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ORIGINAL RESEARCH

Parkinson's disease managing reversible neurodegeneration

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Abstract: Traditionally, the Parkinson's disease (PD) symptom course has been classified as an irreversible progressive neurodegenerative disease. This paper documents 29 PD and treatment-induced systemic depletion etiologies which cause and/or exacerbate the seven novel primary relative nutritional deficiencies associated with PD. These reversible relative nutritional deficiencies (RNDs) may facilitate and accelerate irreversible progressive neurodegeneration, while other reversible RNDs may induce previously undocumented reversible pseudo-neurodegeneration that is hiding in plain sight since the symptoms are identical to the symptoms being experienced by the PD patient. Documented herein is a novel nutritional approach for reversible processes management which may slow or halt irreversible progressive neurodegenerative disease and correct reversible RNDs whose symptoms are identical to the patient's PD symptoms.

Keywords: Parkinson's disease, L-dopa, carbidopa, B6, neurodegeneration

Introduction

This study does not document a new Parkinson's disease (PD) treatment, but discusses effective and novel side effect management associated with the most effective PD treatment known: L-dopa (L-3,4-dihydroxyphenylalanine). The following approach definitively addresses PD, L-dopa, and carbidopa-associated side effects and adverse reactions which interfere with achieving optimal L-dopa results.

PD is classified as a "progressive neurodegeneration" (PN) disease.[1,2] With PD, irreversible brain damage involving the post-synaptic substantia nigra dopamine neurons[3] induces fine motor control dysfunction[4] (herein referred to as "electrical damage").

A relative nutritional deficiency (RND) occurs when an optimal diet does not meet nutritional requirements.[5–11] This paper demonstrates how the reversible PD symptoms induced by newly identified RNDs have been allowed to accumulate because of the disease process or traditional treatment. These symptoms have traditionally been exclusively attributed to irreversible PN. This novel approach breaks PN down into three subcategories: irreversible PN, reversible facilitated PN (FPN), and reversible pseudo-neurodegeneration (RPN).

PD electrical damage dysfunction is classically limited to the post-synaptic dopamine neurons.[12,13] Electrical flow, regulating fine motor control, flows from the pre-synaptic neurons, across the synapse, then through the post-synaptic neurons. It is the novel primary hypothesis that if PD symptoms from post-synaptic neuron damage develop, then compromise at any point in the electrical event chain, to include outside the post-synaptic dopamine neuron focus, may exacerbate and mimic PD symptoms and/or disease progression.

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In PD patients, reversible RNDs may induce PD symptoms which may be inappropriately managed when treated as PN.[9–11] Figure 1 illustrates 29 primary system depletions associated with PD and its treatment. Each depletion induces and represents a significant underlying RND which contributes to PD symptom exacerbation and/or overall irreversible disease collapse. The novel hypothesis is that if a dysfunction resulting from nutrient depletion exists, then one or more underlying RNDs is always present.

With regard to Figure 1, the 29 PD and treatment associated depletions are listed immediately below. The RNDs associated with each are discussed in the following sections prior to the "Materials and methods" section.

1. PD-associated dopamine depletion.[12,13]
2. PD-associated norepinephrine depletion.[14,15]
3. PD-associated epinephrine depletion.[15]
4. PD-associated glutathione depletion prior to symptom onset.[16–18]
5. PD-associated S-adenosylmethionine depletion.[19–21]
6. PD-associated L-cysteine depletion.[22]
7. PD is associated with glutathione depletion.[16–18] Glutathione depletion may induce L-methionine depletion.[23]
8. PD-associated vitamin B6 deficiency.[24]
9. PD-associated serotonin depletion.[25,26]
10. PD associated with 5-********** depletion.[27]
11. PD-associated ******** depletion.[28]
12. PD-associated L-dopa depletion.[29–39]
13. PD associated with L-tryptophan depletion.[31,32]
14. L-dopa-associated L-******** depletion.[33]
15. L-dopa-associated L-tryptophan depletion.[33]
16. L-dopa-associated S-adenosylmethionine depletion.[34–36]
17. L-dopa-associated L-methionine depletion.[36]
18. L-dopa-associated L-******** depletion.[37]
19. L-dopa-associated glutathione depletion.[37]
20. L-dopa-associated serotonin depletion.[33,34,38–40]
21. Carbidopa-associated vitamin B6 depletion.[10,11,41,42]
22. Carbidopa associated serotonin depletion.[43,44]
23. Carbidopa-associated dopamine depletion.[43]
24. Carbidopa-associated norepinephrine depletion.[41]
25. Carbidopa-associated epinephrine depletion.[41]
26. Carbidopa-associated vitamin B6 depletion.[10,11,41,42] Vitamin B6 depletion may deplete glutathione.[45,46]
27. Carbidopa-associated vitamin B6 depletion.[10,11,41,42] Vitamin B6 depletion may deplete glutathione.[45,46] Glutathione depletion may deplete S-adenosylmethionine.[47]
28. Carbidopa-associated vitamin B6 depletion.[10,11,41,42] Vitamin B6 depletion may deplete glutathione.[45,46] Glutathione depletion may deplete L-methinonine.[48]
29. Carbidopa-associated vitamin B6 depletion.[10,11,41,42] Vitamin B6 depletion may deplete glutathione.[45,46] Glutathione depletion may deplete L-********.[48]

