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Review article

Effect of acute hypoxia on cognition: A systematic review and meta-regression analysis

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ABSTRACT

A systematic meta-regression analysis of the effects of acute hypoxia on the performance of central executive and non-executive tasks, and the effects of the moderating variables, arterial partial pressure of oxygen (PaO_2) and hypobaric versus normobaric hypoxia, was undertaken. Studies were included if they were performed on healthy humans; within-subject design was used; data were reported giving the PaO_2 or that allowed the PaO_2 to be estimated (e.g. arterial oxygen saturation and/or altitude); and the duration of being in a hypoxic state prior to cognitive testing was ≤6 days. Twenty-two experiments met the criteria for inclusion and demonstrated a moderate, negative mean effect size ($g = -0.49$, 95% CI −0.64 to −0.34, $p < 0.001$). There were no significant differences between central executive and non-executive, perception/attention and short-term memory, tasks. Low (35–60 mmHg) PaO_2 was the key predictor of cognitive performance ($R^2 = 0.45$, $p < 0.001$) and this was independent of whether the exposure was in hypobaric hypoxic or normobaric hypoxic conditions.

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1. Introduction

The military, mountain rescuers, mountaineers and many other individuals, are required to work and live at high altitudes. With increasing altitude, the barometric pressure decreases exponentially, resulting in a progressive reduction in the ambient partial

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pressure of oxygen (PO_2), termed hypobaric hypoxia. For practical and logistical reasons, normobaric hypoxia is often used as a laboratory alternative to hypobaric hypoxia, whereby the inspired oxygen fraction is reduced to account for the greater barometric pressure and elicit an 'altitude-equivalent' lowering of PO_2 (Conkin, 2011). An underlying assumption with this isohypoxia approach is that PO_2 is the only relevant physiological stimulus, but there is some evidence for physiological differences elicited by hypobaric hypoxia compared to the isohypoxic, normobaric equivalent (Coppel et al., 2015; Normand and Koehle, 2012). Nevertheless, both approaches reduce the slope of the oxygen transport cascade from the atmosphere to the mitochondria, eliciting manifold physiological effects resulting primarily from a lower arterial PO_2 (P_aO_2) and reduced oxyhemoglobin saturation (Marconi and Cerretelli, 2008) The precise nature of the response to hypoxic environments is influenced by the magnitude of the stimulus: altitudes up to ~2000–2500 m are in the flat portion of the sigmoidal oxyhemoglobin dissociation curve, whereas higher altitudes are in the steep portion of the curve and require more pronounced adjustment (Lundby et al., 2008). However, broadly speaking, the initial responses to altitude exposure serve to maintain oxygen supply. Hypoxic stimulation of the carotid bodies increases alveolar ventilation, causing respiratory alkalosis (Marconi and Cerretelli, 2008), and augments sympathoadrenal activity, increasing peripheral epinephrine levels (Epi) (Mazzeo and Reeves, 2013), heart rate and cardiac output (Kahler et al., 1962); while peripheral norepinephrine (NE) levels may progressively increase over the initial six-day exposure (Mazzeo and Reeves, 2003).

Within the first hours of exposure, plasma volume also decreases, possibly due to redistribution of fluid from the extra- to intra-cellular fluid compartment (Hannon et al., 1969). Although this reduces total blood volume, red cell volume is unchanged and the oxygen carrying capacity per unit of blood is increased thus augmenting the oxygen delivery for a given cardiac output. Although, in this study, we concentrate on acute hypoxia ($\leq$6 days), we should note that with chronic hypoxic exposure (acclimatization) the plasma volume is restored and stimulation of erythopoeisis increases the number of erythrocytes (Pugh, 1964), which, in combination with an increased arterio-venous oxygen difference, enables a reduced cardiac output for a given metabolic oxygen demand (Wolfel et al., 1998). Nevertheless, with both acute and chronic hypoxia, the performance of physical work requiring high rates of aerobic metabolism is impaired, relative to the normoxic work capacity (Pugh, 1967), although this decrement may be lower with normobaric than hypobaric hypoxia (Saugy et al., 2016) and is partially attenuated with acclimation and acclimatization (Pugh, 1967).

