

The Ayurvedic Perspective on the Etiopathogenesis of Neurodegeneration

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Abstract

The homeostatic signaling system in Homo sapiens is highly complex involving diverse physiological processes which are what enables the biological regulation of life. Human body is a highly dynamic system, the normal functioning of which is coordinated and maintained by a well-established mechanism of homeostatic regulation. Disorder genesis and progression has an underlying disruption in homeostatic regulation, even though pathophysiology and clinical presentations may vary. Progressive neurodegenerative conditions are an outcome of disrupted homeostatic regulation, which triggers accumulation of dysfunctions and impairment of neuroplasticity.

Ayurveda considers neurodegenerative conditions to be brought by the imbalance of 'Vata', the energy that moves through the brain and the nerves. The scholars behind classical ayurvedic literature considered neural impulses to be a kind of air traveling through the body, controlling both voluntary and involuntary functions. Oxygen is the real time mediator of homeostatic signaling system and defective oxygen transport; thereby impairment in oxygenation is the prime underlying factor in neurodegenerative conditions. The broad spectrum therapeutic effects demonstrated by Withania Somnifera or Ashwagandha are a result of its profound mechanism of enhancement of oxygenation. Also the ayurvedic branch of medicine known as 'Rasa Shastra' uses 'Bhasma', traditionally prepared Nano medicines, some of which shows influential enhancement in oxygenation.

Keywords: Neurodegeneration; Synaptogenesis; Alzheimer's disease; Homeostatic regulation; Parkinson's disease

Abbreviations

COX: Cytochrome C Oxidase; Oxphos-Oxidative phosphorylation; NFT: Neuro fibrillary Tangles; AD: Alzheimers Disease; PD: Parkinsons Disease; DLB: Dementia Lewy Body; CNS: Central Nervous System; Gpx: Erythrocyte glutathione peroxidase; SOD: Superoxide dismutase; CAT: Catalase; MB: Methylene Blue

Introduction

The classical ayurvedic literatures on 'Vata Raktha Chikitsa' [1] clearly suggests that complex disorders affecting nervous system originates from an underlying imbalance of 'vata'. Furthermore, Ayurveda considers human body as a vehicle for spiritual experience which is suggestive of the fact that human consciousness is not locally stored in nervous system. This co-relates with the studies on the underlying mechanisms of cytoskeletal signaling [2]. It has been favored by quantum theory perspectives, that fundamental disturbances in consciousness arises from an underlying disturbance in cytoskeletal system. The micro tubule based concepts of consciousness has been validated in several clinical research studies and implicate aberrant micro tubules as a pathogenetic mechanism in disorders affecting consciousness [3-5]. The cytoskeletal system exhibits dynamic behavior, and it does interacts with hundreds of associated proteins, molecular motors, cross linkers. Also involved in many cell signalling pathways and cytokinesis [6-8]. As described in classical ayurvedic literature, when it comes to the five elements of creation, air is considered to be related to movement and electrical energy. And hence it is suggestive of the fact that oxygen is the fundamental electron

transport mechanism in the universe. It's the way through which the universe is monitoring, recording, maintaining internal stability, obtaining coordinated responses and is managing the ecology of life. All processes of integration and coordination of function in the ecology of life, whether mediated by nervous and hormonal systems comes under homeostatic regulation. The primary target and aim of every disease and disorder in the ecology of life is to impair oxygenation the outcome of which is the disruption of homeostatic regulation. An illness or disease thrives only in an oxygen deficient environment. Impairment in oxygenation implies disruption of homeostatic regulation [9]. Furthermore therapeutic approaches used in ayurvedic medicinal systems for longevity, vitality are suggestive of the underlying mechanism of enhancement of oxygenation. Withania Somnifera or 'Ashwagandha' is showing a similar therapeutic potential. Also certain nanomedicines used in ayurvedic medicinal system prepared in traditional manner which are referred to as 'Bhasma' are demonstrating similar potential [10].