As illustrated in Figure 1, patients with PD suffer from one or more RNDs involving L-cysteine and methionine, vitamin B6, serotonin precursors (L-tryptophan, 5-***), and dopamine precursors (L-********, L-dopa).

Drug-nutrient perspective

The following definitions are required to understand this approach. L-dopa and 5-********** (5-***) are defined as dopamine and serotonin nutrient amino acid pre-cursors, respectively.

The following documented drug-nutrient reference point is required for optimal RND management:

> A nutrient is any substance that facilitates normal system function. A drug is any substance that induces abnormal system function. A nutrient may become a drug. A drug

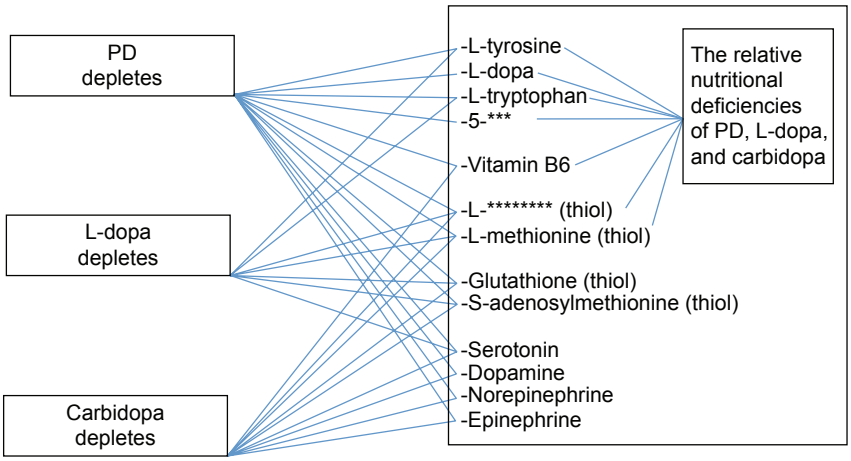

Figure 1 The 29 primary RND-inducing depletions resulting from PD, L-dopa, and carbidopa.
Abbreviations: RND, relative nutritional deficiency; PD, Parkinson's disease; 5-***, 5-**********; L-dopa, L-3,4-dihydroxyphenylalanine.

may not become a nutrient. When the nutrient 5-*** is administered as a single agent, dopamine depletion may occur. If dopamine depletion is induced, 5-*** is no longer functioning as a nutrient; it is a drug. When L-dopa is administered as a single agent, it may deplete serotonin, and would then be considered a drug, not a nutrient.[11]

The following novel hypothesis is required to address the 29 PD RNDs which cause reversible FPN and RPN. If when administered properly drugs have side effects and nutrients have no side effects, then nutrients that display side effects are functioning as drugs.

Under the previous definitions, drugs are substances not normally found in the body which induce abnormal effects. If these abnormal effects are desirable, then the drug is administered. Undesirable effects are labeled side effects. When undesirable effects outweigh desirable ones, drugs may be discontinued. Normal body functions require nutrients. Properly administered L-dopa and other nutrients facilitate normal function without side effects. If L-dopa or 5-*** administration induces side effects, then it is nutrient to drug conversion evidence.

