Cerebral perturbations during exercise in hypoxia

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WITH THE EXCEPTION of very short or static exercises performed at a high percentage of maximal power (15, 19, 83), hypoxia deteriorates exercise performance (7, 82). In particular, the maximal aerobic workload (\( W_{\text{max}} \)) that can be sustained during exercise involving large muscle groups (e.g., cycling) is considerably lower in hypoxia compared with normoxia. The difference between these two environmental conditions increases progressively with the reduction in oxygen inspiratory pressure (\( P_{\text{IO2}} \)) (36) and is affected by subjects’ fitness so that subjects with elevated maximal aerobic capacity are more affected by hypoxia (41).

The origin of exercise performance limitation in hypoxia is still under debate, since the consequences of reduced blood \( O_2 \) affect the whole organism. This limitation has been attributed to a lowered \( O_2 \) partial pressure in arterial blood (\( P_{\text{A,O2}} \)) reducing \( O_2 \) content and \( O_2 \) delivery to tissues with critical consequences on muscle metabolism and contraction (1, 46).

Magnetic nerve stimulation has confirmed the effects of reduced arterial oxygenation on dynamic (12, 111) and static (54) exercise-induced alterations in muscle contractility. Reduced muscle \( O_2 \) delivery and exercise performance may result from impairments in pulmonary gas exchange [e.g., alveolar-capillary \( O_2 \) diffusion limitation (109)], reductions in maximal cardiac output and blood flow to locomotor muscles (17), and respiratory muscle fatigue (23) (for a review see Ref. 20). Calbet et al. (17) demonstrated that the reduction in maximal oxygen consumption during cycling with an inspiratory \( O_2 \) fraction (\( F_{\text{IO2}} \)) of 0.105 was explained by the reduced \( P_{\text{O2}} \), impaired pulmonary gas exchange, and reduced maximal cardiac output and leg blood flow, with each mechanism explaining approximately one-third of the reduction. These factors may, however, not entirely explain the hypoxia-induced reduction in exercise performance (57, 94, 115). Because biochemical, electromyographic (EMG), and mechanical signs of muscle fatigue at exhaustion are reduced in severe hypoxia compared with normoxia (e.g., 13, 56), muscle metabolic fatigue may not be the main factor responsible for impaired whole body exercise performance.
An alternative hypothesis is to consider the effects of hypoxia on the central nervous system (CNS) that may lead to altered central motor command and eventually reduced exercise performance (6). Neurons require continuous O₂ delivery in sufficient quantities to enable vital processes. The responsiveness of neurons to reduced O₂ availability is fast, and they can immediately change their activities in response to hypoxia (29, 72). For example, severe hypoxia can affect cognitive performance (e.g., 59). Some theories and indirect evidence suggest that the CNS may be sufficiently affected during exercise in hypoxia to become a limiting factor for exercise performance. In acute severe hypoxia, CNS alterations may precede the development of peripheral muscle fatigue and underlie the reductions in central motor output and exercise performance (13). This theory is supported by studies showing that hyperoxia at exhaustion quickly restores the ability of subjects to sustain the target workload and increases exercise performance in hypoxia (13, 17, 56, 101). Objective measurements of cerebral perfusion and oxygenation (3, 51, 81, 85, 91, 100, 101, 110) and supraspinal neuromuscular alterations (40, 86, 104, 105) have recently provided indications of brain adaptations to exercise in hypoxia. These results help to understand the mechanisms underlying the effects of hypoxia on central motor command and exercise performance.

This review addresses the main observations in humans regarding the impact of hypoxia on the brain during isolated and whole body exercise as well as questions that need to be addressed. Our approach includes the effects of changes in arterial oxygenation (and potential changes in arterial CO₂) on cerebral blood flow (CBF) and cerebral oxygenation, the impact of changes in cerebral oxygenation and its cellular consequences on neuron excitability, and finally central drive to the muscles. We consider 1) the “direct effects” of acute hypoxia on these different cerebral aspects during exercise, 2) the potential “indirect effects” of acute hypoxia involving interactions between peripheral muscles and the CNS, and 3) the consequences of both direct and indirect effects on maximal voluntary activation and central motor command during submaximal and maximal exercise. The effects of chronic hypoxia (from several hours to several weeks) are also addressed.

DIRECT CEREBRAL EFFECTS OF ACUTE HYPOXIA

Cerebral Blood Flow

The majority of studies assessing changes in cerebral blood flow (CBF) during hypoxic exposure and exercise have used transcranial Doppler methods. This technique provides indirect evaluation of CBF from blood velocity in proximal intracranial or neck arteries. An important consideration is that, in addition to blood velocity, changes in diameter of insonated blood vessels could modulate CBF. The middle cerebral artery diameter (the most frequently measured) is nevertheless assumed to remain relatively constant with changes in blood gases and during exercise (4, 96), although recent data challenge this assumption in severe hypoxia (118).

Hypoxia at rest. Hypoxia per se is a cerebral vasodilator that increases CBF (24), at least beyond a certain threshold, i.e., arterial oxygen saturation (SpO₂) < 90% or PaO₂ < 40–45 mmHg (4). Hypoxic exposure at rest is associated with some degree of hyperventilation that results in hypocapnia. Since hypocapnia reduces CBF by vasoconstriction, changes in CBF result from the opposing effects of hypoxemia and hypocapnia (Fig. 1). Hence, little change in CBF is observed at rest when PaO₂ is reduced (5, 49, 74, 80), slight increases being possible as a function of the level of hypoxia and the amount of hyperventilation-induced hypocapnia. CBF can also be measured by arterial spin labeling (ASL) that magnetically tags blood water and measures its delivery to tissue capillaries to obtain a global or regional measure of tissue perfusion. When FIO₂ is reduced from 0.21 to 0.12, ASL indicates increased whole brain CBF (32) but no difference in the motor cortex (110), potentially due to regional specificity and/or insufficient signal-to-noise ratio.

Normoxic exercise. Consistent increases in middle cerebral artery blood velocity (MCAV) have been observed from rest to
submaximal whole body normoxic exercise (50, 52, 62), whereas other cerebral arteries did not show a similar increase (55). Changes in CBF during exercise depend on cerebral areas being activated and are distributed heterogeneously within the brain (58), global CBF as measured with the Kety-Schmidt method remaining relatively constant from rest to maximal exercise (62). Note that regional CBF decreases near-maximal intensity exercise (39). Mechanisms thought to be involved in CBF regulation during exercise are cerebral autoregulation, i.e., the rapid response of cerebral blood vessels to changes in mean arterial pressure to keep CBF within physiologically tolerable limits and CO₂ vasoreactivity. Thus hyperventilation with concomitant reduction in arterial CO₂ partial pressure (Paco₂) during intense exercise is a potential reason for reduced CBF when approaching maximal exercise (96).

