

## Short Communication

### A Deadly Mistake in Treatment of Parkinson's Disease

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**Citation:** Van Dyke K (2018) A Deadly Mistake in Treatment of Parkinson's Disease. JMBD-108. DOI: 10.29011/JMBD-108.100008

**Received Date:** 31 August, 2018; **Accepted Date:** 05 September, 2018; **Published Date:** 14 September, 2018

#### Abstract

The treatment of Parkinson's Disease (PD) has evolved from drugs that are mostly symptomatic to substances which if used correctly can actually slow down the progression of the disease. The first major discovery for PD was made when Professor Arvid Carlsson suggested the use of L-Dopa for treatment- which increases the amount of the key transmitter dopamine in the dopaminergic nerves in the substantia nigra where brain dopamine is synthesized, stored and released as well as recycled. A variety of scientists have now developed the idea that the Nurr-1 transcription factor and receptor is the controller of the various activities of brain dopamine whose depletion causes PD. But Kim et al. discovered chloroquine which is the first effective agonist which binds to Nurr-1. Chloroquine, an antimalarial drug, actually stimulates the formation of dopamine- while it apparently protects against toxic activity from activated microglia producing harmful peroxides. Using this knowledge, Kim et al. demonstrated that chloroquine or similar antimalarial drugs are effective against animal models of Parkinson's disease. However, a combination therapy (carbidopa/levodopa) presently heavily used today to treat Parkinson's disease rather than decreasing death rate as was observed with L-DOPA alone actually increases the PD death rate 4 fold. The use of Carbidopa (CD) depends crucially on the drug not entering the brain. But PD causes the blood-brain barrier to become leaky as does increasing age and it is herein proposed that if and when carbidopa enters the brain, it prevents the L-DOPA from forming dopamine because CD is an amino acid decarboxylase inhibitor which would prevent L-DOPA from forming dopamine-a necessary neurotransmitter controlling movements and life itself. We propose that this is likely why this drug combination is shortening lives of people with PD. There are approximately 1 million people in the USA with Parkinson's disease most of who are taking the wrong drug combination for their disease. There are many millions more around the world with PD who should change their treatment accordingly. We propose a new combination that can make a difference in possibly prevention but certainly in progression of PD as this has been demonstrated in PD animals at present

