amann et al. (19).

Figure 5.

A - Representative vastus lateralis MEPs evoked at rest at sea level (normoxia), in simulated acute hypoxia (5,260 m; $F_{I}O_2 = 0.105$, $S_pO_2 = 88\%$) and chronic hypoxia (5,260 m; $S_pO_2 = 92\%$). Traces are shown from a representative participant in each condition. **B** - MEP/M_{max} ratio (reflecting corticospinal excitability) evoked at rest in the 3 different conditions. * = $P < 0.05$ vs. chronic hypoxia. Adapted from Goodall et al. (20).