Parkinson’s disease psychosis as a serotonin-dopamine imbalance syndrome

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ISSUE:
Parkinson’s disease psychosis (PDP) is theoretically a serotonin-dopamine imbalance syndrome due to disruption of the normal balance between the serotonergic and dopaminergic neurotransmitter systems in key brain circuits.

Take-Home Points

- Psychosis, especially with visual hallucinations and delusions, may develop in up to half of patients with Parkinson’s disease.
- Parkinson’s disease psychosis (PDP) may be caused in part by deposition of toxic alpha-synuclein–containing Lewy bodies in the cerebral cortex that hypothetically disrupt both serotonin and dopamine neurotransmission, with upregulation and overstimulation of cortical serotonin 5HT2A receptors and excessive release of downstream dopamine in mesolimbic brain circuits.
- Blocking hypothetically excessive serotonin neurotransmission at serotonin 5HT2A receptors in patients with PDP theoretically restores the balance between serotonin and dopamine, reducing visual hallucinations and delusions without worsening motor symptoms.

Introduction
Parkinson’s disease begins with prominent motor symptoms caused by deposition of Lewy bodies containing alpha-synuclein in the substantia nigra,1–3 and then progresses in over half the cases to psychosis with delusions and hallucinations called Parkinson’s disease psychosis (PDP).4–7 Several causes are proposed for PDP, the most prominent theory being the accumulation of Lewy bodies in the cerebral cortex.4–13 Lewy body deposition in the cerebral cortex is also thought to cause Lewy body dementia in patients who have the same visual hallucinations and delusions characteristic of PDP but who do not have early Lewy body deposition in substantia nigra nor motor symptoms of Parkinson’s disease.12–17 Other causes or contributors to PDP may include Alzheimer amyloid plaques/tau pathology in the cerebral cortex15 as well as high dosing of dopaminergic drugs used to treat the motor symptoms of Parkinson’s disease.4,18–21 No matter what the cause, PDP seems to be a serotonin-dopamine imbalance syndrome due to a final common pharmacologic pathway in which serotonin activity at 5HT2A receptors, dopamine activity at D2 receptors, or both, become excessive.

Serotonin-Dopamine Imbalance Due to Cortical Lewy Bodies
Parkinson’s disease starts as a “substantia nigra synucleinopathy” with Lewy body deposition in the substantia nigra that causes motor symptoms.1–3 Parkinson’s disease can progress to a “cortical synucleinopathy” with Lewy body deposition in the cerebral cortex that hypothetically causes PDP.4–13 Although Parkinson’s disease is mostly known as a “dopamine deficiency syndrome” in the dorsal striatum due to loss of substantia nigra neurons thus causing akinesia, rigidity, and tremor,1–3 it can theoretically progress to develop a superimposed “serotonin-dopamine excess syndrome” in the cerebral cortex and ventral striatum that causes PDP.9,10,22 That is, the normal balance between serotonin and dopamine (Figure 1) becomes initially distorted due to loss of substantia nigra projections to the dorsal striatum, causing dopamine deficiency there (Figure 2) and the classical motor symptoms of Parkinson’s disease but not psychosis.
symptoms of Parkinson’s disease. Concomitantly, serotonin neurons in the raphe are also degenerating with initial loss of serotonin (Figure 2), but this is less prominent than the dopamine loss and not clearly linked to motor symptoms, but possibly to nonmotor symptoms.

As Lewy bodies accumulate in the cerebral cortex with the progression of Parkinson’s disease in some patients, pyramidal neurons containing serotonin receptors degenerate, and a well-documented upregulation and thus increase in the number of 5HT2A receptors occurs in the remaining neurons in the cerebral cortex. Upregulation of 5HT2A receptors seems to occur in the motor cortex of Parkinson’s patients whether they have psychosis or not, but upregulation of 5HT2A receptors seems to occur in the prefrontal and visual/temporal cortex areas only in patients with PDP, although not all observers agree. Also in PDP there appears to be an increase in raphe serotonin levels, presumably due to enhanced serotonin turnover despite the loss of serotonergic raphe neurons (Figure 3). The resulting enhanced activity at upregulated 5HT2A receptors in the temporal cortex and visual pathways hypothetically causes visual hallucinations. Indeed, hallucinogenic drugs that stimulate these same 5HT2A receptors also cause striking visual hallucinations. Thus, there is robust pharmacologic rationale to explain why stimulation of 5HT2A receptors causes visual hallucinations, and why blocking hypothetically overstimulated 5HT2A receptors in PDP with the selective 5HT2A antagonist pimavanserin or the nonselective 5HT2A antagonists quetiapine and clozapine reduces visual hallucinations.

