

Title: *Glutathione* in *Parkinson's disease*: a link between oxidative stress and mitochondrial damage?

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Address: California *Parkinson's* Foundation, San Jose 95128.

Source: Ann Neurol, ():

Abstract:

Several links exist between the two mechanisms of neuronal degeneration (i.e., oxygen radical production and mitochondrial damage) proposed to have a role in *Parkinson's disease*. Indeed, mitochondria are critical targets for the toxic injury induced by oxygen radicals, and experimental evidence suggests that mitochondrial damage may cause an increased generation of oxygen radicals. A potentially important link between these two mechanisms of neurodegeneration is *glutathione*. Because of the scavenging activity of *glutathione* against accumulation of oxygen radicals, its decrease in the brains of parkinsonian patients has been interpreted as a sign of oxidative stress; however, this change may also result from or lead to mitochondrial damage. It is conceivable therefore that regardless of whether oxidative stress or mitochondrial damage represents the initial insult, these toxic mechanisms may both contribute to neuronal degeneration via changes in *glutathione* levels.

Publication Type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL

ISSN: 0364-5134

Title: Dopamine turnover and *glutathione* oxidation: implications for *Parkinson disease*.

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Source: Proc Natl Acad Sci U S A, 86(4):1398-400 1989 Feb

Abstract:

Parkinson disease is characterized by a major loss (approximately 80% or more) of dopaminergic nigrostriatal neurons and by an increased turnover of neurotransmitter by surviving neurons of the nigrostriatal tract. In theory, increased turnover of dopamine should be associated with an oxidative stress derived from increased production of hydrogen peroxide. The peroxide is formed during the oxidative deamination of dopamine by monoamine oxidase. In experiments with mice, increased presynaptic turnover of dopamine was evoked by injection of reserpine, which interferes with the storage of dopamine in synaptic vesicles. Loss of dopamine and formation of deaminated metabolites were accompanied by a significant rise (87.8%) in the level of oxidized *glutathione* in brain. This change was observed in the striatum, which is richly innervated by dopamine terminals, but not in the frontal cortex, which receives a much sparser innervation by catecholamine nerve terminals. The rise in oxidized *glutathione* was seen even though dopamine terminals constitute only 1% or less of the mass of the striatum. Clorgyline, an inhibitor of monoamine oxidase type A, blocked the formation of oxidized *glutathione*. These observations confirm that a selective increase in neurotransmitter turnover within nigrostriatal nerve

terminals can evoke a change in cellular redox status. We suggest that an oxidative stress may play a role in the natural history of *Parkinson disease*.

Publication Type: JOURNAL ARTICLE

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Country of Publication: UNITED STATES

Title: Alterations in *glutathione* levels in *Parkinson's disease* and other neurodegenerative disorders affecting basal ganglia [see comments]

Author: Sian J; Dexter DT; Lees AJ; Daniel S; Agid Y; Javoy-Agid F; Jenner P; Marsden CD

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Source: Ann Neurol, 36(3):348-55 1994 Sep

Abstract:

Reduced *glutathione* (GSH) and oxidized *glutathione* (GSSG) levels were measured in various brain areas (substantia nigra, putamen, caudate nucleus, globus pallidus, and cerebral cortex) from patients dying with *Parkinson's disease*, progressive supranuclear palsy, multiple-system atrophy, and Huntington's *disease* and from control subjects with no neuropathological changes in substantia nigra. GSH levels were reduced in substantia nigra in *Parkinson's disease* patients (40% compared to control subjects) and GSSG levels were marginally (29%) but insignificantly elevated; there were no changes in other brain areas. The only significant change in multiple-system atrophy was an increase of GSH (196%) coupled with a reduction of GSSG (60%) in the globus pallidus. The only change in progressive supranuclear palsy was a reduced level of GSH in the caudate nucleus (51%). The only change in Huntington's *disease* was a reduction of GSSG in the caudate nucleus (50%). Despite profound nigral cell loss in the substantia nigra in *Parkinson's disease*, multiple-system atrophy, and progressive supranuclear palsy, the level of GSH in the substantia nigra was significantly reduced only in *Parkinson's disease*. This suggests that the change in GSH in *Parkinson's disease* is not solely due to nigral cell death, or entirely explained by drug therapy, for multiple-system atrophy patients were also treated with levodopa. The altered GSH/GSSG ratio in the substantia nigra in *Parkinson's disease* is consistent with the concept of oxidative stress as a major component in the pathogenesis of nigral cell death in *Parkinson's disease*.

Publication Type: JOURNAL ARTICLE

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Country of Publication: UNITED STATES

Title: *Glutathione* peroxidase in early and advanced *Parkinson's disease*.

