Appendix 2

Abstract of Thesis

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<th>Report number</th>
<th>Name</th>
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<td>☑Ph.D. obtained through coursework and thesis No. 4 2</td>
<td>周禹 (ZHOU YU)</td>
<td>Characterization of imatinib as an anti-parkinsonian agent in mouse models of Parkinson’s disease</td>
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[Background]
Parkinson’s disease (PD) is caused by a progressive degeneration of nigral dopaminergic neurons leading to striatal dopamine deficiency. In the clinic, administration of dopamine precursor levodopa is the gold standard for the treatment of PD. However, long-term exposure to levodopa often causes side effects, such as levodopa-induced dyskinesia. So development of new therapeutic agents for motor deficits is needed in the treatment of PD. In the last decade, an abnormal activity of the Abelson non-receptor tyrosine kinase (c-Abl) was proved relating to the degeneration of nigral dopaminergic cells in PD. Thereby it has been expected that the inhibition of c-Abl activity would exert anti-parkinsonian effects. Moreover, it has also been reported that a c-Abl inhibitor nilotinib showed acute therapeutic potency on motor symptoms in a PD mouse model, possibly with affecting signaling mechanisms in striatum.

[Purpose]
Imatinib, as a c-Abl inhibitor, is currently approved for tumor-related diseases such as human chronic myelogenic leukemia, gastrointestinal stromal tumor and Philadelphia chromosome positive acute lymphoblastic leukemia in clinical use. To examine its potential as a PD therapeutic in this study, I evaluated imatinib in two types of PD models of mice: systemically MPTP-induced PD model mice, and unilaterally 6-hydroxydopamine (6-OHDA)-lesioned hemiparkinsonian mice.

[Results]
When imatinib was systemically administered, the striatum-to-blood concentration ratio of it was about 8%, indicating that peripherally administered imatinib was partially incorporated into the striatum. In MPTP mice, behavioral analysis revealed that a single dose of imatinib (25 mg/kg) could significantly normalized MPTP-induced motor deficits. In western-blot analysis, imatinib significantly reduced the expression of cyclin-dependent kinase 5 (Cdk5) phosphorylated at tyrosine 15 residue (Cdk5-pTyr15) and dopamine- and cAMP-regulated phosphoprotein 32 (DARPP-32) phosphorylated at threonine 75 residue (DARPP-32-pThr75) in striatum, which were increased by MPTP treatment than normal mice. Moreover, I examined the combinatory effects of imatinib and levodopa. Combination of low doses of imatinib (10 mg/kg) and levodopa (5 mg/kg), which were not effective when solely applied, significantly improved the motor activity of MPTP mice in behavioral tests. In western-blot analysis, the expression of active c-Abl phosphorylated at tyrosine 412 residue (c-Abl-pTyr412), Cdk5-pTyr15 and DARPP-32-pThr75 were also significantly reduced by this combination. These results strongly suggest symptomatic effects of acute imatinib treatment on motor deficits in MPTP mice.

I further evaluated imatinib in 6-OHDA-lesioned hemiparkinsonian mice. Essentially, therapeutic effects of imatinib were also obtained on motor deficits and biochemical changes in this model, which were comparable with the results obtained in MPTP model.

[Discussion/Conclusion]
Based on above results, regulating c-Abl/Cdk5/DARPP-32-Thr75 signaling pathway would be important when considering the pathophysiology of motor dysfunctions in PD. I suggest the possibility of a c-Abl inhibitor imatinib as a novel and effective therapeutic agent to treat PD.