Combined effects of hypoxia and exercise. Table 1 summarizes studies that have evaluated the effects of hypoxia on cerebral perfusion during exercise. While the vasodilator effect of hypoxia should accentuate the exercise-induced increase in CBF, reduced Paco₂ due to hyperventilation during hypoxic exercise, probably blunts this effect, and most studies reported similar blood velocity at submaximal or maximal exercise in normoxia and acute hypoxia (2, 49, 81, 101) (e.g., Fig. 1). Keeping end-tidal CO₂ clamped during incremental exercise in acute hypoxia increases CBF but also reduces maximal performance (103). Although this result suggests that CBF is not a limiting factor at maximal exercise, clamping CO₂ also induces respiratory acidosis, increases ventilation and adverse respiratory sensations, potentially limiting exercise performance. Distinguishing the effect of reduced PaO₂ and Paco₂ on hypoxic exercise CBF and performance remains therefore a challenge. In addition to the effect of changes in CO₂ on CBF, cerebral autoregulation may play a role since it is impaired during exercise in acute hypoxia (2). During finger tapping, Tuunanen and Kauppinen (110) reported a similar increase in motor cortex ASL signal intensity in hypoxia compared with normoxia but over a smaller area of the parenchyma. Therefore, CBF during exercise is not enhanced when arterial oxygenation is reduced probably due to the vasoconstrictive effect of reduced Paco₂. Some cerebral regions [including within the motor cortex (104)] may even undergo reduced perfusion potentially impairing O₂ delivery.

Table 1. Changes in cerebral blood flow and oxygenation during exercise in hypoxic conditions compared with normoxic conditions

<table>
<thead>
<tr>
<th>Ref</th>
<th>Hypoxic Condition</th>
<th>Exercise Characteristics</th>
<th>Cerebral blood flow (MCAV*)</th>
<th>Cerebral oxygenation</th>
</tr>
</thead>
<tbody>
<tr>
<td>91</td>
<td>Acute hypoxia (FiO₂ = 0.11, ~4,700 m)</td>
<td>Sustained ankle extension at 40% MVC</td>
<td>↓ HHb and ↓ HbTot</td>
<td></td>
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<tr>
<td>110</td>
<td>Acute hypoxia (FiO₂ = 0.12, ~4,100 m)</td>
<td>Finger tapping (2 Hz)</td>
<td>↓ (MRI ASL signal)</td>
<td>↓ (MRI BOLD signal)</td>
</tr>
<tr>
<td>49</td>
<td>Acute (PiO₂ = 83 Torr, ~4,300 m) and chronic (18 days at 4,300 m) hypoxia</td>
<td>Cycling at low (same absolute workload), middle, and high (same relative workload) intensities for 5 min</td>
<td>↓ at same absolute and relative workload in chronic hypoxia only</td>
<td>=</td>
</tr>
<tr>
<td>2</td>
<td>Acute hypoxia (FiO₂ = 0.14, ~3,000 m)</td>
<td>Cycling at 60–70% of normoxic maximal O₂ uptake for 5 min</td>
<td>↑ at same absolute and relative workload</td>
<td></td>
</tr>
<tr>
<td>86</td>
<td>Acute hypoxia (FiO₂ = 0.10, ~5,300 m)</td>
<td>Cycling at high intensity in hypoxia and at the same absolute or relative intensity in hypoxia</td>
<td>↓ O₂ delivery and PmioO₂ at same absolute and relative workload</td>
<td>↓ HbO₂, ↑ HHb and ↓ HbTot at same relative and absolute (except HbTot) workload</td>
</tr>
<tr>
<td>100</td>
<td>Acute hypoxia (FiO₂ = 0.12, ~4,100 m)</td>
<td>Incremental maximal cycling</td>
<td>↑ at maximal intensity</td>
<td>↓ HbO₂ at same absolute workload</td>
</tr>
<tr>
<td>102</td>
<td>Acute hypoxia (PiO₂ = 79 mmHg, ~4,700 m)</td>
<td>Incremental maximal cycling</td>
<td>= at same absolute and maximal workload</td>
<td>↓ HbO₂ and ↑ HHb at same absolute workload</td>
</tr>
<tr>
<td>81</td>
<td>Acute hypoxia (PiO₂ = 118 mmHg, ~2,500 m)</td>
<td>Incremental maximal cycling</td>
<td>↑ at maximal intensity in chronic hypoxia only</td>
<td>↓ HbO₂ and ↑ HHb at maximal intensity</td>
</tr>
<tr>
<td>101</td>
<td>Acute and chronic (1 wk) hypoxia (PiO₂ = 86 Torr, 4,300 m)</td>
<td>Incremental maximal cycling</td>
<td>↑ at same relative workload (at 4,750 and 5,260 m only)</td>
<td>↑ HHb at same relative workload</td>
</tr>
<tr>
<td>51</td>
<td>Chronic hypoxia (after 24-36 h at 3,610 m, within 9 days at 4,750 and 5,260 m)</td>
<td>Incremental maximal cycling</td>
<td>= at same absolute and relative workload</td>
<td></td>
</tr>
<tr>
<td>93</td>
<td>Chronic hypoxia (2,700 and 3,700 m)</td>
<td>Stepping at moderate intensity (same absolute workload)</td>
<td>↓ Cerebral O₂ saturation (NIRS)</td>
<td></td>
</tr>
</tbody>
</table>

PiO₂, partial O₂ inspiratory pressure; FiO₂, inspiratory O₂ fraction; MCAV, middle cerebral artery blood velocity; HHb, exercise-induced changes in cerebral deoxygenated heme concentration; HbO₂, exercise-induced changes in cerebral oxygenated heme concentration; HbTot, exercise-induced changes in cerebral total heme concentration; PmioO₂, mitochondrial oxygen tension; *except Ref. 110.
cannot be distinguished. Contrary to muscle oxygenation which is maintained, cerebral oxygenation as measured with NIRS at rest is reduced in acute hypoxia (2, 51, 80, 91) suggesting a mismatch between O$_2$ delivery and O$_2$ utilization within the brain, at least in the brain regions under investigation (prefrontal cortex; e.g., Fig. 2). Interestingly, the increase in deoxyhemoglobin concentration did not correlate with changes in MCAV (80), indicating that changes in cerebral oxygenation and CBF at rest in hypoxia are, at least in part, distinct mechanisms.

