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Ascorbic Acid: Therapeutic Implications In Neurodegenerative Diseases

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ABSTRACT:

Ascorbic acid, or vitamin C, is a non-enzymatic antioxidant that dissolves in water. According to research, depending on its dose, vitamin C may have immunomodulatory and antibacterial effects. Ascorbic acid regulates the hypothalamic-pituitary-adrenal (HPA) axis in a critical manner. Therefore, research into ascorbic acid's potential role in the neuro-endocrine interaction is necessary to control neurodegenerative illnesses and behavioral abnormalities. Ascorbate, a reduced form of vitamin C, can scavenge reactive oxygen species (ROS) and nitrogen oxides (NO) produced during synaptic activity and neuronal metabolism in brain tissue. According to a number of studies, ascorbic acid effectively regulates redox balance by increasing the activity of natural antioxidant enzymes such as SOD, CAT, GRx, and GPx. Additionally, it performs crucial roles in protein aggregation, which is unquestionably vital in the pathophysiology of neurodegenerative illnesses including multiple sclerosis, Alzheimer's, Parkinson's, and Huntington's disorders. It's interesting to note that a mouse model showed that lower brain ascorbate could cause oxidative stress at a young age, hastening the onset of pathological alterations such Aβ deposition and the ensuing cognitive deficiencies. In order to maintain synaptic activity, ascorbic acid can change the metabolism of the brain. Thus, based on the fragmented evidence, it may be inferred that redox balance caused by ascorbic acid may serve as a possible target for modulating neurodegeneration, neuroinflammation, and cognitive deficits.

Keywords: Alzheimer's disease, Ascorbic acid, Neurodegeneration, Neuroinflammation, ROS

1. INTRODUCTION

The lowered form of vitamin C, ascorbic acid, is a necessary component for human nutrition. According to research [1], fruits and vegetables are the main source of vitamin C, and diet can help sustain physiological levels of the vitamin. Higher species, such as humans, are dependent on exogenous supplies of ascorbic acid since they lack the functioning enzyme needed for the endogenous production of vitamin C [2, 3]. Its absence results in scurvy. Ascorbic acid is a beneficial antioxidant that plays a significant role in cells. It functions as

an enzymatic cofactor [4], influences synaptic activity and brain metabolism [5], and is involved in detoxification processes [6].
The brain has greater ascorbic acid content [7]. Since the brain's high oxidative metabolism is linked to its high glucose usage [8], antioxidants are necessary to shield it from pathological situations [9]. Redox imbalance and oxidative stress are noted in neurodegenerative illnesses including Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) [10, 11], as well as throughout the aging process of the brain [12, 13].
There is a clear connection between ascorbic acid deficiency and oxidative stress-induced neuronal death during neurodegeneration. As a result, we will specifically examine ascorbic acid's involvement in preventing neurodegenerative disorders in this review.

2. EFFECTS OF ASCORBIC ACID IN NEURODEGENERATIVE DISEASES

2.1. Alzheimer's disease

The most common type of dementia that is recorded is Alzheimer's disease, which is brought on by severe neurodegeneration. It is a complex disorder, with several hereditary and physiological variables influencing its course [14]. Ascorbic acid has been shown to be effective in animal models of Alzheimer's disease. After six months of treatment, Murakami et al. found that ascorbic acid dramatically decreased the development of Aβ oligomers and recovered behavioral impairment [15]. The reduction in the ratio of soluble Aβ42 to Aβ40, which is indicative of the advancement of the disease, and the lessened reaction of Aβ oligomerization lead to less oxidative damage in the brain. Ascorbic acid was shown to reverse the declining brain synaptophysin and phosphorylation of Tau at Ser39 in this study. In rats injected with fibrillar Aβ in the hippocampus (CA1), ascorbic acid therapy decreased proinflammatory cytokines and other markers of oxidative stress. According to other research, ascorbic acid totally eliminated the rise in intracellular calcium and Aβ-induced cell death [16].

