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Review Article

Benefits of N-Acetylcsteine Supplementation in Neurodegenerative Diseases: A Narrative Review

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Abstract

N-acetylcysteine is a precursor to L-cysteine, which in turn is a component of the endogenous antioxidant glutathione, which is a tripeptide composed of glutamate, cysteine and glycine. The objective of this review is to carry out a broad and exhaustive analysis of the available scientific evidence on the role of N-acetylcysteine in the treatment of neurodegenerative diseases. The administration of NAC was analyzed in patients with Alzheimer's disease, Parkinson's disease and multiple sclerosis. In conclusion, comment that the intake of N-acetylcysteine has beneficial effects on neurotransmission, oxidative stress, γ-secretase activity, letter fluency, immediate memory of numbers, memory, the dopaminergic system, glutathione brain, malondialdehyde levels, anxiety, brain glucose levels, cognition and attention.

Keywords: N-acetylcysteine, Alzheimer, Parkinson, multiple sclerosis.

Introduction

N-acetylcysteine (NAC) is an acetylated derivative of the amino acid cysteine. It is widely available as a nutritional supplement with antioxidant properties. NAC (Figure 1) is considered a safe and well tolerated medication that has been used worldwide in a variety of medical conditions over the past decades [1].

Over the past decade, there has been increasing interest in the use of NAC to treat psychiatric and neurological disorders [1].

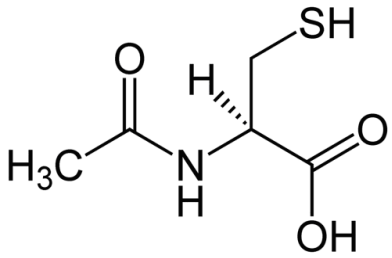

Figure 1. Structure of the N-Acetylcysteine.

Evidence based on preclinical research studies suggests that NAC may modulate pathophysiological processes that are involved in multiple psychiatric and

neurological disorders, including oxidative stress, neurogenesis and apoptosis, mitochondrial dysfunction, neuroinflammation, and dysregulation of glutamate and dopamine neurotransmitter systems [1].

NAC is a precursor of L-cysteine, which in turn is a component of the endogenous antioxidant glutathione, which is a tripeptide composed of glutamate, cysteine and glycine. Glutathione plays an important role in antioxidant activities, cell signaling regulated by the oxidation-reduction reaction, and immune responses. The ratio of reduced glutathione to oxidized glutathione is often used as a measure of oxidative stress. Because cysteine availability is a limiting factor for glutathione synthesis, NAC may help counteract oxidative stress by maintaining or increasing glutathione levels [2]. The actions of NAC are to restore the antioxidant potential of cells by replenishing glutathione depletion by free radicals and scavenging reactive oxygen species. As an anti-inflammatory substance, NAC can limit the release of cytokines in the early stage of the immune response [3].

Oxidative stress is a disturbance in the balance between the production of reactive oxygen species and antioxidant defenses and can occur in response to tissue damage and cause subsequent damage. Given the putative effect of oxidative stress on cognitive function, it is theoretically plausible that the application of an antioxidant agent could mitigate this dysfunction to some extent [4].

NAC is a nutraceutical capable of replenishing brain glutathione and consequently protects against oxidative stress and is likely a neuroprotectant that demonstrates preclinical efficacy in reducing markers of oxidative stress and the severity of cognitive dysfunction in animal models. Similar oxidative responses have been detected in humans, although cognition has not been widely studied [4].

Neurodegenerative diseases (ND) (Figure 2) are a heterogeneous group of complex diseases characterized by neuronal loss and progressive degeneration of different areas of the nervous system. The ND represent a major health problem worldwide, with an increasing incidence rate [5].

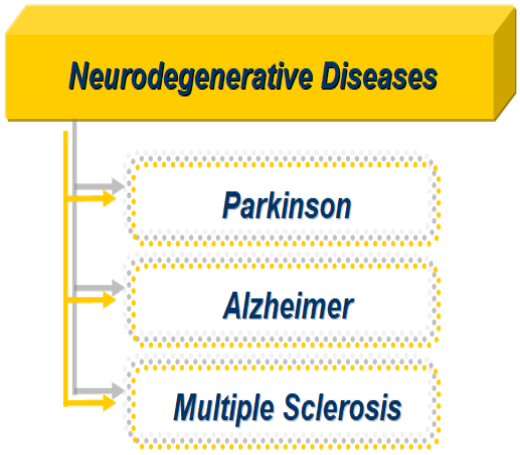

Figure 2. Types of neurodegenerative diseases.

The objective of this review article is to carry out a broad and exhaustive analysis of the available scientific evidence on the role of NAC in the treatment of ND such as: Alzheimer's disease (AD), Parkinson's disease (PD) and sclerosis multiple (SM).

Material and Methods

A descriptive review study has been carried out with the aim of answering the following research question: What effects does NAC supplementation have on improving the symptoms of neurodegenerative diseases?

To do this, a search was carried out in databases such as Pubmed and Google Scholar in February 2024. In order to find as

many articles as possible, the following keywords were used: N-acetylcysteine, parkinson, alzheimer and multiple sclerosis.