In normoxia, prefrontal cortex oxygenation is increased during cycling, whereas muscle oxygenation is reduced (92). At near-maximal exercise, however, cerebral oxygenation decreases (92), potentially because of an imbalance between a slight reduction in regional CBF and increased cerebral metabolic rate and O$_2$ uptake. Table 1 summarizes studies that have evaluated the effects of hypoxia on cerebral oxygenation during exercise. NIRS during exercise in hypoxia shows consistently reduced cerebral oxygenation both at submaximal (e.g., Fig. 2) and maximal intensities (2, 51, 81, 91, 93, 100–102). This reduction has been observed even in cases of enhanced CBF (51, 101), and no correlation was observed between changes in prefrontal oxygenation and MCAV during exercise (2). An elevated cerebral metabolic rate associated with greater O$_2$ consumption may explain this reduction in cerebral oxygenation during whole body exercise in hypoxia (101). In hypoxia, whole body exercise and isolated contractions differ regarding cerebral oxygenation since the former accentuates cerebral deoxygenation (13, 100, 101), whereas the later is associated with some degree of cerebral reoxygenation (40, 91) compared with hypoxic resting levels. While most previous studies have only evaluated prefrontal oxygenation, Subudhi et al. (102) showed using multichannel NIRS that cerebral oxygenation during hypoxic exercise is well correlated between the prefrontal, premotor, and motor regions, although at maximal exercise deoxygenation of the prefrontal cortex was greater than in other regions.

Functional magnetic resonance imaging showed a linear increase in the blood oxygen level-dependent (BOLD) signal (reflecting changes in blood oxygenation, blood flow, and/or blood volume) of the sensorimotor cortex during graded activation of small muscle mass (finger tapping) (53). Liu et al. (60) reported during fatiguing submaximal constant-load handgrasp contractions in normoxia, a progressive increase in the BOLD signal which then reached a plateau toward the end of the task. This plateau, in line with the NIRS reduction in cerebral oxygenation near-maximal exercise reported above (92), can be interpreted as an altered central motor command, i.e., the so-called central fatigue. Such an interpretation should take into account that modified BOLD signals can reflect changes in neuronal input and/or processing and changes in inhibitory and/or excitatory inputs (84). In some parts of the cortex involved in motor task performance in normoxia (supplementary motor areas, the supramarginal gyrus and parts of the motor cortex), BOLD changes during finger tapping are strongly attenuated by hypoxia, further suggesting that hypoxia may not uniformly affect all brain regions (110). Techniques allowing regional assessment of cerebral perfusion and oxygenation (such as MRI and multichannel NIRS) will be helpful in better describing the topographic localization of cerebral perturbations associated with isolated and whole body exercise in hypoxia.

**Brain Mitochondrial Oxygen Tension and Cerebral Metabolism**

Mitochondrial oxygen tension (P$_{mitoO_2}$) and metabolic response of the brain to exercise can be estimated from the arteriovenous differences and CBF (25, 85). It has been speculated that a reduction in P$_{mitoO_2}$ of more than 6–7 mmHg (no absolute P$_{mitoO_2}$ can be measured with this method), because of reduced arterial oxygenation and/or CBF, may be associated with impaired cerebral aerobic metabolism (85). Strenuous exercise in normoxia could induce a drop in P$_{mitoO_2}$ remaining slightly below this threshold (39). When exercise is performed under acute hypoxic conditions, the reduction in P$_{mitoO_2}$ may be exacerbated due to the combination of reduced arterial O$_2$ delivery and unchanged maximal O$_2$ extraction fraction (75). Rasmussen et al. (86) confirmed that P$_{mitoO_2}$ during intense cycling in hypoxia is further reduced (−11 mmHg) compared with cycling in normoxia both at the same absolute workload.

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**Figure 2.** Changes in brain (prefrontal) and muscle oxyhemoglobin (A), deoxyhemoglobin (B), and total hemoglobin (C) concentrations during normoxic and hypoxic (hatched columns) conditions at rest and during submaximal cycling. Values are means ± SD. *Different from muscle (P ≤ 0.05); † Different from hypoxic rest at all time points (P ≤ 0.05); ‡ Different from preexercise (P ≤ 0.05) (from Ref. 2).
(+3 mmHg) and at maximal intensity (−8 mmHg), thus potentially impairing cerebral mitochondrial ATP production.

Brain metabolism during exercise has been expressed as the cerebral metabolic ratio of O₂ vs. substrates (MR = CMR<sub>O₂</sub>/CMR<sub>glucose</sub> + 1/2lactate) (25). During intense exercise in normoxia, CMR<sub>glucose</sub> + lactate increases out of proportion to CMR<sub>O₂</sub>, thereby reducing MR (39, 114), possibly due to the role of glycolysis and lactate in fueling neuronal activity (25). Rasmussen et al. (86) reported reduced CMR<sub>O₂</sub> during intense whole body exercise in hypoxia compared with low (i.e., at same absolute workload) or maximal intensity exercise in normoxia. A greater reduction in MR from rest to exercise was found in hypoxia compared with normoxia at the same absolute workloads, while the MR reduction was similar for comparable relative workloads. Similar results were reported by Volianitis et al. (114), i.e., comparable reductions in MR during 2,000-m all-out rows performed with F<sub>IO₂</sub> of 0.17, 0.21, and 0.30. This finding suggests that hypoxia alters MR for a given absolute work output (possibly due to greater cerebral activation to increase central drive to cope with larger muscle fatigue) but not at similar relative intensities.

Rasmussen et al. (86) showed net cerebral lactate uptake during intense exercise in normoxia but not in hypoxia despite similar arterial lactate concentrations. Volianitis et al. (114) also reported significantly reduced arteriojugular venous lactate differences during intense exercise in hypoxia compared with normoxia. This suggests a modified balance between brain lactate uptake and release during intense exercise in hypoxia, with reduced lactate uptake and/or greater lactate release compared with normoxia (75). The potential role of the hypoxia-induced changes in brain lactate exchange and metabolism on neuronal function in the context of central fatigue remains to be elucidated.

