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Role of Level of Neuroglobin in Understanding the Disease Progression of Neurodegenerative Diseases

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Abstract: ***Oxygen is the lifeline of variety of organisms present on the earth. It is one of the basic elements that are involved in the formation of the functional unit of a living being. Various intricacies and mechanisms are there inside the organism that transports the oxygen to each and every cell of the body. Failure of oxygen to reach the brain leads to various kinds of neurodegenerative disease. Here we have discussed about the role of oxygen carrier moieties and their role in neurodegenerative diseases.***

Keywords: Oxygen, Neuroglobin, Alzhimers, Neurodegenrative disease, Brain

1. Introduction

Oxygen is an indispensable element required by living beings to survive and carry out all the metabolic reactions. Various forms of life have successfully adapted to varying levels of oxygen available in their niches. Mammals being the most advanced form of life have various proteins that function in storage and transport of oxygen in body.

Maintaining adequate oxygen level is important, failing to do so result in improper cellular energy production leading to life threating conditions to mammals. Tissues like nerve cells that are metabolically most active are more sensitive to reduced oxygen levels. Shortage of oxygen in human body for even few minutes result in a state of unconsciousness or acute conditions like cerebral ischemia or stroke whose function can't be restored. Thus it is important to understand the adaptations evolved by mammals that lead them to survive in varying oxygen levels. (1)

For a very long time it was thought that Myoglobin and Haemoglobin are the only two forms of globin proteins that are present in erythrocytes and muscles respectively. (2) The functions of these two globins are very well understood. But recently two more globin, namely Neuroglobin and Cytoglobin have been discovered that have oxygen affinities comparable to that of myoglobin.

2. Neuroglobins and Cytoglobins

Neuroglobin (Ngb) which was discovered by Thorsten Burmester et al. is expressed in the brain and despite being hexacordinated (in contrast to Mb andHb which are pentacordinated). Neuroglobin is present in neurons of central and peripheral nervous system as well as endocrine system. It binds reversibly to O_2, CO and NO (3). The concentration of Ngb is directly proportional to metabolic rate and oxygen consumption in that area, the highest concentration being present in the neuronal retina which has the highest rate of oxygen consumption. (1) Ngb acts as a stress responsive sensor for signal transduction in brain; it senses O_2/NO ratio in the cell seems to act as a sensor of O_2/NO ratio in the cell. It may also function as a terminal oxidase that regenerates NAD+ under anaerobic conditions, thereby sustaining ATP production; also it acts as scavenger of Reactive Oxygen Species which are known to be generated under hypoxic conditions, thus involved in neuro-protection from damage by hypoxia or ischemia in vertebrates. The capacity of Ngb to scavenge the superoxide anion and hydrogen peroxide was comparable to that of vitamin C. (5).

Cytoglobin on the other hand is present in various parts in the body although at varying levels, mainly fibroblast cells and certain neurons. The exact functions of Cytoglobins are not understood, but they are essentially involved in oxygen supply to the cells and ROS defence (3).

It has been found out that marine animals- whales, dolphins living in hypoxic conditions have 3-10 times greater amount of Ngb as compared to terrestrial vertebrates, this might be the reason that they never suffer from stroke and have longer life span compared to humans and tolerate even prolonged duration of hypoxia. (3).

3. Neuroglobins - Neuroprotectors

Study on Ngb has important implications in understanding the neurodegenerative diseases like Alzheimer's, Parkinson disease and ALS (Amyotrophic lateral sclerosis).

Alzheimer's is a very complex neuro-degenerative disease, characterized by deficits in short-term memory, loss in reasoning ability and emotional imbalances. About 30 million people are believed to be affected worldwide and to date no effective drugs exist to stop its progression. Two hallmarks of Alzheimer's are abnormal level of amyloid and tau proteins in brain. Beta-amyloid is formed when BACE1 enzyme that cuts long harmless amyloid protein into small plaque-forming moeities. The plaques cause brain cells to die. According to a recent study, mouse kept in hypoxic conditions developed twice as many beta-amyloid plaques as compared to mice kept in normal conditions. Also it has been shown that Ngb decreases the Beta amyloid production in animal models of AD. The varying Ngb levels co-relates with the risk of developing AD. The inefficient Ngb protein doesn't provide protection against neuro-toxicity of Beta amyloid. The levels of Ngb decreases with aging brain, also the levels of Ngb has been found to be lower in females than in males making them

more prone to diseases like AD. Women are two times more prone to developing AD as compare to male. (6)

More-over Ngb expression has been found to be upregulated in the cerebellum of rat pups exposed to maternal epileptic seizures thus indicating the protective role of Ngb against seizures. Ngb has also been found to be upregulated and protect retinal ganglion cells(RGC) against ocular hypertension and glaucomatous damage, (7)

The growing body of literature has confirmed the role of Ngb in neuroprotection against AD which has paved the way for the future research on other neuro-degenrative diseases like Parkinson's and ALS. (10).

4. Role of Ngb in Parkinson-Speculation

Parkinson's involves the death of vital nerve cells in the area of brain called substantia nigra. Some of the dying neurons produce dopamine, a neurotransmitter that sends signal to the part of the brain that controls movement and coordination. With the disease progression the amount of dopamine goes down leaving the person unable to control the movement normally. The hallmark of Parkinson disease is clumps of a protein alpha-synuclein, which are also called Lewy Bodies-, are found not only in the mid-brain but also in the brain stem and the olfactory bulb. (9)

No exact mechanism of disease development is known but a number of evidence indicates that oxidative stress plays a major role in progression of Parkinson's disease. Oxidativestress contributes to the cascade leading to dopamine cell degeneration in Parkinson's disease (PD). Mitochondrial dysfunction and the consequent increase in reactive oxygen species also trigger a sequence of events that leads to cell demise.

It has been estimated that 6.3 billion people worldwide of all races and cultures have been suffering from Parkinson's syndrome and the numbers are expected to double by 2016. As per Brain Repair Centre at Dalhousie University, brain disease and disorders (like Parkinson's disease) will surpass cancer and heart disease as the leading cause of death and disability by 2040 yet at present, there is no strategy to address this growing concern. All these facts and figures draw the attention for understanding Parkinson's and finding out a preventive measure.

Understanding the role of Ngb in Parkinson's disease progression will help us finding the strategies to not only control Parkinson's but also other neurodegenerative diseases whose mechanisms are too complex to be understood.

5. Future Prospects

The study would give a better insight to the novel preventive therapies for the neurodegenerative disorders. It would also help in understanding a lot of oxidative stress related disorders like cardiovascular diseases, cancer and other neurodegenerative diseases like ALS (*Amyotrophiclateralsclerosis)*. It would help in establishing a relationship between ageing and Ngb levels. Understanding Ngb might help us to retrain the human brain to improve our own survival. We don't know yet, but it's certainly intriguing and worth investigating.

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