Drugs cannot treat RNDs. In the USA L-dopa is concomitantly packaged with carbidopa as a drug and administered with side effect expectations.[47] In the USA there is no single ingredient prescription L-dopa form without carbidopa available. When L-dopa is indicated while intolerable carbidopa side effects develop the non-prescription nutritionally sourced L-dopa found in *M***** ******** (synonym for *M***** **********) is the only option.[10,11] Ayurvedic medicine has prescribed *M.* ******** for 3,500 years.[48]

Competitive inhibition

Competitive inhibition is the interaction between serotonin and dopamine along with their precursors in synthesis, transport, and metabolism. In the endogenous state, where no or insufficient serotonin or dopamine precursors are ingested, competitive inhibition does not exist.[5–11,49–56]

Synthesis

Aromatic-L-amino acid decarboxylase (AADC) metabolizes L-dopa to dopamine, 5-*** to serotonin, histidine to histamine, and phenylalanine to phenylethylamine. Competitive inhibition may exist between the four precursors for metabolism by AADC. Administering L-dopa without balanced serotonin precursor concentrations may decrease AADC serotonin synthesis. This causes a L-dopa-induced serotonin precursor RND, Figure 2.[5–11,49–56]

Transport

Organic Cation Transporters (OCT) transport the centrally acting monoamines (serotonin, dopamine, norepinephrine, and epinephrine) and their precursors bidirectionally across cell membranes. OCT transports precursors into the cellular structures where AADC metabolism occurs. Newly synthesized centrally acting monoamines are transported extracellularly by OCT to effect functional regulation. There is a direct correlation between L-dopa administration and dopamine concentrations. Increasing only L-dopa and dopamine concentrations induces competitive inhibition at the transporter, an event that may exclude serotonin precursor transport leading to synthesis inhibition. Subsequent serotonin depletion represents a serotonin precursor RND.[5–11,49–56]

Metabolism

The monoamine oxidase-A catalyzes centrally acting monoamine metabolism. Increasing dopamine concentrations with L-dopa enhances monoamine oxidase-A activity which may deplete serotonin, inducing a serotonin precursor RND.[5–11,49–56]

Reversible PD phenomenon

The PD clinical course is typically described as irreversible PN. The following is based on 18 years of data collection

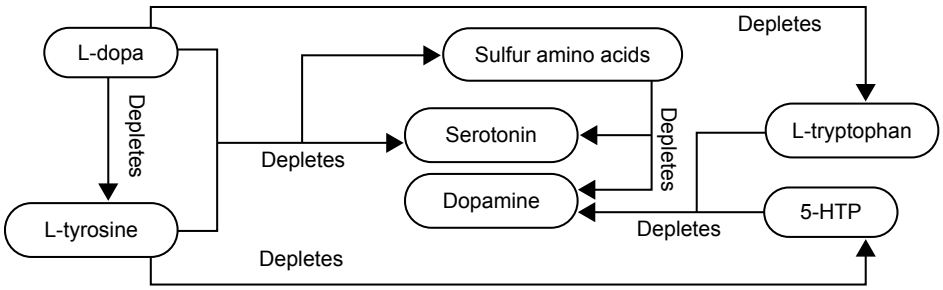

Figure 2 With competitive inhibition administering one precursor in excessive concentrations may induce depletion and one or more RNDs.
Note: Copyright ©2014. Dove Medical Press. Reproduced from Hinz M, Stein A, Uncini T. Parkinson's disease: carbidopa, nausea, and dyskinesia. *Clin Pharmacol.* 2014;6:189–194.[11]
Abbreviations: RND, relative nutritional deficiency; 5-***, 5-**********; L-dopa, L-3,4-dihydroxyphenylalanine.

from several hundred medical clinics. This data was used to define reversible RNDs whose symptoms are identical to PD symptoms and/or facilitate irreversible PN.

