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COMMENTARY

THE POSSIBLE RELATION OF GLUTATHIONE, MELANIN AND 1-METHYL-4-PHENYL-1,2,5,6-TETRA-HYDROPYRIDINE (MPTP) TO PARKINSON'S DISEASE

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Although the treatment of Parkinson's Disease has advanced significantly in the last twenty years, the etiology and possible means of prevention of this disease remain obscure. As recently outlined [1], three general hypotheses regarding the etiology of Parkinson's Disease have been put forward: genetic factors, aging of the nervous system and environmental factors such as infections and/or toxins. Calne and Langston [1], after reviewing the available evidence, concluded that genetic factors and normal aging of the central nervous system can be excluded as adequate causes for the majority of cases of Parkinson's Disease. These authors suggest that, in most cases, the cause of Parkinson's Disease may be exposure to environmental toxins superimposed on the normal decline of substantia nigra dopamine (DA) cells that occurs during aging. Reactive and highly toxic oxygen radicals (such as superoxide radicals and hydrogen peroxide) are produced by normal cellular metabolism, including the oxidative metabolism of catecholamines. These oxygen derivatives are normally eliminated by a number of scavenger systems including superoxide dismutase (in the case of superoxide radicals) and catalase and glutathione (GSH) peroxidase (in the case of hydrogen peroxide). Neurotoxins which induce irreversible parkinsonism, such as 6-hydroxydopamine and manganese, may cause the accumulation of reactive oxygen derivatives in the DA cells of the substantia nigra [2, 3]. The concentration of GSH may be limiting in the process of hydrogen peroxide detoxification (see Ref. 4). As recently reviewed [1, 4], an inverse relationship between cigarette smoking and the incidence of Parkinson's Disease is established. It has been suggested that smokers may maintain a slight but sustained increase in brain concentrations of reducing agents such as carbon monoxide, which would further protect DA cells from the oxidized products of DA metabolism [1, 4]. These data have been interpreted as suggesting that the concentrations of reducing agents such as GSH normally present in DA cells may be suboptimal.

Perry and colleagues [4] have shown that the amount of GSH at autopsy in human substantia nigra (that brain area containing most DA cells) is low compared to other brain areas examined, and that GSH concentrations are further and significantly reduced in the substantiae nigrae of individuals dying of Parkinson's Disease. The authors cite the autopsy data as support for the hypothesis that a relative GSH deficiency may exist in human substantia nigra, affording insufficient protection from cytotoxic metabolites of DA metabolism and, under some circumstances, leading to DA cell death and Parkinson's Disease.

Recently, the accidental induction of Parkinson's Disease by self-administration of a meperidine analogue (1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine; MPTP) has been reported [5–7]. A primate model of MPTP-induced Parkinson's Disease has been developed [8]; however, the mechanism of action of MPTP in causing Parkinson's Disease remains obscure. It is well established that GSH can be readily conjugated both *in vivo* and *in vitro* with a wide variety of conjugated, unsaturated molecules [9, 10]. MPTP is a highly conjugated aromatic compound, and we suggest that MPTP may act to conjugate brain GSH *in vivo*. The postulated resultant decrease in GSH concentration in DA cells would increase the susceptibility to toxic by-products of DA metabolism. This might account for the observed DA cell death and development of Parkinson's Disease after MPTP.

It is interesting that the two neuronal groups primarily affected in Parkinson's Disease, namely midbrain DA cells and locus coeruleus norepinephrine-containing cells, are highly pigmented. MPTP induces DA cell death in humans and primates (whose substantiae nigrae contain much of the pigment melanin), but has substantially less effect in lower species (whose substantiae nigrae contain much less melanin [11]) [8]. The concentration of melanin, a pigment resulting from the oxidation and polymerization of the DA precursor, dopa [12], may in fact provide an index of the relative inability of DA cells to prevent the accumulation of oxidized by-products of DA metabolism. In melanocytes, increased melanin synthesis is associated with an increased vulnerability to cell injury and death [13], perhaps because the quinone intermediates in melanin synthesis are highly reactive with many cell constituents, including GSH [12]. Manipulations which alter melanin production also affect intracellar GSH production