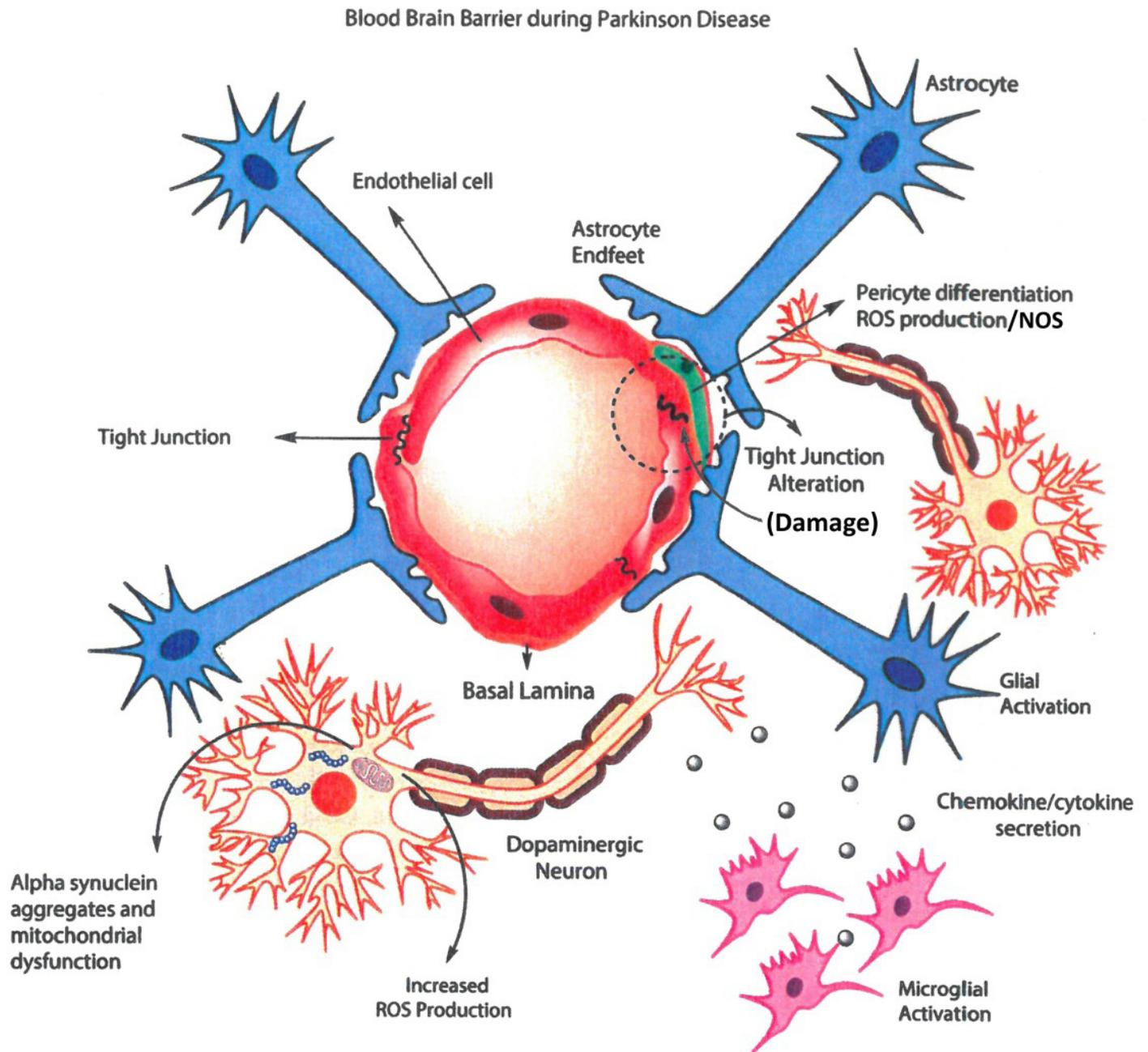
**Keywords:** Carbidopa; Chloroquine; EPA; Fish Oil- DHA; Parkinson's Disease; L-DOPA

#### Introduction

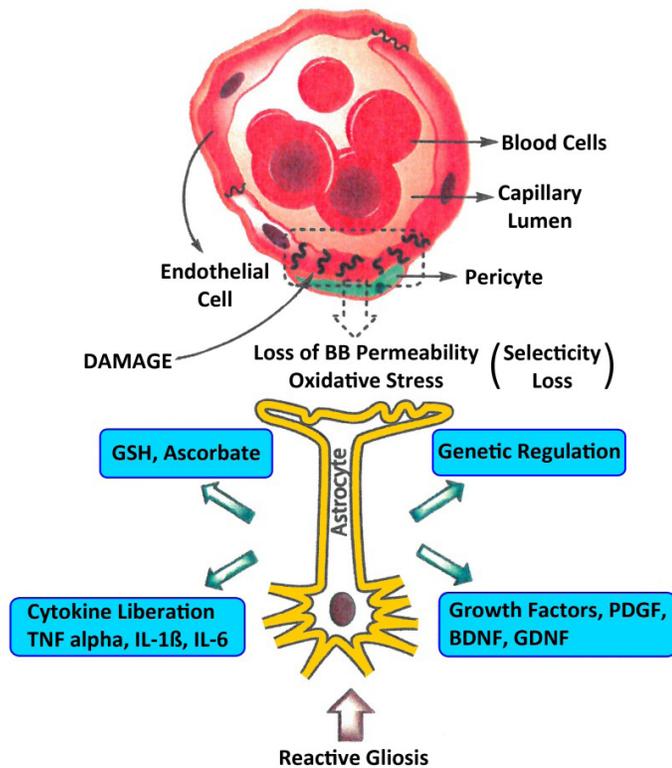
The Blood-Brain-Barrier (BBB) is the important interface between the Central Nervous System (CNS) which regulates molecular movement in and out of the brain creating CNS homeostasis. Its composition is mainly endothelial cells, pericytes, and astrocytes thus creating a neurovascular unit surrounded by adjacent neurons. Astrocytes are crucial both in formation and maintenance of the BBB by secreting factors leading to adequate and strong association of the cells of the BBB and strong junction formation. Various disease states eg. Alzheimer's, Parkinson's, multiple sclerosis and different forms of dementia, brain trauma,

