

Commentary

Possible causes of Parkinson's disease

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1. Abstract

Parkinson's disease, in most patients, is possibly caused by natural oxidative stress in dopaminergic neurons, insufficient exercise and galactose induced oxidative stress. Dopamine oxidizes to produce oxygen radicals that damage neurons. Exercise generates lactic acid and myokines that are essential for brain health. Galactose produces oxidative stress in the brain. These factors change with age and lifestyle. It is likely that lifestyle interventions, including daily exercise and much less alcohol and milk consumption, can delay or prevent Parkinson's disease.

2. Introduction

Dopaminergic neurons in the midbrain substantia nigra are lost in Parkinson's disease which causes an imbalance in the brain circuitry controlling movement [1]. Pa-

tients have difficulty walking, rigidity, tremors and other symptoms of an inability to control movement. By the time symptoms appear, 50–90% of the dopaminergic neurons in the substantia nigra have been lost. Dopamine has a propensity to oxidize in processes that produce oxygen radicals [2–4]. This oxidative stress damages dopaminergic neurons and causes a progressive, age related loss of these neurons.

Dopamine is produced from tyrosine in the brain since dopamine cannot cross the blood brain barrier. Tyrosine hydroxylase, an iron containing enzyme, inserts an oxygen into tyrosine making levodopa. The enzyme also produces oxygen radicals (Table 1) and is the rate limiting step in dopamine production [5]. Levodopa is metabolized by dopa decarboxylase to make dopamine which is rapidly sequestered into vesicles where it is inert by vesicular monoamine transporter type 2 [6]. The release of dopamine into the synapse is followed by reuptake into

Table 1. Compounds important in Parkinson's disease.

Compound	Parkinson's disease risk	Activity
Dopamine	Decreases or Increases	Oxygen radical formation due to tyrosine hydroxylase, monoamine oxidase, aldehyde dehydrogenase
Pesticides	Increases	Several mechanisms
Propranolol	Increases	Inhibits tyrosine hydroxylase activity, decreases dopamine release, induces α -synuclein gene
Alcohol	Increases	Increases blood visfatin levels
Galactose	Increases	Increases brain oxidative stress
Nicotine, high dose	Increases	Damages the blood brain barrier
Nicotine, low dose	Decreases	Increases dopamine release, induces tyrosine hydroxylase
Salbutamol	Decreases	Increases dopamine release, down regulates α -synuclein gene
Caffeine, theophylline, theobromine	Decreases	Increases dopamine receptor activity
Lactic acid	Decreases	Essential nutrient for brain cells
Cathepsin B	Decreases	Induces brain derived neurotrophic factor
Uric acid	Decreases	Decreases vascular endothelial growth factor synthesis
Vitamin E	Decreases	Protects the blood brain barrier
Ibuprofen	Decreases	Decreases dopamine turnover

the presynaptic terminal where it is either repackaged into vesicles or oxidized in mitochondria by monoamine oxidase A in dopaminergic neurons or monoamine oxidase B in astrocytes and endothelial cells with the formation of oxygen radicals [7]. This dopamine oxidation also makes 3,4-dihydroxyphenylacetaldehyde which is oxidized by aldehyde dehydrogenase to make oxygen radicals [8]. Dopamine can also spontaneously oxidize with the formation of 6-hydroxydopamine [2]. However, this is a minor pathway.

3. Environmental causes

The discovery that manganese miners develop a parkinsonian syndrome led to the hypothesis that Parkinson's disease is caused by an environmental factor [9]. This was backed up by the discovery that a contaminant of meperidine like drugs, MPTP causes a parkinsonian syndrome [10]. MPTP is metabolized by monoamine oxidase B to produce 1-methyl-4-phenylpyridine (MPP+) that induces oxidative stress by several mechanisms [11] including redox cycling in a two electron, hydride transfer, mechanism [12]. It is also a weak, reversible inhibitor of mitochondrial respiration. Several years of searching for environmental causes of Parkinson's disease have not found a definite cause of the disease. However, exposure to pesticides is considered a risk factor for developing the disease [13].