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[12, 14]. However, suggesting a causal relationship would be highly speculative: could it be that decreased GSH levels allow more dopaquinone formation and subsequent conversion to melanin, or might an initial increase in dopaquinone production lead to a secondary decrease in GSH through a direct conjugation of GSH to this melanin precursor? Either way, we suggest that melanin-rich, GSH-low brain DA cells may be more susceptible to the postulated GSH-depleting effects of MPTP.

In fact, since the initial drafting of this commentary, Lyden and colleagues [15] have directly demonstrated that MPTP binds with high affinity to dopamine melanin *in vitro*. Thus, DA cell melanin may act as a site for the accumulation and local release of MPTP in the human and primate substantia nigra. This might help to explain the relatively selective and potent effect of MPTP on DA cells [8].

Concluding remarks

The recent autopsy data of Perry and coworkers [4] lend support to the hypothesis that a relative deficiency in substantia nigra GSH results in insufficient protection of DA cells from oxidized products of DA metabolism. This hypothesis can be tested experimentally. Drug-induced GSH synthetase inhibition should lead to DA cell death, which in turn should be prevented by the administration of sulfhydryl compounds which bypass GSH synthetase. The proposed mechanism of action of the Parkinson's Disease-inducing chemical MPTP can likewise be assessed by studying GSH–MPTP conjugation (*in vivo* and *in vitro*), the effect of MPTP injection on substantia nigra GSH concentration and the localization of MPTP *in vivo*. The interrelationship between melanin, MPTP and GSH can be further addressed in melanocytes and in DA neurones in culture. If more data in support of these hypothesis are forthcoming, treatment of individuals in the early stages of (or at risk of developing) Parkinson's Disease with sulfhydryl compounds or other antioxidants may be warranted.

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REFERENCES

1. D. B. Calne and J. W. Langston, *Lancet* 1457 (1983).
2. R. E. Heikkila and G. Cohen, *Science* **172**, 1257 (1971).
3. J. Donaldson, D. McGregor and F. LaBella, *Can J. Physiol. Pharmac.* **60**, 1398 (1982).
4. T. L. Perry, D. V. Godin and S. Hansen, *Neurosci. Lett.* **33**, 305 (1982).
5. G. C. Davis, A. C. Williams, S. P. Markey, M. H. Ebert, E. D. Caine, C. M. Reichert and I. J. Kopin, *Psychiat. Res.* **1**, 249 (1979).
6. J. W. Langston, P. Ballard, J. W. Tetrud and I. Irwin, *Science* **219**, 979 (1983).
7. J. W. Langstom and P. A. Ballard Jr., *New. Engl. J. Med.* **309**, 310 (1983).
8. R. S. Burns, C. C. Chiueh, S. P. Markey, M. H. Ebert, D. M. Jacobowitz and I. J. Kopin, *Proc. natn. Acad. Sci. U.S.A.* **80**, 4546 (1983).
9. E. Boyland and L. F. Chasseaud, *Biochem. J.* **104**, 95 (1967).
10. E. Boyland and L. F. Chasseaud, *Biochem. J.* **109**, 651 (1968).
11. C. D. Marsden, *J. Anat.* **95**, 256 (1961).
12. G. Prota, *J. invest. Derm.* **75**, 122 (1980).
13. J. M. Pawalek and A. B. Lerner, *Nature, Lond.* **278**. 627 (1978).
14. K. Yonemoto. G. A. Gellin, W. L. Epstein and K. Fukuyama, *Biochem. Pharmac.* **32**, 1379 (1983).
15. A. Lyden, V. Bondesson, B. S. Larsson and N. G. Lindquest, *Acta pharmac. tox.* **53**, 429 (1983).