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Ari Rappoport *

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A Galactose Theory of Parkinson's Disease

Ari Rappoport

The Hebrew University of Jerusalem, Israel; ari.rappoport@mail.huji.ac.il

Abstract: I present a complete theory of Parkinson's disease (PD). PD involves an abundance of gut microbiota that degrade mucin, resulting in elevated brain uptake of galactose (a mucin component) and reduced uptake of glucose. Since galactose is not efficiently used for glycolysis, this decreases the production of glutathione, which is essential for countering oxidative iron toxicity. The brain cells that are most sensitive to this effect, as attested by their expression of the iron chelator neuromelanin, are those that continuously secrete dopamine and norepinephrine, and they eventually degenerate. This account explains the etiology, symptoms (including prodromal autonomic symptoms), pathology and risk factors of the disease. The theory is supported by strong evidence, and gives rise to several relatively simply directions for early identification and treatment of the disease.

Keywords: Parkinson's disease; galactose; mucin-degrading gut bacteria; oxidative stress

1. Introduction

Parkinson's disease (PD) is the main movement disorder [1,2]. Movement symptoms result from the degeneration of brain dopamine (DA) neurons, mainly in the substantia nigra pars compacta (SNc). Locus coeruelus (LC) norepinephrine (NEP) neurons also degenerate early [3]. The cognitive impairment shown by many PD patients can be explained by reduced NEP [4] and DA. Although substantial empirical data has been gathered about PD during the last decades, there is still no complete theory explaining the disease. In particular, a theory of PD must explain why gut symptoms such as constipation precede onset by more than a decade [5], and the specific vulnerability of DA and NEP neurons [3].

Here I present a complete theory of PD (T*PD). It is complete in the sense that it explains its etiology, symptoms, pathophysiology, and treatment. The theory is supported by strong evidence, and points to novel optimal treatment directions.

Theory overview. PD patients have a higher gut abundance of mucin-degrading bacteria (e.g., Akkermansia Muciniphila (akkm)), which can be due to (epi)genetic reasons (e.g., higher mucin production), maternal transfer during birth, diet (e.g., milk consumption), infections, pollution, antibiotics treatment, etc. Since galactose is a major component of mucin and competes with glucose for transport and uptake, this results in higher than normal brain galactose uptake, and lower than normal brain glucose uptake. Galactose undergoes oxidative metabolism like glucose, but it is a less efficient substrate for glycolysis. As a result, glutathione (GSH) production, which depends on glycolysis and the pentose phosphate pathway (PPP), is decreased. GSH is the main anti-oxidant that counters the oxidative damage induced by iron, and its deficiency leads to cell death by ferroptosis [6].

Neuromelanin (NM) is a pigment produced via iron-mediated oxidation of catecholamines [7], protecting cells from iron-induced oxidative stress (oxis) [8]. SNc DA neurons and LC NEP neurons have a substantially higher NM expression than other brain cells [7], indicating that they have the highest sensitivity to iron toxicity. Hence, they are the first to suffer the results of decreased GSH. These neurons manage to protect themselves for many years (e.g., via alpha-synuclein (aSyn) and NM), but this protection eventually collapses, due to the general aging-related decrease in the efficiency of cellular processes and to aSyn and NM accumulation.

Glycolysis-oxphos imbalance in PD can also be caused or enhanced by mutations in genes involved in mitochondrial oxphos and iron metabolism.

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2. T*PD Theory of PD

T*PD explains PD as follows.

1. PD involves an imbalance between galactose and glucose in favor of the former. This yields reduced glycolysis.
2. The main source for this imbalance is a higher abundance of mucin-degrading bacteria in the gut microbiome (GMB).
3. The imbalance yields GSH deficiency, exposing cells to oxidative iron toxicity. The cells that are most sensitive to this are those that continuously secrete catecholamines and express neuromelanin.
4. The phenomenon is a small-scale one, and the main damage occurs with the deterioration of cellular defenses with aging, and with the accumulation of NM and alpha-synuclein (aSyn).
5. Some genetic mutations can enhance these processes.

Here I elaborate on each of these points.

