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Dopamine transporter knockout mice in experimental neuropharmacology

Raul R. Gainetdinov
Department of Cell Biology
Duke University
Durham, NC 27710

ABSTRACT OF TALK

The monoaminergic neurotransmitter dopamine (DA) has been implicated in multiple brain disorders including schizophrenia, attention deficit hyperactivity disorder (ADHD), addiction and Parkinson's disease. Dopamine transporter (DAT) is a major regulator of both the intensity of extracellular dopamine (DA) signaling and presynaptic neuronal homeostasis. By deleting the gene encoding the DAT, a strain of mice lacking the mechanism to provide re-uptake of extracellular DA has been developed. In DAT knockout mice (DAT-KO), extracellular levels of DA in the striatum are persistently increased 5-fold and this hyperdopaminergia manifests behaviorally as a pronounced locomotor hyperactivity. This hyperactivity is accompanied by specific perseverative patterns of locomotion and significant impairments in cognitive functions as well as sensorimotor gating mechanisms. Thus, DAT-KO mice may represent an animal model in which hyperdopaminergic related endophenotypes of some psychiatric disorders can be recapitulated, thereby providing test subjects for future treatment developments. Several pharmacological approaches to counteract consequences of increased central dopaminergic function have been tested in DAT-KO mice. Recently, these mice were used to develop a novel model of acute DA deficiency, creating the possibility to screen for drugs efficient in restoring locomotion in a DA-independent manner. Lack of DAT prevents recycling of released DA into the presynaptic terminal thereby resulting in a 20-fold depletion in intraneuronal storage of DA. The remaining DA is highly dependent on its de novo synthesis and pharmacological blockade of the DA synthesis in DAT-KO mice results in fast and effective disappearance of striatal DA. Dopamine-depleted DAT-KO mice (DDD mice) display striking behavioral phenotype including akinesia, rigidity and tremor reversible by L-DOPA and non-selective DA agonists. DDD mice represent a simple model of acute DA deficiency that can be used to screen for novel antiparkinsonian drugs. Furthermore, the ability to rapidly eliminate DA in DDD mice can serve as an effective in vivo approach to study modalities of neuronal activity and DA receptor signaling. In particular, DAT-KO and DDD mice were instrumental to uncover role of AKT/GSK-3 signaling cascade in the actions of dopamine. This approach could be also highly valuable in studies aimed at further defining the role of DA in the neuronal circuitry involved in the motor control. Thus, DAT-KO and DDD mice provide a unique opportunity to create extreme levels of dopaminergic dysfunction in vivo and thereby can be used as valuable tools to understand role of DA in physiology and pathology.