Research Article

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Intrathecal Administration of Melatonin via Implanted Pump for the Management of Neurodegenerative Disorders, Including Alzheimer's Disease: A Mechanical Pineal Gland Approach.

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ABSTRACT

Numerous studies have demonstrated that severe oxidative and free radical damage to the brain is a common feature of human neurodegenerative illnesses, including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, and cerebellar ataxias. Actually, a wealth of data points to oxidative stress as the primary cause of neuronal cell loss and apoptosis in these types of illnesses.The brain possesses an intricate antioxidant system that has developed over time to continuously eliminate harmful free radicals and reactive oxygen species. It has long been hypothesized that a significant portion of the cognitive deterioration that comes with aging is connected to progressive oxidative damage to neurons. Nevertheless, regardless of the origin of these diseases, treatment approaches for their shared pathologic outcome, as a redox issue in the brain have been deficient. Oral or parenteral delivery of antioxidants has been the mainstay of antioxidant therapeutic options in human neurodegenerative illnesses; however, these approaches are likely limited in their ability to appreciably "reduce" the central nervous system due to the blood-brain barrier. In this article, I examine the data in favor of investigating intrathecal melatonin for neuroprotection and disease modification in neurodegenerative illnesses like Alzheimer's disease.

INTRODUCTION

While the exact etiology of neurodegenerative diseases like Alzheimer's disease is still unknown, oxidative damage to neurons is a well-established common theme in their pathogenesis. In fact, there is so much evidence supporting the oxidative stress theory in neurodegenerative illnesses that a textbook on the subject was written and published in 1997, 20 years ago [1]. Nonetheless, the brain's oxidative imbalance has not received much attention in terms of therapeutic interventions. Oxidative stress is most likely to affect the brain. Due to its high energy requirement (1/5 of total oxygen consumption and 1/6 of cardiac output), the brain is especially vulnerable to damage from free radicals. high levels of polyunsaturated fatty acids and a lot of transition metals, such iron, which could function as a catalyst to produce reactive oxygen species (ROS) and free radicals [2-4]. ROS include superoxide radical (O2-), hydroxyl radical (OH), and hydrogen peroxide (H2O2). Some ROS are free radicals, which are defined as having one or more unpaired electrons, as indicated by the dot notation, while others are not. Reactive nitrogen species (RNS) like peroxynitrite (ONOO-) can also cause oxidative stress since they can easily damage proteins, lipids, carbohydrates, and DNA [1]. About 98% of molecular oxygen is used by the mitochondria at the cytochrome c oxidase complex during physiological conditions, and ROS are mostly produced by mitochondria during normal cellular respiration.

Age-related cognitive loss has been hypothesized to be mostly caused by oxidative damage to the brain, which worsens with age [6, 7]. The oxidative damage theory more clearly explains why neurons die in neurodegenerative illnesses, despite the fact that aberrant protein accumulation has received a lot of attention in these conditions. Free radicals, reactive oxygen species, and other reactive oxygen species (RNS) can cause necrosis and apoptosis in neuronal cells by destroying proteins, nucleic acids, carbohydrates, and lipids within a cell. Specifically, it has been determined that oxidative damage is the cause of cell suicide or apoptosis, and that anti-oxidant

enzyme overexpression and the addition of antioxidants can prevent apoptosis in neuronal cell lines [8–10]. Neurons possess many defense mechanisms to fend off hazardous oxidative products resulting from regular metabolism under normal circumstances. These redundant defense mechanisms include of non-enzyme substances (coenzyme Q, glutathione, and melatonin) as well as enzymes (superoxide dismutase, catalase, glutathione peroxidase, and phospholipid hydroperoxide glutathione peroxidase).

Hypothesis

One of nature's most powerful antioxidants and free radical scavengers for the central nervous system, melatonin, can be administered intrathecally through a pump to treat a variety of neurodegenerative diseases, including Alzheimer's.

The etiology of Parkinson's disease (PD) appears to be strongly associated with ROS-induced oxidative stress. Neuroinflammation, mitochondrial dysfunction, and dopamine metabolism have all been connected to ROS in Parkinson's disease [15]. Significantly lower levels of reduced glutathione, elevated superoxide dismutase enzyme (which suggests a compensatory response to elevated superoxide radicals), elevated products of free radical lipid damage, such as lipid hydro peroxides and malondialdehydes, and elevated levels of DNA oxidative damage products, such as 8-hydroxyguanosine, have been found in the substantia nigra, the primary region of selective dopaminergic cell loss in Parkinson's disease (PD) [1]. The herbicide rotenone, which causes oxidative stress and the death of dopaminergic neurons in the substantia nigra, can induce experimental Parkinson's disease in rats [16]. MPTP, This results in complex I inhibition in the mitochondrial electron transport chain, which in turn produces high amounts of reactive oxygen species (ROS) and causes Parkinsonism in humans and primates [17]. Furthermore, it has been observed that PD patients have a specific increase in free iron in the substantia nigra, which is thought to catalyze the Fenton reaction, which produces ROS [18, 19]. Since dopamine can auto-oxidize to produce dopamine quinones and free radicals, it may be regarded as an unstable chemical. Impaired dopamine metabolism may also contribute to ROS in Parkinson's disease. Last but not least, PD-related proteins like alpha-synuclein have a tendency to congregate when reactive oxygen species (ROS) are present, and they can also promote ROS generation via influencing mitochondrial activity.

Lastly, oxidative stress in the central nervous system has been strongly linked to a number of neurodegenerative disorders, including cerebellar ataxias, Huntington's disease, and amyotrophic lateral sclerosis, in addition to the most common neurodegenerative disorders that have been covered thus far [22–24]. Thus, addressing oxidative stress has emerged as a viable treatment approach for a variety of neurodegenerative conditions.

Neurodegenerative Diseases and Melatonin

It has been shown that melatonin (5-acetyl-5-methoxytryptamine) is an ancient chemical that reduces the metabolic threshold for oxygen [26]. Melatonin lowers oxidative damage through a variety of pathways, and evidence suggests that it has been conserved during billions of years of evolution in all living forms, including microbes. Melatonin has several anti-oxidant properties, such as direct free radical scavenging, promoting antioxidative enzymes, raising mitochondrial oxidative phosphorylation efficiency, lowering free radical production, and enhancing the effectiveness of other antioxidants [27]. In 1993, melatonin's potential as an antioxidant was first identified [28]. It is primarily delivered to the brain by direct secretion into the cerebrospinal fluid of the brain ventricular system, namely the third ventricle. It is produced in the vertebrate pineal gland and retina.

CONCLUSION

The pathophysiology of neurodegenerative disorders like Parkinson's and Alzheimer's disease is similar in that they are caused by oxidative brain damage. The brain may be more susceptible to age-related cognitive loss and neurodegenerative processes as a result of the age-related decrease in cerebrospinal melatonin, a crucial antioxidant mechanism in the central nervous system. A straightforward and innovative approach to disease modification in neurodegenerative illnesses is to increase the CSF melatonin concentration in a nocturnal temporal manner using an implanted intrathecal pump and catheter system. This approach merits clinical investigation.

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