Author: Johannsen P; Velandar G; Mai J; Thorling EB; Dupont E

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Source: J Neurol Neurosurg Psychiatry, 54(8):679-82 1991 Aug

Abstract:

A defective antioxidant scavenging system plays a major role in one of the theories of the pathogenesis of *Parkinson's disease*. The aim of this study was to investigate whether there is a general difference in antioxidant activity between early and advanced cases of *Parkinson's disease*. Twenty five recently diagnosed patients, without any clinical fluctuations (group A), and 25 patients in a late phase of the *disease* with severe fluctuations in response to levodopa therapy (group B) were included in the study. Erythrocyte *glutathione* peroxidase was determined as a measure of antioxidant activity and significantly lower values were found in group B than in group A. Regression analyses in groups A and B showed significant correlation between *glutathione* peroxidase and duration of *disease*, but not between *glutathione* peroxidase and age of patients.

Publication Type: JOURNAL ARTICLE

ISSN: 0022-3050

Country of Publication: ENGLAND

Title: Reduced intravenous *glutathione* in the treatment of early *Parkinson's disease*.

Author: Sechi G; Deledda MG; Bua G; Satta WM; Deiana GA; Pes GM; Rosati G

Address: Department of Neurology, University of Sassari, Italy.

Source: Prog Neuropsychopharmacol Biol Psychiatry, 20(7):1159-70 1996 Oct

Abstract:

1. Several studies have demonstrated a deficiency in reduced *glutathione* (GSH) in the nigra of patients with *Parkinson's Disease* (PD). In particular, the magnitude of reduction in GSH seems to parallel the severity of the *disease*. This finding may indicate a means by which the nigra cells could be therapeutically supported. 2. The authors studied the effects of GSH in nine patients with early, untreated PD. GSH was administered intravenous, 600 mg twice daily, for 30 days, in an open label fashion. Then, the drug was discontinued and a follow-up examination carried-out at 1-month interval for 2-4 months. Thereafter, the patients were treated with carbidopa-levodopa. 3. The clinical disability was assessed by using two different rating scale and the Webster Step-Second Test at baseline and at 1-month interval for 4-6 months. All patients improved significantly after GSH therapy, with a 42% decline in disability. Once GSH was stopped the therapeutic effect lasted for 2-4 months. 4. Our data indicate that in untreated PD patients GSH has symptomatic efficacy and possibly retards the progression of the *disease*. <

Publication Type: CLINICAL TRIAL; JOURNAL ARTICLE

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Country of Publication: ENGLAND

Title: Mitochondrial impairment as an early event in the process of apoptosis induced by *glutathione* depletion in neuronal cells: relevance to *Parkinson's disease*.

Author: Merad-Boudia M; Nicole A; Santiard-Baron D; Saill e C; Ceballos-Picot I

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Source: Biochem Pharmacol, 56(5):645-55 1998 Sep 1

Abstract:

In *Parkinson's disease* (PD), dopaminergic cell death in the substantia nigra was associated with a profound *glutathione* (GSH) decrease and a mitochondrial dysfunction. The fall in GSH concentration seemed to appear before the mitochondrial impairment and the cellular death, suggesting that a link may exist between these events. The relationships between GSH depletion, reactive oxygen species (ROS) production, mitochondrial dysfunction and the mode of cell death in neuronal cells remain to be resolved and will provide important insights into the etiology of *Parkinson's disease*. An approach to determine the role of GSH in the mitochondrial function and in neurodegeneration was to create a selective depletion of GSH in a neuronal cell line in culture (NS20Y) by inhibiting its biosynthesis with L-buthionine-(S,R)-sulfoximine (BSO), a specific inhibitor of gamma-glutamylcysteine synthetase. This treatment led to a nearly complete GSH depletion after 24 hr and induced cellular death via an apoptotic pathway after 5 days of BSO treatment. By using the reactive oxygen species-sensitive probe 2',7'-dichlorofluorescein, we observed that the rapid GSH depletion was accompanied, early in the process, by a strong and transient intracellular increase in reactive oxygen species evidenced after 1 hr with BSO, culminating after 3 hr when the GSH level decreased to 30% of normal. GSH depletion induced a loss of mitochondrial function after 48 hr of BSO treatment. In particular, the activities of complexes I, II and IV of the respiratory chain were decreased by 32, 70 and 65%, respectively as compared to controls. These results showed the crucial role of GSH for maintaining the integrity of mitochondrial function in neuronal cells. Oxidative stress and mitochondrial impairment, preceding DNA fragmentation, could be early events in the apoptotic process induced by GSH depletion. Our data are consistent with the hypothesis that GSH depletion could contribute to neuronal apoptosis in *Parkinson's disease* through oxidative stress and mitochondrial dysfunction.

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