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Advances in Research on The Effects of Hypoxia on Cognitive Abilities of People Living Permanently on The Plateau

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Abstract

Cognitive ability refers to an individual's ability to acquire information, store it and process it, and a decline in cognitive function can be influenced by several factors. The high altitude environment is most notably characterized by low oxygen, and with approximately 140 million people living at high altitude worldwide, chronic hypoxia is thought to be a factor affecting cognitive function. Studies on the effects of short-term exposure to high altitude on cognitive function in migrant populations are a current hot topic, but there are fewer studies on the changes in cognitive function in highland resident populations due to chronic low-pressure hypoxic environments. In addition, the results of existing studies are susceptible to inconsistent results depending on the duration of residence, altitude, ethnic composition, cognitive measures, and other factors, which are reviewed in this paper.

Keywords

High altitude; Cognition; Hypoxia.

1. CHARACTERISTICS OF THE EFFECTS OF LONG-TERM PLATEAU HYPOXIA ON COGNITIVE FUNCTION

1.1. Effects of prolonged plateau hypoxia on executive function

Executive function is an important higher cognitive function that integrates different cognitive processes in the course of an individual's behavior, mainly consisting of three elements: working memory, cognitive flexibility, and inhibitory control. Numerous studies have shown that chronic hypoxia on the plateau hurts executive functioning in people who live on the plateau for long periods [1]. A study conducted in Tibet using the Wechsler Intelligence Scale with a total of 45 high school students in Jiuji and Lhasa showed that the high altitude group had significantly lower working memory scores compared to the low altitude Beijing group [2]. The results of another study using the n-back test combined with event-related potentials on university students who had moved to Tibet for three years showed that their spatial working memory was impaired compared to those who had never been to high altitude before [3]. In contrast, Ma Hailin et al. combined n-back testing with EEG analysis on a Tibetan heritage-dwelling population at different altitudes to show that long-term high altitude exposure only negatively affected the spatial working memory abilities of heritage-dwelling respondents at an altitude of 4,200 m. This study suggested that an altitude of around 4,000 m may be a threshold for spatial working memory impairment in Tibetans [4]. Cognitive flexibility is the ability of an individual to freely change cognition in response to different stimuli or environmental changes [5], and a study by Rimoldi et al. showed that cognitive flexibility was significantly reduced in students who lived at high altitude for long periods compared to the low altitude group [6].

ISSN: 2472-3703 DOI: 10.6911/WSRJ.202307_9(7).0027

Inhibitory control is responsible for the ability to exclude or reduce the interference of irrelevant information with the information currently to be processed and thus adapt to changing situations, and refers to an extra-linguistic inhibitory control network [7]. ViruĂŠs study of European children and adolescents aged 11 to 17 years using the Attention Network Test found that the long-term high-altitude exposure group performed significantly worse in inhibitory control than the short-term exposure group and the lowland altitude group [8]. The neurobiological mechanisms associated with chronic hypoxia-induced impairment of executive function have not yet been fully elucidated. A study conducted in Tibet on a migrant population found that subjects had reduced shell nucleus grey matter volume and reduced regional homogeneity, which may be associated with reduced executive function [9].

1.2. The effect of long-term plateau hypoxia on attention

Attention is a response to an objective stimulus, which is the direction and concentration of a person's mental activity on something in the outside world, and is a prerequisite for acquiring knowledge, mastering skills and performing operations, and is the basis for information processing and other mental activities [10]. Most current research classifies attention according to its function: attentional alertness, attentional concentration, attentional allocation, and attentional orientation. The alerting network, the orienting network and the executive network. Dans et al. showed that subjects in high altitude counties scored lower on the digital breadth test than those in the low altitude group, in other words, people living at high altitude in a low oxygen environment (3,700m above sea level) had significantly lower attention spans compared to those living at low altitude [11]. In contrast, a study conducted by Zhang et al. using the SDMT test showed no significant difference in attention between those in the low altitude group (1,700m above sea level) and those in the high altitude group (4,300 above sea level). So whether the effect of altitude on attention is due to differences between the populations investigated or whether it is due to inadequate measurement tools needs to be further investigated.

