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Forum Editorial

Oxidative Damage in Parkinson's Disease

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PARKINSON'S DISEASE (PD) is a progressive neurodegenerative disease characterized by motor symptoms, as well a variety of nonmotor manifestations. The pathological hallmarks of PD are relatively selective degeneration of the nigrostriatal dopaminergic system and formation of cytoplasmic inclusions composed of protein aggregates that are known as Lewy bodies (20). The pathogenic process in PD is not understood completely, but almost certainly involves an interaction between genetic and environmental factors. Despite this etiological uncertainty, studies of both PD patients and model systems have suggested an important role for oxidative damage in PD. Oxidative damage may contribute to both nigrostriatal dopaminergic degeneration and the development of protein aggregates. As summarized in this issue by Shults (19), these recent advances have led to an investigation into the potential clinical use of antioxidant therapies in PD.

OXIDATIVE DAMAGE IN PD

There is substantial evidence for oxidative stress in brains of PD patients (8). Elevated oxidative damage to lipids, protein, and DNA has been observed in the PD substantia nigra. Additionally, there are reduced levels of antioxidant enzymes in PD brain. Przedborski and Ischiropoulos review data indicating an important role for oxidative damage in animal models of PD (15). For example, mice treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) have elevated brain levels of reactive oxygen species (ROS), and antioxidants protect against MPTP toxicity (15). In another model of PD, rats exposed to rotenone show selective oxidative damage across brain regions (18). Taken together, these results strongly suggest an important role for oxidative damage in PD pathogenesis. However, both the source of this oxidative damage and the cellular consequences remain to be determined unambiguously.

POTENTIAL SOURCES OF OXIDATIVE DAMAGE IN PD

Mitochondrial oxidative metabolism is a major source of oxidative damage. Electrons that leak from sites along the electron transport chain (ETC) can react with molecular oxygen, leading to production of superoxide and hydrogen peroxide. Partial reductions in the activity of complex I of the ETC, which have been observed systemically in PD patients, can enhance ROS production (9, 11, 14, 16). Local ROS production can further damage complex I, resulting in a feed-forward cycle of complex I impairment and elevated ROS synthesis. Additionally, both MPP^+ (1-methyl-4-phenylpyridinium; the active metabolite of MPTP) and rotenone, two toxins used in PD models, act as inhibitors of mitochondrial complex I, and result in increased oxidative damage (6, 12). These results demonstrate that mitochondria may be an important source of oxidative damage in PD.

Oxidative damage may also be derived from activated microglia adjacent to affected neurons. PD is characterized by extensive microglial activation particularly in the nigrostriatal pathway. Microglia are the resident immune cells of the brain and, in response to injury, they produce potentially neurotoxic ROS through activation of the enzyme, NADPH oxidase. Hong and colleagues have shown in this issue and elsewhere that mixed neuronal–microglial cultures are more sensitive to MPTP, rotenone, and paraquat than neuronal enriched cultures that lack microglia (4, 22). This enhanced toxicity is attenuated by antioxidants and is reduced in mice lacking NADPH oxidase (15). Furthermore, inhibiting microglial activation may prevent MPTP toxicity (21). Thus, microglial activation in PD may contribute to the oxidative damage seen in the PD brain.

Dopamine itself may contribute to the oxidative damage and cell type-selective vulnerability in PD. The most affected neurons in PD use dopamine as their neurotransmitter. Dopaminergic neurons may be specifically sensitive

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to oxidative damage. Normal dopamine metabolism by monoamine oxidase produces hydrogen peroxide (10). Additionally, in the presence of iron (abundant in the substania nigra), hydrogen peroxide is converted to the highly reactive hydroxyl radical. Dopamine may also be oxidized enzymatically and nonenzmatically to form reactive dopamine semiquinones (5). For these reasons, it is probable that dopaminergic neurons exist in a constant state of oxidative stress and, as suggested in this issue by Hastings and colleagues, endogenous dopamine may render neurons more vulnerable to additional oxidative stressors (3).

Finally, oxidative damage may result from environmental factors that may contribute to PD. Increased occurrence of PD has been associated epidemiologically with rural living and pesticide exposure. Paraquat (PQ), an herbicide with chemical structure similar to MPTP, reproduces features of PD in mice. As pointed out by Di Monte *et al.* in this issue, the neurotoxicity resulting from PQ or diquat (another herbicide) may result from redox cycling of the compound itself, leading to oxidative stress (1).

OXIDATIVE DAMAGE AND PROTEIN AGGREGATION

Lewy bodies, the pathological hallmark of PD, are cytoplasmic aggregates containing a number of proteins, including α-synuclein, ubiquitin, and neurofilament. Norris and Giasson review the data indicating that oxidative damage may also contribute to the formation of Lewy bodies in PD (13). In PD brain, α-synuclein becomes oxidatively damaged and insoluble, increasing aggregation. Furthermore, it has been determined that there is selective and specific nitration of α-synuclein in PD.