For the selection of articles, inclusion criteria were used such as: articles published in any country, articles published in English, articles where the ingestion of NAC is carried out in subjects with diagnosed ND and articles where the research is carried out in vivo; The following exclusion criteria were established: articles that do not clearly show the intake of NAC in subjects with PD, AD and MS, articles that do not refer to NAC supplementation in ND.

Results

NAC supplementation in Alzheimer's disease

In a study conducted by Dodd et al. in 43 participants, NAC (50 mg/kg/day) was administered to 23 patients with AD in a 24 week randomized double-blind trial. To evaluate the memory level of the participants, the Wechsler Memory Scale was used. The results were not statistically significant with respect to the control group (n=20), however the results were better in the experimental subjects [6].

Raghu et al. performed a study where the effect of NAC intake on neurotransmission in AD was investigated where it was demonstrated that the use of NAC has beneficial effects on the balance of amino acids [7].

In the study carried out by researchers Robinson et al. the antioxidant activity of the use of NAC as therapy for AD was evaluated in different disease progressions in mice; the use of NAC in mice showed protection against oxidative stress by acting by eliminating free radicals. Research showed that NAC treatment has significant brain protective effects [8]. The authors Hsiao et al. demonstrated that NAC can be effective for the treatment of AD because it decreases the activity of γ-secretase, favoring improvement in patients with AD [9].

In a study conducted by Adair et al. the administration of NAC was performed in patients with advanced stage AD over a period of six months. Subjects tolerated the treatment well and demonstrated significantly improved performance in letter fluency and immediate number recall on the Wechsler Memory Scale. On the other hand, blood oxidative stress levels did not obtain significant results [10].

NAC intake in patients with Parkinson's disease

In a study carried out by Monti et al. the biological and clinical effects of NAC intake were evaluated in 42 patients with PD. Twenty-eight subjects received a weekly administration of 50 mg/kg of NAC intravenously and 2 oral doses of 500 mg per day for 3 months. The other 14 participants took only the standard PD treatment. The results suggest that NAC may positively affect the dopaminergic system in PD patients, with corresponding positive clinical effects [11].

Coles et al. performed a 4 week prospective study using oral administration of 6000 mg NAC/day for 28 days in 5 patients with PD and 3 healthy subjects. In the results obtained there were no significant increases in brain glutathione, which may be related to a low bioavailability after oral ingestion of NAC [12].

In a study conducted by researchers Katz et al. in 12 PD patients who received an oral dose of NAC twice daily for 2 days. Three doses were compared: 7 mg/kg, 35 mg/kg and 70 mg/kg. Measurement of NAC, cysteine, and glutathione in cerebrospinal fluid (CSF)

was performed at baseline and 90 minutes after the last dose. Cognitive and motor functions were assessed before and after NAC administration using the Montreal Cognitive Assessment (MoCA) and the motor subscore part III of the Unified PD Rating Scale (UPDRS-III). Oral NAC produced an increase of the NAC concentrations in CSF, and the highest dose of NAC produced a higher NAC concentrations in CSF. On the other hand, NAC had no effect on motor or cognitive function. The results obtained by the researchers showed the feasibility of NAC intake as a possible complementary therapy in PD disease [13].

NAC in patients with multiple sclerosis

Khalatbari et al. conducted a randomized clinical trial in 42 patients with MS with an experimental group of 21 participants and a control group of 21 participants. The experimental group received 600 mg of NAC twice a day for 8 weeks and the control group received a placebo with the same amount. Malondialdehyde (MDA), nitric oxide and glutathione levels were evaluated. Additionally, the Hospital Anxiety and Depression Scale (HADS) was used to evaluate symptoms of depression and anxiety in the participants. The results showed that in the experimental group serum concentrations of MDA and anxiety decreased significantly, however the rest of the variables did not suffer significant changes between the experimental group and the control group [14]. In a study carried out by Monti el al. in 24 MS patients, the experimental group (n=12) was administered NAC intravenously once a week and orally for the next 6 days over a period of 2 months. The results showed a significant increase in brain glucose metabolism in several brain regions in the experimental group compared to the control group. Scores related to cognition and attention also improved significantly in the experimental group compared to the control group [15].

Krysko et al. conducted a study in patients with progressive MS whose objective was to evaluate the effect of NAC on the changes in fatigue and antioxidant biomarkers that occur in patients with progressive MS. The experimental group (n=15) ingested 1250 mg of NAC three times a day for 4 weeks, while the control group (n=5) ingested the same as the experimental group but with placebo. The results of the study showed that the reduction in fatigue was similar in both groups, and there were no significant changes in antioxidant biomarkers in the blood between the experimental group and the control group [16].

Conclusions and Future Directions

As conclusions of this review, it is highlighted that the intake of NAC has beneficial effects on AD in the improvement of neurotransmission, in the protection against oxidative stress, in the decrease of the activity of γ-secretase, in the improvement of the level letter fluency and immediate number recall and memory; on PD in the improvement of the dopaminergic system and the increase in brain glutathione; on MS in the reduction of malondialdehyde levels and anxiety, in the improvement of brain glucose levels, in cognition and attention.

The number of studies carried out with NAC in ND is very limited in the scientific literature, so more studies are needed on the influence of NAC intake in patients with AD, PD and MS.

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