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Effect of Hypobaric Hypoxia on Cognitive Functions and Potential Therapeutic Agents

Sangu Muthuraju[1], Soumya Pati[2]

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[1] *Laboratory of Neuropsychopharmacology, FFCLRP, Universidade de São Paulo, Campus USP, Ribeirão Preto, SP 14049-901, Brazil; Instituto de Neurociencias e Comportamento, Avenida do Café, 2450, Ribeirão Preto, SP 14050-000, Brazil*

[2] *Departments of Pediatrics-Neurology and Neuroscience, Program in Developmental Biology, Program in Structural and Computational Biology and Molecular Biophysics, Baylor College of Medicine, Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital, 1250 Moursund Street, Room 1250, Houston, TX 77030, USA*

Abstract

High altitude (HA), defined as approximately 3000–5000 m, considerably alters physiological and psychological parameters within a few hours. Chronic HA-mediated hypoxia (5000 m) results in permanent neuronal damage to the human brain that persists for one year or longer, even after returning to sea level. At HA, there is a decrease in barometric pressure and a consequential reduction in the partial pressure of oxygen (PO_2), an extreme environmental condition to which humans are occasionally exposed. This condition is referred to as hypobaric hypoxia (HBH), which represents the most unfavourable characteristics of HA. HBH causes the disruption of oxygen availability to tissue. However, no review article has explored the impact of HBH on cognitive functions or the potential therapeutic agents for HBH. Therefore, the present review aimed to describe the impact of HBH on both physiological and cognitive functions, specifically learning and memory. Finally, the potential therapeutic agents for the treatment of HBH-induced cognitive impairment are discussed.

Keywords: *high altitude, hypoxia, therapeutics*

Introduction

High altitude (HA)

Exposure to HA, or approximately 3000–5000 m, considerably alters physiological and psychological parameters within a few hours (1,2). At HA, individuals are commonly confronted with disorders such as acute mountain sickness (AMS) (3), HA pulmonary oedema (HAPE) (4), and HA cerebral oedema (HACE)(5). The learning and memory deficits induced by HA exposure draw special concern because these deficits incapacitate or compromise an individual's performance of highly demanding mental functions. Prolonged exposure of human volunteers to HA decreased their verbal working memory (6). At HA, there is a decrease in barometric pressure and a consequential reduction in the partial pressure of oxygen (PO_2), an extreme environmental condition to which humans are occasionally exposed (7). This state in which the partial pressure of oxygen is reduced is termed hypobaric hypoxia (HBH), which reflects the most unfavourable characteristics of HA. HBH causes an imbalance of oxygen availability to tissue, causing severe physiological and psychological dysfunction in humans and other animals. Here, we summarise some of the experimental data concerning the effect of HBH on physiological functions.

Hypobaric hypoxia (HBH)

HBH exposure leads to severe abnormalities in physiological and psychological functions. Exposure to HBH is known to cause sleep disturbances (8), hypophagia (9), oxidative stress (10), and alterations of acetylcholine neurotransmitter (11). Chronic exposure to HBH for 31 days via gradual decompression in a hypobaric chamber from sea level to the altitude equivalent of 8848 m resulted in significant changes in mood (12). Exposure to HBH ranging between 4 200 and 4700 m for a duration from a few hours to almost one month significantly affected mood and cognitive performance in an elevation-dependent manner. The severity of these effects dramatically increases at 4700 m altitude (13) due to an imbalance in physiological activities, resulting in impaired cognitive functions, specifically learning

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and memory functions. The negative effects of HBH on cognitive functions depend on the duration of exposure and the altitude. However, before describing the effects of HBH on cognitive functions, it is essential to describe in the context of learning and memory.

Cognitive Functions

Cognitive functions comprise learning and memory functions. Learning is defined as the acquisition of knowledge via experience or study. Memory is defined as the process by which individuals retain newly acquired information over time. The formation of a memory "engram", a representation of memory in the brain, involves time-dependent consolidation (14). Based on the period in which information can be sustained, memory is categorised into three fundamental types or stages: sensory, short-term and long-term memory (15). The incoming information is initially and very briefly maintained in sensory storage, either as visual sensory memory (iconic memory) or auditory sensory memory (echoic memory). Most of the information in sensory memory is lost within a fraction of second, thus enabling only a small portion of this information to be transmitted to short-term memory storage. The processing of incoming sensory information occurs in the cortical areas that are responsible for the initial perception of sensory stimuli, i.e., in the primary auditory and visual cortices (Figure 1) (16).

