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Research progress on reducing cognitive impairment under high-altitude hypoxia conditions by improving sleep awakening cycle through nasal insulin pretreatment

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Abstract: *The special geographical environment and climate characteristics of the plateau can have many impacts on human physiology and psychology, and in severe cases, it can also endanger life and health. Previous studies have shown that as altitude increases, problems such as sleep disorders, changes in brain function, and anxiety continue to emerge among officers and soldiers stationed at high altitudes. Among them, sleep disorders and cognitive impairment are two particularly prominent issues, which have received much attention from military occupational medicine. Cognitive impairment (CI) often coexists with sleep disorders and is highly destructive, directly affecting the combat effectiveness of the military. Therefore, prevention and treatment measures can be sought to improve sleep disorders and cognitive impairment caused by altitude hypoxia through intervention. Existing research has clearly shown that enhancing the insulin effect of the central nervous system can improve learning and memory functions in both animals and humans, especially hippocampus dependent (declarative) memory. After intranasal administration of insulin, it can bypass the blood-brain barrier, pass through the extracellular nerve gap of the trigeminal nerve and the olfactory nerve pathway, and quickly reach the central nervous system through paracellular transport and endocytosis, increasing the central insulin concentration distributed in the space around cerebral blood vessels. It inhibits the secretion of the hypothalamic pituitary adrenal axis by acting on the hypothalamic nucleus and marginal structures (such as the hippocampus) that can express a large number of insulin receptors, improving sleep cycle disorders and cognitive impairment. This article will provide a review of nasal insulin, sleep awakening cycle, and cognitive impairment.*

Keywords: *cognitive impairment, high-altitude, hypoxia, sleep awakening cycle, nasal insulin*

1. Introduction

The plateau region covers a wide area in China and holds an important economic and military strategic position. Every year, a large number of soldiers rush to the plateau. The plateau region has special geographical and climatic conditions, such as low pressure, low oxygen, high cold, dryness, large temperature difference between day and night, and strong solar radiation [1]. As one of the organs with the highest oxygen consumption in the human body, the brain is highly susceptible to hypoxia damage [2]. When military officers and soldiers enter plateau areas from plain areas, as the altitude increases, the oxygen content in the air gradually decreases, which can lead to insufficient oxygen intake by the body and a decrease in tissue oxygen supply, resulting in varying degrees of damage to brain tissue, affecting the process of brain information processing, and ultimately leading to damage to human body function and cognitive function [3]. However, there is currently no effective prevention and control measures for this phenomenon, which is an urgent problem that needs to be solved. At present, insulin delivery to the brain has become an important treatment for cognitive disorders related to abnormal brain energy metabolism [4]. Research has shown that enhancing the insulin effect of the central nervous system can improve learning and memory functions in both animals and humans, especially hippocampus dependent (declarative) memory [5]. The study of insulin in the brain relies on its intranasal application, as intranasal

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delivery of insulin can bypass the blood-brain barrier and quickly reach the central nervous system, rarely reaching the peripheral circulation and not causing peripheral hypoglycemia [6-7]. Therefore, nasal administration of insulin can increase insulin levels in the brain, which may have a protective effect on cognitive impairment under high-altitude hypoxia conditions.

