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MEETING ABSTRACT

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Lentiviral-mediated local siRNA-induced inactivation of Gpr88 in the medium spiny neurons modulates the behavioral and molecular effects of striatal dopamine depletion induced by 6-OHDA lesions in the rat
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Gpr88, a G protein-coupled orphan receptor, is highly and almost exclusively represented in the GABAergic medium spiny neurons (MSN) of the striatum. The expression of Gpr88 in this structure is regulated by dopamine (DA) and glutamate as well as psychotropic drugs. Interestingly, changes in Gpr88 mRNA reported in rats after 6-OHDA lesions are also reversed by L-DOPA. In addition, Gpr88 knock-out mice exhibit a schizophrenic-like phenotype with deficits that are normalized by antipsychotics. These findings support a role of GPR88 in the pathophysiology of basal-ganglia-related diseases and in the response to drugs that modulate dopamine and glutamate neurotransmission.

We have recently shown that lentiviral-mediated knock-down (KD) of Gpr88 expression by a specific shRNA in ventral striatum (nucleus accumbens) reduces amphetamine-induced motor hyperactivity and ameliorates cognitive deficits in a rat model of schizophrenia. Furthermore, the Gpr88 KD modifies the expression of the dopamine and cAMP-regulated phosphoprotein of 32 kDa (Darpp-32), suggesting cross-talk between dopamine signaling and Gpr88 [1]. In order to further evaluate the interaction between Gpr88 and dopamine signaling, Gpr88 expression was inactivated in the dorsal striatum after unilateral injection of 6-OHDA in the medial forebrain bundle in rats. As expected, the loss of DA neurons induced by 6-OHDA and the concomitant depletion of DA in the striatum resulted in a strong amphetamine-induced turning behavior ipsilateral to the lesioned side and increased, as assessed by in situ hybridization, the expression of glutamic acid decarboxylase 67 (GAD67), a key marker of the activity of the MSN. Moreover, as assessed by western blot analysis, striatal DA depletion decreased the expression of Darpp32 while increased protein levels of the GluA1 subunit of the AMPA receptor. Inactivation of Gpr88 in the dorsal striatum ipsilateral to the 6-OHDA lesion significantly reduced amphetamine-induced turning behavior and restored the normal expression of GAD67. Furthermore, the Gpr88 KD restored toward normal levels the expression of both Darpp32 and GluA1 in lesioned animals. In conclusion, these observations show that extinguishing expression of Gpr88 moderates the impact of DA loss on MSN activity and suggest that Gpr88 could be a relevant target for modulating dopaminergic neurotransmission.

Reference

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