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Dopaminergic Medications for Parkinson's Disease

Javier Carlos*

Biomedical Research Centre, Oxford University, New York, USA

Introduction

Parkinson's disease (PD) is a neurological disorder that worsens over time. The pathogenesis and aetiology are still not fully understood. Since there are no disease-modifying medications for PD, medical care mostly focuses on using medications to control the motor symptoms. Due to the long-term nature of the illness, patients may adopt complex pharmaceutical regimens intended to manage the motor symptoms, albeit there is a chance that these medications will have unfavourable side effects. The selective loss of neurons in the substantia nigra pars compacta, which results in a reduction in dopamine levels in the striatum, is a major cause of Parkinson's disease (PD), a movement condition. The core of PD treatment now consists on dopaminergic medicines made to mimic the effects of dopamine in the depleted striatum. Drugs that are converted to dopamine activate the dopamine receptor, or stop the breakdown of endogenous dopamine can all help with this. There is no perfect treatment plan; instead, drug regimens are individualised for each patient based on the intensity and duration of their symptoms as well as any adverse effects they may encounter [1].

About the Study

Dopamine must be created in the central nervous system (CNS) in order to work in the striatum because it cannot cross the blood-brain barrier (BBB). Dopamine is largely produced in dopaminergic neurons in the brain, while it is also produced in minor amounts in the medulla of the adrenal glands. L-dihydroxyphenylalanine, often known as levodopa or L-DOPA, is the direct metabolic precursor of dopamine in the traditional biosynthetic pathway. It is produced either directly from the non-essential amino acid tyrosine or indirectly from the amino acid phenylalanine (an essential amino acid). In the liver, the enzyme phenylalanine hydroxylase (PH) converts L-phenylalanine into L-tyrosine in the presence of oxygen, iron, and tetrahydrobiopterin as cofactors. An active transport mechanism then delivers the tyrosine that is created in the liver to the brain's dopaminergic neurons.

Following this, the enzyme tyrosine hydroxylase hydroxylates L-tyrosine at the phenol ring to produce L-DOPA (TH). The enzyme L-3,4-dihydroxyphenylalanine decarboxylase (DOPA decarboxylase) then decarboxylates L-DOPA in the pre-synaptic terminal to produce 3,4-dihydroxyphenethylamine (dopamine). Due to its action on all naturally occurring aromatic L-amino acids in addition to L-DOPA, DOPA decarboxylase is also known as aromatic-L-amino acid decarboxylase (AADC). In addition, a secondary pathway that converts L-tyrosine into p-tyramine (initiated by AADC) and then hydroxylates that p-tyramine into dopamine using the enzyme CYP2D6 (Cytochrome P450 2D6) present in the substantia nigra of the human brain can also produce dopamine under certain circumstances [2].

Following reuptake into glial cells or dopaminergic neurons, dopamine is processed. It undergoes oxidative deamination to form reactive aldehyde 3,4-dihydroxyphenylacetaldehyde, which is catalysed by the enzyme monoamine oxidase (MAO) in the presence of flavin adenine dinucleotide (FAD) (DOPAL). Alcohol dehydrogenase (ADH) or aldehyde dehydrogenase (ALDH) can convert DOPAL into 3,4-dihydroxyphenylethanol (DOPET) or 3,4-dihydroxyphenylacetic acid (DOPAC), respectively, to render it inactive. The enzyme catechol-O-methyl transferase then converts DOPAC to the physiologically inactive metabolite homovanillic acid (HVA) (COMT). Instead, dopamine is broken down by COMT into 3-methoxytyramine, which is then changed into 3-methoxy-4-hydroxyacetaldehyde by MAO. This is changed into HVA by the aforementioned ALDH, which is then eliminated in the urine.

