

# MONOAMINE TRANSPORTER AS A TARGET MOLECULE FOR PSYCHOSTIMULANTS

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Methamphetamine (MAP), a drug of abuse known worldwide for its addictive effects and neurotoxicity, causes somatic and psychiatric disorders. MAP enters terminals/neurons via monoamine transporters, displaces both vesicular and intracellular monoamines, and facilitates the release of monoamines into the extraneuronal space through synaptic transport via the monoamine transporters. Chronic psychostimulant abusers exhibit psychotic features, including delusions and auditory hallucinations. The dopamine transporter (DAT) and the vesicular monoamine transporter 2 (VMAT2) play pivotal roles in the action of MAP, including locomotor effects. The deletion of DAT attenuates the locomotor effects of MAP and may play larger role in behavioral responses to MAP compared to the deletion of VMAT2. MAP produces hyperthermia and/or neuronal toxicity in most species. The effects of MAP in DAT or serotonin transporter (SERT) single knockout (KO) mice and DAT/SERT double KO mice suggested that DAT and SERT are key molecules for hyperthermia and neuronal toxicity of MAP.

## I. Introduction

Methamphetamine (MAP) is a psychostimulant that induces enhanced arousal and euphoria acutely, and psychosis and addiction chronically. MAP enters the terminals/neuron via the monoamine transporters (dopamine transporter: DAT, serotonin transporter: SERT, or norepinephrine transporter: NET), displaces

both vesicular and intracellular monoamines, and facilitates release of monoamines into the extraneuronal space by synaptic transport in the monoamine transporters (Seiden *et al.*, 1993). The large release of monoamine produced by psychostimulant is thought to contribute to the drug's effects in the brain.

## II. MAP-Induced Behavioral Sensitization

The acute and chronic pharmacological consequences of MAP in human users have been observed in behavioral experiments in animals, including both hyperactivity and sensitization of locomotor responses (Segal and Schuckit, 1983). Behavioral sensitization is a phenomenon whereby repeated intermittent exposure to MAP-like psychostimulant elicits a progressive enhancement of those responses, which persists for extended time periods following withdrawal from the drug and are easily reinstated by exposure to the drug or psychosocial stress (Robinson and Becker, 1986). This process closely resembles the course of the relapse in MAP-induced psychosis or schizophrenia, thus sensitization in animals has been suggested to model these psychoses (Sato *et al.*, 1983). Behavioral sensitization is thought to be an early and enduring manifestation of neuronal plasticity associated with changes in mesolimbic dopamine neurotransmission (Kalivas *et al.*, 1993). MAP induces dopamine release through exchange diffusion of plasma membrane DAT (Seiden *et al.*, 1993), and release of vesicular dopamine into the cytosol by acting on the vesicular monoamine transporter 2 (VMAT2) (Sulzer *et al.*, 2005). The dopamine releasing effect of MAP has been postulated to mediate its locomotor stimulant and rewarding effects (White and Kalivas, 1998). Therefore, DAT and VMAT2 should play pivotal roles in the mechanisms underlying the actions of MAP.

DAT knockout (KO) mice and VMAT2 KO mice have been used to investigate the roles of DAT and VMAT2 in dopamine neurotransmission and pharmacological mechanisms underlying the actions of psychostimulants. Homozygous deletion of the DAT gene has been reported to produce a 10-fold increase (Shen *et al.*, 2004) or fivefold elevation (Jones *et al.*, 1998) of extracellular dopamine concentrations in the striatum measured by *in vivo* microdialysis, while heterozygous deletion of DAT was not found to significantly increase extracellular dopamine (Shen *et al.*, 2004) or to produce a smaller twofold elevation (Jones *et al.*, 1998) of dopamine in the striatum. Homozygous DAT KO mice show growth retardation and hyperactivity, whereas heterozygous DAT KO mice did not show gross abnormalities in either development or baseline behavioral parameters (Sora *et al.*, 1998). Habituated homozygous DAT KO mice do not show any significant cocaine-induced increase in locomotion (Sora *et al.*, 1998, 2001; Uhl *et al.*, 2002).

We examined locomotor activity and sensitization in heterozygous DAT KO ( $\text{DAT}^{+/-}$ ), heterozygous VMAT2 KO ( $\text{VMAT2}^{+/-}$ ), double heterozygous DAT/VMAT2 KO ( $\text{DAT}^{+/-}$   $\text{VMAT2}^{+/-}$ ), and wild-type (WT) mice to evaluate the roles of DAT and VMAT2 in MAP-induced locomotor behavior (Fukushima *et al.*, 2007). In  $\text{DAT}^{+/-}$   $\text{VMAT2}^{+/-}$  mice, all of MAP-induced behavioral responses were similar to those in  $\text{DAT}^{+/-}$ , but not  $\text{VMAT2}^{+/-}$  mice. The behavioral effects of both acute and chronic MAP administration were suppressed in heterozygous DAT KO mice, whether or not it was combined with heterozygous VMAT2 KO. Contrary to the effect observed in heterozygous DAT KO mice, acute MAP administration produced greater locomotor responses in heterozygous VMAT2 KO mice. These findings indicate that the half deletion of DAT plays a major role in both acute and chronic behavioral responses to MAP, while the effect of the half deletion of VMAT2 is less prominent.

### III. MAP-Induced Hyperthermia and Neuronal Toxicity

MAP abuse causes serious health hazards including irreversible neuronal degeneration, seizures, hyperthermia, and death in human and experimental animals (Davidson *et al.*, 2001). Among these side effects, MAP produces hyperthermia and/or dopaminergic neurotoxicity in most species. Clinical reports and animal studies indicate that lethality by MAP closely correlates with hyperthermia, which may be the primary cause of death. Animal studies suggest that dopamine receptor activation is crucial for MAP-induced hyperthermia (Broening *et al.*, 2005) and lethality (Bronstein and Hong, 1995). There has also been an assumption that the hyperthermia that follows MAP administration is serotonin receptor-mediated (Green *et al.*, 2003).

We examined hyperthermic and lethal toxic effects of MAP in DAT, SERT, and DAT/SERT double KO mice to elucidate the role of these two transporters in MAP-induced hyperthermia and lethality (Numachi *et al.*, 2007). MAP caused significant hyperthermia even in the mice with a single DAT gene copy and no SERT copies ( $\text{DAT}^{+/-}$   $\text{SERT}^{-/-}$  mice). Mice with no DAT copies and a single SERT gene copy ( $\text{DAT}^{-/-}$   $\text{SERT}^{+/-}$  mice) showed significant but reduced hyperthermia when compared to WT mice after MAP. These results demonstrate that MAP exerts a hyperthermic effect via DAT, or via SERT, in the absence of DAT. DAT gene deletion in mice strikingly increased  $\text{LD}_{50}$  of MAP by 1.7–1.8 times that of WT mice, suggesting that the lethal toxic effect of MAP is mainly dependent on DAT. Although DAT and SERT were shown here to be involved in both the effects of MAP on temperature as well as MAP lethal toxicity, the mechanisms are nonetheless different; DAT single KO mice exhibited hyperthermia but greatly reduced MAP lethality, and the lethality was no different from

DAT/SERT double KO mice that had hypothermic responses to MAP. Thus, although the lethal toxic effect of MAP is mainly dependent on DAT, with some contribution from SERT, hyperthermia is not prerequisite for MAP-induced lethality.

In conclusion, these findings lead us to hypothesize that DAT variants may have more profound effects than VMAT2 or SERT variants on the clinically important consequences of acute and chronic MAP abuse in humans.

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