ポスター

[1P]F. 神経系の疾患 2

2022年6月30日(木) 13:00 ～ 14:00 ポスター会場2 (宜野湾市民体育館)

[1P-210]線条体神経細胞の過活動抑制によるジスキネジアの治療

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キーワード：Parkinson's disease, L-dopa induced dyskinesia, striatum, medium spiny neuron

Background: Loss of nigrostriatal dopamine in Parkinson’ s disease (PD) causes dysregulation of medium spiny neurons (MSNs) in the striatum. However, long-term dopamine replacement fails to efficiently modulate MSNs. Previous studies showed that recordings in animal models of advanced PD and patients have revealed significant hyperactivity of MSNs, and that hyperactive MSNs respond to dopaminergic stimulation with unstable firing changes, which are associated with the development of L-dopa induced dyskinesias (LIDs). **Objective:** The present study was aimed at examining whether decreasing the baseline MSN firing frequency would reduce the development of LIDs. **Methods:** To test acute pharmacological reduction of the MSN activity, a selective NMDAR antagonist (LY235959) or vehicle (aCSF) was infused into one side of the putamen of advanced parkinsonian non-human primate (NHPs, n=3). The antagonist was infused in the “ off” state, and L-Dopa methyl ester plus benserazide was injected s.c. after the infusion. To test chronic reduction of the MSN activity, the inhibitory DREADDs (designer receptor exclusively activated by designer drugs) hM4Di was expressed in the striatum of hemiparkinsonian rats. rAAV-hSyn-hM4D(Gi)-mCherry or the control virus (rAAV-hSyn-GFP) was injected into the left striatum of rats with 6-hydroxydopamine lesions of the left nigrostriatal pathway (n=9). After 4 weeks, rats received daily clozapine N-oxide treatment to activate DREADDs and L-Dopa to induce abnormal involuntary movements (AIMs) for 2 weeks. The whole motor responses and LIDs/AIMs were assessed using standardized rating scales for NHP and rodents, respectively. **Results:** The NMDAR antagonist infusion in parkinsonian NHPs significantly reduced LID scores on the contralateral side without affecting the antiparkinsonian action of L-Dopa (motor disability scores of “ on” state). Chronic activation of inhibitory DREADDs in rats significantly reduced AIMs scores when compared with those of the control group. **Conclusions:** These results indicate that strategies to reduce the hyperactivity of MSNs may inhibit the development of LIDs. Together data strongly support the reduction of MSN firing to improve L-Dopa responses and restore functionality in PD patients.