The presence of these inclusions has focused attention on the role of the ubiquitin proteasome system (UPS) in PD. The case for involvement of the UPS in PD has been bolstered by studies of familial PD that are associated with mutations in specific components (parkin, UCLH-1) of the UPS. The mechanism accounting for reduced UPS function in PD brain is unknown. However, as shown by Zeevalk and Bernard in this issue, and by Shamoto-Nagai *et al.,* oxidative stress alters UPS activity, resulting in increased ubiquitination and protein aggregation (17, 23). Additionally, O'Malley and colleagues show that, following an oxidative challenge, expression of proteins involved in protein degradation is altered (7). It is also possible that decreased proteasome function may result in elevated oxidative stress through a yet unknown mechanism.

FUTURE DIRECTIONS

Although there is clear evidence of a role for oxidative damage in PD, many questions remain. Novel two-dimensional gel analysis and mass spectrometry will allow the determination of which proteins are specifically targeted for oxidative damage in the disease. For example, recent studies have determined that specific components of the UPS may be oxidatively altered in PD (2). Are other families of proteins affected? This analysis will provide a more detailed understanding of the role of oxidative damage in PD pathogenesis.

The involvement of oxidative stress in PD also leads to an investigation into the use of antioxidant therapy. Antioxidant and spin trap agents are protective in animal models of the disease. A more thorough understanding of the sources of ROS will allow for the design of better antioxidant compounds. Additionally, many antioxidant compounds, such as vitamin E, that have been proposed as therapy have poor brain bioavailability, and high doses or chronic treatment regimens may be required. However, a recent clinical trial showed the promise of antioxidant treatment. In this small, randomized, placebo-controlled, double-blind study conducted by Shults, the antioxidant coenzyme Q_{10} may have shown the potential to slow PD progression (19). The examination of oxidative damage in PD may uncover more promising treatments for this devastating disorder.

ABBREVIATIONS

ETC, electron transport chain; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; PD, Parkinson's disease; PQ, paraquat; ROS, reactive oxygen species; UPS, ubiquitin proteasome system.

REFERENCES

1. Bonneh-Barkay D, Langston WJ, and Di Monte DA. Toxicity of redox cycling pesticides in primary mesencephalic cultures. *Antioxid Redox Signal* 7: 649–653, 2005.
2. Choi J, Levey AI, Weintraub ST, Rees HD, Gearing M, Chin LS, and Li L. Oxidative modifications and down-regulation of ubiquitin carboxyl-terminal hydrolase L1 associated with idiopathic Parkinson's and Alzheimer's disease. *J Biol Chem* 279: 13256–13264, 2004.
3. Dukes AA, Korwek KM, and Hastings TG. The effect of endogenous dopamine in rotenone-induced toxicity in PC12 cells. *Antioxid Redox Signal* 7: 630–638, 2005.
4. Gao HM, Hong JS, Zhang W, and Liu B. Distinct role for microglia in rotenone-induced degeneration of dopaminergic neurons. *J Neurosci* 22: 782–790, 2002.
5. Hastings TG. Enzymatic oxidation of dopamine: the role of prostaglandin H synthase. *J Neurochem* 64: 919–924, 1995.
6. Hensley K, Pye QN, Maidt ML, Stewart CA, Robinson KA, Jaffrey F, and Floyd RA. Interaction of alpha-phenyl-*N-tert*-butyl nitrone and alternative electron acceptors with complex I indicates a substrate reduction site upstream from the rotenone binding site. *J Neurochem* 71: 2549–2557, 1998.
7. Holtz WA, Turetzky JM, and O'Malley KL. Microarray expression profiling identifies early signaling transcripts associated with 6-OHDA-induced dopaminergic cell death. *Antioxid Redox Signal* 7: 639–648, 2005.
8. Jenner P. Oxidative mechanisms in nigral cell death in Parkinson's disease. *Mov Disord* 13(Suppl 1): 24–34, 1998.

