Loss of NMDA receptor-dependent activity of dopaminergic neurons leads to development of depressive-like symptoms in mice

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Affective disorders are associated with dysfunctions in reward processing, which manifest as anhedonia, altered sensitivity to reinforcement, a reduced ability to exert effort or decreased incentive motivation. These functions depend on the brain’s reward system and are mainly mediated by dopamine signaling. Nevertheless, the role that dopamine signaling plays in affective disorders is often regarded as secondary to other monoamines. We show that inactivation of NMDA receptors on dopaminergic neurons in adult mice leads to the development of affective disorder-like symptoms.

A mouse with no NMDA receptor-dependent bursting of dopamine neurons

We have generated a mutant mouse strain (NR1DATCreER²) with inducible inactivation of NMDA receptors on dopamine neurons.

![Diagram showing DAT/Cre expression and NR1 expression]

Depressive-like behaviors

NR1DATCreER² mice showed increased immobility in the forced swim test and decreased social interaction with a non-familiar conspecific. These behaviors bear resemblance to some of the symptoms associated with depression.

Social interaction with an unfamiliar conspecific

Forced swim test

Open field arena

Mutant mice showed less horizontal activity in an illuminated open field arena.

Sweet taste preference

Mutants consumed less saccharin solution but they were not significantly different in preference of saccharin vs. water. When the access to saccharin was progressively more difficult, mutants showed normal discounting of preference.

0.1% saccharin preference

male mice, individual cages

0.1% saccharin preference

female mice, mixed cage

Ratio discounting

Female mice, hotLab

Motivation and effort discounting

NR1DATCreER mice were slower to reach the same number of instrumental responses as controls when learning food self-administration under (FR1) schedule, but performed equally under a PR schedule.

Instrumental food self-administration in operant conditioning chambers

Mutant mice were not significantly different from controls in a T-maze based effort discounting task. However, a trend toward greater discounting was observed, which could be in line with the role of dopamine signaling in control of motivation and vigor.

Loss of NMDA receptor-dependent activity caused the development of despair-like behaviours: reduced social activity and reduced saccharin intake. These changes were not associated with significantly altered sensitivity to reinforcement, and the results indicated only a trend toward greater effort discounting.

Additional data for the saccharin preference experiment

Acknowledgements

This project is supported by the grant HARMONIA 2012/06/M/NA4/00143 from the Polish National Science Centre. If you want a copy of the poster, please scan the QR code on the left. Or write me at janrod@if-pan.krakow.pl, I am happy to answer any questions.