The second stage, short-term memory, is responsible for the acquisition and conscious processing of information to be subsequently transmitted to long-term memory storage or forgotten (15). The period for which short-term memory is responsible for maintaining information is elastic, varying from seconds to 10–20 minutes, depending on the type of information and the task used to assess memory. The third stage of memory, long-term memory, is considered persistent memory (16). The maintenance of long-term memory depends on synaptic plasticity. Long-term memories can be disturbed under stress or disease conditions. Particularly, HBH strongly disturbs memory in altitude-dependent manner. At present, few mechanisms underlying the HBH-mediated deficits in learning and memory function have been identified.

Effects of HBH on Cognitive Functions

Hypobaric hypoxia (HBH) at HA is known to disrupt cognitive functions in humans (13). Cognitive functions, such as learning and memory, are adversely affected by exposure to HBH (11). Short-term memory decreased following exposure of human volunteers to acute, mild or moderate hypoxia for 1 h at 4 400 m, and these effects were exacerbated at increasing altitudes (17). Studies of mountaineers and volunteers subjected to simulated HBH have suggested that impairments in psychomotor function and visual reaction time were associated with HA hypoxia (18). Titus et al., 2007 suggested that hippocampal dendrite atrophy following exposure to HBH could represent a potential mechanism underlying these cognitive deficits (19). Exposure to acute HBH induced cognitive deficits, along with oxidative stress (20). At the behavioural level, postnatal exposure to HA hypoxia at 7000 m for 19 days impaired spatial memory (21).

Further, Barhwal et al., 2007 (22), and 2009

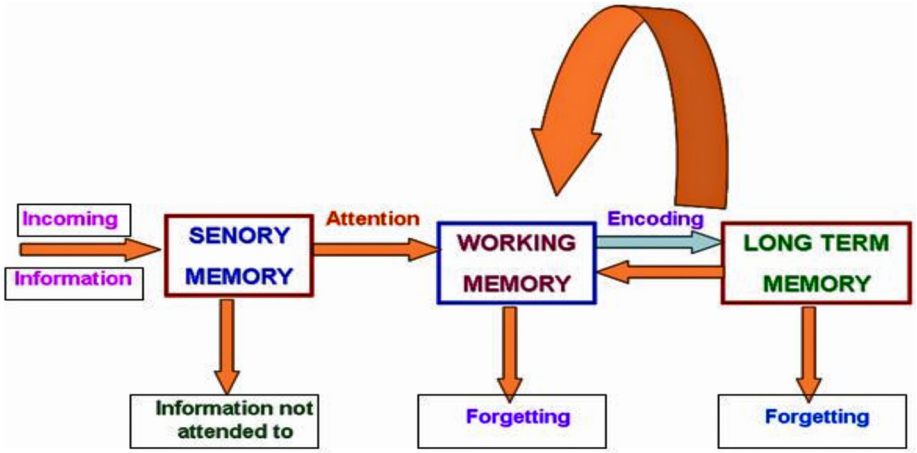


Figure 1: Schematic diagram of the types of memory.

(23), reported that 3 and 14 days after exposure to HBH impaired working and reference memory, respectively, via increased oxidative stress and apoptotic cell death. In another study, Barhwal et al. 2009 (24), identified the role of the L-type calcium channel in spatial memory impairment induced by exposure to HBH for 3 or 7 days. In addition, learning ability and memory retrieval were both impaired at 25 000 ft (25). Maiti et al. 2008 (26), and 2008 (27), suggested that spatial memory was impaired after 3 or 7 days of exposure to HBH, which was associated with neuronal damage. Rats exhibited significant deficits in spatial working memory following exposure to HBH for 3 days (28). Hota et al. 2008 (29), demonstrated that memory retrieval was delayed after exposure to HBH for 14 days due to glutamate-mediated neuronal excitotoxicity. Also, Baitharu et al. 2012 (30), and 2013 (31), found that corticosterone and glucocorticoid may serve as factors that cause memory impairment after exposure to HBH at 25000 ft for 7 days. Several lines of evidence reported the effect of HBH on cholinergic system. Muthuraju et al. 2009 (32), reported that the effects of exposure to HBH for 7 days on relearning and memory retrieval depend on the impairment of cholinergic systems. In another study, Muthuraju et al. 2010 (33), examined learning ability after exposure to HBH and revealed impairment in learning ability and an increased level of acetylcholinesterase activity. Further more, the alteration of acetylcholine synthesis following HBH exposure causes impairments in memory ability and memory consolidation (11,34). Other studie that targets to evaluate role of HBH on hippocampal neurons. Hippocampal neurodegeneration leads to cognitive impairment following exposure to HBH (35). Based on the available evidences, we conclude that the HBH-mediated learning and memory impairments, could be involvement of oxidative stress, alter in acetylcholine system, glutamate-mediated excitotoxicity, and corticosterone imbalance. Among these studies, some investigators evaluated the ability of potential therapeutic agents to ameliorate HBH-induced learning and memory impairments.