Galactose. Galactose is a monosaccharide found in milk products (as lactose, containing one galactose molecule and one glucose molecule), fruits and vegetables [9]. It is absorbed by intestinal endothelial cells via the sodium-glucose linked transporter type I (SGLT1), and released into the circulation via glucose transporter type 2 (GLUT2). Normally, most of the ingested galactose remains in the liver, with a small amount entering the brain (via GLUT3 and GLUT4) and other organs [10]. However, a higher load reduces liver clearance [11], and following an intraperitoneal galactose load, brain uptake is higher than the livers', retaining galactose for a longer duration than the liver and that of brain glucose [10].

The main metabolic pathway of galactose is the Leloir pathway, where it is converted to UDP-Gal and UDP-Glc. Through these, galactose can be used for glycogen synthesis, glycolysis, and glycosylation. However, it fuels glycolysis at a much slower rate than glucose does [9,12,13]. As a result, its contribution to the PPP, which is essential for GSH synthesis, is smaller, it induces higher oxidative stress and oxphos gene transcription than glucose [14], and reduces glycogen synthesis.

Two additional metabolic pathways, used in case of excess, are the galactonate pathway and galactitol. Galactitol does not diffuse across the cell membranes, and when it accumulates, it leads to depletion of NADPH, decreased glutathione reductase activity, and increased oxis. Galactitol accumulation exerts negative feedback on the first step of the Leloir pathway, increasing its accumulation [9].

Thus, galactose decreases anabolic processes and increases oxidative stress. Indeed, there is a rodent model of aging in which chronic subcutaneous galactose injections induce mitochondrial dysfunction, oxidative stress, inflammation, apoptosis, and decreased neurotrophic factors [13]. These effects are ameliorated by alpha-lipoic acid, an iron chelator [15].

The galactose aging model also shows increased GSK3b, which suppresses glycogen synthesis [16]. Note that (i) glycogenolysis is required for the astrocyte Na^+/K^+-ATPase [17], (ii) the glutamate-glutamine cycle depends on K^+ and Na^+ gradients, and (iii) glutamate is used for GSH production. These data imply that glutamate uptake may be impaired in PD, leading to excitotoxicity.

Mucin-degrading gut bacteria. The human gut microbiome (GMB) is comprised of a large number of species and sub-species. Several of these can degrade mucin, the protective mucus layer of the gut and the respiratory tract [18,19]. Galactose is a fundamental component of mucin. The main mucin-degrading bacterium is akkm (the only member of verrucomicrobia present in humans), which clearly plays an important part in PD and has all of the prototypical properties needed for explaining it. Other species include bacteroidetes, bifidobacteria, firmicutes, and lactobacteria.

Unlike some mucin-degrading bacteria, akkm liberates mucin but does not use it [20]. In parallel, akkm increases the thickness of the gut mocus layer [21], and upregulates genes involved in maintaining the intestinal barrier [22]. These effects increase galactose absorption and decrease glucose absorption [23].

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High GMB akkm may be secondary to increased mucin production due to (epi)genetic reasons, diet effects (e.g., consumption of particular milk products), and other inherited or acquired alterations of the GMB. For example, akkm is increased in the galactose-induced aging mouse model [24]. Importantly, mucin production is enhanced by gut infections [25]. Since akkm is highly heritable [26], a family or personal history of infections can trigger PD in many people.

Neuromelanin, iron. One clearly unique aspect of brain DA and NEP cells is that they are the only ones with substantial expression of neuromelanin (NM). NM is a pigment resulting from the oxidation of catecholamines by iron(III) to o-quinones, which yield NM [7]. NM is not degradable and it is insoluble, accumulating in cells. Thus, the expression of NM indicates a state with a high reactive iron potential. Indeed, SNc DA neurons have higher basal oxphos and oxis than ventral tegmental area (VTA) DA neurons, which are less sensitive in PD [27].

Ferroptosis is an iron-dependent, caspase-independent cell death pathway whose key features are GSH depletion and lipid peroxidation [6]. The PPP, which depends on glycolysis, is essential for the production of GSH [28]. GSH binding to iron prevents the oxidation of iron(II), maintaining iron solubility and preventing the generation of the hydroxyl radical from hydrogen peroxide (the fenton reaction) [6]. Hydroxyl radicals are highly potent agents of lipid peroxidation. GSH depletion allows iron to yield hydroxyl radicals, lipid peroxidation, and ferroptosis.

