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Relationship among hypoxia, sleep and cognitive functions

Relación entre hipoxia, sueño y funciones cognitivas

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ABSTRACT: The scientific literature shows that the reduced oxygen supply (O2) induced by acute or chronic exposure to high altitudes stimulates the organism to adapt to new physiological and psychological conditions imposed by hypoxia. Sleep can suffer partial fragmentation due to exposure to high altitudes, and these changes can be responsible for impaired cognitive functions. Therefore, this study aimed to explore the relationship between hypoxia, sleep and cognitive functions. We conducted a literature review in the period from 1978 to 2020. In that way, we concluded that hypoxia can impair sleep patterns and, consequently, cognitive functions, including memory, attention, executive functions, decision making and reaction time.

KEY WORDS: Hypoxia, sleep, cognitive functions.

INTRODUCTION

Every year a large number of people travel to different parts of the world, such as Machu Picchu (over 2500 m), the Bolivian Andes (over 3500 m) and the Swiss Alps (can reach up to 4000 m), for work, leisure or to practice sports, including hiking, mountaineering, skiing and climbing, both in Brazil and in other countries (Magalhães *et al.* 2002; Muhm *et al.* 2007; Gutwenger *et al.* 2015). High altitude locations can alter both physiological and cognitive functions and increase the risk of accidents and deaths for people less acclimatized to these conditions (Loewenstein, 1999; Kurtzman & Caruso, 2018).

At sea level, the barometric pressure (BP) is about 760 mmHg; As it progresses to higher altitudes, the pressure decreases to 523 mmHg at 3000 m; and for 330 mmHg at 6800 m (Sellera & Ghorayeb, 2005). Trying to respond to the breakdown of homeostasis resulting from hypoxia, the body produces responses in various systems, so different adjustments need to take place, ranging from the cardiovascular system to the skeletal muscle, passing through the endocrine, nervous and immune systems, until reaching the brain, which can change the sleep pattern (Bolmont *et al.*, 2000; Du *et al.* 2019).

According to Johnson *et al.* (2010) and Liu *et al.* (2019) sleep can be impaired at altitudes above 3500 m. Wickramasinghe & Anholm (1999) explain that sleep at high altitudes become of poor quality and has an increase in nighttime awakenings due to hypoxemia. Besides, changes in sleep architecture are also observed, with an increase in the percentage of stage 1 and 2 of sleep and a decrease in slow-wave sleep and REM, which can impair cognitive functions.

In addition to the deprivation caused by sleep due to the partial reduction of environmentally inspired O2, Imray *et al.* (2011) and Shanjun *et al.*, (2020) emphasizes that cognitive impairment also occurs at altitudes ranging between 2500m and 5000m, including memory, attention, decision making, learning and executive functions impairments.

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Thus, it is believed that hypoxia alters the sleep pattern and, consequently, negatively influences cognitive performance. Therefore, this review aims to explore the relationship between hypoxia, sleep and cognitive functions in healthy people.

MATERIAL Y METHOD

For this study, we conducted a systematic and integrative review of the literature, using source articles indexed by the ISI database, PubMED, and MEDLINE by searching for books that addressed specific aspects related to altitude/ hypoxia, sleep and cognitive functions during the period from 1978 to 2020. The keywords searched were "hypoxia," "sleep and hypoxia," "sleep and altitude," "cognition and hypoxia," and "cognition and altitude,". These descriptors were used in a Boolean-specific basis to obtain various arrangements thought to maximize both the coverage and quality of the search. No restrictions were made regarding age or gender.

Development

Hypoxia

Hypoxia can be classified into different types, including the most well-known and studied hypoxia in universities, which is hypoxic hypoxia, simulated hypoxia, or in a mountain environment (Coppel *et al.* 2015). The other three types of hypoxia that exist are less frequent in scientific studies, but, once this subject is discussed, the details of the concepts become important. Stagnant hypoxia is characterized by low blood flow, due to vessel constriction or reduced cardiac output. Anemic hypoxia is a decrease in the amount of hemoglobin due to some type of blood loss (Morita *et al.*, 2003), genetic failure, or in cases of carbon monoxide poisoning. And finally, Histotoxic hypoxia, which is caused by poisoning, such as cyanide (Hutter-Paier et al, 1998). Thus, hypoxia represents a preponderant risk factor that promotes physical and brain changes, which can cause a series of impairments to humans, depending on the partial reduction of O2 in the body (Ortega *et al.* 2004; Mazzeo, 2008).