**Effect of Cerebral Oxygenation on Exercise Performance: Lessons From Hyperoxia**

To determine to what extent the reduction in cerebral oxygenation can impair exercise performance, some studies have evaluated the effect of increasing F<sub>IO₂</sub> during whole body exercise on cerebral oxygenation and performance (13, 81, 101). Subudhi et al. (101) increased surreptitiously F<sub>IO₂</sub> to 0.60 at W<sub>max</sub> of incremental cycling tests performed in normoxia and hypoxia (P<sub>EO₂</sub> = 86 Torr, ~4,300 m). Hyperoxia increased cycling time in hypoxia only and improved both cerebral and locomotor muscle oxygenation assessed by NIRS over the frontal lobe and vastus lateralis, respectively (Fig. 3). Similarly, Peltonen et al. (81) reported improved performance with enhanced cerebral and muscle perfusion when subjects were switched to hyperoxia at the end of a maximal incremental cycling test in hypoxia (P<sub>EO₂</sub> = 118 mmHg, ~2,500 m). In both studies, the greater effect of switching to hyperoxia was observed on cerebral oxygenation compared with muscle oxygenation (Fig. 3). Peltonen et al. (81) suggested that tissue-specific control mechanisms may underlie differences between cerebral and muscle tissues regarding hypoxia-induced perfusion and oxygenation changes, although the mechanisms responsible for such differences remain to be elucidated. Because of the simultaneous and rapid effect of hyperoxia at exhaustion on cerebral oxygenation and exercise tolerance, cerebral deoxygenation is thought to be an important factor underlying exercise performance limitation in hypoxia (6). However, a potential role of mechanisms other than cerebral reoxygenation inducing increased exercise performance in hyperoxia cannot be ruled out (e.g., cardiovascular changes). The effect of low brain oxygenation (and reoxygenation) on performance during other types of exercise protocols limiting the influence of large cardiovascular changes (e.g., prolonged submaximal whole body exercise or isolated muscle exercise) needs to be investigated.

**Cortex excitability.** Transcranial magnetic stimulation (TMS) is a noninvasive technique that allows stimulation of small brain areas. Stimulation of the motor cortex can evoke short-latency excitatory EMG (motor-evoked potential, MEP) and mechanical (twitch) responses in many muscles. When TMS is delivered during a voluntary contraction, MEPs are followed by a period of EMG silence called the cortical silent period (CSP) reflecting intracortical inhibition. During fatiguing muscle contractions in normoxia, increased MEP amplitude (reflecting greater corticospinal excitability) and CSP shortening (reflecting greater intracortical inhibition) are observed (37).
In acute severe hypoxia at rest (20–30 min with FIO2 = 0.12, SpO2 \sim 75\%), Szubski et al. (104) showed unchanged MEP amplitudes, a reduced resting motor threshold (RMT), and shorter CSP compared with normoxia, suggesting that acute hypoxia may increase cortical excitability and decrease intracortical inhibition. Conversely, after 10-min wash-in periods at rest with various gas mixtures (FIO2 = 0.10–0.21), Goodall et al. (40) reported that corticospinal excitability and inhibition were similar in hypoxia and normoxia. Differences between studies regarding the effects of hypoxia at rest on corticospinal excitability may arise from differences in the muscle group tested (first dorsal interosseus vs. quadriceps muscles) or the length of exposure to hypoxia. Regarding the latter, the effect of hypoxemia on cerebral tissue oxygenation has relatively prolonged kinetics, i.e., 10–20 min of hypoxic breathing may be insufficient to reach a cerebral deoxygenation steady state (e.g., Fig. 2, or Fig. 3 in Ref. 40). Therefore, a more prolonged wash-in period with the hypoxic gas (>30 min to reach steady-state cerebral oxygenation, personal data) should be used to observe the effect of acute hypoxia on neuronal excitability. Szubski et al. (105) reported after a 90-s maximal voluntary contraction (MVC) of the first dorsal interosseous muscle that MEP amplitude increased and CSP decreased to a similar extent in normoxia and hypoxia, indicating similar responses in corticospinal excitability and intracortical inhibition. Millet et al. (67) observed no difference in MEP or CSP between normoxia or hypoxia (FIO2 = 0.09–0.14) during intermittent isometric submaximal (40% MVC) contractions of the elbow flexors under vascular occlusion. Goodall et al. (40) found no change in corticospinal excitability during exercise using TMS on the knee extensors before or after intermittent isometric submaximal (60% MVC) leg extensions to task failure in normoxia or hypoxia (FIO2 = 0.10–0.16). Based on these studies (40, 67, 104, 105), hypoxia may change corticospinal excitability at rest, whereas during fatiguing exercise with small muscle mass, it does not impair the responsiveness of neurons involved in central motor drive to a greater extent than normoxia.

Arguments in favor of hypoxia-induced perturbations of cerebral neuron activity also come from electrophysiologic recordings indicating reduced activity in hypoxia compared with normoxia both at rest (78) and during mental tasks (79).Animal and in vitro studies suggest that alterations in CNS neurotransmitter turnover [e.g., acetylcholine, dopamine, norepinephrine, and serotonin (38, 77)], ion homeostasis, and channel activity [reduced ion channel and pump activity (42, 73)] might underlie hypoxia-induced changes in brain neuronal excitability.

INDIRECT CEREBRAL EFFECTS OF ACUTE HYPOXIA

Afferent Signals From Working Muscles

Sensory feedback from the fatigued locomotor muscles to the CNS may be a determinant of central motor drive and therefore exercise performance. This hypothesis is supported by both the increased motor drive during the first half of a normoxic 5-km cycling time trial performed with impaired cortical projection of opioid-mediated muscle afferents by intrathecal fentanyl injection and the excessive development of locomotor muscle fatigue observed during the time trial (11). Spinal opioid receptor muscle afferents may influence cerebral adaptations to exercise by facilitating intracortical inhibition (45). Consequently, under moderate hypoxic conditions, muscle fatigue may represent a key factor responsible for impaired central drive in hypoxia through enhanced muscle inhibitory afferent signals because of an accelerated development of locomotor muscle fatigue (12, 54). This statement is supported by the parallel hypoxia-induced (FIO2 = 0.15) reductions in integrated EMG (iEMG) and power output during a 5-km cycling time trial, while peripheral muscle fatigue at exhaustion does not differ (7). Discharge of group III/IV afferents in cats is higher during muscle contractions in hypoxia compared with normoxia, as a consequence of both a higher baseline firing frequency and an additional increase during exercise triggered by hypoxia-induced accumulation of muscle metabolites (44). Increased activity of peripheral muscle afferents in hypoxia (44) could alter brain activity as suggested from recordings of electroencephalographic activity in a cat model (14). Therefore, in addition to CNS hypoxia per se, the effect of hypoxia on central motor drive may also involve changes in afferent signals from both locomotor and respiratory muscles [facing an increased work of breathing (23, 111)] to the CNS. These mechanisms may be critical up to an acute level of SpO2 > 70%, whereas below this level the aforementioned direct effects of hypoxia on cerebral function appear to dominate the regulation of muscular performance (6, 13). Whereas blockade of neural feedback from working muscles with epidural anesthesia does not impair hypoxia-induced increases in systemic cardiovascular and neuroendocrine responses (57), evaluation of the central motor drive during hypoxic exercise when manipulating muscle afferent signals is needed to confirm their impact on the CNS in hypoxic conditions. This should include selective blockade of ascending sensory pathways and avoid the confounding effect of motor nerve activity or maximal force output impairments (10, 11, 57).