Thus, the following picture emerges. When GSH production is sufficient, it prevents the formation of iron(III) and lipid peroxidation. When GSH diminishes (e.g., with aging), iron(III) is formed and drives the formation of NM, which neutralizes iron toxicity, including the production of toxic catecholamine metabolites and of the hydroxyl radical [29]. Indeed, reactive iron is not present in NM-containing neurons, while neurons without NM have reactive iron deposits [7]. With severe GSH deficiency, as in PD, there is lipid peroxidation and eventually ferroptosis.

Aging. Age is the leading risk factor for PD. In over 75% of patients, the age of onset is older than 65 years, and in 90-95% it is older than 50 years [30]. Aging involves a general decrease in the efficiency of brain cellular processes, inducing an increase in relevant harmful processes such as lipid peroxidation, mitochondrial dysfunction, and dysregulated metabolism [31]. Moreover, the specific causal processes discussed above are also affected by aging. The capacity of the liver for galactose elimination decreases with aging, starting around 63 years [32]. The galactose-based aging model shows many of the characteristics of normal aging [13]. GSH synthesis significantly decreases with aging [33]. Both oxidative iron [34] and NM [7] increase with aging. Lipid peroxidation is increased 2-fold in SNc DA neurons vs. the basal ganglia and prefrontal cortex in aging [35].

Alpha-synuclein (aSyn). PD has been traditionally strongly associated with aggregates of aSyn in the degenerating neurons. However, it is now recognized that such aggregates are also present in many other neurons and tissues [30]. aSyn is recruited by increased oxis [36] and iron (via an iron-responsive DNA element) [37]. There is higher aSyn accumulation in NM cells [38]. Monomeric (but not fibrillar) aSyn prevents lipid peroxidation [39], and knockout neurons are more vulerable to oxis [40]. aSyn converts large spherical vesicles into very small ones with higher curvature [41], inhibits membrane fusion, and induces mitochondria fragmentation [42]. It is present in mitochondria-associated endoplasmic reticulum membranes, streamlinining Ca^{2+} transfer [43]. Finally, it promotes glucose uptake and glycolysis [44,45].

Thus, the role of aSyn seems to be to protect cells from excessive oxphos- and iron-induced oxis. It is easily activated in basically all cell types (in fact, the kinases promoting its Ser129 phosphorylation are constitutively active [46]), indicating that it is the first line of defense against such toxicity. As explained above, cells that continuously secrete catecholamines are more vulnerable than other cells, and need further defenses in the form of NM. In PD, higher chronic oxis induces chronic aSyn recruitment, misfolding, and phosphorylation, which eventually lead to its aggregation. This further impairs mitoch function and promotes degeneration.

Genetic mutations. In a minority of patients, PD is associated with gene mutations (in parkin (park2), DJ1 (park7), pink1, LRRK2). All of these genes are essential for mitochondria function,

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specifically with respect to oxis [47]. For example, parkin overexpression decreases oxis, protects from DA- or 6-OHDA-induced apoptosis, and mutants are associated with increased lipid peroxidation [47]. DJ1 is protective against H2O2, 6-OHDA, rotenone, and MPTP (widely used animal models of PD). DJ1 also enhances GSH levels [47].

Another associated gene is GBA, which shows decreased activity in sporadic PD [48]. GBA breaks down glucosylceramide to glucose and ceramide. Decreased activity implies decreased glucose around membranes, exacerbating the imbalance problem in PD.

It is not clear whether these mutations require higher mucin-degrading bacteria to cause the disease. They may be able to do so on their own, or alternatively, it is possible that they do require a basic galactose problem, and their presence only accelerates disease onset.

Animal models. There are several animal models for PD, based on rotenone, paraquat, 6-OHDA, MPTP/MPP+, etc. [1]. These models mimic the oxis and mitochondria aspects of PD, but not the galactose aspect.

3. Evidence

T*PD is supported by strong evidence.

3.1. Gut Bacteria, Mucin

Mucin-degrading bacteria. Increased abundance of mucin-degrading bacteria, mainly akkm, is consistently reported in PD [49,50]. Other relevant bacteria include some bifidobacterium, bacteroides, lactobacillus and christensenellaceae species.

Constipation. PD patients show gut-related prodromal symptoms, mainly constipation, which precede movement symptoms by decades. Akkm and high gut mucin are associated with constipation [51,52].

