IS THERE ROOM FOR NON DOPAMINERGIC TREATMENT IN PARKINSON DISEASE?

Abraham Lieberman
Muhammad Ali Parkinson Center, Movement Disorders Barrow Neurological Institute, Phoenix Arizona, USA

The introduction of levodopa in 1967 revolutionized the treatment of Parkinson Disease (PD). Levodopa combined with carbidopa to block levodopa's metabolism in the periphery and drive more levodopa into the brain, or levodopa/ carbidopa combined with entacapone or tolcapone to drive even more levodopa into the brain, or levodopa/ carbidopa combined with rasagiline or selegiline to prolong the duration of the dopamine formed from levodopa, or the use of synthetic dopamine analogues, dopamine agonists, are variations on a the theme of levodopa as a treatment for PD. While levodopa and its iterations (decarboxylase inhibitors, catechol-O-methyl transferase inhibitors, monoamine B- oxidase inhibitors, and dopamine agonists) have improved PD, it has not cured PD, and many unmet needs remain. These include intractable tremor, balance difficulty, falls, freezing of gait (FOG), cognitive impairment, memory loss, levodopa induced dyskinesias and dystonias, levodopa induced psychoses, hallucinations, agitation, delusions and paranoia, autonomic nervous system insufficiency, especially orthostatic hypotension, apathy, akinesia and sleep disturbances. Although it's simplistic to think that alterations in a single or in several neurotransmitters will restore damaged or impaired circuits nonetheless alterations in cholinergic, serotonergic, glutaminergic, and noradrenergic activity have, indeed, met or show promise of meeting many of the unmet needs.

Prior to the introduction of levodopa, centrally acting anti-cholinergic drugs were a mainstay of treatment relieving, in part, tremor and PD induced dystonia. The drugs are thought to block "excessive" cholinergic activity in the putamen. Since the introduction of levodopa, cholinomimetic drugs, drugs that block the breakdown of acetyl choline in the cortex, have gained a real but limited role in improving cognition and memory loss. And, recently, cholinomimetic drugs, have gained another real but limited role in improving balance, freezing of gait (FOG), and decreasing falls (1 -4). Presumably these effects are achieved by increasing cholinomimetic transmission in the pedunculopontine nucleus (PPN), a cholinergic nucleus in the brainstem.

Serotonin, 5-hydroxytryptamine, 5-HT, like dopamine, is a major neurotransmitter in the brain Drugs that block the re-uptake of serotonin have played a prominent role in the treatment of anxiety and depression in PD. In addition to a role in emotion, serotonin has a role in behavior. Serotonin receptors, 5-HT3 and 5-HT2A receptors in cortical and subcortical regions are involved in behavior. LSD, a major hallucinogen is an agonist at 5-HT2A receptors. Ondansetron, a 5-HT3 antagonist, an anti-emetic, has a small role in countering hallucinations associated with levodopa (5). Recently, pimavanserin, a specific 5-HT2A antagonist, has shown promise in countering the delusions, the hallucinations, and the paranoia associated with levodopa (6).

Glutamate is the major excitatory neurotransmitter in the brain. Excess glutamate or enhanced glutamate sensitivity has been implicated in the involuntary movements, chorea and dystonia, of Huntington Disease. And excess glutamate or enhanced glutamate sensitivity may be implicated in levodopa induced dyskinesias and dystonias. Amantadine, an antagonist at fast acting NMDA glutamate receptors and talampanel, an antagonist at fast acting AMPA glutamate receptors, have demonstrated a limited ability to reduce levodopa induced dyskinesias and dystonias. Recently, a drug that is an allosteric modulator of slow acting, metabotropic glutamate 5-receptors has shown promise in reducing levodopa induced dyskinesias and dystonias in rodents and primates, and in, a limited trial, in humans with PD (7-10).

Norepinephrine (NE), like dopamine, acetyl- choline, serotonin and glutamate is a major neurotransmitter in the brain In PD, the loss of NE neurons in the locus ceruleus, the main NE nucleus in the brain, is greater and occurs earlier than the loss of dopaminergic neurons in the substantia nigra. The locus ceruleus has major projections to the sub-cortex and cortex and to the brainstem. The loss of NE neurons and NE tone has been implicated in the apathy, the akinesia, and the sleep disturbances in PD. The loss of NE neurons and NE tone has also been implicated in the ANS insufficiency of PD, especially in orthostatic hypotension and supine hypertension. NE reuptake inhibitors have played a prominent but limited role in the depression of PD, especially the apathetic depression. Dihydroxyphenylserine, DOPS, Droxidopa, Northera-TM is an artificial amino acid and is a precursor of NE. As L-dopa is converted by dopa- decarboxylase into dopamine, droxidopa is converted by dopa-decarboxylase into NE. Inhibitors of

dopa-decarboxylase such as carbidopa and benserazide, inhibitors that do not cross the blood brain barrier, block the conversion of droxidopa to NE in the periphery (11, 12), resulting in an increased entry of NE into the central nervous system (CNS). The increased entry of NE into the CNS may be responsible for the reported improvement in ANS insufficiency, apathy, and akinesia (11, 13 – 15).

No one denies the benefits of levodopa and dopaminergic therapy in PD, such benefits do not, however, exclude a role for other neurotransmitters including acetyl choline, serotonin, glutamate and norepinephrine.

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