1.3. Effects of prolonged plateau hypoxia on memory

Memory is the consolidation and reproduction in the human mind of objects and phenomena that have been perceived in the past. Memory is of great importance in the intellectual development of children. If there is no memory, then what the child has observed cannot be traced in the brain and intelligence cannot be developed. a study by Rimoldi et al. showed that long-term residence at high altitude affects the visual-spatial memory capacity of children and adolescents and that it is more impaired than in the acutely exposed group [6]. And ViruĂŠs et al. found that digital short-term memory was impaired in the high-altitude group. Impairment of memory function is a major aspect of hypoxia-induced cognitive impairment, and chronic hypoxic exposure is currently thought to primarily impair memory storage and retrieval functions [12].

1.4. Effects of prolonged plateau hypoxia on fluid intelligence

Fluid intelligence refers to the ability to solve problems without relying on previous knowledge and experience when solving novel, abstract problems. Fluid intelligence not only underpins the acquisition of other cognitive abilities but also plays a key role in the way we solve everyday work and life problems to adapt to new environments [13]. Another study on the Tibetan Plateau also showed lower fluid intelligence scores in adolescents at a higher altitude of 4300m compared to the 2800m altitude group [14]. The two studies were conducted with different populations and used different tests, the former using Raven's test and the latter using the standard Raven’s Progressive Matrices Test, and the two studies involved different altitudes, so the reasons for this need further investigation.

ISSN: 2472-3703 DOI: 10.6911/WSRJ.202307_9(7).0027

1.5. Effects of prolonged plateau hypoxia on processing speed

Processing speed characterizes how fast or slow individuals can perform different cognitive operations. The impairment of processing speed by prolonged residence at high altitudes has been shown in studies by Rimoldi and Hill et al [6, 15]. Hogan et al. also showed impairment of processing speed by prolonged residence at high altitudes [16]. Zhu et al. found that the processing speed of Tibetan adolescents in the high-altitude group was significantly lower than that of Han adolescents at ground altitude [2]. From the results of the current study, there is more uniformity in the findings that long-term altitude hypoxia can impair processing speed.

1.6. The effect of prolonged plateau hypoxia on language comprehension and expression

Language is the medium through which information is transmitted and is the most important tool for communication. Childhood is a critical period for language development. Zhu Xiaohan et al. found that the comprehension index of Tibetan adolescents in the high altitude group was lower than that of Han adolescents at ground altitude [2]. A study by Yaqing Zhang showed that Tibetan adults at an altitude of 4300m had lower verbal fluency compared to Tibetan populations at lower altitudes [17]. Davis [18] et al. similarly found that Ecuadorians living at high altitudes had a higher level of verbal fluency or were affected by chronic hypoxia at high altitudes. Thus, both language comprehension and language fluency may be affected by high altitude hypoxia.

1.7. Prolonged high altitude hypoxia and dementia

Alzheimer's disease (AD), vascular dementia(VaD), mixed dementia, and other dementias [19] are manifestations of brain dysfunction in the elderly. Studies on the pathogenesis of AD have not been well studied, and chronic hypoxia is a risk factor for AD [20]. A study by Yuan Bin [21] et al. found that the prevalence of AD was significantly higher in plateau areas than in plain controls. The occurrence of chronic hypoxia-induced AD may be related to the damage to brain cells caused by oxidative stress due to chronic hypoxia. And as the plateau is a stable hypoxic environment, the study of AD in plateau areas may be important for the discovery of the etiology and mechanism of dementia.

2. MECHANISMS OF THE EFFECTS OF CHRONIC PLATEAU HYPOXIA ON COGNITIVE FUNCTION

In summary, chronic hypoxia at high altitudes has a negative effect on the cognitive function of people who have lived on the plateau for a long time. There is no definite conclusion as to the mechanism, and the mechanism may be as follows.

