Serotonin 5-HT_4 receptor agonists improve facilitation of contextual fear extinction in an MPTP-induced mouse model of Parkinson's disease

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Previously, we found that 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced Parkinson's disease (PD) model mice (PD mice) show facilitation of hippocampal memory extinction via reduced cyclic adenosine monophosphate (cAMP)/cAMP-dependent response element-binding protein (CREB) signaling, which may cause cognitive impairment in PD. Serotonergic neurons in the median raphe nucleus (MnRN) project to the hippocampus, and functional abnormalities have been reported. In the present study, we investigated the effects of the serotonin 5-HT_4 receptor (5-HT_4R) agonists prucalopride and velusetrag on the facilitation of memory extinction in PD mice, because 5-HT_4R, which is a Gs protein-coupled receptor that activates adenylate cyclase, is highly expressed in the hippocampus. We found that 5-HT_4R agonists restored facilitation of contextual fear extinction in PD mice by stimulating the cAMP/CREB pathway in the dentate gyrus (DG) of the hippocampus. These findings suggest that 5-HT_4R agonists could be potentially useful as therapeutic drugs for treating cognitive deficits in PD by improving the cAMP/CREB signaling pathway in the hippocampal DG.