N-acetylcysteine and neurodegenerative diseases: basic and clinical pharmacology

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Abstract

Increasing lines of evidence suggest a key role of oxidative stress in neurodegenerative diseases. Alzheimer's disease, Parkinson's disease, myoclonus epilepsy of the Unverricht-Lundborg type, spinocerebellar degeneration, tardive dyskinesia and Down's syndrome have been associated with several mitochondrial alterations. Oxidative stress can decrease cellular bioenergetic capacity, which will then increase the generation of reactive oxygen species resulting in cellular damage and programmed cell death. First, this review examines the mechanisms of action of N-acetylcysteine (NAC), an antioxidant and a free radical-scavenging agent that increases intracellular GSH, at the cellular level. NAC can act as a precursor for glutathione synthesis as well as a stimulator of the cytosolic enzymes involved in glutathione regeneration. The chemical properties of NAC include redox interactions, particularly with other members of the group XIV elements (selenium, etc.) and ebselen, a lipid-soluble seleno-organic compound. Second, NAC has been shown to protect against oxidative stress-induced neuronal death in cultured granule neurons. Recent findings on the protective effect of NAC against 4-hydroxynonenal (HNE)-induced toxicity in cerebellar granule neurons are summarized. Finally, the protective pharmacokinetics of NAC in humans and the possible usefulness of NAC for the treatment of neurodegenerative diseases are discussed with reference to basic and clinical studies.

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