Concurrence for Blood Flow

A plateau or slight reduction in CBF near-maximal exercise in normoxia has been suggested to be due to 1) competition for blood flow between working muscles and the brain and/or 2) a plateau or decline in cardiac output (47, 90). Also, respiratory muscle work during normoxic exercise can reduce blood flow to the locomotor muscle, enhance locomotor muscle fatigue, and impair exercise performance (43, 89). By changing FIO2 and/or the work of breathing (by using pressure-assisted ventilation) during exercise, it has been demonstrated that the increased work of breathing during hypoxic exercise independently enhances locomotor muscle fatigue during cycling, probably by reducing blood flow to the legs (9). Given these results, it can be hypothesized that brain perfusion during high-intensity hypoxic exercise might be compromised by 1) competition for blood flow distribution in face of increased locomotor muscle perfusion compensating for reduced arterial oxygenation (17), and 2) the increased work of breathing potentially impairing blood flow to other regions of the body (9). In support, greater alteration in brain versus muscle oxygenation (as determined by NIRS) in hypoxia compared with normoxia was reported during rest and exercise (2, 102), leading the authors to suggest that a “steal” of blood from cerebral circulation to the muscle may occur in hypoxia. The potential competition for blood flow between the brain and other parts of the body during hypoxic exercise remains to be specifically investigated.
CONSEQUENCES OF ACUTE HYPOXIA ON MOTOR DRIVE

Voluntary Activation

Peripheral nerve stimulation. The central component of neuromuscular function can be assessed from the level of maximal voluntary activation (VA). VA is measured with peripheral nerve stimulation and the twitch interpolation technique, leading to the definition of central fatigue as an activity-induced decline in the ability to activate a muscle voluntarily (37). In normoxia, reductions in VA have been reported following isolated muscle contractions (107) and whole body exercise (65).

Goodall et al. (40) and Romer et al. (87) observed significant reductions in VA after exhaustive normoxic exercise and compared these alterations in central motor drive in hypoxic conditions. Goodall et al. (40) observed no difference in VA reduction (estimated by femoral nerve stimulation) at task failure following isometric submaximal knee extensions between normoxic and hypoxic (FIO2 = 0.10–0.16) conditions, but VA was not assessed for the same exercise duration. Romer et al. (87) measured VA before and after constant-load cycling at 92% of normoxic Wmax in normoxia and hypoxia (FIO2 = 0.13); the reduction in VA observed at exhaustion in hypoxia was only slightly greater than in normoxia for the same exercise duration (−10 vs. −5%, P = 0.11), while similar to the reduction observed at exhaustion in normoxia. In endurance athletes at sea level, preventing exercise-induced hypoxemia (SpO2 = 92% on average) by increasing FIO2 from 0.21 to 0.27 reduces locomotor muscle contractile fatigue and also postexercise reduction in VA (88), indicating that even slight hypoxemia can exacerbate exercise-induced activation deficit. These data suggest a greater impairment in the ability of the CNS to maximally activate muscles following a given fatiguing exercise performed in hypoxia compared with normoxia, potentially contributing to exercise performance impairment. This reduced central drive could be due to an effect of hypoxia on α-motoneuronal responsiveness, but α-motoneurons are relatively insensitive to hypoxia (33). It is also unlikely that the reduced VA can be attributed to alteration of the peripheral nerves since hyperexcitability has been reported in peripheral nerves (117). Reduced Hoffmann reflex responses in acute (20 min) hypoxia at rest suggested an inhibitory effect on the spinal motoneurons via descending influences (117), but this was not confirmed in another study (27) and definitive conclusions cannot be made.

The fact that all results do not confirm a greater VA reduction following hypoxic exercise may be due to limitations of this variable to detect central fatigue (37) including 1) the task specificity of VA (i.e., VA is measured during isometric MVC while whole body exercise performance involves repetitive submaximal contractions), 2) its inability to distinguish spinal and supraspinal factors, 3) the delay between the end of exercise (e.g., cycling) and the time VA is measured on a dedicated ergometer (e.g., quadriceps chair), and 4) nonlinearity of the voluntary force–VA relationship.

Cortical stimulation. Maximal voluntary activation can also be evaluated with TMS during submaximal and maximal voluntary contractions (108); i.e., providing assessment of cortical VA. During fatiguing muscle contractions in normoxia, cortical VA is reduced (108), confirming that part of neuromuscular fatigue in some normoxic conditions [e.g., during sustained submaximal isometric elbow flexion (98)] can be attributed to suboptimal drive from the motor cortex (37).

Szubski et al. (105) and Goodall et al. (40) assessed cortical VA following a fatiguing exercise in hypoxia. After a 90-s MVC of the first interosseus muscle, Szubski et al. (105) reported similar reductions in normoxia and hypoxia in the force increment evoked by TMS during MVC expressed as the percentage of the mean voluntary force immediately before the stimulation. In the study of Goodall et al. (40), short-term (10 min) hypoxic exposure at rest did not impair cortical VA. Only severe hypoxia (FiO2 = 0.10) reduced the time to task failure during intermittent isometric submaximal leg extensions compared with normoxia (from 24.7 ± 5.5 to 15.9 ± 5.4 min) and induced a distinct pattern of fatigue compared with the other conditions. Whereas quadriceps contractile fatigue at task failure was attenuated compared with normoxia, the reduction in cortical VA was greater (Fig. 4), being responsible for more than half the decrease in maximal voluntary strength. Also, a correlation (r = 0.93) for group mean values between postexercise cortical VA and cerebral oxygenation (assessed by NIRS) was observed. This study indicates that reduced cerebral oxygenation and subsequent alterations in central drive play a key role in isolated muscle exercise limitation in acute severe hypoxia [contrary to moderate hypoxia (105)].

