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Review Article

Intrathecal Melatonin Administration via Implanted Pump for Treatment of Alzheimer's Disease and Other Neurodegenerative Disorders: A Mechanical Pineal Gland Strategy

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Abstract

Decades of research has supported those human neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease and cerebellar ataxias share in common severe oxidative and free radical damage to the brain. In fact, there is an abundance of evidence that oxidative stress is the ultimate trigger for apoptosis and neuronal cell death in such diseases.The brain has a complex anti-oxidant system which has evolved to constantly scavenge detrimental free radicals and reactive oxygen species and it has been long proposed that much of cognitive decline associated with aging may be linked with progressive oxidative damage to neurons. However, strategies to treat the shared pathologic endgame of these diseases, regardless of etiology, as a brain redox problem have been lacking. Anti-oxidant treatment strategies in human neurodegenerative diseases have repeatedly focused on oral or parenteral administration, which are likely hampered by the blood brain barrier from significantly "reducing" the central nervous system. Here I review the evidence to support a study of intrathecal melatonin for disease modification and neuroprotection in the neurodegenerative disorders such as Alzheimer's disease.

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Background

Although the causes of neurodegenerative disorders such as Alzheimer's disease remain unknown, oxidative damage to neurons is a well-established common theme in the pathophysiology of these disorders. In fact, the abundance of evidence towards this oxidative stress hypothesis in neurodegenerative diseases gave rise to an entire textbook on the topic published 20 years ago in 1997 [1]. However, there have been relatively few attempts to therapeutically address oxidative imbalance in the brain. The brain is the most susceptible organ to oxidative stress. The brain is particularly sensitive to free radical damage due to its high energy demand (1/5 of total oxygen consumption and 1/6 of cardiac output), high concentration of polyunsaturated fatty acids and abundant transition metals such as iron which may catalyze the production of free radicals and reactive oxygen species (ROS) [2-4]. ROS include hydrogen peroxide (H_2O_2), hydroxyl radical ($OH^{\cdot}$), superoxide radical ($O_2^{-\cdot}$) and some ROS are free radicals (have one or more unpaired electrons denoted by the dot notation) while others are not. Oxidative stress is also engendered by Reactive Nitrogen Species (RNS) such as peroxynitrite ($ONOO^-$) which also readily oxidizes proteins, lipids, sugars and DNA [1]. ROS are primarily generated by mitochondria during normal cellular respiration and under physiological conditions about 98% of molecular oxygen is consumed by the mitochondria at the cytochrome c oxidase complex [5].

Oxidative damage to the brain increases with age and has been hypothesized to be a major cause of age-related cognitive decline [6,7]. Although there has been considerable focus on the accumulation of abnormal proteins in neurodegenerative diseases, the oxidative damage hypothesis more directly explains why neurons die in these disorders. By damaging proteins, nucleic acids, carbohydrates and lipids within a cell, ROS, RNS and free radicals can lead to neuronal cell death by both necrosis and apoptosis. In particular, oxidative damage has been identified as a culprit for triggering cell suicide or apoptosis and apoptosis can be inhibited in neuronal cells lines by adding anti-oxidants and overexpressing anti-oxidant enzymes [8-10]. Under normal conditions, neurons have multiple defense mechanisms against the toxic oxidative products which are generated from normal metabolism. These defense mechanisms are redundant and include both enzymes (superoxide dismutase, catalase, glutathione peroxidase and phospholipid hydroperoxide glutathione peroxidase) and non-enzyme molecules (coenzyme Q, glutathione and melatonin) [1,4,11,12].

Hypothesis

Intrathecal pump delivery of melatonin, one of nature's oldest and most potent central nervous system free radical scavengers and anti-oxidants may prove beneficial in the treatment of various neurodegenerative disorders including Alzheimer's disease.

Oxidative Stress and Neurodegenerative Diseases

The pathologic hallmarks of Alzheimer's Disease (AD) are the abnormal deposition of amyloid beta peptide and intracellular accumu-

lation of hyperphosphorylated tau proteins. Oxidative damage in AD includes advanced glycation end products, nitration, lipid peroxidation adduction products, carbonyl-modified neurofilament protein and free carbonyls. Markers of oxidative damage in the brain of patients with AD, particularly lipid peroxidation, are increased compared to normal controls and AD patients also shown increased levels of transition metals such as iron and copper in the neuropil which catalyze the formation of ROS [13]. The hyperphosphorylation of tau proteins has been linked to oxidation and amyloid beta peptide has also been shown to have pro-oxidant effects [13,14].