4. Evidence from epidemiology

Epidemiologic research on Parkinson's disease has found at least eleven factors that are important in causing or preventing the disease [13–15]. Pesticides, non-selective β adrenergic receptor antagonists and consump-

tion of dairy products are risk factors. Factors that protect against developing the disease are smoking, coffee, tea, physical activity, gout, using vitamin E, nonsteroidal anti-inflammatory drugs and β 2 adrenergic receptor agonists. These factors provide clues about the causes of Parkinson's disease.

5. Pesticides

Organochloride insecticides such as dieldrin are known to accumulate in fat deposits in the body which may lead to persistent effects. The Parkinson's disease hazard ratio for dieldrin is 1.95 ($p < 0.003$). However, the epidemiologic evidence did not find an increased hazard for developing Parkinson's disease with other organochlorine pesticides [15]. The data on paraquat exposure found an increased risk of developing Parkinson's disease with a hazard ratio of 1.64 and was statistically significant [16]. There is also animal experimental work that demonstrates paraquat is deleterious to dopaminergic neurons [17]. Paraquat stimulates microglial cells to release inflammatory factors such as tumor necrosis factor- α , IL-1 β and IL-6 that damage dopaminergic neurons [18].

Dieldrin has been tested in isolated dopaminergic neurons and is proposed to induce endoplasmic reticular stress leading to mitochondrial dysfunction [19]. This appears to involve transcription of the Chop/Gadd153 gene (DNA damage inducible transcript 3). Tyrosine hydroxylase activity was not altered by the pesticide. Dieldrin treatment in mice resulted in a loss of dopamine transporter activity, but no loss of dopaminergic neurons [20].

6. β 2 adrenergic receptor agonists/antagonists

Alpha-synuclein is a protein that may be involved in the regulation of dopamine and other neurotransmitter release which are important in Parkinson's disease [19]. Abnormal accumulations of α -synuclein, such as in Lewy bodies, occurs in patients expressing mild to severe symptoms of Parkinson's disease [21]. However, these abnormal accumulations are also found in patients who do not have symptoms of Parkinson's disease. Alpha-synuclein accumulates in the brain with age. There is no correlation between dopaminergic neuron loss and Lewy body load [22]. B-Adrenergic receptor antagonists, such as propranolol, induce the gene for synuclein synthesis and increase the risk of Parkinson's disease [23–25]. B-Adrenergic receptor agonists down regulate the gene and decrease the risk of Parkinson's disease [23].

The ability of noradrenergic neurons to regulate dopaminergic neurons may be involved in these drug effects. It is known that dopamine can interact with β receptors [26]. Norepinephrine can also interact with dopamine receptors [26]. These interactions may be involved in the disease process. B-Adrenergic blockers such as propranolol inhibit the release of dopamine from dopaminergic nerve terminals [27, 28]. B-Adrenergic receptor agonists increase the release of dopamine [27, 28]. Propranolol is also an inhibitor of tyrosine hydroxylase [29]. This is undoubtedly important in Parkinson's disease and may explain the ability of these drugs to increase or decrease the risk of developing Parkinson's disease.

Drugs that are purported to remove α -synuclein from the brain are being tested in clinical trials. Many of these drugs are antibodies or monoclonal antibodies. A major goal of these studies must be to demonstrate that the antibodies or monoclonal antibodies can cross the blood brain barrier. A study of a monoclonal antibody BIIB054 has produced preliminary results [30]. The drug was found to penetrate across the blood brain barrier and was safe. Clinical trials to determine its efficacy in Parkinson's disease have not been reported. Other antibodies, such as ABBV-0805, NPT200-11, PRX002, MEDI1341, AFFITOPE and PRX002 have been studied in preliminary clinical trials [31]. The results of randomized, placebo controlled clinical trials of these drugs in Parkinson's disease have not been reported [32].