One study (86) has evaluated the relationship between brain metabolism and cortical VA during whole body exercise in hypoxia. During intense cycling in hypoxia (FiO2 = 0.10) and low (i.e., at the same absolute workloads) and maximal intensity cycling in normoxia (FiO2 = 0.21), cortical VA of the elbow flexor muscles (i.e., a muscle group not involved in cycling) was measured with TMS. While low-intensity exercise in normoxia did not modify maximal elbow flexor strength and cortical VA, cycling in hypoxia at the same absolute power output and maximal cycling in normoxia reduced maximal elbow flexor strength and cortical VA. Since no signs of contractile fatigue of the elbow flexors in response to muscle electrical stimulation were observed in any condition, the fatigue in hypoxia and during maximal exercise in normoxia was attributed to central origin. These results suggest that

![Fig. 4. Cortical voluntary activation measured using transcranial magnetic stimulation (TMS) at baseline in normoxia (BL), after a 10-min wash-in period with the test gas (Wash-in), at the end of the fatiguing protocol (0) and up to 45 min after intermittent knee extensions to task failure performed with various inspiratory O2 fractions (from 0.10 to 0.21). Values are means ± SE. *P < 0.05, all conditions vs. BL. †P < 0.05, FiO2 = 0.10 vs. FiO2 = 0.21 (from Ref. 40).](http://ajpregu.physiology.org/)
inadequate oxygenation of the brain and subsequent perturbation of cerebral metabolism may underpin central fatigue and the reduction in VA. Concomitant measurement of brain oxygenation and metabolism and cortical VA of the muscle mass involved in a fatiguing exercise is needed to better evaluate the impact of cerebral alterations on performance.

Central Motor Command

Central motor command can be evaluated from EMG signals measured during muscle contractions. Although EMG evaluations are frequently used, important limitations should be taken into account regarding interpretations with fatigue (30). EMG responses can give an insight into central motor drive during voluntary contractions, provided this variable is normalized to the maximal M-wave, i.e., the EMG response to a single supramaximal stimulus, especially during fatigue studies (66). The reduction in $W_{\text{max}}$ during whole body exercise in hypoxia complicates the comparison between normoxic and hypoxic conditions since for a given absolute workload the relative intensity, and therefore the cardiorespiratory and muscular constraints, is higher in hypoxia. Isolated exercise protocols involving a small muscle mass have the advantage of being carried out at the same relative intensity in normoxia and hypoxia since acute hypoxia has no effect on MVC (83) and does not involve the cardiorespiratory system to a great extent (21). Table 2 summarizes studies using surface EMG signals to assess the effect of hypoxia on central motor drive during exercise and at exhaustion.

EMG responses to isolated exercise. During intermittent submaximal contractions of the knee extensors, Fulco et al. (35) and Katayama et al. (54) showed that acute hypoxia ($F_i O_2 = 464$ Torr and $F_i O_2 = 0.11$, respectively) accelerates the increase in iEMG from the beginning to the end of exercise. This increase in iEMG is interpreted as an increase in motor command to recruit additional motor units and/or to increase motoneuron discharge rate to compensate for contractile failure in active muscle fibers. Since contractile fatigue is enhanced during leg extensions in hypoxia (54), the greater increase in iEMG during submaximal contractions in hypoxia may illustrate an increased motor command compensating for the development of contractile fatigue (40). This increase in EMG during isolated submaximal contractions in hypoxia was not observed in other studies that reported similar EMG changes during sustained submaximal (55) or maximal (31) muscle contractions in hypoxia and normoxia. During sustained contractions (26, 31, 55), high intramuscular pressure causes substantial ischemia (both in normoxia and hypoxia) that may induce comparable contractile failure and therefore similar increase in EMG and central motor drive in normoxia and hypoxia (55).

To separate the central and peripheral effects of hypoxia, including the potential inhibitory effect of sensory feedback from working muscles, Millet et al. (64) induced ischemia of the exercising muscles, therefore maintaining a similar metabolic state within the working muscle independent of changes in $F_i O_2$. Subjects performed an intermittent isometric knee extension protocol (at 50% MVC) in normoxia or hypoxia ($F_i O_2 = 0.11$), with or without leg circulation occlusion (with a 250-mmHg cuff inflated proximally on the thigh). No effect of hypoxia on the rate of increase in EMG root mean square (RMS) of the knee extensors during exercise with the cuff inflated was observed. Similar stimulation of muscle afferents with leg circulation occlusion may explain this result and therefore supports a link between changes in central drive andafferent signals during hypoxic exercise. The maximum number of knee extensions with the cuff on was reduced during hypoxia compared with normoxia (8.2 $\pm$ 2.6 vs. 9.4 $\pm$ 3.1 repetitions), suggesting a specific though modest effect of CNS hypoxia on performance. In a recent study, Millet et al. (67) evaluated the effect of more severe hypoxia ($F_i O_2 = 0.09$) in a similar setting for the elbow flexors. They showed a significant, yet modest, performance reduction with circulation occlusion in severe versus moderate hypoxia and normoxia while peripheral muscle fatigue and oxygenation (NIRS) were similar in all three conditions, further demonstrating the direct cerebral effect of severe hypoxia, at least during such isolated muscle exercise.

EMG responses to whole body exercise. When comparing iEMG during cycling at the same absolute workload in normoxia and hypoxia, greater iEMG increases for the same exercise duration have been reported in hypoxia (12, 13, 106), similar to the results during leg extensions. Therefore, during submaximal whole body exercise in acute hypoxia, the CNS is able to increase motor drive above levels observed in normoxia to sustain the workload to compensate for increased levels of contractile fatigue (87). The severity of hypoxia plays a critical role regarding the ability of the CNS to increase motor drive during exercise. Amann et al. (13) showed that severe ($F_i O_2 = 0.10$), but not moderate ($F_i O_2 = 0.15$) hypoxia, the iEMG increment during intense constant-load cycling is reduced compared with normoxia, whereas hyperoxia at exhaustion prolonged exercise duration with a concomitant increase in iEMG (Fig. 5). Thus, in acute severe hypoxia, cerebral alterations due to hypoxia may precede the development of peripheral muscle fatigue [(13), Fig. 5] and lead to reduced central drive and muscle power output. Whether under such conditions (i.e., whole body exercise in severe hypoxia) impaired neuronal excitability is one of the mechanisms underlying the reduced central drive remains to be investigated.

EMG during maximal voluntary contractions. MVC can either be sustained or performed repeatedly before and after submaximal contractions to assess the development of fatigue. During MVC without fatigue, acute hypoxia has no effect on maximal EMG, in accordance with unchanged maximal voluntary strength (83). When comparing the evolution of maximal iEMG during MVC after submaximal contractions at the same absolute intensity, similar [after 3 sets of isometric leg extensions (54) and after 10 min of cycling (106)] or greater [after dynamic leg extensions to exhaustion (35)] reductions in MVC iEMG have been reported in hypoxia compared with normoxia. A greater reduction in MVC iEMG may reflect some alterations in central neural pathways, partly explaining the greater reduction in MVC observed under hypoxic conditions (35). However, as explained above, one cannot interpret changes in EMG during MVC as alterations of the central motor drive only because of amplitude cancellation (30) and potential alterations at the spinal, neuromuscular junction, or sarcocellular levels. In this context, EMG or mechanical responses to electrical and/or magnetic stimulation are needed to better understand how hypoxia affects maximal activation of motor units.

