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論　文　内　容　要　旨

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学位論文題目	Characterization of imatinib as an anti-parkinsonian agent in mouse models of Parkinson's disease （パーキンソン病モデルマウスにおけるイマチニブの薬効評価）		

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.

Imatinib, as a c-Abl inhibitor, is currently approved for tumor-related diseases such as human chronic myelogenic leukemia, gastrointestical 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-hyroxydopamine (6-OHDA)-lesioned hemiparkinsonian mice.

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 phosphoproten 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.

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.