Olfaction. PD patients also show very early prodromal olfactory symptoms [1]. Mucin is expressed at the respiratory tract, including the nasal cavity, which hosts mucin-degrading bacteria [53].

aSyn. Patients show aSyn pathology in the gut and olfactory mucosa [54].

Pneumonia. Respiratory diseases are very common in PD [55], and have been reported to be the leading cause of death [56,57]. Usually explained via swallowing difficulties, it is possibly better explained via respiratory mucin expression.

HPL infection. Helicobacter pylori (HPL) is a gut bacterium, associated with increased PD risk [55]. HPL degrades mucin and liberates galactose [58].

Pollution. Exposure to air pollution increases risk (but not in all studies) [59]. Environmental pollution and pesticides enhance oxis burden in the respiratory tracts and increase gut mucus [60].

3.2. Galactose

Milk. Consumption of dairy products, mainly milk, is a PD risk factor [61]. Milk increases the amount of gut galactose. Many mucin-degrading bacteria, including akkm, bacteroides, and bifidobacteria can degrade human milk oligosaccharides [62].

Galactitol. There is some direct evidence for excessive galactose in PD. CSF galactitol, whose production indicates excessive galactose, is increased by 1.26x in PD [63]. Galactitol is increased 3.1x in most brain areas in PD with cognitive decline [64]. In preonset PD, plasma galactitol is decreased [65] (with a similar trend reported as well [66]). This may show higher brain intracellular accumulation.

Glycosylation. Abnormally high glycosylation and glycation are common [67].

Galactosemia. Galactosemia is a disease that involves accumulation of galactose due to reduced function of an enzyme that breaks it down. A high percentage of patients show motor problems, mainly tremor and dystonia [68], and progressive worsening is common [68,69]. Striatal dopamine denervation has been reported in one case report, and L-dopa improved tremor in another [70,71].

Both galactosemia [72] and PD patients [73] show decreased bone mass and bone problems.

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3.3. Glucose

Reduced glucose. Patient CSF shows decreased glucose and lactate [74,75]. Lower blood glucose elevation following food intake is associated with increased PD risk [76]. This supports lower glucose gut absorption.

Glycolysis. G6PD and 6PGD (PPP-supporting enzymes) are decreased in the putamen in early PD stages [77]. Patient SNc DA cells show decreased glycolysis [78]. Plasma PPP and glycolysis are dysregulated compared to essential tremor patients [79].

Glycogen. GSK3b, which suppresses glycogen synthesis, is found in patient Lewy bodies in midbrain and pons neurons[80]. Glycogen synthesis rate is decreased in patient visual cortex [81].

Glycolysis medication. Glycolysis-enhancing drugs decrease PD risk [82].

Uptake. PET imaging studies consistently report reduced glucose uptake in non-degenerating brain areas [83–85]. This supports excess of ATP in brain cells (in T*PD, due to galactose), since ATP excess is the main factor that downregulates glucose receptors.

Reduced glucose uptake in olfaction pathways is correlated with olfactory dysfunction in patients [86].

Diet. Patients eat significantly more carbohydrates preonset [87], and show sweet craving [88,89], showing that the brain does not receive sufficient amounts of glucose.

Diabetes. People with type 2 diabetes (DM2) have a higher PD risk, but PD patients have a lower risk of DM2 [90]. T*PD explains this as follows. In DM2, there is reduced cellular uptake of glucose, and a higher PD risk indicates that this might be part of the problem in PD. In PD, there is lower blood glucose (due to competition with galactose for gut absorption), which reduces DM2 risk.

Note that gut bacteria such as akkm are usually viewed as beneficial in DM2 and inflammatory bowel disease, because they reduce blood glucose and enhance barrier function. In T*PD, such bacteria are the main culprits.

BMI. PD patients are commonly underweight, with a significant proportion fulfilling criteria for malnutrition [91]. Conversely, being underweight (prodromally) increases risk [92]. Mucin reduces gut absorption of nutrients used for fat storage, and galactose poorly supports growth processes.

3.4. Oxidative Stress

Mitochondria. There is overwhelming evidence showing mitochondria (especially complex I) damage in PD [2]. Factors that impair mitochondria function (e.g., pesticides) are associated with increased PD risk [61]. Higher mitochondria oxis is also present in patient skin fibroblasts [93].