Parkinson's Disease (PD) pathophysiology also seems closely linked with oxidative stress due to ROS. ROS in PD have been linked to dopamine metabolism, mitochondrial dysfunction and neuroinflammation [15]. In PD, the substantia nigra, the primary region of selective dopaminergic cell loss has been shown to have significantly decreased levels of reduced glutathione, elevated superoxide dismutase enzyme which suggests a compensatory response to elevated superoxide radicals, elevated products of free radical lipid damage including lipid hydro peroxides and malondialdehydes, elevated levels of DNA oxidative damage products including 8-hydroxyguanosine [1]. Experimental PD can be created in animals by the pesticide rotenone which destroys dopaminergic neurons in the substantia nigra via oxidative stress [16]. MPTP, which causes Parkinsonism in humans and primates also causes complex I inhibition in the mitochondrial electron transport chain and there by generates high levels of ROS [17]. In addition, selective increase of free iron in the substantia nigra has been found in patients with PD and is believed to catalyze the production of ROS via the Fenton reaction [18,19]. Dopamine may be considered an unstable molecule since it can undergo auto-oxidation to form dopamine quinones and free radicals and impaired dopamine metabolism may also contribute to ROS in PD. Finally, the PD-related proteins such as alpha-synuclein tend to aggregate in the presence of ROS and they can contribute to increased ROS production by affecting mitochondrial function [20,21].

Finally, in addition to these most common neurodegenerative disorders discussed so far, other neurodegenerative disorders including amyotrophic lateral sclerosis, Huntington's disease and cerebellar ataxias have been strongly associated with oxidative stress in the central nervous system [22-24]. Thus, targeting oxidative stress has become a promising strategy in the treatment of numerous neurodegenerative disorders [25].

Melatonin and Neurodegenerative Diseases

Melatonin (5-acetyl-5-methoxytryptamine) has been described as an ancient molecule which makes oxygen metabolically tolerable [26]. By numerous mechanisms melatonin reduces oxidative damage and there is evidence to suggest that it has been evolutionarily conserved for billions of years and can be found in all life forms including bacteria. Melatonin's function as an anti-oxidant include direct free radical scavenging, stimulation of antioxidative enzymes, increasing the efficiency of mitochondrial oxidative phosphorylation and reducing free radical generation and augmenting the efficiency of other antioxidants [27]. Melatonin was first discovered to be a potent anti-oxidant in 1993 [28]. It is produced in the vertebrate pineal gland and retina and the major route of delivery to the brain is likely direct secretion into the cerebrospinal fluid of the brain ventricular system, particularly the 3rd ventricle [29]. CSF melatonin concentration is considerably higher than blood melatonin concentrations and melatonin-rich CSF bathes the entire central nervous system via Virchow-Robin perivascular spaces and diffuses deeply into the neural parenchyma [29,30].

This may be the main antioxidant system of the central nervous system and CSF melatonin levels decrease with age. Multiple studies have shown that CSF melatonin concentrations in AD are several-fold lower than those in age-matched non-AD control subjects and CSF melatonin levels in AD are negatively correlated with disease severity [30-33]. Melatonin is lipophilic and easily passes the blood-brain barrier. Preliminary clinical studies of melatonin in humans with AD and in AD animal models have been promising but have not taken advantage of CSF delivery [34,35].

Why Intrathecal Delivery?

Melatonin is a powerful free radical scavenger and antioxidant which is secreted by the pineal gland into the cerebrospinal fluid. Despite passing readily through the blood brain barrier, the bioavailability of oral melatonin is poor and variable [36,37]. Melatonin is safe even at high doses but delivery via an intrathecal pump would more closely mirror the physiologic endogenous delivery of melatonin in humans. Another great benefit of intrathecal pump delivery is the programmable option which could permit CSF delivery of melatonin only during evening hours, similar to the physiologic pineal-secreted delivery of melatonin - a mechanical pineal gland strategy. The flex-dose programming of available intrathecal pumps (Synchromed II, Medtronic, Inc.) could allow continuous delivery of melatonin into the CSF for multiple hours during just the evening, which may reduce side effects such as alteration of circadian rhythms. This synergy of a safe and powerful endogenous CSF anti-oxidant and a well-established, implantable and programmable human CSF delivery system would take advantage of biomimicry and would not require the extensive safety testing required for novel small molecules or proteins engineered for the treatment of neurodegenerative diseases.

Conclusion

The neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease share oxidative damage to the brain in their pathophysiology. The age-related decrease in cerebrospinal melatonin - an important central nervous system anti-oxidant system - may predispose the brain to age-related cognitive decline and neurodegenerative processes. Augmenting the CSF melatonin concentration in a nocturnal temporal manner via implantable intrathecal pump and catheter system is a simple and novel strategy for disease modification in the neurodegenerative disorders and deserves clinical trial.

Conflict of Interest

The author reports no conflict of interest.

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