Rasmussen et al. (85) evaluated the effect of inhaling gas mixtures with $F_i O_2$ from 0.10 to 1.0 and concomitant changes in brain oxygenation on motor performance evaluated by maximum handgrip strength. Stepwise forward-regression analysis showed that the best predictor of maximal handgrip strength

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Review
Table 2. **EMG changes during exercise in hypoxic conditions compared with normoxic conditions**

<table>
<thead>
<tr>
<th>Ref</th>
<th>Hypoxic Condition</th>
<th>Exercise Modality</th>
<th>Exercise Intensity, Duration</th>
<th>EMG Changes in Hypoxia vs. Normoxia</th>
</tr>
</thead>
<tbody>
<tr>
<td>35</td>
<td>Acute hypoxia (barometric pressure = 464 Torr, ~4,300 m)</td>
<td>Dynamic 1-leg knee extension (90-150°, 1 Hz), MVCs every 2 min during the test</td>
<td>Submaximal constant load at the same absolute load (21 ± 3 W, i.e., 62 ± 3 and 79 ± 2% of 1-leg peak work rate for normoxia and hypobaria, respectively) to exhaustion</td>
<td>Greater rise in iEMG during submaximal contractions and greater fall in iEMG during MVCs at isotime; similar iEMG changes during submaximal contractions and MVC at exhaustion</td>
</tr>
<tr>
<td>54</td>
<td>Acute hypoxia (FiO2 = 0.11, ~4,700 m)</td>
<td>Intermittent (5 s on - 5 s off) isometric 1-leg knee extension, MVCs before and after each set</td>
<td>Submaximal constant load (at 62% MVC), 3 sets of 9 contractions</td>
<td>Greater rise in iEMG during submaximal contractions and similar fall in iEMG during MVCs at isotime</td>
</tr>
<tr>
<td>55</td>
<td>Acute hypoxia (FiO2 = 0.10-0.12, ~4,700 m; target ŜpO2 = 75-80%)</td>
<td>Intermittent (5 s on - 5 s off) isometric 1-leg knee extension</td>
<td>Submaximal intensity (60% MVC) to exhaustion</td>
<td>Greater rise in iEMG at isotime and at exhaustion</td>
</tr>
<tr>
<td>31</td>
<td>Acute hypoxia (FiO2 = 0.15, ~2,500 m)</td>
<td>Sustained isometric 1-leg knee extension</td>
<td>Submaximal intensity (60% MVC) to exhaustion</td>
<td>Similar rise in iEMG at isotime and at exhaustion</td>
</tr>
<tr>
<td>64</td>
<td>Acute hypoxia (FiO2 = 0.11, ~4,700 m)</td>
<td>Intermittent (10 s on; 10 s off) isometric 1-leg knee extension</td>
<td>Submaximal intensity (50% MVC) to exhaustion</td>
<td>Similar increase in RMS</td>
</tr>
<tr>
<td>56</td>
<td>Chronic hypoxia (1 mo at 5,050 m)</td>
<td>Dynamic forearm flexion (5-cm amplitude, 0.5 Hz)</td>
<td>Submaximal constant-load test (at 30% 1-RM) to exhaustion MVC for 1 min</td>
<td>Similar rise in iEMG at isotime and at exhaustion</td>
</tr>
<tr>
<td>34</td>
<td>Chronic hypoxia (43 days at 5,050 m)</td>
<td>Sustained knee or elbow extension</td>
<td>Similar reduction in RMS</td>
<td></td>
</tr>
</tbody>
</table>

**Isolated exercise**

<table>
<thead>
<tr>
<th>Ref</th>
<th>Hypoxic Condition</th>
<th>Exercise Modality</th>
<th>Exercise Intensity, Duration</th>
<th>EMG Changes in Hypoxia vs. Normoxia</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>Acute hypoxia (FiO2 = 0.15, ~2,500 m)</td>
<td>Cycling</td>
<td>Submaximal constant-load intensity (same absolute workload in normoxia and hypoxia: 52% normoxic maximal power output) for the same duration (= maximal duration in hypoxia)</td>
<td>Greater rise in iEMG at isotime</td>
</tr>
<tr>
<td>106</td>
<td>Acute hypoxia (FiO2 = 0.12, ~4,100 m)</td>
<td>Cycling, MVCs before and after</td>
<td>Submaximal constant-load intensity (same absolute workload in normoxia and hypoxia: 77% normoxic age-predicted maximal heart rate) for 10 min</td>
<td>Greater rise in iEMG at isotime, similar iEMG during MVCs before and after cycling</td>
</tr>
<tr>
<td>13</td>
<td>Acute hypoxia (FiO2 = 0.10 and 0.15, ~4,700 and ~ 2,500 m)</td>
<td>Cycling</td>
<td>Submaximal constant-load intensity (same absolute workload in normoxia and hypoxia: 81% normoxic maximal power output) to exhaustion</td>
<td>Greater rise in iEMG at isotime and smaller rise at exhaustion in severe hypoxia only</td>
</tr>
<tr>
<td>7</td>
<td>Acute hypoxia (FiO2 = 0.15, ~2,500 m)</td>
<td>Cycling</td>
<td>5-km time-trial</td>
<td>Smaller iEMG</td>
</tr>
<tr>
<td>56</td>
<td>Chronic hypoxia (1 mo at 5,050 m)</td>
<td>Cycling</td>
<td>Local maximal workload (workload hypoxia = approximately 80% workload normoxia) to exhaustion</td>
<td>Blunted rise in iEMG at isotime and at exhaustion</td>
</tr>
</tbody>
</table>

**Whole body exercise**

FiO2, inspiratory O2 fraction; MVC, maximal voluntary contraction; iEMG, integrated EMG signal; RMS: root mean square of EMG signal; NS: nonsignificant.

was cerebral oxygenation measured by NIRS. However, the impact of cerebral oxygenation on maximal motor drive remains to be confirmed since such a reduction in maximal voluntary strength is not a universal finding (83).

