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Dopamine Receptor Agonists and Levodopa and Inducing Psychosis-Like Behavior in the MPTP Primate Model of Parkinson Disease

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The relative propensity for levodopa and dopamine receptor agonists to cause psychosis or neuropsychiatric symptoms in patients with Parkinson disease (PD), including compulsive symptoms such as pathological gambling or stereotypies (termed punding), is unknown.[1,2] Although, the dopamine D3 preferring agonist pramipexole has been suggested to cause pathological gambling in PD,[3] we have recently shown that pathological gambling in PD is associated with all dopamine agonists rather than levodopa or any one specific dopamine agonist.[4] However, clinical studies are difficult to interpret because of confounding factors such as differences in disease severity, concomitant medications, and comorbidities. In addition, most patients take a combination of both levodopa and dopamine agonists, so the relative contributions of individual agents to induce symptoms are therefore unknown.

To investigate these issues, we assessed the relative propensity of clinically available dopaminergic drugs to induce neuropsychiatric symptoms in the recently described nonhuman primate model of psychosis-like behaviors in parkinsonism where agitation, stereotypies, and hallucinatory-like and obsessive-compulsive behaviors are seen in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)–lesioned primates after long-term levodopa therapy.[5] These psychosis-like behaviors can be rated using the MPTP-lesioned marmoset psychosis-like behavior rating scale.

METHODS

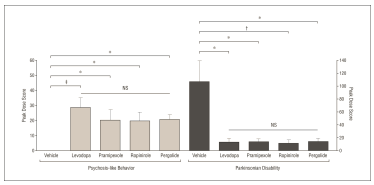
The long-term, levodopa-treated, MPTP-lesioned marmoset model of PD was used as described previously.[6] Animals were housed in groups and cared for under an approved local institution protocol (University Health Network 02/053). Levodopa with benserazide (as Prolopa; Hoffman-La Roche, Mississauga, Ontario; 12.5 mg/kg) (n = 7), pergolide (0.01 mg/kg) (n = 7), ropinirole (0.16 mg/kg) (n = 7), pramipexole (0.06 mg/kg) (n = 6), and vehicle (n = 7) were administered by mouth and the animals placed into observation cages. Doses used were defined as those producing an equivalent full reversal of parkinsonism. Parkinsonian disability, dyskinesia, and psychosis-like behaviors were scored for 10 minutes every 30 minutes using previously described rating scales[5,6] with post hoc video analysis by a rater blinded to the treatments. For each drug or vehicle, each parameter was rated for 90 minutes at the peak antiparkinsonian effect, between 40 and 130 minutes for levodopa and pergolide and between 70 and 160 minutes postdose for pramipexole and ropinirole. Scores were cumulated to give a total peak-dose score and expressed as a median score (and range). Statistical analysis was performed using a nonparametric Kruskal-Wallis (KW) test followed by a Dunn multiple comparison test with GraphPad Prism version 4 (GraphPad Software, San Diego, Calif). Significance was assigned as $P<.05$.

RESULTS

There was a significant effect of treatment on parkinsonian disability and psychosis-like behaviors. All drugs significantly reversed peak-dose parkinsonian disability. The median score with vehicle was 110 (range, 60-139) compared with 13 (range, 3-22) with levodopa, 14 (range, 4-20) with pramipexole, 11 (range, 2-19) with ropinirole, and 14 (range, 4-19) with pergolide ($KW_{(4,29)}$ = 16.92, n = 7, for all treatments except pramipexole, n = 6, P<.01) (Figure). There was no difference in peak-dose antiparkinsonian action between levodopa, pramipexole, ropinirole, and pergolide (all P>.05).

Figure.

Effects of clinically available dopamine agonists and levodopa on psychosis-like behaviors in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)–lesioned marmoset model of Parkinson disease. Figure shows total peak-dose psychosis-like behaviors (left y-axis) and parkinsonian disability (right y-axis) as measured using rating scales following administration of levodopa (as Prolopa; Hoffman-La Roche, Mississauga, Ontario) (n = 7), pramipexole (n = 6), ropinirole (n = 7), pergolide (n = 7), and vehicle (n = 7) by mouth. Data show mean total peak-dose scores (± SD). NS indicates not significant; *, P<.05; †, P<.01; and ‡, P<.001 by Kruskal-Wallis test followed by a Dunn multiple comparison test.



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All drugs significantly induced peak-dose psychosis-like behaviors; the median score with vehicle was 0 (range, 0) compared with 29 (range, 14-33) with levodopa, 21 (range, 17-35) with pramipexole, 20 (range, 15-30) with ropinirole, and 21 (range, 18-27) with pergolide ($KW_{(4, 29)}$ = 18.96, n = 7, for all treatments except pramipexole, n = 6, P<.001) (Figure). There was no difference in peak-dose psychosis-like behavior between levodopa, pramipexole, ropinirole, and pergolide (all P>.05). Subscore analysis revealed there was no significant difference in any peak-dose subscores (agitation, stereotypies, hallucinatory-like and obsessive-compulsive behaviors) between levodopa and the dopamine agonists. However, stereotypies were significantly increased with levodopa and ropinirole compared with vehicle; the median peak-dose scores were 8 (range, 2-24) and 14 (range, 0-23) compared with 0 (range, 0), respectively ($KW_{(4,29)}$ = 14.84, n = 7, for all treatments except pramipexole, n = 6, P<.01, P<.05, respectively). In addition, hallucinatory-like behaviors were significantly increased with levodopa compared with vehicle; the median peak-dose score was 17 (range, 1-23) compared with 0 (range, 0) ($KW_{(4,29)}$ = 15.99, n = 7, for all treatments except pramipexole, n = 6, P<.01). All drugs also induced peak-dose dyskinesia ($KW_{(4,29)}$ = 19.01, n = 7, for all treatments except pramipexole, n = 6, P<.001).

COMMENT

Dopamine receptor agonists and levodopa have similar potential to elicit neuropsychiatric symptoms when given as monotherapy at doses with equivalent antiparkinsonian actions in the MPTP-lesioned marmoset model of PD. These findings suggest that the nature of the dopaminergic agent employed may not be a major factor determining the degree of the comparative neuropsychiatric adverse effects of antiparkinsonian therapies that have been recently highlighted.

ARTICLE INFORMATION

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