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Glutathione and Parkinson's disease: is this the elephant in the room?

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Abstract

At least 2 decades have past since the demonstration of a 40-50% deficit in total glutathione (GSH) levels in the substantia nigra in patients with Parkinson's disease (PD). The similar loss of GSH in the nigra in Incidental Lewy body disease, thought to be an early form of PD, indicates that this is one of the earliest derangements to occur in the pre-symptomatic stages of PD. Oxidative damage to lipids, protein and DNA in the nigra of PD patients is consistent with the loss of the antioxidant functions contributed by GSH. Past clinical trials that have used an antioxidant approach to treatment have used antioxidants that might substitute for GSH but these have shown modest to little benefit. More recent studies of the functions served by GSH in cells include in addition to its well-known participation in H(2)O(2) and toxin removal, such roles as modulation of protein function via thiolation which may control physiological and pathophysiological pathways to include DNA synthesis and repair, protein synthesis, amino acid transport, modulation of glutamate receptors and neurohormonal signaling. These multifunctional aspects to the workings of GSH in the cell would suggest that its loss perturbs many different processes and that replenishment and maintenance of GSH per se may be the best approach for preventing progressive damage from occurring. Despite this, few studies have been directed at specifically restoring GSH, although, as discussed herein, its unsanctioned use in PD is growing in popularity. This review will focus on glutathione in PD; the various functions carried out by glutathione and possible consequences of its depletion, as well as measures to elevate GSH in the CNS and its use in humans. Consideration of how the CNS generates and handles the substrates for GSH synthesis is also addressed with the view in mind that this may provide insights into control and maintenance of intracellular glutathione.

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