Responses to hypoxia can be chronologically divided into acute and chronic. A few moments after the beginning of exposure to hypoxia, an increase in ventilatory response, heart rate, and cardiac output can be observed. When exposure is prolonged, we have chronic responses including an increase in the number of erythrocytes and hemoglobin and a decrease in muscle mass (Magalhães *et al.*; Bourdillon *et al.*, 2017).

Exposure to hypoxia for humans refers to the permanence in high altitude conditions, which can lead to the risk of death, such as helicopter pilots and their passengers, as reported (Smith, 2005; Vavricka *et al.*, 2016; Mulchrone *et al.* 2020). Thus, it is observed that in these conditions of low O2 concentration, people may suffer undesirable consequences, especially above 3000 m, since, above this altitude, the decrease in barometric pressure reduces the amount of O2 molecules per unit volume, which results in a decrease in oxyhemoglobin saturation leading to more intense effects of hypoxia (Ohkuwa *et al.* 2003; Ortega *et al.* 2006; Bosco *et al.* 2019).

In addition to the symptoms of Acute Mountain Sickness, other changes in the body can be triggered, including the emergence of even more important clinical problems such as brain edema, retinal hemorrhages, pulmonary edema, and generalized edema, as well as changes in sleep and cognitive functions (Sellera & Ghorayeb; Garrido *et al.* 2020). Windsor *et al.*, (2009) reported that above 6000 m altitude there is a serious health risk as well as trauma, high altitude illness, cold injury, avalanche burial and sudden cardiac death.

Sleep

Sleep is a reversible and cyclic behavioral state and is responsible for the physiological and cognitive maintenance of the organism (Nicolau *et al.* 2000). Besides, sleep has the function to recover the body from a possible energy output established during waking time. Other functions assigned to sleep is mantention of body's homeostasis, regulating neurotransmitters involved in sleep-wake cycle, cognitive functions, thermoregulation, and most of neuroendocrine functions such as Growth Hormone (GH), Cortisol, Prolactin, Thyroid Stimulating Hormone (TSH), Testosterone among others (Van Cauter *et al.* 2008; Kessler *et al.* 2010). The cardiovascular system including systemic hypertension and heart rate is also influenced by sleep due to autonomic regulation (Somers *et al.* 1993; Narvaez-Guerra et al, 2018; Grandner 2020). Besides, the immune system regulation is also associated with sleep, for example the proinflammatory cytokines play an important role in sleep regulation (Krueger, 2008). Some cytokines have an antisomnogenic action by decreasing prosomnogenic cytokine production, while others cytokines have the opposite effect (Besedovsky *et al.*, 2012; Haspel *et al.* 2020).

During a night's sleep, 90-minute cycles of NREM and REM sleep occur between four to six times per night. Thus, a healthy young adult has the following distribution in sleep staging: NREM sleep occupies between 75% to 80% of sleep time, stage N1 from 2% to 5%, stage N2 varies from 45% to 50%, stage N3 between 18% to 25% and REM sleep between 20% to 25% (Dement, 2000; de Zambotti *et al.* 2017). Too many during NREM sleep, there is a reduction in heart rate, cardiac output, and blood pressure. During REM sleep there is an increase in blood pressure and heart rate, but in general mainly during the phasic events that occur intermittently during REM sleep, including rapid eye movements, clitoral and penile tumescence, in addition to there is probably a generalized vasoconstriction seen in skeletal muscles during phasic REM sleep (Iber *et al.* 2007; Silber *et al.* 2007).

Cognitive Functions

Cognition can be defined as higher intellectual processes, including thinking, memory, learning, attention, and executive functions which is the ability to plan, organize and execute a given task and the more complex processes of perception (Sperry, 1993; Wang & Bi, 2019).

Concerning learning, there is an association with memory because, to learn, the brain pass through a process of consolidation of something we have learned, which will later make the person remember some fact or situation and repeat it (Takahashi, 2011; Kim & Kaang, 2017). In this sense, it is important to emphasize that all animals, especially humans, adapt to environments through learning. From a behavioral point of view, the learning process can be characterized by classical or operant conditioning (Skinner, 1978).

Through this process of learning, the memory allows the person to be situated in the present, taking into account the past and the future, which plays an important role in the capacity to store information, providing the necessary support for all human knowledge and the skills and goals that are determinants of behavior (Sanvito, 1991; Gisquet-Verrier & Riccio, 2018).