Treatments

Levodopa-based preparations, intended to replenish the dopamine in the depleted striatum, are the cornerstone of contemporary PD treatment. Dopamine itself cannot cross the BBB and hence cannot be utilised to treat Parkinson's disease, as was previously stated. Levodopa, a precursor to dopamine, can be provided as a therapeutic since it can pass through the BBB. After passing through the BBB and being absorbed, DOPA decarboxylase transforms it into the neurotransmitter dopamine. Levodopa dosages are often started for patients at modest levels and then increased over time based on how well they respond to treatment and any side effects they may suffer. The majority of people need a dosage of 150–1000 mg per day, split into many doses.

The chance of negative side effects becoming problematic increases with dose. Levodopa typically has a rapid onset and a prolonged clinical effect, especially in the early stages of the disease. However, as the condition progresses, the drug's effects typically wear off sooner and a higher dosage frequency is frequently needed.

Despite its effectiveness, levodopa has serious adverse effects that, especially in cases of severe disease, play a substantial role in the patient's sickness. Levodopa is converted to dopamine by DOPA decarboxylase outside of the central nervous system (CNS), which causes some of its negative effects. Levodopa is administered along with peripheral inhibitors of DOPA decarboxylase to lessen these side effects, as will be covered below. Prolonged use can cause serious motor issues, such as dyskinesias, and extremely unpredictable motor swings [3].

Involuntary twisting hyperkinetic movements are known as dyskinesias, and they typically happen when a medication is at its highest dose (but may also occur as the drug is wearing-off or even during off-periods). Levodopa dosage decrease may be used to treat problematic dyskinesias, therefore it's important to find a delicate balance between maximising the management of motor symptoms and limiting side effects. Deep brain stimulation may be used to treat motor symptoms while using a lower dose of levodopa in individuals who had previously reacted well to the medication but had developed troublesome dyskinesias.

The term "on-off phenomenon" describes how advanced Parkinson's disease (PD) patients may suffer sudden changes in their motor performance. When a patient is in the "on" state, their motor symptoms are generally under control, but when levodopa's effects quickly wear off, they enter the "off" state, which is characterised by severe Parkinsonian motor characteristics. These variations can drastically restrict function and be quite harmful. Variable drug absorption and transit through the BBB, along with the resulting changes in pre-synaptic and post-synaptic dopamine levels in the nigrostriatal pathway,

***Address for Correspondence:** Javier Carlos, Biomedical Research Centre, Oxford University, New York, USA, E-mail: josephweinberg@edu*

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are the most likely causes of these motor symptoms. Orthostatic hypotension and gastrointestinal disorders like nausea and vomiting are prominent additional adverse effects. Dopamine acting in extranigral brain may have "off-target" effects that cause neuropsychiatric symptoms including anxiety and hallucinations [4].

Anticholinergics

All of the medications that have been mentioned thus far aim to boost striatal dopaminergic activity. There are only a few medications used to treat PD that work via non-dopaminergic mechanisms. The anticholinergic drug class is one example of this. By acting as antagonists at cholinergic receptors, these lessen the neurotransmitter acetylcholine's activity. Even though their usefulness is restricted and they are no longer widely administered, they might help with PD stiffness and tremor. Anticholinergic medications may help restore and maintain the usual balance between these two neurotransmitters in the brain after loss of dopaminergic neurons, which results in disruption of the two neurotransmitters' normal interaction [5].

Conclusion

These medications are primarily used in young patients with early disease stages to treat mild movement symptoms, particularly tremors and muscle stiffness. Anticholinergic medications have a greater impact on tremor-predominant Parkinson's disease (PD), where they may initially be used as monotherapy. But when anticholinergics are used, it's typically in conjunction with levodopa and the other drugs listed above. Due to a higher risk of confusion with this class of medications, they are typically avoided in older patients or those with cognitive issues. Preparations come in tablet and oral suspension forms. Anticholinergic drugs include, for instance, procyclidine, trihexyphenidyl, orphenadrine, and benztropine (Benzhexol).

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Conflict of Interest

The author shows no conflict of interest towards this manuscript.

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