2.1. Damage to brain structures

Low-pressure hypoxia in the plateau leads to reduced synaptic plasticity, degradation of neuronal chromatin, neuronal apoptosis, and a decrease in the number of neurons, resulting in structural changes in the brain [22]. Acute hypoxia can lead to reduced synaptic plasticity and death of specific neurons through various mechanisms such as oxygen radical toxicity, mitochondrial dysfunction, disruption of calcium homeostasis, and increased glutamate release, thus causing cognitive impairment [23]. In addition, experimental animal studies have found that exposure to 6000 m altitude induces the cortical autophagy effector protein Beclin-1, hypoxia-inducible factor In addition, animal studies found that exposure to 6000 m altitude induced an increase the expression of the cortical autophagy effector protein Beclin-1, hypoxia-inducible factor-1α (HIF-1α), and microtubule-associated protein 1 light chain 3-II, and a significant increase in autophagy and apoptosis of cortical neurons, resulting in extensive neurological damage in experimental mice [24]. permanent damage. Neuronal damage affects the processes of synthesis, uptake, and release of central neurotransmitters, thereby affecting

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the transmission of excitatory neurotransmitters between neurons, affecting synaptic plasticity and ultimately causing memory and cognitive dysfunction [26]. Prolonged hypoxia in the plateau can also keep the already highly oxygen-depleted brain tissue in a constant state of hypoxia, and neuronal damage induced by oxidative stress generated by chronic hypoxia may be the cause of cognitive impairment due to chronic hypoxic exposure [27]. In addition, chronic hypoxia induces increased HIF-1α activity and activates cAMP response element binding protein (CREB), a transcription factor mainly involved in the regulation of learning processes and neuronal plasticity, which inhibits the activity of brain-derived neurotrophic factor (CAMP) [28]. The expression of brain-derived neurotrophic factor (BDNF) is inhibited by CREB, a transcription factor mainly involved in the regulation of learning processes and neuronal plasticity, which ultimately leads to neuronal damage by these mechanisms [29], and may be related to cognitive impairment in hypoxia at the plateau.

2.2. Sleep disorders

Sleep is a self-protective mechanism in the human body and is a physiological process necessary for survival [30]. There is a correlation between sleep and cognitive function, and many studies have shown that sleep disorders can lead to a decline in different cognitive functions [31-33]. Hypoxia is likely to be the main cause of sleep disturbance at altitude [34], as hypoxia-induced impairment of cerebral blood circulation leads to impairment of cerebral energy metabolism, which further affects the excitatory or inhibitory transmission of neurons in the brain, thus interfering with neural activity and leading to sleep disturbance [35]. Decreased sleep quality and disturbed sleep structure are often seen in those who enter the plateau acutely [36-39]. In contrast, studies conducted among officers and soldiers of troops stationed on plateaus have shown that sleep quality remains a problem after more than six months on the plateau [40]. Studies on the effects of sleep in a highland-dwelling population have shown that sleep disorders are common among elderly nursing home residents at high altitudes [41]. Sleep disorders can cause disturbances in the hypothalamus-pituitary-adrenal gland, which affects the functioning of neurotrophic factors in the brain and is thought to be a possible cause of cognitive impairment [42]. Sleep disorders also cause a decrease in blood flow to the prefrontal cortex, which impairs cognitive function by affecting the prefrontal cortex [43], so that hypoxic cerebral blood flow disorders in the plateau cause sleep disorders that further lead to altered cerebral blood flow, creating a vicious cycle that affects cognition.