Since oxygen is the mediator of electron-transport mechanism, a dysfunction in the electron-transport mechanism is suggestive of disrupted homeostatic regulation. And a lot of experimental and clinical studies favor a major disruption in homeostatic regulation in neurodegenerative conditions. Respiratory chain deficits, mitochondria dysfunction, exacerbated reactive oxygen species production, low hemoglobin levels, deficiency in the terminal complex of the mitochondrial electron transport chain-cytochrome c oxidase (COX), defects in oxidative phosphorylation (Oxphos) has been observed in the pathophysiology of neurodegenerative conditions. These observations suggests that impairment in oxygenation is at the core of neurodegeneration. Its quite interesting that a rejected theory on neurodegeneration, which had considered 'circle of willies-atherosclerosis' as a contributing factor to Alzheimer's disease, neuritic

plaques and neurofibrillary tangles. This was conceptualized based on vascular hypothesis. From this also it can be presumed that impairment in oxygenation can contribute to pathophysiology of neurodegeneration. The mechanisms of oxygen sensing and homeostatic regulation is contributed by several intracellular signaling systems. Even a slight disruption in the normal environment can result in mild to severe disruption on homeostatic regulation.

Background

Homeostasis refers to stability, balance or equilibrium; its an attempt to maintain a constant internal environment. Maintaining a stable internal environment requires constant monitoring and adjustments as conditions change. This adjusting of physiological systems within the body is called homeostatic regulation. Since oxygen is the mediator of homeostatic regulation, defective oxygen transport causes disruptions in homeostatic regulation. There are several underlying physiological processes that eventually contributes in maintaining homeostatic regulation which governs life. Imbalances in these underlying processes as a result of impaired oxygenation there by results in disrupted homeostatic regulation.

When we look into the pathogenesis of neurodegeneration, it can be seen that a wide array of neurodegenerative conditions are caused by intraneuronal accumulations of intracellular or extracellular protein aggregates. Disorder genesis and pathological changes involve proteins which are subject of altered post-translational modifications, including truncation and cleavage, which promote abnormal solubility, aggregation, and fibril formation. As a result, most degenerative diseases of the nervous system including Alzheimer's disease (AD) and Parkinson's disease (PD) are recognized by the end-products accumulated in the brain. These abnormal aggregates form amyloid plaques and neurofibrillary tangles (NFT) composed of hyperphosphorylated tau in AD, pre-tangles and alpha synuclein inclusions named Lewy bodies in PD and related synucleinopathies such as dementia with Lewy bodies (DLB) [11-16]. This inturn occurs as a result of disruption in homeostatic regulation governing life. While in the case of Amyotrophic Lateral Sclerosis whose clinical features suggests a pathogenesis of upper and lower motor neuron degeneration. The motor neurons serve as the controlling units and vital communication links between the nervous system and the voluntary muscles of the body. And hence their degeneration can result in wide range of disabilities. Even though the disease doesn't affect a person's mind or intelligence, several recent studies suggests that ALS can also cause decline in cognitive functioning. When it comes to homeostatic regulation, it encompasses all forms of integration and coordination of functions, whether mediated by nervous and hormonal systems. And so impairment in homeostatic regulation, suggests a vast array of underlying factors that contributes in the pathophysiology and progression, such as impairment in the regulation through HPA and HPG axis. Several studies reported the dysfunction of prominent functions performed by neuroendocrine systems in the pathophysiology of neurodegeneration [17-21].

Homeostatic regulation of neuronal excitability refers to the collective phenomena by which neurons alter their intrinsic or synaptic properties to maintain a target level of electrical activity. Dysfunction of these fundamental processes could thereby contribute to the pathophysiology of neuropsychiatric presentations as observed in neurodegenerative conditions. [22,23]. The term neuroplasticity relates to diverse processes of vital importance by which the brain perceives, adapts and responds to a variety of internal and external stimuli. The

manifestations of neuroplasticity in the adult CNS have been characterized as including alterations of dendritic function, synaptic remodeling, long-term potentiation (LTP), axonal sprouting, neurite extension, synaptogenesis, and even neurogenesis [24,25]. There are several underlying mechanisms which regulates neuroplasticity which is a part of the homeostatic regulation system. Disruptions in these mechanisms of homeostatic regulation contributed by impairment in oxygenation thereby results in dysfunctions in neuroplasticity. Previous studies shows the presence of hemoglobin alpha-chain and beta-chain in neurons of the rodent and human brain thus indicating that hemoglobin is a normal component of nerve cells and that hemoglobin may play a role in intraneuronal oxygen homeostasis.[11]. Also several studies have suggested deficiency in the terminal complex of the mitochondrial electron transport chain, cytochrome *c* oxidase (COX), in platelet mitochondria of Alzheimer's disease (AD) patients [26]. Also low hemoglobin level has shown to have been associated with AD [27]. Parkinson's disease also has been associated with defects in oxidative phosphorylation (Oxphos) [28]. Also a study reported defects of respiratory chain complexes were considered as possible pathogenetic mechanisms in Parkinson's disease (PD) [29,30]. Multiple studies also reported an association between anemia experienced early in life and the later development of Parkinson disease [31].

