

SFB 35 Colloquia in Membrane Transport

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"Monoamine transporters as the targets of psychostimulants"

Cocaine is a powerful psychostimulant and an addictive drug of abuse. There are three known high-affinity targets for cocaine: the dopamine transporter (DAT), the serotonin transporter (SERT), and the norepinephrine transporter (NET). Decades of studies support the dopamine (DA) hypothesis that the blockade of DAT and the subsequent increase in extracellular DA primarily mediate cocaine reward and reinforcement. Contrary to expectations, DAT knockout mice (DAT-KO), and SERT or NET knockout mice still display the rewarding property of cocaine. These studies indicate that none of these transporters are required for the cocaine effects and led to the re-evaluation of the DA hypothesis and the proposal of redundant reward pathways. However, the knockout mice have very significant adaptive changes during development to compensate for the complete absence of a critical protein, which might have altered how cocaine produces its effects in these mice. Therefore, we have engineered a functional but cocaine-insensitive mutant of DAT and generated a knock-in mouse line carrying this DAT mutant (DAT-CI mice). Normal doses of cocaine still block SERT and NET but have little effect on DAT in these mice which provide a unique tool to study the role of DAT in mediating cocaine effects. In DAT-CI mice, cocaine did not elevate extracellular DA in the nucleus accumbens (NAc), cocaine did not stimulate locomotor activity but suppressed it, and cocaine failed to produce reward as measured by conditioned place preference and by drug self administration. In contrast, amphetamine, another psychostimulant, was able to stimulate locomotor activity and produce reward, indicating that the reward system functioned well in these mice. In addition, re-introducing wild type DAT back into the brains of fully developed DAT-CI mice restored the ability of cocaine to stimulate locomotor activity and to produce conditioned place preference. Our results indicate that cocaine blockade of DAT is required for the stimulating and rewarding effects of cocaine in mice with a functional DAT. Furthermore, we are now in the process of generating mouse lines carry a cocaine-resistant SERT or NET mutant to study the roles of these transporters in the complex cocaine effects.