

## The Role of DOPAL in Parkinson's Disease

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Parkinson's disease is an incurable, neurodegenerative disease. The cause is still not fully understood. It is the second most common neurodegenerative disease and affects people all around the world<sup>1</sup>. Parkinson's affects approximately 500,000 Americans. There are about 60,000 new cases diagnosed every year<sup>2</sup>. The symptoms of this disease include slow movement, resting tremors, rigidity, and rapid eye movement sleep behavior disorder. There are many risk factors that influence this disease such as, genetic factors, environmental factors, and age-related factors<sup>1</sup>. Although some evidence suggests that some cases of Parkinson's disease are hereditary, most cases are random.

Parkinson's disease is characterized by the destruction of dopamine-producing (dopaminergic) neurons in the substantia nigra of the midbrain and neuron terminals in the striatum causing a dopamine deficiency in the putamen. Dopamine is a catecholamine that functions as one of the main neurotransmitters in the brain<sup>1</sup>. Lewy bodies are the pathological hallmark of this disease. Lewy bodies are abnormal aggregates of a misfolded form of the protein, alpha-synuclein, which develop inside the nerve cells<sup>3</sup>. The Lewy body is a hallmark because the misfolded form of alpha-synuclein is one of the end products of the metabolism of dopamine that characterizes Parkinson's.

The best proposed hypothesis for these characterizations is the catecholaldehyde hypothesis. This hypothesis proposes that the buildup of a toxic metabolite from dopamine, 3,4-dihydroxyphenylacetaldehyde (DOPAL), is detrimental to dopaminergic neurons in the substantia nigra of the brain and leads to Parkinson's disease<sup>4</sup>. This hypothesis has been confirmed by many studies. In a 2010 study<sup>4</sup>, researchers were able to determine the effects of DOPAL on the survival of dopaminergic neurons and motor functions in rats in order to confirm that DOPAL was in fact the toxic metabolite that is responsible for pathological characteristics of Parkinson's disease.

In this experiment<sup>4</sup>, researchers injected an overall 800 nl of DOPAL (1µm/200nl) per rat in the substantia nigra at three different sites while injecting control rats similarly with phosphate buffered saline. They analyzed the motor functions via rotational behavior and counted the neurons of the substantia nigra. They also found the optical density, using immunohistochemistry, of striatal tyrosine hydroxylase, an enzyme that catalyzes the conversion of one of the precursors, tyrosine, to dopamine. The rotational behavior was assessed to determine the effects of the selective disruption of dopaminergic neurons on circuitry. Rotational behavior was hypothesized to depend on the balance between dopamine release and sensitivity of dopamine receptors on both sides. Thus, disruption of the circuitry on one side of the brain would result in altered rotational behavior. The results showed the rats injected with DOPAL prefer to rotate toward the same side the DOPAL was injected significantly more than control rats supporting the notion of disruption of circuitry. The amount of dopaminergic neurons in DOPAL injected rats was significantly lower than the controls. The neurons immunostained for tyrosine hydroxylase were counted and found to be significantly lower than that of the controls confirming significant loss of dopaminergic neurons. Thus, it was confirmed that DOPAL selectively destroys dopaminergic neurons in the substantia nigra and triggers behavioral changes in rats supporting the catecholaldehyde hypothesis<sup>4</sup>.

DOPAL can be metabolized via various pathways. Some of these pathways contribute to its toxicity; protein cross-linking, oxidation to quinones, production of hydroxyl radicals, and alpha-synucleinopathy are a few of these pathways. Normally, if dopamine is leaked into the cytosol, it is recycled back into vesicles by the type 2 vesicular monoamine transporter (VMAT2). In the case of Parkinson's disease, it escapes this recycling. Consequently, there is a loss of dopamine because the dopamine in the cytosol is deaminated by the enzyme monoamine oxidase-A to produce DOPAL. DOPAL can be detoxified by a mechanism that uses a major pathway requiring aldehyde dehydrogenase (ALDH) to form 3,4-dihydroxyphenylacetic acid (DOPAC) or a minor pathway requiring aldehyde/aldehyde reductase (AR) to form 3,4-dihydroxyphenylethanol (DOPET). The loss of dopamine is replaced by its biosynthesis from the precursor dihydroxyphenylalanine (DOPA). DOPA is a precursor to many