and chronic cerebral ischemia there is a disruption of the BBB creating a loss of proper permeability of the carrier and concomitant physical changes in endothelial cells and astrocytes. Reactive gliosis is a common astrocytic feature during BBB damage which affects barrier function and neuronal survival.

Damage to BBB function is a fundamental characteristic in various diseases and in physical damage to the brain. Since the BBB functions to allow certain nutrients and ions to enter the brain, it also functions to keep out cells and materials that could be detrimental to the brain. It is generally known that for every 100 drugs used by humans only 2 of the 100 actually are allowed to penetrate into the brain so there is a clear selectivity for different substances entering the brain. See (Figure 1) and (Figure 2) which demonstrate the damage to the BBB from either diseases or trauma to the brain.



**Figure 1:** Blood Brain Barrier (BBB) destruction in Parkinson's disease. As Parkinson's disease develops oxidative and nitrosative stress occurs generating reactive oxygen and nitrogen species. This produces an overload of calcium which is toxic to mitochondria causing apoptosis and necrosis and neuronal death. Apparently both astrocytes and microglia become activated causing cytokine release which damages tight endothelial cell junctions pericyte phenotype and permeability of BBB causing leakiness.



**Figure 2:** Astrocyte release during BBB disruption. As PD progresses the BBB becomes leaky allowing entrance of toxic inflammatory substances and even infiltration of immune cells. Reactive oxygen / nitrogen species cause reactive gliosis and cell death. Damaged astrocytes release glutathione and ascorbic acid, vitamin E and other antioxidants and generate growth factors like BDNF and GDNF creating angiogenesis. Astrocytes release Occludin and ZO-1 affecting endothelial cell tight junctions. Cytokines are released from astrocytes tumor necrosis factor alpha interleukins 1-Beta and IL-6 which are important in microglial activation and neuronal death during brain damage.

One aspect of the BBB which is not always appreciated is that this barrier functions a little differently in some people than others. For example, the newer H1 antihistamines are not supposed to penetrate the BBB and therefore they cannot make you sleepy. However, it is well known that some people that are normal otherwise do get sleepy from these drugs, indicating that these H1 antihistamines do get into their brains. Another aspect of the BBB that is not always appreciated is that as people get older the BBB becomes leaky. Naturally many older people begin to have chronic diseases after the age of 50, and either the change in years or the disease or the combination of the two- cause an increase in BBB leaking. Parkinson's Disease (PD) is a chronic and progressive neuro-inflammatory disorder caused by the death of the dopaminergic neurons in the substantia nigra. This is a movement disorder which includes asymmetrical bradykinesia

(slow movement), rigidity, resting tremor, and postural instability. The initiation and progression of the disease is likely caused by oxidative/nitrosative stress and mitochondrial dysfunction and apoptosis and necrosis with increases in autophagy.

Our original patented idea was that a continual and sustained use of a mixture of various antioxidants with inosine could actually slow the progression of neurodegenerative diseases like PD (Van Dyke, [1,2]. Schwarzschild [3] et al. demonstrated that inosine does actually slow disease progression in men. Early treatments with sustained release vitamin C, Vitamin E (tocotrienols), sustained release inosine or inosine at the correct doses will likely act synergistically to help slow progression of the early disease.