2. Overview of cognitive impairment at high altitude

Cognitive function refers to various spiritual activities that humans always exist in an awakened state, are controlled by self-awareness. These activities are both simple and complex, such as sensory perception, audiovisual perception, attention, etc., while complex activities include understanding, judgment, reasoning, abstract generalization, complex calculations, etc.[8]. The plateau region of China is vast, with an average altitude of over 4000m. There are unfavorable factors such as low pressure, low oxygen, high altitude, and strong radiation, and individuals need special protection to cope. Moreover, these special environments are often closed and relatively isolated from the outside society. All of these factors may have an impact on individuals' cognitive function. Soldiers shoulder the heavy responsibility of safeguarding their country and need to be stationed at high altitudes to carry out various tasks. Basic cognitive functions such as reaction speed and accuracy, memory, and attention are the foundation for them to complete various complex cognitive tasks. Any impairment of cognitive function may bring serious consequences to themselves and the collective [9]. Cognitive impairment is mainly divided into two types, one is mild cognitive impairment between normal aging and mild dementia, and the other is vascular cognitive impairment with risk factors for cerebrovascular disease or cerebrovascular disease [10]. However, officers and soldiers stationed in high-altitude training generally have mild cognitive impairment, mainly manifested as decreased attention span and attention transfer ability, poor short-term memory, complex thinking judgment and delayed thinking flexibility, which affects physical and mental efficacy[11]. At present, most studies on brain cognitive impairment caused by rapid altitude entry use animal models, evaluated through behavioral and pathophysiological experiments. Zhong Z et al. found that long-term living in high-altitude areas can significantly impair cognitive function, and the levels of neurotransmitters and cognitive abilities may change during long-term high-altitude exposure, with a causal relationship. After chronic hypobaric hypoxia exposure in rats, there is a correlation between the levels of neurotransmitters dopamine, serotonin, 5-HIAA, and glutamate in the peripheral plasma and brain neurotransmitter levels. Ji W et al.[13] determined the role of N-methyl-d-aspartate (NMDA) receptor mediated excitatory toxicity in neuronal damage and cognitive impairment caused by chronic hypobaric hypoxia exposure by feeding Sprague-Dawley rats at three different altitudes (4300, 2260, and 450 m) for 8 weeks and evaluating their behavioral changes through Morris water maze testing using morphological, molecular biological, and biochemical tests, It has been found that exposure to chronic low-pressure hypoxia in high-altitude areas can lead to cognitive impairment, damage to neurons in the hippocampus and cortex, increase cell apoptosis, and lead to abnormal expression of Caspase-3 protein. Simultaneously NMDA and α- The expression of amino-3-hydroxy-5-methyl-4-isoxazolic acid (AMPA) receptors, oxidative stress, and levels of free radicals were significantly increased. Although there have been few human experiments on cognitive impairment caused by rapid altitude entry, as early as the 1990s, a large number of scientific researchers have conducted research on mountaineers, confirming that low-pressure and hypoxic environments at high altitudes can lead to cognitive impairment in the human body. Lemos et al. [14] placed 10 men aged 23-30 in a simulated low-pressure oxygen chamber at an altitude of 4500 meters to observe the changes in sleep, mood, and cognitive function after 24 hours of exposure. The results showed that hypoxia reduced total sleep time, sleep efficiency, slow wave sleep, and rapid eye movement. Under hypoxic conditions, depression, anger, and fatigue can increase, while vitality, attention, visual and working memory, attention, and executive function deteriorate. In addition, Shi Juhong et al. [15] conducted a survey and analysis of 2037 officers and soldiers stationed at high altitudes. After systematically understanding the cognitive status and influencing factors of officers and soldiers stationed at high altitudes, they also found that long-term low pressure and hypoxia can affect normal cognitive function, and poor sleep quality or insomnia are important risk factors for mild cognitive impairment. For officers and soldiers stationed at high altitudes, attention should be paid to strengthening training in psychological perception, psychological movement speed, and attention ability, as well as optimizing accommodation environments, Strive to create a harmonious sleeping atmosphere and improve their cognitive function. Therefore, the issue of cognitive impairment in the brain caused by rapid entry into high altitude is urgently needed for further research.

The pathogenesis is mainly related to calcium homeostasis disorders, glutamate toxicity, NO neurotoxicity, oxygen free radical response, cell apoptosis and necrosis mechanisms, and sleep awakening cycle disorders [16-17]. At present, based on the pathological and physiological mechanisms