**Effects of Chronic Hypoxia**

Over the first hours of hypoxic exposure, minor changes in CBF have been observed (48, 74, 99), depending on hyperventilation-induced hypocapnia (74) and the level of hypoxia. With more prolonged hypoxia (several days), CBF at rest returns to values observed in normoxic conditions (48, 61, 71), probably due to the combination of changes in blood gases, cerebrovascular reactivity, and cerebrospinal fluid acid-base status with acclimatization (16, 61, 97). Compared with normoxia, increased MCAV during exercise has been reported in chronic hypoxia (51, 101), but whether this change is different from that in acute hypoxia is uncertain (48, 101). On one hand, smaller increase in CBF during exercise with chronic exposure to low PaO2 may be due to 1) improved arterial oxygenation with acclimatization making the increase in flow to preserve brain O2 supply unnecessary, and 2) greater hyperventilation-induced hypocapnia after acclimatization that may blunt the increase in CBF during exercise (49). On the
other hand, the reduction in cerebrovascular reactivity to CO₂ with acclimatization may attenuate the hypocapnic-mediated reduction in CBF (101).

Cerebral deoxygenation measured by NIRS is greater at the same absolute work load and at maximal exercise during chronic versus acute hypoxia (4,300 m), while muscle oxygenation is unchanged (101). The authors suggested that this greater cerebral deoxygenation is due to the combined effect of differences in cerebrovascular responses and elevated cerebral metabolic rates. Insufficient brain oxygenation may still contribute to performance limitation during maximal exercise despite acclimatization to high altitude since acute reoxygenation at peak exercise during chronic severe hypoxia (5,050–5,260 m) enables subjects to continue exercise and increase their maximal workloads (18, 56).

Evaluation of motor cortex excitability by TMS after 3–5 days at 4,554 m (SpO₂ ~84%) suggests a hypoexcitability of both the excitatory and inhibitory cortical circuits, with higher RMT and lower short-interval intracortical inhibition (SICI) as well as tendencies toward lower MEP and intracortical facilitation compared with normoxia (68). The severity of acute mountain sickness and SpO₂ at altitude correlated with the changes in RMT and SICI, respectively. Thus cerebral alterations associated with hypoxic exercise may show interindividual differences analogous to acute mountain sickness sensitivity, although the underlying mechanisms may differ (99).

Changes in cortical excitability observed in hypoxicemic patients with chronic respiratory insufficiency further suggest that chronic hypoxia can induce alterations in cerebral neuronal excitability (70, 76). In patients suffering from chronic obstructive pulmonary disease, motor threshold is increased (70) and MEP is unchanged (70, 76). The effect on CSP is controversial (70, 76). Moreover, motor cortex adaptations observed in chronic obstructive pulmonary disease patients were reversed by 3 mo of oxygen therapy (76), supporting that the observed cortical changes were induced by hypoxia. Since hypoxemia can alter the synaptic inhibitory γ-aminobutyric acid (GABAergic) transmission (69) that underlies intracortical inhibition and CSP (116), the cortical effect of chronic hypoxia may be associated with GABAergic dysfunction (8, 76), although other mechanisms may also be involved (73).

Similar to acute hypoxia, no significant change in MVC is observed in chronic hypoxia (83). Conversely, the increase in EMG signal during isolated submaximal contractions reported in acute hypoxia was not observed after 1 mo at 5,050 m by Kayser et al. (56), who reported similar iEMG changes during intermittent submaximal forearm exercise compared with normoxia. Esposito et al. (34) also reported similar reductions in EMG RMS during a 1-min MVC of knee or elbow extensors performed at sea level and after 43 days at 5,050 m. Changes associated with acclima-
tization [e.g., myoelectrical alterations, muscle structural and/or metabolic adaptations (22)] may explain why changes in EMG observed in acute hypoxia compared with normoxia are not observed anymore in chronic hypoxia. Conversely, during cycling exercise at sea level or at altitude $W_{\text{max}}$, Kayser et al. (56) observed a smaller rise in quadriceps iEMG in chronic hypoxia compared with normoxia both for the same exercise duration and at exhaustion. The authors suggested that central drive might be limited in hypoxia during exercise involving a large as opposed to small muscle mass and that performance limitation may be centrally mediated during this type of exercise. The difference between studies having observed greater iEMG signals in acute hypoxia (12, 13, 106) and the study by Kayser et al. (56) may arise from 1) differences in characteristics of the hypoxic stress, i.e., chronic and severe hypobaric hypoxia in Kayser’s study (1 mo at 5,050 m) vs. acute moderate normobaric hypoxia in the other experiments ($F_{\text{IO}_2} = 0.12$ or 0.15) and 2) differences in exercise intensity (local $W_{\text{max}}$ in Kayser’s study versus the same submaximal absolute workload in the other studies). To better understand the cerebral effects of chronic hypoxia, its impact on VA both in unfatigued and fatigued states remains to be investigated. Only one study in chronically hypoxic patients reported reduced VA compared with age-matched healthy controls (113).

The effect of hypoxia on the brain can also be observed in terms of anatomy. Several hours of hypoxia is able to modify brain volume by inducing edema (95), whereas several days or weeks at high altitude may be associated with changes in brain morphology, including the motor cortex (28). Whether these changes associated with chronic hypoxia lead to changes in cerebral responses to exercise is unknown.

Conclusion. Several aspects of cerebral function are impaired during hypoxic exercise compared with either normoxic exercise or hypoxia at rest, indicating that the CNS is important for exercise performance limitation in hypoxia. Impaired cerebral perfusion and/or oxygenation during hypoxic exercise can underpin reduced central drive to the locomotor muscles although the intermediate neuronal mechanisms remain to be elucidated (Fig. 6). The integration of the different cerebral alterations observed during hypoxic exercise (perfusion, oxygenation, metabolism, neuronal excitability, and electrical activity) is required and would benefit from a combination of methodologies offering complementary insights into the brain in hypoxia. Besides the direct cerebral effects of hypoxia that are believed to mostly play a major role in severe hypoxia, afferent signals from working muscles to the CNS appear to be important for reduced central drive during hypoxic exercise (Fig. 6). In addition to seeking neuronal cellular mechanisms and a more integrated view of cerebral alterations during hypoxic exercise, research should consider 1) potential interindividual differences regarding cerebral alterations associated with hypoxic exercise, analogous to the sensitivity to acute mountain sickness and 2) the interconnection of the cerebral alterations with psychomotor (e.g., decision making) and cognitive factors since they may participate to exercise performance limitation and share common cerebral mechanisms (63, 112).

Perspectives and Significance

Impairment of several aspects of the cerebral function has been demonstrated during hypoxic exercise, suggesting that the brain may be a critical factor underlying exercise performance limitation under this condition. Further studies are needed to provide a more integrated view of the impact of hypoxemia on the brain from cerebral blood flow to central motor command. This will be of value for a better understanding of exercise limitation at altitude but also relevant for exercise response in hypoxic patients.

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DISCLOSURES

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AUTHOR CONTRIBUTIONS


REFERENCES


