Dopamine dysregulation syndrome-like behavior in bilateral dorsal striatum 6-hydroxydopamine lesioned Parkinson's disease model mice

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Background: Parkinson's disease (PD) is a neurodegenerative disorder often accompanied by psychiatric symptoms. Long-term dopamine replacement therapy (DRT) in PD can lead to impulse control disorders (ICDs). Among ICDs, dopamine dysregulation syndrome (DDS) is characterized by a dependence or craving for DRT. The detailed pathogenesis of DDS is unclear, and its treatment is limited to DRT reduction, which may result in poor control of motor symptoms. Moreover, there are only a few reports of animal models of DDS. In this study, we investigated DDS caused by continuous DRT administration using a PD mouse model created by local brain lesioning with 6-hydroxydopamine (6-OHDA), which induces dopaminergic neuronal loss. **Methods:** We allocated 8-week-old male C57/BL6J wild-type mice (n=40) to 6-OHDA (n=23) or sham (n=17) groups. The 6-OHDA group received bilateral administration of 4 μg/1 μL of 6-OHDA dissolved in 0.25% ascorbic acid (AA) in saline, while the sham group received 1 μL of 0.25% AA in saline alone, both into the dorsal striatum. Before and 3 weeks after 6-OHDA lesioning, we conducted the rotarod, pole, and balance beam tests to evaluate motor function decline, reflecting the PD model. After 2 weeks of 6-OHDA lesioning, all mice received 12 mg/kg L-dopa intraperitoneally every weekday in the morning and afternoon for 3 weeks to induce dependence on L-dopa. Subsequently, a conditioned place preference test (CPP) was performed to evaluate dependence on L-dopa. After the experiment, brain tissues were harvested and paraffin-fixed, and paraffin sections were prepared and immunostained for tyrosine hydroxylase. **Results:** Three mice from the 6-OHDA group died postoperatively. At 3 weeks after 6-OHDA lesioning, the 6-OHDA group exhibited impairments in the rotarod test (before lesioning: 220.09 [mean] ± 68.12 [SD] s; after lesioning: 129.75 ± 52.06 s; $P<0.001$), pole test Tturn (time taken by mice placed on top of the pole with their head oriented upward to orient downward; before: 2.25 ± 0.73 s; after: 3.24 ± 1.30 s; $P<0.001$), pole test Tdown (total time taken to turn and descend the pole; before: 9.22 ± 1.34 s; after: 11.43 ± 2.73 s; $P<0.001$), and balance beam test (before: 9.60 ± 2.58 s; after: 11.96 ± 2.40 s; $P<0.01$). In contrast, the motor function test results of the sham group did not change significantly with vehicle administration. Therefore, the 6-OHDA group showed motor dysfunction, reflecting PD symptoms. In the CPP, three mice in the 6-OHDA group and five in the sham group were excluded from the evaluation because of a biased preference for one side of the chambers seen in the pre-test result. The CPP score, calculated by subtracting the time spent in the chamber of the L-dopa administration side during the post-test from the time during pre-test, was significantly higher in the 6-OHDA group (348.20 ± 766.58 s) than in the sham group (-376.75 ± 1048.69 s, $P<0.05$), suggesting that L-dopa dependence was induced in the 6-OHDA group. Pathological

evaluation of this condition is still under investigation. **Discussion:** Continuous L-dopa administration in 6-OHDA lesioned mice induced L-dopa dependence, indicating DDS. As the administration of 6-OHDA into the bilateral dorsal striatum does not disrupt dopaminergic neurons in the ventral tegmental area, the remaining dopaminergic neurons may contribute to dependency induction. We will additionally report the results of the pathological evaluation in the presentation.

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