neurotransmitters other than dopamine and is produced from tyrosine (Y) by action of tyrosine hydroxylase (TH). It is then acted on by L-aromatic-amino-acid decarboxylase (LAAAD) to produce dopamine. When DOPAL is not detoxified, it can auto-oxidize into quinones, which increase the generation of reactive oxygen species (ROS). This increase in ROS results in lipid peroxidation. An intermediate of this peroxidation, 4-Hydroxynonenal, inhibits the detoxifying enzyme ALDH. This yields to increased levels of toxic DOPAL. DOPAL can also enter a mechanism in which it forms cross links with proteins and increases alpha-synuclein oligomerization<sup>5</sup>. Alpha-synuclein is the protein abundant in Lewy bodies, the hallmark of Parkinson's disease. This is what first linked DOPAL to Parkinson's disease<sup>3</sup>.

In hopes of better understanding the role of DOPAL in Parkinson's disease, research has been done to determine the cause of DOPAL buildup after dopamine metabolism. In 2013, a study was conducted in which neurochemical data was collected from post-mortem human putamen tissue of the brain and mice striatum tissue of the brain by measuring the levels of critical metabolites and precursors<sup>5</sup>. The tissue samples were extracted, uniformly mixed with a 20:80 mixture of 0.2 phosphoric acid and 0.2 acetic acid, and then assayed by liquid chromatography with series electrochemical detection. After finding the amounts, researchers determined the ratio of DOPAL to DA, DA to DOPA, and DOPAC to DOPAL in a Parkinson's diseased brain as well as an unaffected (control) brain and then graphed them. The ratio of DA: DOPA was used to determine if low vesicular intake was the cause of DOPAL buildup. DOPAC: DOPAL used to determine if inefficient detoxification by ALDH was the cause of DOPAL buildup. DOPAL: DA was used to determine the efficiency of the minor detoxification mechanism involving AR in the case of a faulty ALDH. Researchers were very hopeful that it was one of these that causes the buildup<sup>5</sup>.

The results showed that all the levels of metabolites and precursors decreased but some more than others. The levels of DOPAC and DA in Parkinson's diseased brain were extremely decreased from the control levels by about 94%. The levels of DOPAL and DOPET were decreased 79% and 83%; not as

much as DOPAC and DA. DOPA was decreased by 65%. These varying changes in the levels of metabolites and precursors caused the ratios to vary from the control. There was a higher ratio of DOPAL to dopamine as well as a lower than normal DOPAC to DOPAL level, which researchers determined was due to both low vesicular uptake and inefficient detoxification by ALDH. They also found that the minor mechanism of detoxification was not enough to balance out the inefficient ALDH mechanism<sup>5</sup>.

Although there is no cure, there are various treatments available that can help manage some of the symptoms of this disease. There are noninvasive therapeutic options but if the symptoms cannot be adequately controlled, there are some invasive therapeutic options available as well<sup>6</sup>.

Levodopa/Carbidopa is the most effective noninvasive drug treatment for Parkinson's right now<sup>2,6</sup>.

Levodopa is converted into dopamine which helps replace that which is lost. This helps with the rigidity and slow movement symptoms of Parkinson's<sup>6</sup>. By itself, Levodopa is not as effective because a lot of it is metabolized by catechol-O-methyl transferase before it can pass the blood brain barrier and affect the central nervous system. Carbidopa is an inhibitor of this enzyme and allows a greater proportion of Levodopa to effect the central nervous system. It helps with the effectiveness of Levodopa while also reduces some of its side effects. Invasive treatments include deep brain stimulation and internal drug pumps inserted in the patients intestines. Both of these have large benefits but are very invasive and have various side effects such as nausea, dizziness, and possibly hallucinations. All of these treatment results vary depending on the patients<sup>6</sup>. Not all patients respond well to treatments; the treatments don't always decrease the Parkinson's symptoms. None of these currently available treatments target DOPAL directly but researchers are working towards this.

Overall, although the cause of Parkinson's disease is still not completely understood, great advances have been made in understanding the aspects of this disease that we know. It has been shown that DOPAL has a rather important role in Parkinson's disease. It is the toxic metabolite responsible for the characteristic loss of dopaminergic neurons in the substantia nigra and terminals in the striatum causing dopamine depletion in Parkinson's disease. Its buildup is due to low vesicular intake by VMAT2

and low efficiency of ALDH in detoxifying DOPAL. This is what allows DOPAL to enter its other toxic pathways, specifically protein cross linking and alpha-synuclein oligomerization. By determining the role of DOPAL in Parkinson's disease, researchers hope this information will help with finding more effective treatments and ultimately, a cure.

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