Opinion

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Neuroactive Agents with Antiparkinsonian Potential

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Description

Due to its distinctive motor characteristics, Parkinson's disease is referred to as a movement disorder. The current treatments for Parkinson's disease only treat symptoms and become less effective as the disease progresses. The unique characteristics of the zebrafish, a vertebrate that has been used as a model for Parkinson's disease, make it possible to identify molecules that have antiparkinsonian properties. An antiparkinsonian potential neuroactive agent screening assay was developed in this area. First, we tested the effects of known antiparkinsonian medications to pharmacologically validate the phenotypes of the 6-hydroxydopamine zebrafish model. Whole-mount immunohistochemistry on TH+ neurons and confocal microscopy in the dopaminergic diencephalic cluster of zebrafish were also used to test these drugs for their ability to treat diseases. The 6-hydroxydopamine zebrafish model was used to optimize a phenotypic screening, and 1600 bioactive drugs that had been approved by the FDA were tested. Levodopa, rasagiline, isradipine, or amantadine can restore bradykinetic and dyskinetic behaviors in zebrafish larvae that have been lesioned with 6-hydroxydopamine. A higher number of TH+ neurons in 6-OHDA-lesioned zebrafish larvae treated with this compound compared to untreated lesioned larvae confirmed that isradipine rescued dopaminergic cell loss. We were able to find a number of compounds that had been predicted to cause Parkinson's disease through phenotypic screening, as well as new molecules that might have antiparkinsonian properties. We chose stavudine, tapentadol, and nabumetone as the most promising options among these. Our findings highlight novel molecules with antiparkinsonian potential and highlight the functional similarities between the motor impairments seen in 6-hydroxydopamine-lesioned zebrafish, PD models, and PD patients.

Progressive Decrease in Dopamine Produc-tion

More than 1% of people over the age of 65 worldwide suffer from Parkinson's disease, which is a neurodegenerative, chronic, and progressive disease of the Central Nervous System (CNS). Motor symptoms like resting tremor, rigidity, bradykinesia, and postural instability are the main clinical features of Parkinson's disease. The accumulation of misfolded alpha-synuclein protein and a progressive decrease in dopamine production in the nigrostriatal pathway are the histopathologic hallmarks of Parkinson's disease. It has been hypothesized that Parkinson's disease, other neurodegenerative diseases like Alzheimer's and some neurological diseases like epilepsy may have intrinsically related etiologies. Neuronal loss, elevated excitotoxicity, elevated oxidative stress and pro-inflammatory activity, and increased production of apoptotic cytokines are among the pathological mechanisms that these diseases share. The dopamine precursor levodopa (LD), the dopadescarboxilase inhibitors, the dopaminergic receptor agonists, the catechol-O-methyltransferase (COMT) inhibitors, the monoamine oxidase B (MAO-B) inhibitors, and, to a lesser extent, the anticholinergic drugs are currently available on the pharmaceutical market for the treatment of Parkinson's disease. However, serious adverse effects may occur with some anti-Parkinson's medications. The ergotic alkaloid dopaminergic agonists like bromocriptine were linked to fibrotic reactions, the non-ergotic derivatives to sleep tendencies, and the dopamine precursor levodopa was linked to increased oxidative stress (Fenton reaction). Selegiline and rasagiline are irreversible inhibitors in the MAO-B inhibitors group. Additionally, the production of neurotoxic amphetamine metabolites is linked to selegiline. Constipation, urinary retention, cognitive impairment, and other well-known side effects of anticholinergic medications pose a serious issue for elderly patients. The aforementioned issues call for the creation of safer and more effective medications. A brand-new selective and reversible monoamine oxidase-B inhibitor that raises dopamine levels outside of cells in the striated body is called safinamide. The utilization of MAO-B inhibitors possessing adenosine A2A receptor antagonist activity in conjunction with multi-target strategies for the treatment of Parkinson's disease is also under investigation.

Subsequent Decarboxylation Reaction

A substrate-specific hydroxylase catalyzes the first step in the parallel biosynthesis of dopamine and 5-hydroxytryptamine, but the subsequent decarboxylation reaction appears to involve the same enzyme, aromatic l-amino-acid decarboxylase. Although it has been suggested that AADC is encoded by a single gene, there may be multiple isoforms of the protein. However, when l-3,4-dihydroxyphenylalanine and l-5-hydroxytryptophan are utilized as substrates, the numerous biochemical properties that clearly distinguish AADC have not yet been adequately explained. As a result, not only are the two enzymes distributed

differently in brain regions and subcellular tissue fractions, but they also have distinct optimal conditions for pH, temperature, and substrate concentration. It has been proposed that AADC may be a single enzyme with distinct recognition and regulatory sites for l-DOPA and 5-HTP in order to accommodate these seemingly contradictory molecular biological and biochemical data. DOPA decarboxylase, also known as DDC, was once thought to be an uninteresting, unsaturated, and unregulated enzyme. However, the discovery that the activity of DDC is subject to both pre- and post-translational regulation has fundamentally altered this view. Dopamine replacement therapy with l-DOPA may eventually lose its efficacy if DDC disappears as a result of the degeneration of nigrostriatal dopamine neurons, so the ability to increase DDC activity may be crucial to the clinical treatment of Parkinson's disease. Therefore, it may be possible to co-administer drugs that maintain or even increase the activity of residual DDC in the basal ganglia to prevent DDC from becoming rate-limiting in Parkinsonism. Dopamine receptor antagonists were shown to modestly increase DDC activity in mice, but their use would exacerbate the condition of dopamine-deficient Parkinsonism patients. On the other hand, we and others have found that a number of N-methyl-d-aspartate receptor antagonists significantly increased DDC in the nigrostriatal dopamine pathway in rats. This suggests that these compounds could be used in conjunction with l-DOPA to improve Parkinson's disease pharmacotherapy. In dopaminergic neurons, l-DOPA is not only decarboxylated by DDC, but also by 5-HTP decarboxylase, also known as 5-HTPDC, in 5-HTergic neurons. It is highly possible that 5-HT systems in the parkinsonian brain are crucially involved in "dopamine replacement" with l-DOPA because 5-HT neurones sprout to occupy synapses vacated by dopamine axons in the dopamine-lesioned brain. We observed that 5-HTPDC in this brain region responded differently to various NMDA antagonists than DDC during studies into the effects of glutamate antagonists on the decarboxylation of l-DOPA by the nigrostriatal dopamine system in the reserpine-treated rat. This study will demonstrate that glutamate blockade significantly enhances DDC but not 5-HTPDC, indicating that glutamate regulates the two decarboxylase forms in different ways.