The problems

This approach rests on the hypothesis that dysfunction resulting from inadequate nutrient concentrations, even when an optimal diet is consumed, results in a nutritional precursor RND. The RNDs associated with PD and its precursors include:

- "Total glutathione loss" which is known to occur before PD symptoms develop.[16,57] This represents a novel glutathione precursor RND involving L-******** and/or L-methionine,[57] the normal dietary glutathione precursor source.
- PD-induced serotonin, dopamine, norepinephrine, and epinephrine depletion represents novel serotonin and dopamine precursor RNDs.[5]
- L-dopa-induced competitive inhibition depletes serotonin with an associated novel serotonin precursor RND.[5]
- Melanin steal, which has been documented and discussed in the "Other impacts" section, induces dopamine fluctua-tions that represent an L-dopa and L-*** RND.[51]
- L-dopa induces a glutathione precursor RND.[36]

The most potentially devastating RND is caused by carbidopa which irreversibly binds to and then deactivates vitamin B6 (B6) and all B6-dependent enzymes causing a drug-induced B6 RND that may compromise function involving over 300 enzymes and proteins. When the B6-dependent enzyme AADC collapses, this may compromise metabolism of L-dopa to dopamine, 5-*** to serotonin, histidine to histamine, and phenylalanine to phenylethylamine. Carbidopa-induced B6 depletion may compromise the two B6-dependent enzymes (histadine decarboxylase and AADC) which metabolize histadine to histamine inducing a profound antihistamine effect. Carbidopa-induced B6 depletion can deplete glutathione. The B6-dependent enzymes cystathione-beta-synthetase and cystathione-gamma-lyase metabolize homocysteine to L-********. L-******** is the rate limiting step in glutathione synthesis.[10,11,43,58]

The primary PD RND

The primary PD RND involves the inability to obtain adequate dopamine precursors from the diet. Under normal conditions dietary L-t******* and L-dopa metabolism meet the synaptic dopamine requirements for optimal electrical transfer across the synapse which facilitates optimal fine motor control regulation. When PD symptoms are present, an optimal diet cannot facilitate dopamine synthesis at the levels required for adequate increase in post-synaptic electrical flow.[5]

Increased L-dopa intake may facilitate synaptic dopamine levels which enhance post-synaptic electricity flow. The subsequent decrease in PD symptoms is due to the dopamine-induced improvement in fine motor control regulation. Increasing synaptic dopamine levels is analogous to increasing the post-synaptic voltage which regulates fine motor control.[10]

An exception to the assumed "more is better concept" was documented in 2014. In the competitive inhibition state, administering too much or too little L-dopa can display exactly the same PD symptoms with identical intensity. The previously documented pill stop technique is required to determine optimal dosing.[9]

AADC freely metabolizes L-dopa to dopamine without biochemical feedback regulation. With adequate AADC, ingesting unlimited L-dopa will yield unlimited dopamine. Under the traditional PD treatment medical care standard, the L-dopa daily dosing value limiting factor is usually L-dopa-induced side effects and/or tachyphylaxis. Typically, less effective drugs, such as dopamine agonists, are prescribed first to delay dealing with inevitable and escalating L-dopa side effects. This is a practice that ignores the primary PD RND, inadequate dopamine precursor intake, which is a reversible dietary deficiency. As discussed in the following section, this RND has RPN symptoms that are identical to irreversible PN.[5,49]

Facilitated irreversible progressive neurodegeneration

It is postulated that the primary PD etiology is lipophilic neurotoxin-induced post-synaptic dopamine neuron damage.[56,59–66] The body's most powerful and abundant protection against lipophilic neurotoxins is glutathione.[67,68] Total glutathione loss prior to PD symptom onset is documented.[16,57,68] The hypothesis is, if glutathione depletion facilitates and potentiates lipophilic neurotoxin damage, then the first step in halting or slowing the irreversible PN is establishing glutathione at optimal levels. The medical care standard does not address the glutathione precursor RND. To the contrary, as discussed in the following section, many medical actions and inactions facilitate glutathione collapse which in turn may potentiate and accelerate FPN. FPN occurs when a reversible process, if left unchecked, enhances and/or accelerates irreversible PN.

Glutathione depletion

With regard to Figure 3, L-******** is the rate-limiting step in glutathione synthesis.[70] Under normal conditions the gluta-thione precursor L-******** and/or its precursor L-methionine are obtained from the diet in adequate amounts to facilitate optimal glutathione synthesis.