7. Alcohol

Long term alcohol abuse increases the risk of developing Parkinson's disease with a hazard ratio of 3.48 [15, 33]. Alcohol induces sterol regulatory element binding protein and is an obesogen that causes visceral fat accumulation [34]. However, obesity has not been shown to be a risk factor for Parkinson's disease. Visceral fat se-

cretes a number of adipokines that are bad for health and the brain. An adipokine that is elevated in Parkinson's disease is visfatin, also known as nicotinamide phosphoribosyltransferase [35]. This adipokine is involved in damaging the blood brain barrier by increasing oxygen radical formation in the lumens of brain capillaries [36, 37]. The blood brain barrier is essential to brain health since it regulates the penetration of nutrients into the brain and waste products out of the brain. A leaky blood brain barrier may become inflamed which leads to brain inflammation [38].

8. Dairy products

Milk contains lactose, lactalbumin, casein, fat and other constituents. It can be contaminated with bacteria, especially unpasteurized raw milk. These bacteria can be dangerous, especially Salmonella bacteria. The bacteria found in milk include Escherichia coli, Salmonella species, Aeromonas species, Yersinia species, Listeria species and Cronobacter species [39–41]. Salmonella in milk may have been responsible for causing red skin disease and the deaths of 15 million Aztecs [42]. Streptomyces bacteria produce a toxin that damages dopaminergic neurons [43].

Lactose is metabolized in the gut by lactase to liberate glucose and galactose. Lactase is not produced in adulthood in 30–70% of adults [44], which results in lactose intolerance. Milk consumption, 3 or more glasses per day over a 20-year period, in adults leads to more bone fractures in women and more mortality in men and women [45]. A measure of oxidative stress, blood 8-iso-prostaglandin F₂ α , also increases. Three glasses of milk corresponds to about 15 g of galactose.

Galactose metabolism should be studied more. It is oxidatively metabolized by galactose dehydrogenase in the presence of NAD and produces D-galactonolactone [46]. However, the existence of mammalian galactose dehydrogenase has been disputed [47]. In bacteria, galactose oxidase metabolizes galactose with the production of oxygen radicals [48]. Galactose oxidase is not found in humans. Gut bacteria contain galactose oxidase and produce gut oxidative stress following galactose ingestion [49]. Altered gut microbiota by galactose changes the digestion of foods and the absorption of plant derived nutrients that are essential for brain health. Chronic galactose ingestion in rodents leads to memory loss, brain damage and peripheral oxidative stress [50]. In fact, chronic galactose ingestion is used as a model of accelerated aging in rodents [51]. Caffeine inhibits galactose induced oxidative stress in a rodent model [52]. Humans born with galactosemia exhibit many symptoms of brain oxidative stress including neurodegeneration, motor imbalances, gait irregularities and tremor [53]. These symptoms also occur in Parkinson's disease.

Galactose is reductively metabolized by aldose reductase to form galactitol [53]. The major pathway of galactose metabolism is phosphorylation by galactokinase

to form galactose-1-phosphate [53]. This forms UDP conjugates which are eventually converted to glucose.

The oxidative metabolism of galactose may be responsible for reactive oxygen species formation and oxidative stress. Little is known about the mechanism of catalysis of galactose dehydrogenase except that it performs hydride transfers [54]. Hydride is a proton and two electrons. Hydride transfer to oxygen makes hydrogen peroxide. This implies the enzyme forms hydrogen peroxide which is a powerful oxidant that crosses cell membranes, damages nuclear DNA and other macromolecules as discussed above. Hydride transfers can be important causes of oxidative stress [12]. It is not known if galactose dehydrogenase exists in the brain. It is clear that high blood levels of galactose damage the human brain [53]. The mechanism involved in this damage is open to discussion. It is known that galactosemia patients excrete galactonate in the urine [55]. Galactonate is a product of the spontaneous or enzymatic degradation of galactonolactone made by galactose dehydrogenase [56]. This implies that galactose dehydrogenase exists in humans.