2.3. Altering cerebral blood flow affects cerebral metabolism

The weight of the brain accounts for only 2% of body weight, but cerebral blood flow can account for 15%-20% of systemic blood flow, oxygen consumption accounts for 20%-25% of the body, and energy consumption accounts for about 25% of the body. The stability of cerebral blood flow is directly related to the normal functioning of the central nervous system [44]. Acute low-pressure hypoxia may alter the cerebral hemodynamics of the body, causing increased cerebral blood flow and cerebral arterial vasodilation [45, 46]. M Pagani et al. found that after 40 minutes of acute low-pressure hypoxia experiments, a significant increase in posterior cerebral arterial blood flow was observed, suggesting that the body may compensate for the priority of maintaining cerebral blood flow and blood oxygen supply after entering a low-pressure hypoxic environment [45]. However, when the body loses its compensatory capacity for cerebrovascular response, cerebral blood volume increases, intracranial pressure rises, and the blood-brain barrier is disrupted, leading to brain damage in severe cases [47], which in turn results in cognitive impairment. Despite prolonged hypoxic compensation, cerebral blood flow is reduced by hypoxia due to high blood viscosity and blood concentration, increased cerebrovascular resistance to blood, and slow blood flow in sedentary inhabitants. The results of a study conducted in Bolivia showed that the cerebral blood flow velocity in the main arteries of the brain was significantly lower in the high-altitude group compared to the plains [48],

ISSN: 2472-3703 DOI: 10.6911/WSRJ.202307_9(7).0027

especially in the basilar artery [16]. Jiang Dong et al. found that cerebral blood flow in the normal population at high altitude was significantly different from that in the normal population on the plains, with lower and higher blood flow velocities in all age groups and lower velocities in the normal population at high altitude compared to the plains, as well as reduced compliance, reduced elasticity and increased peripheral resistance of the cerebral arteries in the normal population at high altitude compared to the plains [49]. In addition, studies conducted on the Tibetan plateau have shown a higher incidence of ischaemic cerebrovascular disease than on the plains [50]. This suggests that the Tibetan population also suffers from alterations in cerebral blood flow due to plateau hypoxia.

The relative lack of cerebral blood flow perfusion may affect the metabolic processes associated with two of the brain's most important nutrients, namely oxygen, and nutrients. Mitochondria are the hub of cellular energy metabolism in the brain, and 95% of the brain's energy is produced by mitochondria with the involvement of oxygen. Previous studies have found that imbalance in mitochondrial homeostasis in the hippocampus is crucial in cognitive dysfunction [51], and hypoxia causes swelling of mitochondria, disruption of mitochondrial membrane structure, and vacuolization of the mitochondrial interior, resulting in an imbalance in mitochondrial homeostasis, which may underlie the pathology of cognitive dysfunction due to hypoxia. In addition, insufficient cerebral blood perfusion leads to inadequate glucose supply ultimately resulting in reduced glucose utilization [52] and impaired amino acid and energy metabolism in brain cells, which may be the metabolic basis for the reduced cognitive function due to hypoxia [53].

2.4. Epigenetic mechanisms

Human cognitive function is shaped by the interaction of genetic and environmental factors. While human genes, as genetic material, are unlikely to change in a relatively short period in response to environmental changes, gene expression can change through epigenetic regulation. Epigenetic inheritance refers to the regulation of gene expression through "acquired" modifications such as DNA methylation, histone modifications, and RNA interference, without changes in DNA sequence, resulting in heritable changes in gene expression [54]. Epigenetic modifications have profound effects on human health and disease, including phosphorylation, guanylate, ubiquitination, carbonylation, proline isomerization, ADP ribosylation, succinylation, crotonylation and malonylation [55-58], and more than 100 different histone modifications have been identified to date [59]. An increasing number of studies have found that epigenetic mechanisms regulate brain function, and epigenetic modifications have been shown to play an important role in many neuronal functions, from synaptic plasticity to learning and memory [60-62], with histone acetylation modifications being strongly associated with altered cognitive function [63]. Chromatin is the close link between genomic DNA and histones, the physiological form of our genome, and the substrate that regulates the process of cellular gene expression. The basic repetitive unit of chromatin is the nucleosome, which consists of approximately 147 bp of superhelical DNA wrapped around the octameric surface of a highly conserved core histone (two copies each of H2A, H2B, H3, and H4). Histone acetylation, as one of the acetylation modifications, is important for the epistatic transcriptional regulation of genes and is regulated by both histone acetyltransferases (HATs) and histone deacetylases (HDACs) to maintain a relatively stable state. (for lysine acetyltransferase) [64]. It is thought that KAT acetylates lysine residues at the N-terminal end of histones, leading to DNA unwinding and relaxation of chromatin structure, thereby activating transcription and promoting gene expression; HDACs cause chromatin sequestration, inhibit transcription, and down-regulate gene expression. Since 2004, when Levenson and his team first linked the regulation of H3 and H4 acetylation to cognitive processes such as learning and memory [65], studies relating histone acetylation levels to cognitive function have continued to emerge, and it is now believed that the