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of its occurrence, the main intervention measures include: 1) Hyperbaric oxygen therapy: if stationed officers and soldiers undergo hyperbaric oxygen therapy before completing high-altitude tasks, it can effectively improve gas exchange, increase oxygenation capacity, increase blood oxygen tension, increase tissue oxygen content and reserve, accelerate lactate clearance, reduce tissue damage caused by hypoxia, enhance the physical fitness and resistance of high-altitude officers and soldiers, and improve work efficiency. 2) High altitude acclimatization: The process of gradually adapting the body to high altitude hypoxia through hypoxic preconditioning; Through stepwise adaptation training, the body is allowed to stay at a certain altitude for a period of time while undergoing appropriate physical fitness training; Perform appropriate hypoxic tolerance training before entering the plateau, such as adaptive physical fitness training such as long-distance running, weight-bearing stretching, or mountain climbing. 3) Drug treatment: Traditional Chinese medicine preparations: such as Polygonatum polysaccharides, Rosa roxburghii polysaccharides, ginger ethanol extract, Shenqi Hongzao decoction, Ginkgo biloba extract, Scutellaria baicalensis water extract, Rhodiola Tibet extract, Spirulina, Saffron water extract, Puerarin injection, and Compound Angelica injection; Antioxidant drugs: indapamide, verapamil, melatonin, etc; Cholinesterase inhibitors: physostigmine and galanthamine, etc; Calcium channel blockers: nimodipine and iradipine, etc; Neuroprotective drugs: acetyl L-carnitine, etc; Sleep medications: zolpidem, zaleplon, and acetazolamide. 4) Health education and psychological counseling: Enhance the psychological adaptability of high-altitude external training officers and soldiers to work in high-altitude environments, and have a positive promoting effect on cognitive function [16,18-20]. However, the current prevention and treatment methods for cognitive impairment caused by high-altitude hypoxia are far from satisfactory. For example, the stepwise adaptation training method is not suitable for emergency situations such as military exercises, disaster rescue, and helicopter driving, so drug prevention is important. In drug prevention, acetazolamide can cause side effects such as metabolic acidosis, hyperventilation, and decreased exercise ability [21-22], while the use of hormones has systemic side effects that may cause symptoms to rebound after discontinuation. Therefore, the use of acetazolamide and acetazolamide as drugs for preventing cognitive impairment caused by high altitude hypoxia is not ideal. In addition, the traditional Chinese medicine commonly used in China to prevent cognitive impairment caused by high altitude hypoxia has not yet been internationally recognized. In summary, up to now, there are no satisfactory drugs available to prevent cognitive impairment caused by high altitude hypoxia. Therefore, it is particularly urgent to conduct in-depth research on the core mechanisms of cognitive impairment caused by high-altitude hypoxia and find new safe, effective, and convenient prevention and treatment measures for cognitive impairment based on this.

3. Overview of Intranasal Insulin Administration

In 1921, Frederick Grant Banting and others first discovered insulin. Insulin is a type of insulin produced by the pancreatic islets β A small molecule protein composed of 51 amino acid residues secreted by cells, with a molecular weight of 5808 Da. It is also the first energy regulatory factor discovered by humans and the only hypoglycemic hormone in the body, controlling the storage and metabolism of three major nutrients: protein, sugar, and fat [23]. Previously, due to the presence of the blood-brain barrier, it was often believed that insulin could not enter the brain[24]. Therefore, the role of insulin in the brain has never been paid attention to, but its role in regulating the dynamic stability of glucose metabolism in peripheral tissues (such as adipose tissue, muscle and liver) has attracted extensive attention. But since Harankova et al.[25] detected insulin in cerebrospinal fluid using radioimmunoassay in 1978, the role of insulin in the central nervous system has attracted attention. With the deepening of research, people have also discovered that insulin in the brain has unique effects that are different from those in the periphery. These effects include influencing dietary behavior, cognition, systemic metabolism, cerebrovascular function, and the selective transmission of substances by the blood-brain barrier[26].

Research has found that insulin in the brain mainly comes from two pathways. The first is that nerve cells synthesize and secrete insulin into the cerebrospinal fluid circulation; The second type is pancreatic islets β After secretion, cells enter the bloodstream and eventually enter the brain through the blood-brain barrier[27]. The study of exogenous insulin in the brain mainly relies on nasal application. Compared to other drug delivery routes, the advantages of nasal drug delivery include non-invasive, easy self administration, rapid absorption and onset, and avoidance of liver first pass elimination[28]. Due to its low bioavailability (approximately 3-8% of intravenous injection), nasal administration of insulin is less likely to cause systemic side effects, such as hypoglycemia[7,29-30]. Compared to subcutaneous injection of insulin, the bioavailability ratio of brain and plasma after nasal delivery is about 2000 times, indicating that the nasal delivery pathway can prioritize insulin delivery to the brain[4]. After intranasal administration of insulin, it can quickly reach the brain through the extracellular nerve gap and olfactory

