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MINIREVIEW

Glutathione, oxidative stress and neurodegeneration

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There is significant evidence that the pathogenesis of several neurodegenerative diseases, including Parkinson's disease, Alzheimer's disease, Friedreich's ataxia and amyotrophic lateral sclerosis, may involve the generation of reactive oxygen species and mitochondrial dysfunction. Here, we review the evidence for a disturbance of glutathione homeostasis that may either lead to or result from oxidative stress in neurodegenerative disorders. Glutathione is an important intracellular antioxidant that protects against a variety of different antioxidant species. An important role for glutathione was proposed for the pathogenesis of Parkinson's disease, because a decrease in total glutathione concentrations in the substantia nigra has been observed in preclinical stages, at a time at which other biochemical changes are not yet detectable. Because glutathione does not cross the blood–brain barrier other treatment options to increase brain concentrations of glutathione including glutathione analogs, mimetics or precursors are discussed.

Keywords: Alzheimer's disease; amyotrophic lateral sclerosis; glutathione; neurodegeneration; Parkinson's disease.

The etiology of neuronal death in neurodegenerative diseases remains mysterious. These illnesses are insidious and subtle in onset and run a gradually progressive, inexorable course. They are exemplified by illnesses such as Alzheimer's disease (AD), Huntington's disease (HD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), hereditary spastic paraplegia and cerebellar degeneration. Recent advances in both molecular genetics and neurochemistry have improved our knowledge of the fundamental processes involved in cell death, including oxidative stress and mitochondrial dysfunction. Both processes may interfere with each other.

In this issue, Dringen and colleagues [1] review the potential of the antioxidant glutathione to detoxify reactive oxygen species (ROS) with special emphasis on its metabolism in neurons and glia. In this review we focus on the evidence that oxidative stress is involved in the pathogenesis of neurodegenerative disease and discuss the specific role of glutathione. Of all neurodegenerative diseases, evidence for a dysfunction of glutathione metabolism based on post mortem examinations, animal and cell culture models is strongest in PD.

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Abbreviations: AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; BSO, buthionine sulfoximine; CSF, cerebral spinal fluid; DOPAC, 3,4-dihydroxybenzoic acid; GSH, glutathione; GSSG, glutathione disulfide (oxidized glutathione); γGT, γ-glutamyltranspeptidase; HNE, 4-hydroxynonenal; H_2O_2, hydrogen peroxide; HVA, homovanillic acid; MPP^+, 1-methyl-4-phenylpyridinium; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; $NO^{\cdot}$, nitric oxide; $^{\cdot}OH$, hydroxyl radical; 6-OHDA, 6-hydroxydopamine; 8OH2′dG, 8-hydroxy-2′-deoxyguanosine; PD, Parkinson's disease; ROS, reactive oxygen species; SNpc, substantia nigra pars compacta.

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INTRACELLULAR SOURCES OF REACTIVE OXYGEN SPECIES

The observation that biomolecules, which consist primarily of carbon, hydrogen, oxygen, nitrogen and sulfur, are disrupted by the presence of oxygen (O_2) is an evolutionary paradox for aerobic life [2]. A wide variety of ROS can be found in biological systems. These ROS differ in their site of formation, their physiological function, their reactivity and their biological half-life. Mitochondria, nitric oxide synthase, arachidonic acid metabolism, xanthine oxidase, monoamine oxidase and P450 enzymes are sources of ROS in the brain. The high metabolic rate of neurons implies a high baseline ROS production. Correspondingly, healthy brain cells possess high concentrations of both enzymatic and small molecule antioxidant defenses (Fig. 1). The enzymes include CuZn-superoxie dismutase and Mn-superoxide dismutase, GSH peroxidase and catalase, as well as the small molecules glutathione, ascorbic acid, vitamin E and a number of dietary flavonoids. Under normal physiological conditions cells thereby cope with the flux of ROS. Oxidative stress describes a condition in which cellular antioxidant defenses are insufficient to keep the levels of ROS below a toxic threshold. This may be either due to excessive production of ROS, loss of antioxidant defenses or both (Fig. 1).

OXIDATIVE STRESS AND THE SHAPE OF CELL DEATH

Loss of glutathione and oxidative damage have been suggested to constitute early, possibly signaling events in apoptotic cell death [3,4]. In thymocytes, a decrease of GSH and disruption of the mitochondrial transmembrane potential preceded the onset of apoptosis [5,6]. A rapid loss of GSH was found recently in IL3 withdrawal-induced apoptosis of FL5.12 cells. Efflux of GSH constitutes a step of Fas-induced apoptosis [7,8].

Strong evidence that glutathione depletion causes cell death comes from cell culture studies by Li and colleagues [9]. Using