It is clear that galactose metabolism changes with aging [57]. Galactose dehydrogenase has not been reported to change with aging. Elderly people have lower activities of galactokinase and galactose-1-phosphate uridyl transferase, which forms galactose UDP conjugates. This causes blood galactose levels to increase after galactose ingestion and makes elderly people much more susceptible to galactose induced oxidative stress by galactose dehydrogenase.

9. Smoking

Smoking supplies nicotine to the brain, a highly addictive substance that interacts with various receptors as discussed below. Smoking is a major health crisis in the world today. Smoking small amounts of tobacco versus large amounts of tobacco has very different effects on Parkinson's disease. The dose response relationship for tobacco and Parkinson's disease is not well described in the literature. Nicotine, at appropriate, small doses, stimulates dopamine release in the brain [58, 59]. This may be part of the reward system that drives nicotine addiction. This dopamine release is also useful in Parkinson's disease and appears to delay onset. However, heavy smoking and current smoking increase the onset of Parkinson's disease with a hazard ratio of 3.2 [14, 15]. This may be because nicotine damages arteries including the blood brain barrier due to stimulation of non-neuronal nicotinic acetylcholine receptors (NACHR) which enhances oxygen radical formation [60]. Nicotine also down regulates GTP cyclohydrolase 1 [61] which is essential for endothelial cell health. This enzyme is the rate limiting enzyme in tetrahydrobiopterin synthesis, a required cofactor for tyrosine hydroxylase. The effects of nicotine on tyrosine hydroxylase activity involve glucocorticoids. Nicotine elevates glucocorticoid levels in

the midbrain. These glucocorticoids induce tyrosine hydroxylase synthesis [62]. This is beneficial in the prevention of Parkinson's disease.

10. Coffee

Coffee protects against Parkinson's disease with a hazard ratio of 0.52 [15] and contains chlorogenic acids, kahweol, cafestol and other phenolics [63]. It also contains alkaloids such as caffeine and trigonelline [63]. Other secondary metabolites are present as well. Coffee has a number of health effects against: cardiovascular disease, type 2 diabetes, cancer, depression, Parkinson's disease and more [63]. Caffeine inhibits the adenosine A_{2A} receptor and is neuroprotective in an MPTP mouse model of Parkinson's disease [64]. In the brain, adenosine A_{2A} receptors form heteromers with dopamine receptors such that inhibition of the adenosine A_{2A} receptor increases the activity of dopamine receptors [65]. Caffeine also indirectly stimulates tyrosine hydroxylase activity [66]. This is important in preventing Parkinson's disease.

11. Tea

Several alkaloids are found in tea including theophylline, caffeine and theobromine [67]. A number of glycosides are present. Polysaccharides, monoterpenoids, minerals, theanine and other constituents have been reported in tea [67]. The alkaloid activities are discussed above under caffeine. The polyphenol content of tea possesses antioxidant and other activities [68]. Theanine decreases sleep latency and anxiety while increasing cognitive skills in a placebo-controlled study [69]. Theanine enhances dopamine D1/5 receptor activity [70] and may add to the protective effects of the alkaloids in Parkinson's disease.

12. Physical activity

Physical activity stimulates lactic acid production, an essential nutrient to brain neurons, endothelial and other cells [71]. Lactic acid also inhibits transient receptor potential cation channel vanilloid 1 in endothelial cells, thereby decreasing oxygen radical formation and protecting the blood brain barrier [72]. There is a muscle brain axis because nutrients and myokines released by exercising muscle cells are beneficial to the brain [73]. Myokines secreted by muscle that cross the blood brain barrier and benefit the brain are: cathepsin B, irisin and fibroblast growth factor 21 [73]. Cathepsin B induces brain derived neurotrophic factor synthesis in the brain. There is an age-related loss of muscles, sarcopenia, that makes exercising more difficult with age.