Potential Therapeutic Agents

It has been clearly demonstrated that HBH causes learning and memory impairments. However, few studies have identified therapeutic agents that improve cognitive functions under HBH conditions. The factors that are involved in the HBH-mediated learning and memory impairments may include neuronal damage, oxidative stress and neurotransmitter alterations. Jayalakshmi et al. 2007 (28), reported that N-acetyl cysteine (NAC) administration during HBH exposure ameliorated the hypoxia-induced impairments in spatial working memory function. In addition, NAC supplementation decreased oxidative stress, increased the antioxidant status, and reduced free radical production during HBH. Other study suggests that acetyl-L-carnitine supplementation improved the spatial working memory deficits of rats chronically exposed to HBH (24). Additionally, Barhwal et al. 2009 (23) suggested that L-type calcium channels and glutamate receptors play an important role in learning and memory functions during HBH. They reported that isradipine, an L-type calcium channel blocker, may serve as a useful therapeutic agent to improve spatial memory during HBH. Further more, bacosides ameliorated the memory impairment induced by exposure to HBH (25). Also, bacosides upregulated NCAM, enhanced cytochrome c oxidase activity, and improved memory during HBH. Hota et al. 2008 (29), concluded that ceftriaxone ameliorated HBH-induced cognitive impairment. Alternatively, Baitharu et al. 2012 (30,31), suggested that corticosterone plays a role in learning and memory functions during HBH. They reported that the administration of the corticosterone synthesis inhibitor metyrapone and Withania somnifera root extract improved cognitive functions during HBH. Besides, Muthuraju et al. 2009, 2010, and 2011 reported that physostigmine and galantamine ameliorated the increase in the level of acetylcholinesterase during and after HBH exposure and enhanced cholinergic system function. This facilitation of the cholinergic system may help to improve learning and memory during HBH. Prasad et al. 2013, reported that Quercetin reverses cognitive impairment by reducing the level of oxidative stress. Furthermore, Vishal et al. 2012 (36), found that an enriched environment prevented HBH-induced memory impairment. Based on these studies, the aforementioned therapeutic agents may ameliorate HBH-induced cognitive impairment.

Conclusion

The current review has collectively considered the importance of several important factors associated with the effect of HBH on cognitive functions and the potential therapeutic agents. Recently, the disruption of cognitive functions associated with HBH has been considered a

serious mental health issue. The experiments and findings that have associated HBH with learning and memory deficits should be of great interest to researchers, particularly with respect to the future development of interventions. Additionally, this review of the literature emphasises the importance of considering the direct impacts of HBH on cognitive function. Accumulating experimental evidence implicates oxidative stress, the cholinergic system dysfunction, and alterations in the glutamate and corticosterone levels in the effects of HBH. Animal data confirm that the aforementioned therapeutic agents ameliorate oxidative stress and modulate the neurotransmitter and corticosterone levels. In the future, further investigations must confirm these changes during HBH and must determine the efficacy of these therapeutic agents against HBH-mediated abnormalities.

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Conflict of Interest

None.

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Authors' Contributions

Conception and design, drafting of the article, collection and assembly of data: SM, SP

Correspondence

Dr Sangu Muthuraju
PhD (Bharathiar University)
Laboratory of Neuropsychopharmacology
FFCLRP, Universidade de São Paulo
Campus USP, Ribeirão Preto, SP 14049-901
Brazil
Tel: +5516-3602 3788
Email: muthuraju67@gmail.com

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