Upregulated 5HT2A receptors in the prefrontal cortex hypothetically lead to downstream changes in the cortical-striatal and cortical-brainstem projections regulating dopamine release in the ventral striatum in patients with PDP (Figure 3). When dopamine release is enhanced there, positive symptoms of psychosis are thought to be the consequence, namely delusions and auditory hallucinations. This is the same pathophysiology long postulated for psychotic symptoms of schizophrenia in the so-called dopamine hypothesis. Overall, this formulation comprises robust pharmacologic rationale to explain why
blocking hypothetically overstimulated 5HT2A receptors in PDP would improve serotonin-dopamine imbalance, and thereby stop psychotic symptoms.

Serotonin-Dopamine Imbalance Due to Dopamine Treatments

Psychosis in Parkinson’s disease can also be associated with dopaminergic therapies, since it can correlate with dosing and blood levels of the drugs and improve with dose reduction.\(^\text{18-21}\) This may not necessarily occur only in Parkinson patients with Lewy body accumulation the cortex (Figure 3), but also for various additional and unknown reasons in certain other vulnerable patients (Figure 4).\(^\text{4,18-21}\) That is, in the usual patient with Parkinson’s disease (Figure 2), administration of L-DOPA and similar dopamine stimulating agonists and agents appears to improve motor symptoms without causing psychosis. In these patients, stimulation of dopamine terminals in the dorsal striatum thus provides therapeutic benefit for motor symptoms but any concomitant stimulation of dopamine terminals in the ventral striatum does not cause psychosis, presumably due to the presence of a therapeutic window in these patients.\(^\text{1-4,18-21}\)

However, in vulnerable Parkinson patients who may have early age of onset of their Parkinson’s disease, have a long duration of illness, or are in the later stages of the illness with severe motor symptoms, the improvement of motor symptoms by dopaminergic therapy can come at the expense of inducing concomitant positive psychotic symptoms such as delusions and auditory hallucinations, also just like those seen in schizophrenia.
the dorsal and the ventral striata now respond to stimulation by dopamine.\textsuperscript{20} Too much dopamine stimulation of the dorsal striata may manifest as unwanted movement disorders such as dyskinesias or the on-off phenomenon whereas too much dopamine stimulation in the ventral striatum hypothetically manifests as positive symptoms of psychosis just as postulated to occur when this area of the brain is overstimulated in patients with these same symptoms who have schizophrenia. Dose reduction of dopaminergic stimulants or administration of D2 dopamine antagonists traditionally utilized for the treatment of schizophrenia may improve the psychosis of excessive dopaminergic therapy in Parkinson’s disease, but often at the expense of worsening motor behavior.

Pharmacologic Mechanism of Action of 5HT2A Antagonism in PDP: No Longer Between a Rock and a Hard Place

Traditional treatments for PDP included dose reduction of dopaminergic therapy if that was a contributing factor, or administration of antipsychotics, especially quetiapine or clozapine, assumed initially to work by blocking D2 dopamine receptors just as they do in schizophrenia.\textsuperscript{18–21,38,39} However, this often put both PDP patients and their clinicians between a rock and a hard place when trying to balance simultaneously the treatment of both PDP and motor symptoms of Parkinson’s disease, since what was good for psychotic symptoms was generally bad for motor symptoms.

Pimavanserin is a potent antagonist at 5HT2A receptors without any D2 dopamine antagonist properties.\textsuperscript{34} It is the first agent with proven antipsychotic actions for PDP and is effective for psychotic symptoms worsening motor symptoms.\textsuperscript{34–37} This antipsychotic efficacy of pimavanserin in PDP was at first surprising because longstanding dogma about the pharmacology of psychosis assumed that psychosis was due to excessive dopamine activity (such as that shown in Figure 4),\textsuperscript{40,41} and the only way to treat psychosis was therefore to reduce dopamine activity directly either by dose reduction of dopamine stimulants or by administration of dopamine antagonists. However, pimavanserin appears to exert its antipsychotic effects in PDP without worsening motor symptoms by correcting the theoretical serotonin-dopamine imbalance in PDP that causes psychosis via direct interaction with 5HT2A receptors,\textsuperscript{34} leading to indirect actions on downstream dopamine release (Figure 3)\textsuperscript{40} without disrupting the serotonin-dopamine balance associated with motor symptoms (Figure 2).\textsuperscript{34,40}

Summary

PDP is associated with upregulated 5HT2A receptors in the cerebral cortex that presumably are the result of cortical Lewy body deposition and that theoretically set off a serotonin-dopamine imbalance syndrome associated with visual hallucinations and delusions. Blocking 5HT2A receptors improves PDP without worsening motor symptoms, hypothetically restoring balance in serotonin and dopamine neurotransmitter systems. Since 5HT2A receptors are also upregulated in dementia with Lewy bodies, it is possible that pimavanserin will also be effective in treating the visual hallucinations of Lewy body dementia.

References:

15. Jacobson SA, Morshed T, Dugger BN, et al. Plaques and tangles as well as Lewy-type alpha synucleinopathy are associated with...


