

## Effect of Chronic Hypoxia in Cognition on Childhood: Review Article

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### ABSTRACT

**Background:** Hypoxia is defined as the reduction of the normal oxygen supply. The hypoxia is traditionally classified as acute and chronic. Chronic hypoxia was classified into three subgroups: *diffusion-limited hypoxia*, *hypoxemic hypoxia*, and *hypoxia due to a compromised perfusion of leaky micro vessels*. Serious hypoxic-ischemic events are known to have an adverse impact on cognitive function. **Aim:** to review the evidence concerning the effect of chronic hypoxia on childhood cognitive outcomes including development and academic achievement.

**Materials and Methods:** We used scientific websites such as PubMed, Google Scholar, and Research Gate to get related articles about this subject.

**Results:** There were 15 articles included in this review including both research and review articles.

**Conclusion:** It has been suggested that cognitive function including knowledge, attention, memory and Oxygen supply to the brain tissue may be decreased under hypoxia. Thus, brain desaturation and resultant biological process may be responsible for the impairment of cognitive function although the underlying mechanisms are still unclear

**Keywords:** Chronic Hypoxia, *Diffusion-limited hypoxia*, *Hypoxemic hypoxia*.

### INTRODUCTION

The oxygen gas (O<sub>2</sub>) is a necessary element for obtaining the life of aerobic organisms. In the mitochondrial respiratory chain the oxygen is the final receptor of electrons <sup>[1,2]</sup>. This allows the ultimate process of oxidative phosphorylation and the generation of cellular energy, in the form of adenosine triphosphate (ATP). The most metabolic pathways requires the ATP molecules as a major source of energy hence ATP molecules are necessary to maintain cellular viability.

Under normoxial conditions a cell continuously maintains a high and constant ratio of cellular ATP/ADP in order to survive this reflect the dependence on oxygen. Therefore, a reduction of the normal oxygen supply (hypoxia) will have consequences on the cell viability <sup>[2]</sup>. Hypoxia is encountered not only in different conditions including the patho-physiological conditions, such as atherosclerosis, obstructive sleep apnea, mountain sickness, ischemic diseases (stroke) and cancer, but also in physiological processes, such as embryonic development <sup>[3]</sup>.

### MATERIALS AND METHODS

We used scientific websites such as PubMed, Google Scholar, and Research Gate to get related articles about this subject. The research process involved specific keywords "effect of chronic hypoxia on cognition among children, classification

of chronic hypoxia and management of chronic hypoxia" to find

more articles on the subject. We were more concerned about English published articles only which published from 1995 to 2017.

### Classification of Chronic hypoxia

This traditional classification of hypoxia into only two subgroups (chronic and acute) is based on empirical observations solely and widely discounts the multiple pathogenetic processes involved <sup>[4]</sup>. Chronic hypoxia was classified into three subgroups: *diffusion-limited hypoxia*, *hypoxemic hypoxia*, and *hypoxia due to a compromised perfusion of leaky microvessels* <sup>[5]</sup>. Diffusion-limited chronic hypoxia is very common in solid tumors. In neoplastic tissues increased cell proliferation frequently outpaces angiogenesis, resulting in tumor cells extending beyond the oxygenation zones that surround blood vessels. This is exacerbated by the high metabolic demands of tumor cells, and unreliable vessel perfusion <sup>[6,7]</sup>.

Reduced oxygenation elicits activation of Hypoxia-Inducible Factors (HIFs), representing an evolutionarily conserved physiological response which coordinates a range of adaptive changes in gene expression and cross-communicates with other signaling pathways <sup>[6,8]</sup>.