Mitochondria are one of the major producers of ROS and are also the main targets of oxidative damage, mitochondrial dysfunction and exacerbated ROS production is generally associated with neurodegenerative disorders. It has been observed that mitochondrial dysfunction, inflammation, iron dysregulation and apoptosis have a crucial role in the pathogenesis of several neurodegenerative disorders. [32-34]. Iron, Copper, Zinc and Magnesium has prominent roles in biological electron transport and oxygen transportation. Iron (Fe) is an essential element that is imperative for the redox-driven processes of oxygen transport, electron transport, and DNA synthesis. Previous studies which evaluated the status of plasma essential trace elements magnesium (Mg), copper (Cu), zinc (Zn), iron (Fe) and selenium (Se) concentrations and their some related antioxidant enzyme activities, erythrocyte glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase (CAT) activities in patients with Alzheimer's disease (AD) suggested alterations in essential trace elements and their related enzymes may play a role in the etiopathogenesis of AD. Also, there is a defect in the antioxidant defense system, which may lead to oxidative damage in patients with AD [35]. However it has been observed that, in the absence of appropriate storage or chelation, excess-free Fe readily participates in the formation of toxic-free radicals, inducing oxidative stress and apoptosis. The brain shares with other organs the need for a constant and readily available supply of iron and has a similar array of proteins available to it for iron transport, storage, and regulation. In a number of common neurodegenerative disorders, there appears to be an excess accumulation of iron in the brain that suggests a loss of the homeostatic mechanisms responsible for regulating iron in the brain. The disruptions in such mechanisms of homeostatic regulation is brought by the impairment in oxygenation. As a result of a loss in iron homeostasis, the brain becomes vulnerable to iron-induced oxidative stress. The disrupted expression or function of proteins involved in iron metabolism increases the concentration of iron in the brain. Disturbances can happen at any of several stages in iron metabolism. Increased brain iron triggers a cascade of deleterious events that lead to neurodegeneration [32-34]. Also this disrupted expression or

functions of proteins thereby suggests a disruption in homeostatic regulation governing life.

Also it's an interesting fact to know that several medications that have proven to improve oxygenation provided benefits in neurodegenerative conditions including Alzheimer's Disease. This is suggestive of benefits obtained from 'Methylene Blue' (MB). Several studies suggested MB hold a therapeutic potential for Alzheimer's disease. MB activated Amyloid Beta clearance, increases in proteasome function and ameliorated AD-like pathology *in-vivo*. [36,37]. In Ayurvedic medicinal system, therapeutic approaches used in neurodegenerative conditions suggest a similar mechanism of action, which is by enhancing oxygenation. One of the best candidate showing such a potential is 'Withania Somnifera' or 'Ashwagandha' which have shown to have potent hematonegic, immune enhancing effects [38-43]. Withania Somnifera is known to alter the oxidative stress markers of the body, found to have neuroprotective activity, free radical scavenging activity and has found to significantly reduce the lipid peroxidation and increase the superoxide dismutase (SOD) and catalase activities. Ashwagandha for its benefits have been used since thousands of years in Ayurvedic medicinal systems for neurodegenerative conditions. The synergistic effects thus produced by Ashwagandha is suggesting its profound mechanism of enhancement of oxygenation. Also it has been observed that drinking oxygenated water has shown to enhance the immune status [44]. This is suggestive of the fact that enhancing oxygenation is improving homeostatic regulation. The involvement of glymphatic system in neurodegenerative conditions are very prominent. Enhancement of oxygenation can activate glymphatic clearance pathways and can produce multiple target actions which has promising effects in delaying progression and furthermore in the promotion of neurogenesis. Through enhancement of oxygenation, the disruptions in homeostatic mechanisms governing life can be re-established which can induce healing and can be used in prevention of diseases. This is also suggestive of the benefits associated with a vegetarian diet. A diet rich in green leafy vegetables, fruits promotes enhanced oxygenation and thereby aids in maintaining the homeostatic regulation. Also the intended results from intermittent fasting suggests an underlying mechanism of enhanced oxygenation. Also its interesting to know the fact that moderate exercise is an antioxidant. It has been observed that exercise causes oxidative damage when its exhaustive. It has been observed that moderate exercise results in activation of underlying signaling pathways that results in useful adaptations in cells. These underlying signaling has shown to up regulate several potential antioxidant enzymes [45]. There lies a similar concept in the 'Vata Raktha Chikitsa', that exhaustive physical activities can have adverse effects in health. This is also suggestive of results obtained in aerobic exercises and yoga. It has been observed that tailored 'Tai -chi' program improved postural instability in patients with Parkinson's disorder [46].