In 1960, Professor Arvid Carlsson [4] introduced dihydroxyphenylalanine (L-DOPA) into clinical treatment of PD. From 1960-1975, the death rate from Parkinson's disease actually decreased. However, L-Dopa was partially converted to dopamine outside the brain (in the periphery) causing side effects- nausea and low blood pressure etc. Merck Sharpe and Dohme introduced carbidopa to be taken in combination with L-DOPA- and in Europe benserazide is added to L-DOPA instead of carbidopa –both of which partially alleviate side effects of L-DOPA. However, 40% of these patients using the combination of the two drugs used in Europe or the USA also caused motor fluctuation and dyskinesia. In addition, and more importantly- from 1975-to present day 2018- the death rate of Parkinson's patients taking the combinational drugs increased 4 fold. This is an unacceptable situation, created by drug manufacturers and governments not watching PD death rate figures of patients using these combinational drugs compared to L-DOPA alone. One wonders why retrospective studies have not been done on these drug combinations. It is likely that drug acceptance has escaped scrutiny because acceptance happened so long ago.

Hinz and Cole [5] mentioned that carbidopa and benserazide both react with vitamin B6 via Schiff base formation. Once this covalent complex is formed, the vitamin B6 cannot react with amino acids to create important amino acid transamination reactions. Normally, there are 9 essential amino acids, but 20 amino acids are needed. The 20 amino acids have to be produced using biochemical changes to the 9 essential amino acids and if vitamin B6 is bound to the one of the two drugs, this essential transamination cannot occur. This creates a nutritional disaster. But, can it be the main cause of the increased death rate? It certainly could be a contributing factor. But, since many of the Parkinson's disease patients are over the age of 65, it is quite likely that a leaky blood-brain barrier may play a large role because it is known that age and PD can become an important factors in blood-brain barrier leakiness [6]. If either carbidopa or benserazide entered the brain through a leaky barrier- it could inhibit the amino acid decarboxylase which forms dopamine from L-DOPA. Without sufficient dopamine, life cannot

exist. Further the tachyphylaxis effect of l-DOPA or (its dwindling effect) could be explained because less dopamine would be formed over time and this produces a deficient amount of dopamine. In other words, if there is less production of dopamine, it could be related to less actual hormone produced over time caused by an amino acid decarboxylase inhibitor which can enter the brain.

We suggest a different method to increase the production of dopamine and protect the damage to dopaminergic neurons. First, take orally, L-tyrosine at least 500 milligrams every 8 hours. L-tyrosine is the natural supplement that produces dopamine. It is readily taken into the brain using specific transporters and enters the Nurr-1 complex in the dopaminergic neurons. The enzymes of the Nurr-1 complex convert the tyrosine to dihydroxyphenylalanine (DHA) using tyrosine hydroxylase. The DHA is then decarboxylated using amino acid decarboxylase to form l-dopamine [7]. The dopamine is stored, released and even taken back by reuptake mechanism to be reused. In addition, we propose a more complete list of substances which will help to prevent and control Parkinson's disease.

Ingredients to prevent or slow progression of Parkinson's Disease

1. Inosine -4 grams /day in divided doses inosine or sustained release inosine.
2. Tocotrienols -Special form of Vitamin E capsules -1 capsule every 12 hours. Endurance Products
3. Fish oil with omega 3 fatty acids-DHA/EPA (1000mg/day); coated tablets. Endurance Products
4. Sustained release 5 hydroxytryptophan -500 mg every 12 hours-Endurance Products.
5. L-tyrosine-at least 500 milligram capsules every 8 hours-Endurance Products
6. Astrazanthin capsules 12 mg/day
7. Krill oil- 100-200 mg capsule /day-Endurance Products

8. Tylenol-arthritis formula-sustained release 1 to 2- 650 mg tablets/ every 8 hours

9. N- acetyl cysteine sustained release (NAC-SUSTAIN)- 1-600 mg tablet, take one/day

10. Sustained release niacinamide -500 mg tablets- take 2-3/day available- Endurance products, Oregon

11. Levo-Dopa/Carbidopa dose determined by physician - best avoided because of toxicity. If Levo-Dopa alone would be available this would be a more judicious choice.

12. Chloroquine 200-300 milligrams every third day. The dose and timing should be confirmed by a physician via prescription.

13. Vitamin C -2 grams every 12 hours or sustained release Vitamin C -2 grams every 12 hours-Endurance Products.

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