Chronic hypoxemic hypoxia is caused by long-lasting reduced oxygen content in the blood and extreme longitudinal intravascular oxygen gradients<sup>[9]</sup>. One example is tumor-associated and/or therapy-induced anemia (anemic hypoxia). Another example can be described as “functional anemia” in heavy smokers. The increased carbon monoxide content in the blood of these individuals binds with high affinity to hemoglobin and thus reduces the oxygen transport capacity of hemoglobin by forming carboxy hemoglobin. Another example of chronic hypoxemia can be found in (small) primary or metastatic liver tumors that are mostly supplied by branches of the portal vein containing deoxygenated blood from the splanchnic region<sup>[5]</sup>. Another subtype of chronic hypoxia may (hypothetically) be caused by stagnant flow due to interstitial hypertension as a result of extreme microvessel leakiness and a lack of functional lymphatics. In normal tissues, a perfusion pressure difference between the arterial and venous end of approximately 20 mm Hg drives blood flow through capillaries. Tumor tissues, however, are characterized by dilated, elongated, tortuous, leaky microvessels, nonfunctional lymphatics, and increased interstitial fluid pressure. Transmural coupling between high interstitial fluid pressure and microvascular pressure can result in abolished perfusion pressure differences (approximately 0 mm Hg). The resulting lack in perfusion pressure difference between arterial and venous ends of microvessels does not allow for blood flow and thereby causes hypoxia<sup>[5]</sup>.

### Effect of chronic hypoxia on cognition in childhood

It has been suggested that cognitive function including knowledge, attention, memory and oxygen supply to the brain tissue may be decreased under hypoxia. The exposure to high-altitude may lead to acute altitude sickness, pulmonary and cerebral edema<sup>[10]</sup>. Hypoxia is thought to have the detrimental effects on the central nervous system<sup>[11]</sup>.

It judgment may be impaired under hypoxia. Hypoxia decreases arterial pressure of O<sub>2</sub> (PaO<sub>2</sub>) and arterial saturation of O<sub>2</sub> (SaO<sub>2</sub>)<sup>[12]</sup>. At the cellular level, the turnover of several neurotransmitters seems to be altered under hypoxia despite the preserved state of brain energy stores<sup>[13]</sup>.

For example, the synthesis of acetylcholine is sensitive to oxygen availability<sup>[14]</sup>. Thus, brain desaturation and resultant biological process may be

responsible for the impairment of cognitive function although the underlying mechanisms are still unclear. Notably, the impairment of cognitive function was prominent at high altitude.

As altitude increases and, thus, severity of hypoxia increases, PaO<sub>2</sub> and SaO<sub>2</sub> gradually decrease<sup>[12]</sup>. It is possible that the detrimental effects of hypoxia on cognitive function are exaggerated as the severity of hypoxia increases.

### Management of chronic hypoxia in brain

O<sub>2</sub> shortage is always associated to early signs of failure represented by marked falls in pH and tissue creatine phosphate levels<sup>[15]</sup>, followed by nearly immediate dysfunction of Na<sup>+</sup>/K<sup>+</sup> ATPase that finally leads to lethal ion imbalance<sup>[16]</sup>. The poor brain plasticity in terms of metabolic adjustment and its inability to improve the metabolic efficiency by switching to anaerobic energy-yielding pathways<sup>[17]</sup> lead to a situation whereby the defense of the brain function against O<sub>2</sub> shortage is exploited either through triggering pro-survival pathways, or through improving brain oxygenation.

It should, however, be pointed out that, although the brain is thought to be an insulin-insensitive organ, several studies<sup>[18]</sup> are introducing the concept that insulin may play important roles in the central nervous system too, thereby yielding a new light to glucose-dependent responses to altered O<sub>2</sub> supply/ O<sub>2</sub> demand balance. At present, though, it is difficult to focus on insulin as an anti-hypoxia/hyperoxia molecule.

A growing number of studies support the idea that regular aerobic exercise can improve a number of aspects of cognition<sup>[19, 20]</sup>. These findings demonstrate that high aerobic capacity is beneficial to cognitive function. Hence, oxygen availability may be one of the factors that affect cognitive function at the resting condition. It has been suggested that hypoxia has the potential to impair human brain function<sup>[21]</sup>. Several previous studies have reported that hypoxia impairs cognitive function in the resting state<sup>[22]</sup>. In particular, more pronounced impairments were observed under severe hypoxic conditions<sup>[23]</sup>.

### CONCLUSION

Chronic hypoxia was classified into three subgroups: *diffusion-limited hypoxia*, *hypoxemic hypoxia*, and *hypoxia due to a compromised perfusion of leaky microvessels*. It has been suggested that cognitive function including knowledge, attention, memory and Oxygen supply to the brain tissue may

be decreased under hypoxia. Thus, brain desaturation and resultant biological process may be responsible for the impairment of cognitive function although the underlying mechanisms are still unclear.

The impairment of cognitive functions is improved by the supplement of oxygen.

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