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Organic Cation Transporter 3 Mediates Abuse-Related Properties of Amphetamine

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Abuse of amphetamine-type stimulants poses a significant public health burden with over 56 million users worldwide and growing global trends of abuse. No treatments exist for amphetamine-type stimulant use disorders, underscoring a critical need to identify novel, effective therapeutic targets. It has long been known that amphetamine exerts its actions by targeting high affinity, low capacity 'uptake 1' transporters, particularly the dopamine transporter. Published studies from our lab provide strong support for a significant role of the low affinity, high capacity 'uptake 2' transporter organic cation transporter 3 (OCT3) in the neurochemical and behavioral actions of amphetamine. Here, we use *in vivo* high-speed chronoamperometry coupled with behavioral assays to extend these results. Using a temporally inducible, global OCT3 knockout model, we show that acute inhibition of OCT3 with decynium-22 (D-22) attenuates amphetamine-evoked dopamine release in dorsal striatum of both sexes, an effect lost in mice with OCT3 knockout induced in adulthood. OCT3 knockout did not prolong clearance of amphetamine-evoked dopamine release in dorsal striatum, suggesting blockade of OCT3 allows for selective attenuation of dopamine release. Moreover, we show that the rewarding effects of amphetamine (1 mg/kg) measured by conditioned place preference are attenuated by inhibition of OCT3 with D-22 in both sexes, and that mice with OCT3 knockout induced in adulthood do not develop conditioned place preference regardless of pharmacological pre-treatment. Ongoing studies are assessing the specific contribution of OCT3 on dopaminergic terminals in nucleus accumbens to amphetamine-evoked dopamine release and conditioned place preference. Altogether, these data suggest that OCT3 may be an attractive target for development of novel therapeutics to treat amphetamine-type stimulant use disorders.

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