Glutathione Deficiency in Parkinson's Disease: Intranasal Administration as a Method of Augmentation

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Abstract   *Reduced glutathione (GSH), an abundant essential antioxidant capable of scavenging reactive oxygen species and reactive nitrogen species in both cytosol and mitochondria, is one of the primary antioxidant defence systems of the central nervous system. Among its many roles, GSH is a substrate for glutathione peroxidase, where it inactivates hydrogen peroxide, a mediator of neurodegeneration. GSH holds potential as a neuroprotective strategy capable of reducing radicals, preventing mitochondrial dysfunction, and subsequent cell death. Whereas humans are typically capable of supplying GSH in quantities sufficient for function, the production of GSH appears inadequate in some circumstances. Preliminary data now exists to warrant consideration of supplemental GSH as a conditionally essential nutrient in individuals with evidence of nigrostriatal degeneration, such as in Parkinson's disease. While there are several potential methods for administering supplemental (i.e., exogenous) GSH, intranasal administration might be the preferable method when attempting to augment GSH levels within the central nervous system and to slow neurodegeneration among patients having Parkinson's disease. A safety survey and Phase I study of intranasal glutathione are currently underway to evaluate the safety and tolerability of this novel method of administration.*

Evidence for Glutathione Deficiency

Reduced glutathione (GSH) is a ubiquitous tripeptide found in all eukaryotic cells, including all mammalian tissue. GSH is available to the mammalian organism through cellular synthesis from constituent amino acids, and also through dietary intake. Depletion of GSH in the substantia nigra is one of the earliest reported biochemical events to occur in Parkinson's disease (PD).[1] The GSH content of the substantia nigra in PD has been shown to be approximately 40% lower than controls[2,3] and the degree of disease severity is correlated with the extent of GSH loss.[4] Evidence of glutathione depletion is also evident in related disorders of the nigrostriatal system, such as progressive supranuclear palsy and multiple system atrophy.[5] Post-mortem studies document glutathione deficiency in PD patients, and recently glutathione deficiency has been demonstrated in the cerebrospinal fluid of Lewy body disease patients.[6]

Pathological hallmarks of neurodegenerative diseases include mitochondrial dysfunction, oxidative stress, neuroinflammation, and apoptosis. No medications are available to interfere with this degenerative process; rather, PD therapeutic strategies are targeted solely at dopamine replacement and symptom management. Even with medica-

tion, the disease process ensues.

Given the well-documented cascade of inflammation, degeneration and cell death, intervention strategies should be focused upstream in the pathobiological process. Glutathione deficiency has been shown to precede and contribute to mitochondrial dysfunction, oxidative stress, and dopaminergic apoptosis.[1,7,8] The loss of this primary antioxidant so early in the course of the disease suggests GSH deficiency may be involved with disease initiation,[9] and makes it an ideal candidate for upstream influence on the neurodegenerative process. Despite decades of evidence suggesting glutathione deficiency plays a role in PD, only two intervention studies have attempted to augment glutathione levels in this population.[10-12]

GSH as an Antioxidant

Glutathione is a tripeptide consisting of glycine, cysteine, and glutamate. GSH may quench the majority of known reactive oxygen species in the brain, including hydrogen peroxide, peroxynitrite, and hydroxyl radicals.

Glutathione Deficiency Contributes to Mitochondrial Dysfunction

Mitochondria produce hydrogen peroxide, which is largely detoxified by GSH-dependent mechanisms and a GSH deficit has been shown to exacerbate neuronal damage by impairing mitochondrial function independently of the presence of oxidative stress. Impairment of the GSH defense system thereby compromises the ability of the brain to eliminate hydrogen peroxide, resulting in secondary mitochondrial dysfunction.[13] Several *in vitro* studies demonstrate inhibition of mitochondrial complex I activity following glutathione depletion,[1,7,8] the same portion of the respiratory chain damaged by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, rotenone, and other toxicants associated with the development of Parkinsonism.[14]

Glutathione Supplementation as a Mechanism of Neuroprotection in Parkinson's disease

Only two clinical trials have been conducted to investigate the therapeutic potential of glutathione in Parkinson's disease. In 1996, Italian researchers studied the effects of intravenous (IV) GSH, where 600 mg GSH was administered twice daily to nine patients with early, untreated PD in a 30 day, open-label, uncontrolled trial.[11] All patients improved significantly following IV GSH therapy, with an average 42% decline in disability. The therapeutic effect lasted for 2-4 months following discontinuation of the study medication. The authors concluded that IV GSH has symptomatic effectiveness and possibly retards the progression of the disease.

In a second study, published in 2009,[12] 21 subjects were randomly assigned to receive 1,400 mg of IV GSH or placebo three times a week. The authors concluded that IV GSH was well tolerated, appeared safe, and that the preliminary efficacy data suggested the possibility of a mild symptomatic effect. During the post-treatment period, however, the group that received the IV GSH worsened by a mean of 3.5 units (as per the Unified Parkinson's Disease Rating Scale) more than those in the placebo group.

