Introduction: Oxidative stress

Parkinson's disease (PD) is a progressive neurodegenerative disease that affects 1% of the U.S. population over 60 years of age (1). PD is unique among neurological disorders in that many rational pharmacological and neurosurgical therapies exist to counteract the loss of dopamine neurons; however, there is no cure for PD and therapies provide symptomatic relief rather than disease modification. In addition to motor deficits resulting from the characteristic death of dopaminergic neurons, late-stage symptoms include cognitive dysfunction. Typically, patients find retirement necessary within nine years of diagnosis (2), at a cost of $23 billion annually in the United States (3).

The oxidative stress model of PD pathophysiology has been supported by extensive research in the 50 years subsequent to the discovery of dopamine neuron loss in the substania nigra pars compacta (SNpc) (4). Dopaminergic neurons are believed to be especially sensitive to oxidative damage due to dopamine (DA) oxidation, which forms free radicals and reactive quinones (5). PD patients have reduced levels of glutathione, which can neutralize DA quinone. Additionally, PD pathology is associated with increased lipid peroxidation and increased levels of nonheme iron (6,7) that can reduce oxygen to the superoxide ion, a free radical. Another proposed mechanism for the development of PD is lipid peroxidation via dopamine-iron complexes. Addition of Fe^{3+} to the SNpc in experimental animals kills dopaminergic neurons selectively and induces parkinsonian symptoms (11). Administration of iron-chelating molecules can reduce parkinsonian symptoms in an animal model (12); however, a drug of this class or mechanism is not yet available for PD treatment in humans.

One class of PD medications targets the enzyme monoamine oxidase-B (MAO-B) in an attempt to reduce free radical generation (8). MAO oxidizes the neurotransmitter dopamine, generating hydrogen peroxide. The high level of iron in the SNpc accelerates the Fenton reaction, turning hydrogen peroxide into the highly reactive hydroxyl radicals ($OH^{\cdot}$) (9). Selegilline and rasagiline, MAO-B inhibitors, have both produced symptomatic relief of PD. The latter has provided statistical improvement in the progression of PD and is under further study (10); nevertheless, with our current understanding, it is possible that the therapeutic effect of these drugs is due to the prevention of dopamine breakdown, rather than the reduction of oxidative damage.

To more directly address the oxidative stress model, a placebo-controlled blinded clinical trial was designed to assess the effect of antioxidant supplementation. In this study, vitamin E supplements did not slow the progression of PD (13). One possibility for the failure of this study is that antioxidants are given when the disease is beyond amelioration. PD lacks an inexpensive surrogate marker for dopaminergic cell count in the SNpc, and at clinical presentation, at least 50% of dopamine neurons in the SNpc have been lost (14). The extensive pathophysiology at clinical presentation may make antioxidant-based therapy ineffective; nevertheless, slowing or freezing progression of PD would maintain patients in a disease state that is well managed with current medications. Thus the holy grail of the research community is a rapid and inexpensive

biomarker that would indicate first patients at risk for PD prior to clinical presentation and second indicate the rate of disease progression.

Uric acid: Preventing oxidative stress and iron chelation

Recent epidemiologic data have uniformly indicated that the level of plasma uric acid is indicative of risk for PD. Table 1 is a comprehensive list of these studies and the protective level of uric acid. Moreover, a dose-dependent effect has been found. Individuals with higher levels of uric acid are unlikely to develop PD while those with low levels have increased risk. Finally, the progression of early PD was inversely related to the level uric acid. In sum, PD patients have a low uric acid plasma level and PD patients with the lowest level of uric acid have a rapid progression of the disease process.

Uric acid is the end product of purine metabolism. Uric acid levels may be influenced by both hereditary factors as well as diet. Purines are found in high levels in fish (sardines and mackerel), meat (beef, pork, and poultry), and fructose (honey, apples, pears, grapes, and watermelon). In addition, uric acid plasma levels are raised by thiazide diuretics that decrease uric acid clearance by the kidney (15).

Uric acid is a prevalent water soluble antioxidant in the brain. Additionally, uric acid binds iron, preventing the generation of free radicals (18). In this way, uric acid is ideally suited to combat the dual pathology in SNpc of PD patients: namely, an increase in free radicals, and an increase in free iron. Free iron, typically bound by transferrin or ferritin, is elevated in PD and an iron chelator like uric acid could prevent its destructive effects. MAO generates free radicals in dopamine oxidation and the antioxidant properties of uric acid could neutralize free radicals in an amount sufficient to prevent the neuron death.

Table 1. Comprehensive list of epidemiological studies of plasma uric acid (UA) levels and risk of Parkinson's disease.

	Study type	Country	Population	All subjects	Gender distribution	UA* cutoffs	Rate ratio	CI* (95%)
Davis et al., 1996 (20)	Cohort	United States	Honolulu	7968	100% male	404 umol/l	0.6	0.40-1.00
de Lau et al., 2005 (21)	Cohort	Netherlands	Rotterdam	4695	39% male	374 umol/l	0.71	0.51-0.98
Gao et al., 2008 (22)	Cohort	United States	Health Professionals	1387	100% male	375 umol/l	0.47†	0.30-0.74
Schwarzschild et al., 2008 (25)	Cohort	United States	PRECEPT	804	64% male	399 umol/l	0.51	0.37-0.72
Weisskopf et al., 2007 (23)	Nested case control	United States	Health Professionals	252	100% male	416 umol/l	0.43	0.18-1.02

*CI, Confidence Interval; UA, uric acid. † relative risk

Rate ratio compares the subgroup (quartile or quintile) with the highest level of plasma uric acid to the corresponding subgroup with the lowest plasma uric acid.

