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Dopamine Receptors and Dopamine Transporter in Brain Function and Addictive Behaviors: Insights from Targeted Mouse Mutants

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Dopamine receptors
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Neuropeptide

Abstract
Recent advances in molecular biology have resulted in a number of genetically manipulated mice with defined changes at dopamine receptor and the dopamine transporter (DAT) loci. Mice with targeted mutations at the D1 receptor (D1R) are growth-retarded and show downregulated expression of dynorphin and substance P. Behavioral assessment indicates that mutants have deficiencies in spatial learning and initiating movement, as well as in responding to novel stimuli. D1R mutants do not become locomotor activated with cocaine or show upregulated immediate early gene (IEG) expression, but D2 receptor-dependent IEG changes are intact. Acute cocaine administration increases substance P levels, suggesting that striatal expression of this neuropeptide can be modulated by D1R-independent processes. Failure of locomotor activation is also seen with repeated amphetamine treatment. Surprisingly, D1R-deficient mice retain cocaine-conditioned place preference. In contrast, D2 receptor knockout mice are bradykinetic, show increased striatal enkephalin expression and an absence of opiate rewarding effects. D3 receptor mutants are hyperactive when assessed in an exploratory assay and display reduced anxiety-associated behavior in an elevated plus maze test. The recently described D4 receptor homozygous mutants exhibit a reduction in baseline locomotor activity and were shown to be supersensitive to the locomotor activating effects of alcohol and psychostimulant drugs. As expected, DAT knockout mice are hyperactive and do not respond to cocaine or amphetamine. The observation that D2 and D4 dopamine receptor and DAT mutants show compensatory effects, together with the complicating issue of their hybrid genetic background may temper conclusions regarding the direct effects of the targeted mutation on phenotype.

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