Chronic systemic complex I inhibition by rotenone causes highly selective SNc DA degeneration, associated with hypokinesia and ridigity [94].

GSH. The data with respect to GSH in PD overwhelmingly points to a decrease, in the SNc [95–97], including preonset [98,99], in other brain areas [100], in CSF [101], and in blood [102–104].

Iron. There is excessive total iron and iron(III) accumulation in the SNc in PD [100,105–107], including preonset [108].

Lipid peroxidation. Patients brains show high lipid peroxidation [109–112].

Neuromelanin. Virtually all patients exhibit substantial loss of neuromelanin-containing LC NEP neurons [7]. (See also cancer below.) Lateral SNc neuromelanin positively correlates with posterior putamen DA functionality in patients [113].

3.5. Sympathetic Nervous System

Early sympathetic degeneration. Early sympathetic nervous system (SNS) symptoms (daytime sleepiness, decreased lipolysis, cardiac SNS dysfunction) are very common in PD [114], showing that SNS cells degenerate early.

PD risk is higher with decreased serum triglycerides [115] and long chain fatty acids [116]. Note that this seemingly contradicts the datum stated earlier of being underweight increasing risk. That datum was due to GMB, and the one here to SNS function (lipolysis).

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REM sleep behavior disorder (RBD). RBD involves large movements during the rapid eye movement (REM) phase of sleep ("acting out dreams"). RBD is often one of the prodromal signs of PD [30]. Muscle atonia during REM sleep is normally mediated by projections from the sublateral dorsal nucleus (SLD), located just below the LC. SLD neurons contain NM, and are affected in PD to about the same extent as the LC [117]. This yields prodromal symtpoms like the other sympathetic prodromal symptoms in PD.

3.6. Risk & Protective Factors

Alcohol. Mild alcohol consumption is associated with decreased PD risk [118]. Alcohol depletes akkm, firmicutes, and lactobacteria [119].

Smoking. Smoking is associated with decreased PD risk [120]. Smoking depletes gut mucin-degrading bacteria (akkm, bifidobacteria, bifidobacteria, firmicutes) [119].

Caffeine. Caffeine decreases PD risk [61]. Caffeine has been shown to oppose galactose-induced oxis [121]. Akkm is negatively associated with caffeine consumption [52].

Traumatic brain injury (TBI). TBI increases PD risk [61]. TBI induces iron and reactive oxygen species accumulation, dysfunctional iron metabolism, and upregulates ferroptosis genes and neural degeneration [122].

Infections. Infections increase PD risk [55]. Infections increase gut mucin production [25].

Ibuprofen. Chronic ibuprofen (and to a lesser extent, also other NSAIDs) treatment reduces PD risk [123]. Such treatment is known to increase gut permeability, allowing nutrient entry.

Exercise. Moderate to intense exercise is associated with decreased risk [124]. This either occurs because the capacity of exercising shows an unimpaired SNS (reverse causality), or because exercise is actively helpful, e.g., by enhancing glycolysis.

Cancer. All cancer types are decreased in PD [125], except melanoma, which is increased [126]. The decrease occurs because cancer utilizes aerobic glycolysis, which is reduced in PD due to galactose. Melanoma is increased because melanocytes are specifically sensitive to oxis, as attested by their high melanin expression (however, the precise mechanisms of melanoma are not fully understood).

4. Treatment

Current drug-based treatments attempt to increase brain DA. While these drugs may help movement symptoms (at least for some time), they do not address the real cause of the disease, and are associated with several negative adverse effects.

According to T*PD, the optimal treatment for PD is to reduce galactose load while enhancing glucose metabolism. This needs to be done early, before neurons have been irrevocably damaged. Fortunately, gut symptoms can be easily detected, allowing early screening.

Fecal tests for the relative abundance of mucin-degrading bacteria, blood levels of galactose and its metabolites, and GSH levels in all tissues (including blood and skin cells and fibroblasts) constitute promising biomarkers.

Galactose load can be theoretically reduced via a galactose restricted diet. This is currently the only treatment for galactosemia. In practice, this approach is very difficult, due to the large number of food items that contain galactose. Nonetheless, most milk products should be avoided (high-fat yogurts and some high-fat cheese are low in galactose and can be consumed).