The consolidation of memory is possible due to a sequence of events: a) acquisition or registration - transmission of information to the Central Nervous System (CNS); b) coding - comparison of new memories with previous memories; c) consolidation, retention or storage of information; d) recalling, evoking or retrieving information (Baddley, 1992; Izquierdo, 2002). The major regulators of these steps are level of consciousness, emotions and mood states.

In addition to the process of learning and the ability to store what has been learned, another prominent cognitive function is attention. This process is fundamental to achieve success in learning and in memory capacity. In that way attention is a multidimensional concept associated with a variety of relationships between the external stimulus or tasks and behavioral responses (Bakker *et al.*, 1979; Cohen *et al.*, 2019).

Reaction time (RT) is another important cognitive function that depends on the state of attention and can be defined as the time interval between the presentation of a stimulus and the beginning of a motor action (Shidoji & Matsunaga, 1991; Magill, 2000; Schmidt & Wrisberg, 2001). Schmidt & Wrisberg, (2001) and Tam *et al.* (2015) report that RT is an indicator of the speed of information processing and, in that way, represents a level of neuromuscular coordination.

Hypoxia and sleep

A study by Nussbaumer-Ochsner *et al.* (2011), in which they assessed the sleep of 14 healthy climbers over four consecutive nights in natural mountain conditions, demonstrated that sleep efficiency, sleep latency and total sleep time (TST) have been impaired, that is, they were equal to 490 m as for 4559 m during the first, second, third and fourth night. Other authors such as Johnson *et al.* and Latshang *et al.* (2019) reported that sleep can be impaired at altitudes above 3500 m. Following this line of research, Pedlar *et al.*, (2005) evaluated the effect of simulated hypoxia on sleep in an altitude of 2500 m, in healthy people, showing an increase in apnea and hypopnea rates. However, other parameters evaluated in this study, such as total sleep time (TST), sleep efficiency, and sleep architecture have not been impaired under hypoxia. On the other hand, Normand *et al.*, (1990) have found that altitudes above 4000 m can produce stress responses and impaired sleep. Besides, hypoxia induces changes in mood. Gupta *et al.*, (2009) suggest that sleep changes may be associated with depressed mood. Other authors report that sleepiness may be prevalent in people under hypoxic conditions that, subsequently, may impair behavioral and physiological performance (Shukitt *et al.*, 1988; Ramsohler *et al.*, 2017).

Zieliński *et al.*, (2000) investigated sleep quality in a study carried out on the mountain with nine healthy young males who were evaluated at 760 m, and 3200 m on the first and sixth night. The results showed no significant differences between both first and sixth nights in the following aspects: NREM sleep and REM sleep, TST and sleep efficiency. In contrast, Wickramasinghe & Anholm explained that sleep at high altitudes is characterized by poor quality, increased number of awakenings, and marked by nocturnal hypoxemia and periodic breathing. Besides, the authors also reported that there is an increased latency to initiate sleep, as well as a reduced slow-wave sleep and REM sleep. Although some studies have shown that hypoxia alters sleep patterns, Johnson *et al.*, reported that studies on sleep and its relationship to hypoxia are controversial, and more established methodological standards are necessary. Muhm *et al.* (2009) conducted a study in which they investigated sleep at a simulated altitude of 2438 m with 20 healthy male adults. The results of this study showed that sleep efficiency, awakenings, and sleep architecture, including stages 1, 2, slow-wave sleep, and REM sleep, have not been impaired during a night under hypoxic conditions similar to an altitude of 2438 m.

On the other hand, a study conducted by Reite *et al.*, (1975) showed that the hypoxia response at 3000 m decreases the percentage of slow-wave sleep and stage N3 of sleep. This may be a consequence of increased fragmentation and frequent awakenings during sleep. Corroborating this results of the present study, Przybylowski *et al.*, (2003) reported that REM sleep is also reduced at an altitude above 3800 m. In this sense, some studies showed that hypoxia causes the O2 dissociation curve to decrease and result in lower concentrations of CO2 in arterial blood, which can fragment sleep and thus alter its entire architecture (Mizuno *et al.*, 1993; Hoshikawa *et al.* 2007). Thomas *et al.*, (2007), on the other hand, did not observe an impairment in subjective sleepiness, attention, and memory of 11 healthy young men and women, during two weeks of exposure to simulated hypoxia. In addition to the relationship between hypoxia and sleep, cognitive functions can also be influenced by partial O2 reduction.