While the effects of acute hypoxia on physical performance have been studied extensively, there is comparatively little research into the effects on cognitive skills, such as visual search and decision making. These skills typically require attention, perception, executive functioning and short-term memory (STM). Moreover, few authors have attempted to review the work and, to the best of our knowledge, nobody has sought to systematically review this area using meta-analytical methods. Recently, Taylor and colleagues (2016) completed a narrative review and demonstrated a tendency towards inhibition of cognition by acute hypoxia, however these findings were equivocal and inconclusive. In a review focusing primarily on clinical neuropsychological measures, Virués-Ortega et al. (2004) showed a tendency for acute hypoxia to induce decrements in psychophysiological measures, e.g. P300 latency and amplitude, but this was not always manifest in outcome measures, e.g. reaction time. Although the aforementioned, narrative reviews were unable to provide definitive conclusions, both groups of authors observed similar tendencies, with central executive tasks demonstrating negative effects while the non-executive, perception/attention and short-term memory (STM) tasks showed limited effects. This is in line with studies examining the effects of acute exercise (McMorris and Hale, 2012), heat (Cian et al., 2001; McMorris et al., 2006a) and sleep deprivation (McMorris et al., 2006b) on cognitive function. The findings of Taylor et al. and Virués-Ortega et al. also provide some support for lower PaO_2 resulting in greater inhibition of performance than more moderate levels of PaO_2 (readers not familiar with PaO_2 should note that lower PaO_2 means a greater negative effect of hypoxia than moderate levels of PaO_2). Observation of the studies reviewed by these authors also showed that some studies examined the effect of normobaric hypoxia while others utilized hypobaric hypoxia. Research has suggested that the two conditions may well have different effects on stress due to their differing environmental conditions (Coppel et al., 2015). To summarize the conclusions of Taylor et al. and Virués-Ortega et al., we could say that the empirical literature reviewed provided little strong evidence for a significant effect of hypoxia on cognition but the trend is for an inhibitory effect, especially at low levels of PaO_2 and mainly for central executive tasks.

Given that cognition requires oxygen activation at every stage (Virués-Ortega et al., 2004), one might expect hypoxia to have a resounding negative effect and that the failure of the narrative reviews to demonstrate this unequivocally is counterintuitive. However, animal studies have shown that when PaO_2 falls below ~60 mmHg, chemoreceptors in the carotid body sense the fall and feedback, via the glossypharyngeal nerve, to the nucleus tractus solitarii (NTS), where they activate tyrosine hydroxylase (TH)-containing catecholaminergic neurons. The NTS projects to the ventrolateral medulla (VLM) (Guyenet et al., 2013) and the paraventricular nucleus of the hypothalamus (King et al., 2013; Rinaman, 2011), regions important in the control of autonomic functions. This results in the release of the catecholamine neurotransmitters NE and Epi. Moreover, catecholaminergic neurons also project to the locus coeruleus (LC) (Abbott et al., 2012; Guyenet et al., 2013), which is the main source of NE in the brain. Release of NE has been shown to increase Ca^{2+} signaling in astrocytes, which is associated with the release of vasodilatory astroglial messengers; dilatation of brain microvessels; and, hence, increases in cerebral blood flow (CBF) (Toussay et al., 2013). Similarly, during hypoxia, feedback to the NTS from visceral afferents and carotid body arterial chemoreceptors has been shown to activate non-TH-containing neurons. These non-catecholaminergic neurons project to the rostral VLM (Guyenet et al., 2013) and, also, stimulate the brain's response to hypoxia. Moreover, adenosine, which is released from the carotid body during hypoxia, plays a role in increasing CBF by stimulating the release of nitric oxide (NO) from vascular endothelium vessels (Ray et al., 2002). NO, mediated by its second messenger cyclic guanosine monophosphate, plays a major role in vasodilation during hypoxia (Umbrello et al., 2012). These hypoxia-induced increases in CBF may account for the apparent disparity between the empirical research results reviewed by Taylor et al. (2016) and Virués-Ortega et al. and what one would expect based on the importance of oxygen during cognition and the lack of it during hypoxia. In other words, increased CBF during hypoxia compensates for lower PaO_2. However, several authors have questioned the ability of increases in hypoxia-induced CBF to ensure a sufficient supply of oxygen for proficient performance of many tasks, including cognitive functioning (Binks et al., 2008; Ogoh et al., 2013, 2014).

Examination of the results of the studies reviewed by Taylor et al. (2016) and Virués-Ortega et al. (2004) also raises questions concerning the ability of hypoxia-induced increased CBF to ensure maintenance of cognitive performance. Moreover, that many of the studies reviewed had small sample sizes leads one to question their power and it is distinctly possible that, at least, some of these