Physical activity increases oxygen flux in cells and increases hydrogen peroxide synthesis. Hydrogen peroxide quickly crosses membranes and damages nuclear DNA

[74]. This damage activates poly (ADP-ribose) polymerase that uses NAD as a substrate in an attempt to decrease DNA damage [74]. The mild oxidative stress caused by exercise appears to induce protective mechanisms that benefit the brain. A history of competitive sports protects against Parkinson's disease with a hazard ratio of 0.42 [15].

13. Gout

Gout is caused by hyperuricemia and is more common in obese men. Uric acid is an inflammatory compound that damages kidneys, joints and other tissues. However, uric acid appears to protect the blood brain barrier by decreasing vascular endothelial growth factor synthesis [75]. Protection of the blood brain barrier is critical in the prevention of Parkinson's disease.

14. Vitamin E

Vitamin E is a very lipophilic antioxidant that protects lipids and other lipophilic molecules from oxidative damage. High density lipoproteins deliver vitamin E to brain endothelial cells [76]. Scavenger receptor class B type 1 may be responsible for transporting vitamin E into the brain [76]. This transport mechanism limits the uptake of vitamin E into the brain. Vitamin E protection of the blood brain barrier is important in preventing Parkinson's disease.

15. Nonsteroidal anti-inflammatory drugs

Ibuprofen has saturable penetration into the brain [77]. However, ibuprofen helps alleviate inflammation in the brain caused by peripheral inflammation [78]. Ketorolac does not penetrate into the brain and decreases survival of hypoxic insults to the brain [79]. It appears that the ability of ibuprofen to penetrate into the brain is critical to the prevention of Parkinson's disease. Ibuprofen protects mice against MPTP toxicity perhaps by protecting tyrosine hydroxylase activity and decreasing dopamine turnover [80]. The protective effect of ibuprofen may be to decrease oxygen radical formation by decreasing dopamine turnover. Cyclo-oxygenase 2 is present in substantia nigra dopaminergic neurons where it is involved in oxygen radical formation and synaptic plasticity [81]. The activity of the enzyme increases in Parkinson's disease [81]. This implies that ibuprofen inhibition of cyclo-oxygenase 2 in dopaminergic neurons may be protective in Parkinson's disease.

16. Iron

Deferiprone, an iron chelating agent that penetrates into the brain, has been tested in a phase 2 clinical trial in Parkinson's disease patients [82]. Brain iron concentrations, measured by T2*MRI, decreased in the caudate

nucleus and dentate gyrus after 3 and 6 months of treatment. Iron concentrations in the substantia nigra decreased in 3 out of 22 patients. Disease symptoms did not improve significantly. Changes in iron levels, iron storage proteins and iron transport proteins have been found in Parkinson's disease [83, 84]. These changes may be the result of the disease rather than the cause of the disease.

17. Conclusions

Brain trauma is an uncommon cause of parkinsonism [85]. Uncommon recessively inherited genes and other uncommon genetic risk factors can cause Parkinson's disease [86]. There are ethnic differences in susceptibility to Parkinson's disease [87]. It is possible that Parkinson's disease is caused in most people by several factors that contribute to the damage of dopaminergic neurons in the substantia nigra. This damage increases with age.

(1) Dopaminergic neurons naturally suffer from oxidative stress due to dopamine oxidation.

(2) The brain and blood brain barrier are damaged by lack of physical activity that produces lactic acid and myokines essential for brain health. Alcohol consumption also damages the blood brain barrier.

(3) Excess consumption of foods containing galactose by elderly people may induce brain oxidative stress that adds to the oxidative stress induced by dopamine oxidation.

Lifestyle interventions may help delay or prevent Parkinson's disease. This includes daily physical activity and limiting the intake of galactose. It is clear that only a small percentage of elderly people develop the disease. These lifestyle factors may explain why not everyone comes down with the disease. Some people live healthier lifestyles than others. It is also possible that some people metabolize galactose better than others.

18. Author contributions

This work was entirely done by the author James D. Adams.

19. Ethics approval and consent to participate

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22. Conflict of interest

The author declares no conflict of interest.

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