Hypoxia and cognitive functions

A study conducted by Pavlicek *et al.* (2005) investigated the relationship between cognitive functions in a condition of simulated hypoxia, composed of three groups of seven healthy young males, exposed to continuous hypoxia for two hours under the following conditions for 30 min. each: 450, 1500, 3000 and 4500 m in comparison to the control condition of 450 and 650 m. The results showed that there was no impairment in cognitive aspects including mental flexibility, and decision making. In contrast Bahrke & Shukitt-Hale (1993) performed a literature review to investigate the influences of hypoxia on cognitive functions in simulator chambers, reaching the equivalent of 4000 m.

The results showed that simulated hypoxia induces cognitive changes, including attention, memory and decision making. A study conducted by Abraini *et al.* (1998) with humans, simulated a climb to Mount Everest intending to investigate the effects of altitude on the reasoning processes and psychomotor skills of eight climbers, gradually exposed to 8848 m over a period of 31 days of confinement in an altitude simulator. This results showed no impairment in learning and reaction time at altitudes of up to 5500-6500 m but, in contrast, altitudes above 8000 m showed a worsening in mental efficiency and psychomotor skills. Zhang *et al.* (2011) studied the working and long-term memory of 52 healthy university students, who remained exposed to 2260 m for seven months, with a monthly return to sea level. The findings of this study demonstrated that prolonged exposure to hypoxia have not impaired memory capacity. On the other hand, the hypoxia response to short-term memory was evaluated in 18 healthy men at an altitude equivalent to 2800 m, 3600 m and 4400 m in an altitude simulator for one hour. The results showed that memory has been impaired after exposure to hypoxia equivalent to 2800 m, reaction time increased and memory capacity worsened to 3600-4400 m. Furthermore, in general, cognitive performance worsened 73.7% when compared to the control group (Du *et al.* 1999).

Tsarouchas *et al*., (2008) conducted a study in which they investigated simulated hypoxia equivalent to 4572 m on cognition for 15 min., and observed no changes in cognitive aspects. This study included ten healthy people of both genders, eight men and two women with an average age of 29 years. All volunteers were assessed in terms of normoxia and hypoxia. The results showed that there was no difference in cognition during the entire experiment period, including attention, memory, and visual and psychomotor functions. A study to assess cognitive aspects on Mount Everest at 8000 m monitored the verbalization and attention of a group of healthy climbers. The results showed that altitude worsened verbalization and attention measures (Lieberman *et al*., 2005). Besides that, Ortega *et al.* (2004); Paintal (2004), and Lefferts *et al.* (2019) showed that reaction time, color discrimination, memory, learning, attention and decision making can be impaired under hypoxia. On the other hand, other authors such as Bonnon *et al.* (1999) to study cognitive adaptations and mood states at high altitudes, have recruited seven healthy men to stay under hypoxia in altitude ranging between 3500-4400-5400 m for nine days, and performed a motor and cognitive task three times, in normoxia and under acute and chronic hypoxia. The results showed that when the three conditions were compared, no significant impairment in motor activities, cognitive functions, and mood states were observed.

CONCLUSIONS

The effects of hypoxia alter the sleep pattern, reducing slow-wave sleep and REM sleep, worsening sleep efficiency, and increasing awakenings, apnea and hypopnea rates. From 2500 m the cognitive functions are also impaired, including attention, reaction time, decision making, memory, executive functions, learning, speed, and mental processing, that is, the greater the exposure at high altitudes the worse the changes. In this sense, it is suggested that changes in sleep patterns can modulate cognitive functions regardless of whether the exposure to hypoxia is acute or chronic.

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RESUMEN: La literatura científica muestra que el suministro reducido de oxígeno (O_2) inducido por aumentos agudos o crónicos en la altitud estimula al organismo a adaptarse a las nuevas condiciones fisiológicas y psicológicas impuestas por la hipoxia. El sueño puede sufrir fragmentación parcial debido a la exposición a grandes altitudes, y estos cambios pueden ser responsables de las funciones cognitivas deterioradas. Por lo tanto, este estudio tuvo como objetivo explorar la relación entre la hipoxia, el sueño y las funciones cognitivas. Realizamos una revisión de la literatura en el período de 1978 a 2020. Por lo tanto, se concluye que la hipoxia puede empeorar el patrón de sueño y, en consecuencia, el funcionamiento cognitivo, incluida la memoria, la atención, las funciones ejecutivas, la toma de decisiones y tiempo de reacción.

PALABRAS CLAVE: Hipoxia, sueño, funciones cognitivas.

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