Methods of Glutathione Repletion

Numerous clinicians have made various attempts at exogenous supplementation of GSH. Each of these has its inherent strengths and limitations. No method has been adequately evaluated for central nervous system (CNS) absorption or clinically correlated to disease progression, or lack thereof. **Table 1,** (p.34), summarizes the various methods of GSH augmentation to the author's knowledge.[11,12,15,16]

Intranasal GSH as a Novel Route of Administration

Intranasal delivery of therapeutic agents has recently received attention as a potential means of circumventing the blood-brain-barrier for the delivery of drugs to the CNS.[17-20] Such a pathway exists in animal models, but it is still debatable whether such delivery could be exploited therapeutically in humans.[17-22] Preliminary research on this topic does not describe the direct measure-

ment of the rate and degree of transport into the CNS, but rather indirectly measures the pharmacological effects of drugs on the CNS.[22]

Sprayed or squirted as a fine mist into nasal cavity, a compound might reach the CNS via several mechanisms. The rich vasculature of the nasal membranes permits some molecules to enter circulation, where they later cross the blood-brain-barrier.[22] A second mechanism of entry into the CNS is by direct entry into the olfactory bulb or the cerebrospinal fluid by transport across the olfactory region of the nasal cavity. The absorption of molecules across the nasal pathway is thought to involve several general mechanisms.[22,23] Water-soluble substances, such as glutathione, are well absorbed and nasal absorption probably depends on aqueous channel diffusion (pores).[24] The data indicate that good bioavailability can be achieved for molecules up to 1000 Da (without enhancers) and good availability can be extended to 6000 Da with enhancers.[24,25] Given that glutathione is a water-soluble molecule of low molecular weight (307.33 Da), it is likely that direct transport into the CNS occurs via aqueous channel diffusion across the olfactory epithelial cells.

Table 1. Delivery Methods for GSH: Advantages and Limitations

Intranasal Administration

Advantages	Limitations
Non-invasive, rapid, comfortable	Concentration in various brain structures may vary
No modification of drug is required	Delivery is expected to decrease with molecular size
Reduces systemic exposure	Mucosal irritation may occur
Rich vasculature enhances uptake	Nasal congestion may interfere with delivery
Drug degradation is minimized	Ongoing use could lead to mucosal damage
May bypass the blood brain barrier	

IV Administration

Advantages	Limitations
No modification of drug is required	Invasive – risk of complications
Effectively raises serum glutathione	Expensive – medical staff required for IV administration
Minimal drug degradation	Inconvenient – mobility issues plus frequent visits
Method used in preliminary studies	Non-specific access to CNS
'Standard of care' among CAM clinicians	One report of hepatic injury following IV GSH

Oral Administration

Advantages	Limitations
Convenient	Poor absorption
	Non-specific access to CNS

Nebulized Administration

Advantages	Limitations
Comfortable	Nebulizer is loud and time consuming
	Portion of dose wasted (non-specific dosing)
	Does not reach systemic circulation

Safety and Toxicology of Intranasal GSH

There have been numerous studies published over the last three decades involving exogenously administered GSH to humans; most have used oral, intravenous, and nebulized forms. Recently, the author assisted with the preparation of an FDA investigational new drug application, reviewing and summarizing all published data on glutathione in humans.[26]

When GSH was repeatedly administered to humans in doses up to 5 g per day, both orally and intravenously, no toxicity was observed.[27,28] In contrast, there was a recent report of severe hepatotoxicity in a patient with PD following the use of IV GSH[29] and bronchoconstriction has been reported in asthmatics following administration of nebulized GSH.[15] There are otherwise no reports in the scientific literature indicating any toxicity from the use of glutathione, whether in oral, aerosol, IV, or intranasal forms, in animals or in humans. Established pharmacopeias, such as the European Pharmacopeia,[30] the Merck Index,[31] the Physicians' Desk Reference,[32] Thomson Micromedex,[33] and others, concur that no toxicity has ever been observed from oral use of glutathione in animals or in humans.

The only published study attempting intranasal administration of GSH was conducted in children ranging in age from 3 to 12 years with chronic otitis media. In this placebo-controlled trial, 30 patients received 600 mg of GSH in 4 mL saline aerosolized and administered via a face mask every 3-4 waking hours for two weeks. In the treatment group, 66.6% of the patients improved compared with 8% of the controls. No toxicity was reported.[34]

Conclusion

PD is a debilitating movement disorder, and the incidence is projected to increase with the aging population. Despite tremendous efforts, not a single neuroprotective strategy has been demonstrated to slow progression of this devastating disease. Hundreds of research studies support the notion of GSH deficiency as a major, early pathobiological mechanism of neurodegeneration in PD and related disorders. This orthomolecule has an impressive safety profile and the intranasal method of administration holds promise as a non-invasive mechanism of enhancing delivery to the CNS. The recent documentation of glutathione deficiency in the CSF suggests GSH may have potential as a biomarker and lends further support for the deficiency hypothesis.[6]

In a disease characterized by excessive reactive oxygen species production, it is time to determine whether correcting the deficiency of glutathione has clinical utility in PD. This is the first publication to describe the potential use of intranasal GSH. Both clinicians and researchers should be aware of the reported bronchoconstriction and hepatotoxicity, and should avoid this therapy in asthmatics and routinely check liver enzymes when administering GSH in any form. Two studies, a "Safety Survey of Intranasal GSH" and a "Phase I Study of Intranasal GSH" are underway by the author, both aiming to evaluate the safety and tolerability of this novel method of administration. If determined to be safe, subsequent Phase II studies should focus on the neuroprotective potential of intranasal GSH, alone and in combination with therapies purported to thwart the cascade of neurodegeneration.

Competing Interests

The author declares that she has no competing interests.

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