One treatment approach is to remove or reduce gut mucin-degrading bacteria, especially akkm. This can be done via fecal transplants, or via antibiotics or other drugs that have this effect. Common antibiotics decrease relative akkm abundance, but they also increase other mucin-degrading bacteria. Thus, akkm-specific drugs should be developed. Nonetheless, even common antibiotics may improve PD state, because these other species may not over-enhance gut barrier in the way that akkm does.

It is not clear whether complete eradication of gut bacteria (via non-selective antibiotics) is beneficial, but it can be attempted in the absence of other treatments.

A promising approach is to develop drugs that reduce gut mucin levels by targeting mucin production genes (MUC2, MUC5AC, others). Reducing mucin levels has three benefits. First, it would

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directly relieve galactose load. Second, it would reduce the relative abundance of mucin-degrading bacteria, depriving them of their main nutrients. Finally, it would address olfaction and respiration problems.

Exercise reduces PD risk. However, as explained above, this could be via reverse causality.

Adrenergic receptor agonists relieve the pressure off the SNS, and prodromal beta2-AR is indeed protective in a 1.76M Israeli cohort [127]. Similarly, propranolol (a beta blocker) increases risk 2.6-fold.

5. Discussion

I presented the first complete theory of PD. T*PD is complete in the sense that it explains the etiology, symptoms, pathology and risk factors of the disease. A complete theory can be wrong (partially or fully), but being complete is the minimal requirement from a theory.

In T*PD, PD occurs following a particular composition of the GMB, with an increased abundance of mucin-degrading bacteria. This in turn can result from many events, including infections, diet, inheritance, etc. Mechanistically, this particular composition yields higher levels of galactose and lower levels of glucose in the brain, which increases oxis and decreases glycolysis and GSH production, leaving the cell more exposed to ferroptosis. SNc and LC cells are the brain cells most sensitive to this, as indicated by their uniquely high expression of neuromelanin.

This account unifies the two most important questions about the disease: the gut and olfactory connection (with prodromal symptoms that precede diagnosis by over a decade), and the specific vulnerability of SNc and LC neurons.

Evidence. T*PD is supported by diverse and wide evidence, relating to the GMB, galactose, glucose (glycolysis, diabetes, BMI, imaging), oxis (mitochondria, GSH, iron, lipid peroxidation), the SNS, and risk and protective factors (smoking, alcohol, caffeine, exercise, ibuprofen, traumatic brain injury, infections, and melanoma). One piece of evidence that is relatively small is direct evidence for higher galactose levels in patient blood.

Other theories. A recent large multi-author review of PD did not mention the gut or GMB at all [1]. The idea that PD is an energy disease has been raised but without mechanistic gut and brain details [128]. The idea that the increased risk with milk consumption is due to galactose has been phrased [129,130], again without mechanisms and without linking it to other phenomena. A GMB hypothesis has been formulated, with an emphasis only on aSyn, inflammation, and brain fatty acids [131]. A brain-side hypothesis was raised in which PD involves a toxic feedback loop between iron, oxis, aSyn, and NM [8]. Thus, no existing theory is close to T*PD.

aSyn propagation. One of the established ideas in PD research is that the disease starts in the periphery (gut, olfactory tract) and spreads upwards to the brain [1]. However, this is based on Lewy pathology, whose distribution is not consistent with the disease [132]. As far as I know, the idea that the harmful agents are metabolic agents that spread from the gut through the blood has never been raised.

Treatment. An encouraging aspect of T*PD is that it implies several possible ways of treating the disease, some of which are relatively not difficult to implement. Precise modifications of the GMB are difficult to achieve, but a reduction of mucin degradation is probably possible. This treatment should start before DA and NEP neurons have accumulated too much damage, but fortunately, the presence of prodromal symptoms allows us to identify the risk years in advance.

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List of Abbreviations

akkm	Akkermansia Muciniphila.
aSyn	alpha-synuclein.
GMB	gut microbiome.
GSH	glutathione.
HPL	helicobacter pylori.
LC	locus coeruelus.
NEP	norepinephrine.
NM	neuromelanin.
PD	Parkinson's disease.
PPP	pentose phosphate pathway.
RBD	REM sleep behavior disorder.
SNc	substantia nigra pars compacta.
SNS	sympathetic nervous system.
TBI	traumatic brain injury.
T*PD	the theory of PD presented in this paper.

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