Inadequate glutathione levels can be caused by one or two conditions; The first is an L-******** RND, Figure 3. The second is vitamin B6 RND. The B6-dependent enzymes cystathionine-beta-synthase (4.2.1.22) and cystathionine-gamma-lyase (4.4.1.1) metabolize homo-cysteine to L-********, Figure 3. A B6 RND may profoundly inhibit glutathione synthesis.[45,46]

To properly manage glutathione depletion from car-bidopa or other sources, glutathione precursor status and/or B6 status must be addressed. Under the current PD medical care standard, nothing is done. The hypothesis is, if common PD treatment approaches deplete glutathione, then each facilitates the neurotoxin-induced electrical damage which leads to irreversible PN. The novel hypothesis is if glutathione depletion facilitates irreversible PN, then administering carbidopa may facilitate irreversible PD symptom progression and collapse.

With regard to PD patients, 89% take carbidopa.[71,72] Carbidopa's only indication is L-dopa-induced nausea management.[46] It has no PD efficacy. Carbidopa has one mechanism: it causes a drug-induced B6 RND through irreversible binding to both B6 and the B6 active site found on all B6-dependent enzymes. This includes the B6-dependent enzyme AADC that catalyzes the L-dopa to dopamine reaction and the 5-*** to serotonin reaction. The two B6 enzymes illustrated in Figure 3 metabolize homocysteine to L-********.[10,11,41,42] If carbidopa is not inducing a B6 RND state its clinical effects will not be observed. Supplementing B6 may hinder, reverse or cancel carbidopa's one benefit, its L-dopa anti-nausea effect.[47]

Referring to Figure 2, glutathione depletion may be induced by L-dopa administration which can deplete the glutathione sulfur amino acid (thiol) precursor S-adenosyl-methionine, Figure 3.[34,35,73]

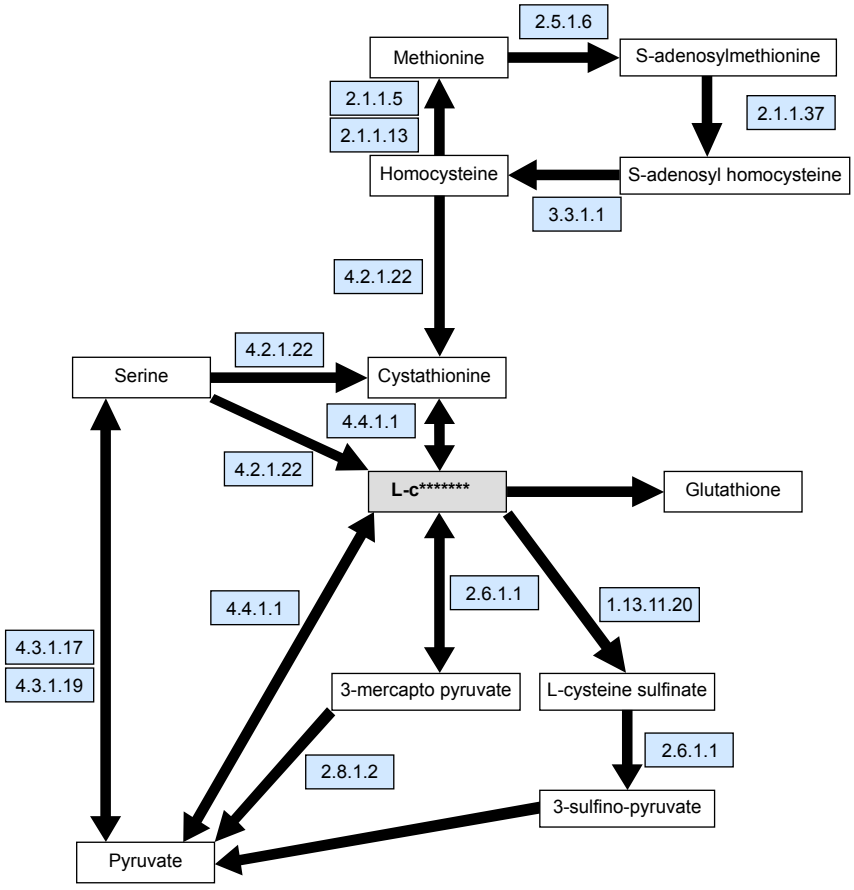

Figure 3 Thiol metabolism.
Notes: Glutathione precursors obtained from the diet are L-methionine and L-********. The enzymes cystathione-beta-synthetase (4.2.1.22) and cystathione-gamma-lyase (4.4.1.1) are vitamin B6-dependent enzymes. Data from Schulz et al[57] and http://www.genome.jp/kegg-bin/show_pathway?hsa00260.[69]