Conclusion

Oxygen is the mediator of homeostatic regulation. Since the rasayana concept emphasizes tissue regeneration and cell renewal, it can be concluded that the synergistic approaches as used in Ayurvedic treatment methods in 'Vata Vyadi' or 'Vata Rakha Chikitsa' is intended in reestablishing homeostatic regulation by enhancing oxygenation. This can lead to clearance pathways for accumulated dysfunctions, and promotion of non-amyloidogenesis. Enhancing the oxygenation capacity by modifying the oxygen transport and delivery, enhancing

factors involving oxygen metabolism can re-establish homeostatic regulation which can further aid in cure and prevention. And hence treatment using nanomedicines capable of enhancing oxygenation can produce outstanding results in progressive neurodegenerative conditions. In the Ayurvedic branch of medicine known as 'Rasa shashtra', the 'Bhasma' which are nanomedicines prepared using traditional methods have been used for centuries. Some of them demonstrates a therapeutic potential resulting in profound hematonegic, immuno modulatory, hemopoietic activity. Moreover the decline in the efficiency of homeostatic regulation due to accumulated dysfunctions can persist and become progressive if the homeostatic regulation is not reestablished. The effects are accumulative over years unless regeneration occurs by re-establishing the disrupted homeostatic regulation. Aging is principally said to be caused by the cumulative damage to tissues by oxygen free radicals and endogenous glycation, which occurs in the body, which is associated with increased oxidative damage. There are underlying mechanisms in human body to counteract oxidative stress by producing antioxidants, which are naturally produced *in situ*. Through enhancement of oxygenation, progressive loss of dopaminergic neurons in substantia nigra and development of intraneuronal accumulations of aggregated proteins, neuro-fibrillary tangles can be hindered, synaptogenesis and neuroregeneration can be induced which can result in regrowth and repair of nervous tissues and brain cells.

When it comes to neurogenesis, the generation of new neurons occurring in adult mammals as classically described in two defined regions of the brain: the subventricular zone of the lateral ventricles and the subgranular zone of the dentate gyrus, where neural stem cells give rise to new neurons and glia, which functionally integrate into the existing circuits under physiological conditions. This mechanism of neurogenesis also indicates a highly dynamic behavior, which is contributed by promotion of several underlying mechanisms. Experimental studies indicate the presence of neurogenic potential in other brain regions also. Neural progenitor and stem cells have been isolated from various areas of the adult brain, including non-neurogenic areas, such as the spinal cord in species including humans [47,48]. This methodology of treating through enhancing oxygenation by modifying the quality, concentration, metabolism, storage and oxygen binding capacity of hemoglobin is also effective in demyelination conditions. This includes enhancement of factors associated with oxygen metabolism such as oxidases, peroxidases, catalases, hydroxylases, and electron transfer-cytochromes. Up-regulation of genetic expression is dependent of oxygen. Genetic predispositions can be corrected by enhancing oxygenation since oxygen is the real time mediator of homeostatic regulation.

When it comes to 'Vata Vyadi', the rasayana concept as explained in classical ayurvedic literature is intended in promoting neurogenesis by reestablishing homeostatic regulation by enhancing oxygenation [1,10,38-43,49,50]. This methodology of modulation of neurogenesis by enhancing oxygenation has been followed in ayurvedic medicinal system since thousands of years. And hence it can be concluded that the ayurvedic medicinal approaches towards neurodegenerative conditions and nervous system disorders are mainly focused on enhancing oxygenation. Novel synergistic therapeutic approaches for enhancing oxygenation would thereby aid in reversing neurodegeneration. This novel approach holds the key to the future of treating neurodegenerative conditions, furthermore the future of life sciences.

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