2.2. Parkinson's disease

Parkinson's disease neuropathology is closely associated with α-synuclein neuropathology, or the protein aggregates called Lewy bodies. This kind of knowledge has the potential to influence the idea of a certain pathophysiology. Studies indicate that ascorbate has a noteworthy ameliorative impact on neuroinflammation produced by α-synuclein. As an illustration, ascorbic acid can convert hazardous clumps of α-synuclein-$Cu2^{+}$ into α synuclein-Cu^{+} and sustain the redox cycle, which converts O_2 into H_2O_2 and constantly depletes cellular redox species [17]. Furthermore, by inhibiting the synthesis of reactive oxygen species in *Saccharomyces cerevisiae* cells, ascorbic acid downregulates the creation of α-synuclein [18]. Furthermore, it has been established that elevated α-synuclein expression makes dopaminergic neurons more vulnerable to oxidative stress, which results in mitochondrial dysfunction [19]. Ascorbic acid may therefore be useful in the treatment of Parkinson's disease. According to research [20], there is evidence that the concentration of lymphocyte ascorbate is lower in the more severe form of Parkinson's disease than in the less severe version. This finding raises the possibility that lymphocyte ascorbate levels could serve as a biomarker for the disease's development. The age of the Parkinson's patients did not, however, correspond with their serum vitamin C levels. Two sizable cohort studies prospectively investigated the relationship between ascorbic acid consumption and the risk of Parkinson's disease [21]. It was shown that eating ascorbic acid in the diet was substantially linked to a lower incidence of Parkinson's disease.

2.3. Huntington's disease

Movement abnormalities and cognitive deficiencies result from Huntington's disease, a genetic neurodegenerative disease marked by a gradual loss of neurons, primarily in the striatum. According to clinical research, Huntington's disease may be associated with a deficiency in the release of ascorbic acid into the striatum, which may have an indirect effect on the release of glutamate by cortical neurones [22]. Research demonstrated that striatal extracellular ascorbate in R6/2 mice was restored to wild-type controls following a 3-day infusion of sodium ascorbate (300 mg/kg) [23]. This finding raises the possibility that ascorbate plays a role in regulating neuronal function in Huntington's disease. According to Acuña et al. [24], astrocytes may not release ascorbate efficiently prior to behavioral symptoms of Huntington's disease, indicating a disruption in ascorbate homeostasis during the presymptomatic phases of a mouse version of Huntington's disease. Furthermore, exogenous ascorbic acid cannot cause the huntingtin-dependent ascorbate transporter SVCT2 translocation to the plasma membrane in mice during the symptomatic stages of Huntington's disease [25].

Given the significance of maintaining ascorbate homeostasis in Huntington's disease, further research should be done on ascorbic acid as a neurodegenerative adjuvant.

2.4 Multiple sclerosis

A long-term inflammatory brain illness that causes demyelination, neurodegeneration, and elevated oxidative stress is multiple sclerosis. In addition to its well-known antioxidant qualities, vitamin C helps produce collagen, this is essential for the production of myelin [26]. Furthermore, Eldridge et al.'s research clearly shows that it plays a critical function in promoting the myelin development of Schwann cells [27]. Because of these benefits, we might speculate that ascorbate may one day be used to treat or prevent multiple sclerosis. Ascorbic acid increased memory for passive avoidance learning, according to Babri et al. [28], but progesterone did not improve memory when combined with ascorbic acid. According to previous research [29, 30], ascorbic acid may influence the cholinergic and serotonergic neurotransmitter systems. Furthermore, it has been observed that ascorbic acid influences the activity of the enzyme acetyl cholinesterase, which is crucial for learning and memory processes [31]. Lastly, the antioxidant qualities of ascorbic acid may also help to prevent and attenuate the effects of multiple sclerosis [32, 33].

3. CONCLUSION

We can infer from the explanation above that ascorbic acid may be used as a drug to treat neurological disorders such as multiple sclerosis, Parkinson's disease, Alzheimer's disease, and Huntington's disease, as well as a preventive strategy. Carefully examining ascorbic acid's neuromodulatory and antioxidant qualities can help develop therapeutic approaches that effectively address neuroinflammation, dementia, cognitive decline, and behavioral changes. Additionally, it can be used as an adjuvant therapy specifically for brain inflammation in combination with other anti-inflammatory medications. Understanding the molecular underpinnings and signaling pathways that ascorbic acid may effectively target as a medicine for a variety of neurodegenerative illnesses should necessitate further research.

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Conflict of interest

All authors declare that there are no conflicts of interest.

Data availability statement

No data was used for the research described in the article.

Author’s contribution

Rajen Dey (RD) participated in the conception of the study. RD and Manojit Bysack (MB) participated in literature searches and extraction. MB and RD wrote the manuscript for submission to this journal.

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