Loss of Neuregulin 3 in dopaminergic neurons leads to dysregulated dopamine transients and cognitive deficits

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Objective

To investigate the function of Nrg3 in midbrain dopaminergic neurons in dopamine transmission and behaviors relevant to schizophrenia.

Background

A large body of genetic and functional studies have showed that Nrg3 mutation is implicated in the pathophysiology of schizophrenia. However, whether mutation of Nrg3 results in the dysbalanced dopaminergic transmission, a major cause of schizophrenia, remains unknown. Here, we hypothesize that ablation of Nrg3 function in dopaminergic neurons lead to dysregulated dopamine transmission and behaviors relevant to schizophrenia.

Methods

We used dopamine specific Cre line (DAT-Cre), to delete the expression of Nrg3 in the dopaminergic neurons. Using fast scanning cyclic voltammetry (FSCV), subsecond spontaneous dopamine transients were recorded in the control and Nrg3 CKO mice. Behavioral tests were used to analyze the working memory and cognitive deficits in the CKO mice.

Results

In situ hybridization data shows that Nrg3 was enriched in midbrain dopaminergic neurons. Knock out expression of Nrg3 in the dopaminergic neurons increased dopaminergic terminals in the prefrontal cortex and Nucleus accumbens, also increased dopamine transients in the core of nucleus acumens (NAcc). In addition, Nrg3 CKO mice exhibited hyperlocomotor activity and impaired working memory in the behavioral tests.

Conclusion

Our data reveals a novel function of NRG3 on the dopaminergic transmission which regulates spontaneous dopamine transients in the NAcc, and deletion of Nrg3 in dopaminergic neurons induces schizophrenia-like behaviors.