Nox1 deficiency alleviated behavioral abnormalities in obsessive-compulsive disorder model mice via inhibition of D_2 receptor/β-arrestin pathway-mediated synaptic facilitation

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Obsessive-compulsive disorder (OCD) is a neuropsychiatric disorder characterized by repeated rising concern (obsessions) and repetitive behaviors to get rid of obsessions (compulsions). Considering the high rate of treatment-refractory patients, novel therapeutic strategies are strongly awaited. Recent clinical researches indicate that antioxidants, such as N-acetylcysteine, enhance treatment response. However, pathological roles of reactive oxygen species (ROS) and the mechanisms of action of antioxidants are poorly understood. In this study, we showed that mRNA expression of NOX1, the catalytic subunit of NADPH oxidase, was significantly increased in the striatum of OCD model mice. *Nox1* deficiency or pharmacological inhibition of NOX1 alleviated OCD-like behavioral abnormalities. *Nox1* deficiency also suppressed D_2 receptor/β-arrestin pathway-mediated synaptic facilitation in the indirect pathway medium spiny neurons (iMSNs) in the central part of the striatum (CS) shown in OCD model mice. These results suggest that NOX1-derived ROS enhance synaptic facilitation in the CS iMSNs via modulation of the D_2 receptor/β-arrestin pathway, leading to OCD-like behavioral abnormalities.