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nerve pathway of the trigeminal nerve, through paracellular transport and endocytosis. It is distributed in the space around cerebral blood vessels and activates insulin receptors (IR) distributed in areas such as the olfactory bulb (with the highest receptor expression), cerebral cortex, hippocampus, hypothalamus, amygdala, septum, cerebellum, thalamus, and pituitary [5-6,27]. The IR in the mammalian brain consists of two α Subunits and 2 β The tetramer composition of subunits is divided into two types: one is peripheral type IR, mainly distributed in glial cells of neurons, with low concentration and related to glucose metabolism; The other type is neural type IR, mainly distributed in neurons with high concentration and related to learning and memory. In summary, after insulin is administered through the nose and reaches the central nervous system, it can combine with different types of IR in different parts of the brain to play a role in regulating metabolism and non metabolism in the brain[31-32].

4. High altitude sleep awakening cycle disorder and cognitive impairment

Due to its unique geographical environment and climatic factors (reduced oxygen supply, low humidity, and low temperature), the plateau can have many adverse effects on the physiological and psychological well-being of the human body[33]. When military officers and soldiers enter plateau areas for training, due to the low-pressure and hypoxic environment at high altitudes, the body's metabolism and immune function can be disrupted, thereby disrupting the balance of the internal environment, leading to changes in various physiological functions of the body, such as headaches, insomnia, chest tightness, asthma, fatigue, etc. Among them, sleep disorders are more prominent, with frequent nocturnal awakening the increase in nightmares and the feeling of dizziness after waking up in the morning pose a more serious threat to the human body than in low altitude areas. The delayed response, decreased stress ability, and decreased cognitive performance caused by sleep disorders also greatly weaken the combat effectiveness of troops, which may have a certain impact on the personality and mental health of soldiers stationed at high altitude[34]. It is generally believed that hypoxia is the main cause of sleep disorders at high altitudes. High altitude hypoxia can lead to changes in sleep structure, leading to insomnia and decreased sleep quality. As a result, it can exacerbate central nervous system dysfunction and reduce its ability to adapt to high altitude environments. As the altitude increases, it will further cause changes in sleep state. Medically, sleep states are divided into non rapid eye movement (NREM) and rapid eye movement (REM). Sleep starts from the non rapid eye movement phase, falls asleep for about 90 minutes, enters the rapid eye movement phase, which lasts for about half an hour, and then returns to the non rapid eye movement phase, alternating for about 6-7 cycles (assuming a sleep time of 7 hours). NREM is divided into stages I, II, III, and IV, with stages I and II being shallow sleep and stages III and IV being deep sleep. Stages III and IV are also known as slow wave sleep (SWS) due to their slow wave electroencephalogram (EEG) appearance. The quality of sleep mainly depends on the duration of deep sleep in stages III and IV. If the sleep in stages III and IV is short or almost non-existent, and mainly in stages I and II, even if you sleep for more than ten hours, you still feel tired and drowsy; If deep sleep is prolonged in stages III and IV, and shallow sleep is scarce in stages I and II, even if you only sleep for five or six hours, you will still be energetic and healthy. High altitude environment can cause sleep and respiratory rhythm disorders, manifested as a decrease in sleep efficiency (SE), a constant total sleep time (TST), but a transition from deep sleep (III and IV) to shallow sleep (I and II) in NREM, a decrease in SWS sleep, frequent awakening, and the occurrence of periodic breathing (PB)[35]; Changes in the rhythms of various waves in the electroencephalogram (EEG) α Rhythmic disorders are predominant[36]; The increase in cerebral blood flow from initial adaptation to a decrease after prolonged hypoxic exposure leads to a decrease in oxygen saturation, leading to dysfunction of the sleep center and affecting its sleep quality[33]. In addition, under high altitude hypoxia conditions, the partial pressure of inhaled oxygen decreases, the content of oxygenated hemoglobin in the blood decreases, and brain cells do not receive sufficient oxygen supply. The metabolic activity of mitochondria in brain nerve tissue cells will be disrupted, resulting in a decrease in ATP production; The increase in intracranial pressure, in turn, hinders brain blood circulation and exacerbates disorders in brain energy metabolism[37], further affecting the excitatory or inhibitory conduction of brain neurons, thereby interfering with the aforementioned neural activities and leading to sleep disorders[38-39]. Insomniac officers and soldiers have difficulty falling asleep, frequent sleep awakening, and reduced slow wave sleep, which directly leads to dysfunction of the hypothalamic pituitary adrenal axis. This affects the nutritional support of brain neurotrophic factors (including brain-derived and glial neurotrophic factors) to neurons and glial cells, leading to cognitive impairment[40]. Insomnia can also damage cognitive function by reducing blood flow to the prefrontal cortex, which is the main area of cognitive activity such as brain execution and behavioral function[41]. Long term sleep restriction and disruption during high-altitude adaptation by officers and soldiers can weaken the cyclic adenosine monophosphate protein kinase A signal transduction of neurons and weaken the plasticity and memory process of hippocampal neurons. When