UA cutoffs reports the subgroup with the highest plasma uric acid.

The role of uric acid in PD pathology was first highlighted by a postmortem study (16). The level of uric acid was decreased in the SNpc of the PD brain relative to controls. The rate of dopamine oxidation was accelerated in the SNpc of parkinsonian brains and addition of uric acid to brain homogenates decreased the oxidation rate. In contrast, while uric acid was depleted in the SNpc of the PD brain, the level of ascorbic acid was unchanged. Uric acid may be better suited to combat PD relative to other antioxidants, like ascorbic acid and tocopherol, due to its unique evolutionary history and dual mechanism of action. In higher primates, the loss of ability to synthesize ascorbic acid coincided with the loss of ability to synthesize uricase (urate oxidase). Uricase is the enzyme for uric acid, which produces hydrogen peroxide as a byproduct of metabolism of uric acid. It has been hypothesized that uric acid may have succeeded ascorbic acid as the antioxidant of the higher primate (17).

Uric acid has rescued in vitro PD models. Adding homocysteine and free iron to cultures of human dopaminergic neurons produced the oxidative stress model. Uric acid prevented apoptosis and reduced dihydrorhodamine, a marker for free radical generation, to baseline levels (19). In dopamine neurons, uric acid has also been demonstrated to prevent apoptosis induced by rotenone, a pesticide linked with PD (19).

Uric Acid Levels and Reduced Risk of PD

After the postmortem study implicated uric acid in PD pathology, several epidemiological studies investigated the role of uric acid in PD morbidity. The first study measured the serum uric acid levels in almost 8,000 men from the Honolulu Heart Program (20). The men with plasma uric acid exceeding the median level had a 40% reduction in developing PD. This study hinted at the possibility that low levels of uric acid were not a consequence of PD pathophysiology, but rather a cause of PD.

The next prospective study improved upon these findings by examining the relationship in both men and women. The Rotterdam Study found a dose-effect relationship between uric acid levels and hazard ratio for PD (21). These results were similar in men and women as well as in smokers and non-smokers.

The final prospective study of uric acid level and PD risk was performed on the Health Professionals dataset (22). This large study of male subjects found a lower relative risk of developing PD (0.47) for the top quintile of plasma uric acid level in comparison with the bottom quintile ($p<0.0008$). Like the previous studies, this finding remained significant after adjustment for age, smoking and caffeine intake. In addition, this study examined the diets of the individuals and found fructose and alcohol to be pro-uricemic while vitamin C and diary products lowered uric acid levels.

Two case-control studies provide additional evidence for the role of plasma concentration of uric acid. The first found a 55% reduction in risk of PD in the top quartile versus the

bottom quartile of plasma uric acid concentration (23). One limitation of this study is the inclusion of only male subjects.

A second case control study found lower uric acid levels in PD patients compared with their spouses (24). This result was in spite of the fact that the PD patients were treated with levodopa, which reduces uric acid clearance by the kidney. This study also examined the diets of the subjects. An inverse correlation between yogurt consumption and plasma uric acid was noted in both PD and controls. The dietary examination provides new insight to an earlier study that found increased diary consumption as a risk factor for developing PD.

Finally, three studies examined the level of uric acid in patients diagnosed with disease. In a re-examination of data from a clinical trial, a test of an ultimately ineffective pharmacological agent, patients with recent diagnosis of PD and upper quintile level of uric acid levels had slower development of PD, as measured by both clinical exam (UPDRS) and neuroimaging measurement of dopamine level (25). Again, the study found this effect only in male subjects; however, this study was not powered for studying gender differences and few female subjects had upper quintile levels of uric acid. A case-controlled study (26) found that male patients with gout, a disease process with toxically elevated plasma level of uric acid, were less likely to develop PD (odds ratio 0.60). Initial results from a metabolic profiling effort found plasma uric acid to be decreased in PD patients (27).

Conclusion

Investigations to date have provided consistent evidence that uric acid plasma levels may be used as a risk factor for both incidence and progression of PD, providing new avenues for treatment.

PD patients with low levels of plasma uric acid had elevated rate of disease progression, and these patients are possible candidates for a dietary intervention that raises uric acid concentration; however, a pro-uremic diet not without risk. A high uric acid plasma concentration is associated with other adverse effects, such as an increased risk for gout, cardiovascular disease, kidney stones, and overall mortality (28). With the current incidence of PD in the elderly population at 1-3%, and the potential adverse risks of adopting a pro-uremic diet, the diet may not be recommended at present. A randomized placebo-controlled trial of patients with recently diagnosed PD is necessary to determine the efficacy and risks of diet modification.

Several issues remain to be resolved regarding the role of uric acid in PD. First, the predictive value of uric acid is inconsistent in female subjects; however, this is likely due to inadequately powered studies to date. Moreover, the studies with larger number of subjects consist exclusively of male subjects. Second, although two studies suggest a dietary link, it is currently impossible to rule out genetic factors that may play a role in ability of individuals to develop elevated plasma concentration of uric acid. Finally, a uric acid level may be correlated with other factors that ultimately provide protection

from PD. For instance, the foods that raise uric acids levels, such as fructose, may induce other changes responsible for dopamine neuron survival.

Although an interventional trial is lacking, the uniformity of results in prospective studies bodes well for the role of uric acid as a risk factor for PD onset and progression. Dietary changes that increase levels of plasma uric acid have the potential to halt the progression of the disease. Alternatively, should dietary increases in uric acid lead to an abundance of adverse effects, uric acid may still remain an effective predictive tool for clinicians. Such a marker, combined with other predictive factors could lead to a revolution in the manner in which PD risk is assessed.

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