9. Kushnareva Y, Murphy AN, and Andreyev A. Complex I-mediated reactive oxygen species generation: modulation by cytochrome *c* and NAD(P)$^+$ oxidation–reduction state. *Biochem J* 368(Pt 2): 545–553, 2002.
10. Maker HS, Weiss C, Silides DJ, and Cohen G. Coupling of dopamine oxidation (monoamine oxidase activity) to glutathione oxidation via the generation of hydrogen peroxide in rat brain homogenates. *J Neurochem* 36: 589–593, 1981.
11. Mizuno Y, Ohta S, Tanaka M, Takamiya S, Suzuki K, Sato T, Oya H, Ozawa T, and Kagawa Y. Deficiencies in complex I subunits of the respiratory chain in Parkinson's disease. *Biochem Biophys Res Commun* 163: 1450–1455, 1989.
12. Nicklas WJ, Vyas I, and Heikkila RE. Inhibition of NADH-linked oxidation in brain mitochondria by 1-methyl-4-phenyl-pyridine, a metabolite of the neurotoxin, 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine. *Life Sci* 36: 2503–2508, 1985.
13. Norris EH and Giasson BI. Role of oxidative damage in protein aggregation associated with Parkinson's disease and related disorders. *Antioxid Redox Signal* 7: 673–684, 2005.
14. Parker WD Jr, Boyson SJ, and Parks JK. Abnormalities of the electron transport chain in idiopathic Parkinson's disease. *Ann Neurol* 26: 719–723, 1989.
15. Przedborski S and Ischiropoulos H. Reactive oxygen and nitrogen species: weapons of neuronal destruction in models of Parkinson's disease. *Antioxid Redox Signal* 7: 685–693, 2005.
16. Schapira AH, Cooper JM, Dexter D, Jenner P, Clark JB, and Marsden CD. Mitochondrial complex I deficiency in Parkinson's disease. *Lancet* 1: 1269, 1989.
17. Shamoto-Nagai M, Maruyama W, Kato Y, Isobe K, Tanaka M, Naoi M, and Osawa T. An inhibitor of mitochondrial complex I, rotenone, inactivates proteasome by oxidative modification and induces aggregation of oxidized proteins in SH-SY5Y cells. *J Neurosci Res* 74: 589–597, 2003.
18. Sherer TB, Betarbet R, Testa CM, Seo BB, Richardson JR, Kim JH, Miller GW, Yagi T, Matsuno-Yagi A, and Greenamyre JT. Mechanism of toxicity in rotenone models of Parkinson's disease. *J Neurosci* 23: 10756–10764, 2003.
19. Shults CW. Antioxidants as therapy for Parkinson's disease. *Antioxid Redox Signal* 7: 694–700, 2005.
20. Wooten GF. Neurochemistry and neuropharmacology of Parkinson's disease. In *Movement Disorders: Neurologic Principles and Practice*, edited by Watts RL and Koller WC. New York: McGraw–Hill, 1997, pp. 153–160.
21. Wu DC, Teismann P, Tieu K, Vila M, Jaskson-Lewis V, Ischiropoulos H, and Przedborski S. NADPH oxidase mediates oxidative stress in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine model of Parkinson's disease. *Proc Natl Acad Sci U S A* 100: 6145–6150, 2003.
22. Wu X-F, Block ML, Zhang W, Qin L, Wilson B, Zhang W-Q, Veronesi B, and Hong J-S. The role of microglia in paraquat-induced dopaminergic neurotoxicity. *Antioxid Redox Signal* 7: 654–661, 2005.
23. Zeevalk GD and Bernard LP. Energy status, ubiquitin proteasomal function, and oxidative stress during chronic and acute complex I inhibition with rotenone in mesencephalic cultures. *Antioxid Redox Signal* 7: 662–672, 2005.

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1. Humberto Rodriguez-Rocha , Aracely Garcia Garcia , Laura Zavala-Flores , Sumin Li , Nandakumar Madayiputhiya , Rodrigo Franco . Glutaredoxin 1 Protects Dopaminergic Cells by Increased Protein Glutathionylation in Experimental Parkinson's Disease. *Antioxidants & Redox Signaling*, ahead of print. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links] [Supplemental material]
2. Dong-Hee Choi , Ana Clara Cristóvão , Subhrangshu Guhathakurta , Jongmin Lee , Tong H. Joh , M. Flint Beal , Yoon-Seong Kim . 2012. NADPH Oxidase 1-Mediated Oxidative Stress Leads to Dopamine Neuron Death in Parkinson's Disease. *Antioxidants & Redox Signaling* **16**:10, 1033-1045. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links] [Supplemental material]
3. Cecilia Hidalgo , Paulina Donoso . 2008. Crosstalk Between Calcium and Redox Signaling: From Molecular Mechanisms to Health Implications. *Antioxidants & Redox Signaling* **10**:7, 1275-1312. [Abstract] [Full Text PDF] [Full Text PDF with Links]
4. H MAO, X FANG, K FLOYD, J POLCZ, P ZHANG, B LIU. 2007. Induction of microglial reactive oxygen species production by the organochlorinated pesticide dieldrin. *Brain Research* **1186**, 267-274. [CrossRef]
5. Kyle M. Sousa, Helena Mira, Anita C. Hall, Lottie Jansson-Sjöstrand, Moriaki Kusakabe, Ernest Arenas. 2007. Microarray Analyses Support a Role for Nurr1 in Resistance to Oxidative Stress and Neuronal Differentiation in Neural Stem Cells. *Stem Cells* **25**:2, 511-519. [CrossRef]
6. Suvi Vartiainen, Petri Pehkonen, Merja Lakso, Richard Nass, Garry Wong. 2006. Identification of gene expression changes in transgenic C. elegans overexpressing human #-synuclein. *Neurobiology of Disease* **22**:3, 477-486. [CrossRef]