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sleep restriction occurs for a long time, hippocampal cell proliferation and neurogenesis decrease, resulting in a decrease in hippocampal volume and impaired cognitive function[42].

5. Intranasal insulin and cognitive impairment at high altitude

With the discovery of the effects of insulin in the brain on synaptic plasticity and cognitive function, the preventive and therapeutic effects of nasal administration of insulin on cognitive dysfunction caused by central nervous system degenerative diseases, anesthesia, and other factors have received widespread attention. Claxton et al.[43] found through clinical trials that intranasal administration of insulin can improve cognitive impairment in adults with mild cognitive impairment or early Alzheimer's disease dementia. Farzampour S[44] also found that nasal insulin therapy can improve amyloidosis β Memory and learning abilities of model rats with Alzheimer's disease. In addition, Chen Y et al.[45] found through animal experiments that nasal insulin can restore insulin signaling, increase synaptic proteins, and reduce A levels in the brain of 3xTg-AD mice β Horizontal and inhibitory activation of microglia. In postoperative cognitive impairment with a similar pathogenesis to Alzheimer's disease, Li X et al.[46] found in animal experiments that nasal insulin therapy can prevent anesthesia induced cognitive impairment, increase the expression level of postsynaptic density protein 95, and microtubule associated protein 2 (MAP-2) in the hippocampal dentate gyrus. At the same time, they also found that nasal insulin therapy can interfere with anesthesia signals by activating the PI3K/PDK1/AKT pathway and weaken anesthesia induced tau protein hyperphosphorylation at multiple AD related sites. Zhang Y et al.[47] treated mice with daily intranasal insulin (1.75U/day) for one week, followed by intraperitoneal injection of propofol to induce anesthesia and inhalation of sevoflurane for 1 hour. After 1-5 days of anesthesia, it was found through Morris water maze measurements that insulin therapy can prevent anesthesia induced spatial learning and memory deficits, while also weakening anesthesia induced high phosphorylation of tau and promoting synaptic protein expression in the brain. In addition, after nasal administration, insulin can directly enter the cerebrospinal fluid circulation and reach the central nervous system. It inhibits the secretion of the hypothalamic pituitary adrenal axis by acting on the hypothalamic nucleus and marginal structures (such as the hippocampus) that express a large number of insulin receptors, improves the phenomenon of sleep cycle disorder, and thus improves memory formation after cognitive impairment[48]. Ritze Y et al.[49] showed a decrease in serum cortisol concentration after 2 weeks of nasal administration of insulin before nighttime sleep, which is beneficial for memory formation. Feld G B et al.[50] studied the effect of nasal insulin on sleep in 16 males and 16 females, and found that brain insulin can improve memory by inhibiting the process of active forgetting during sleep, reducing interference with encoding new information. The above results indicate that nasal administration of insulin may benefit cognitive function by inhibiting the hypothalamic pituitary adrenal axis, reducing the release of cortisol, improving sleep, and ultimately improving cognitive function.

6. Discussion

Based on existing research, we have reason to speculate that nasal insulin can be used for the prevention and treatment of cognitive impairment under high-altitude and hypoxic conditions, and its mechanism may be related to reducing neuronal hypoxic damage and improving sleep awakening cycle disorders.

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