ISSN: 2472-3703 DOI: 10.6911/WSRJ.202307_9(7).0027

relationship between histone acetylation levels and changes in cognitive function is manifested by the fact that histone acetylation can regulate the expression of synapse-associated proteins to alter synaptic plasticity The relationship between histone acetylation levels and changes in cognitive function has been suggested to be that histone acetylation can regulate the expression of synapse-associated proteins to alter synaptic plasticity [66], that neural activity affects cognitive function by influencing the expression of genes that regulate histone acetylation [67], and that KAT affects cognitive and memory function by regulating the acetylation of non-histone proteins and thereby enhancing the expression of other related genes [68].

3. HABITUATION TO HIGH ALTITUDE HYPOXIC ENVIRONMENTS

Regarding studies on the effects of high altitude on cognitive function, one study in Bolivia showed that adaptation to high-altitude environments appears to be independent of ethnicity, but only related to a history of high-altitude residence [16]. Gerard F A Jansen et al. showed that adaptation to high altitude environments in highland-dwelling populations involves different mechanisms, with higher blood flow to the brain in Himalayan-dwelling Tibetan populations[69] and Ji Chen et al. showed that, in addition to adaptation to the plateau environment in plateau-dwelling populations, long-term residents of plateau migrations can also compensate for the effects of prolonged high altitude hypoxia on visual function by affecting hemispheric functional connectivity [70]. et al. showed that brain tissue oxygenation was higher in Tibetans than in Han Chinese during normal exercise, while muscle tissue oxygenation was lower during hypoxic exercise to protect brain function [71]. Although, for adaptation to the plateau environment, different studies from different regions have had different results, however, the current consensus is that the Tibetan population is the most adapted to the plateau environment, therefore studying the impairment and adaptation of cognitive function in the Tibetan population in the plateau environment could potentially provide a viable solution for human research on cognitive impairment disorders caused by chronic hypoxia.

4. HOW TO PREVENT

The impairment of cognitive function in the hypoxic environment of the plateau is due to the inevitable hypoxia caused by low air pressure. And many studies have shown that the effects of altitude on cognitive function are reversible [15]. One option, therefore, is to move teaching to lower altitudes, which may be feasible in some parts of the world. For example, in the Andes of South America, these regions may also have a large difference in altitude even when they are very close together, while others are not applicable, such as the Tibetan Plateau where the overall altitude is high. For those who cannot take these approaches, the oxygen concentration in the room can be increased by oxygen enrichment techniques, which are currently being tested in some areas.

5. LIMITATIONS OF CURRENT RESEARCH

Most of the above studies suggest that the hypoxic environment of the plateau can cause cognitive impairment, however, some studies show that long-term residence at high altitude does not negatively affect the cognitive function of Bolivian-deprived children. A study conducted in Jiuji, Tibet, and Beijing showed that cognitive performance as measured by the Wechsler Intelligence Scale was less related to altitude than to socioeconomic status. Therefore, there is an urgent need for a uniform and scientific measurement tool for large samples to standardize the current findings. In addition, animal experiments have been conducted mainly on white rats, which have a short lifespan and add to the difficulty of experimental studies on chronic hypoxia in the highlands. Due to the current development of brain science, it is still unclear how the effects of chronic hypoxia on cognition in plateau-dwelling populations play a

ISSN: 2472-3703 DOI: 10.6911/WSRJ.202307_9(7).0027

role, and the effects of hypoxia on brain metabolism and brain structure will remain a popular direction for future research. It is believed that with the continuous improvement of experimental tools and techniques, the relationship between a hypoxic environment and cognitive impairment and the related mechanisms will be further elucidated, thus providing new methods and ideas for the prevention and treatment of hypoxic cognitive impairment.

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