**Unfaithful transporters:  Insights into mechanisms of action of therapeutic and abused drugs**

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**Introduction**. Organic cation transporter 3 (OCT3) is emerging as an important player in monoamine neurotransmission and in the actions of psychotherapeutic and abused drugs. Using constitutive OCT3 knockout (KO) mice we showed that OCT3 is a contributor to amphetamine-evoked dopamine (DA) release, and that OCT3-dependent uptake of serotonin (5-HT) undermines the antidepressant-like activity of selective 5-HT transporter (SERT) reuptake inhibitors (SSRIs). Here we use conditional and cell-type specific OCT3 KO mice to build on these findings.

**Aims**. Our aims were to 1) further interrogate OCT3 in the neurochemical and rewarding properties of amphetamine, and 2) investigate the role for OCT3 on 5-HT neurons in fear learning and memory and in 5-HT clearance in the basolateral amygdala (BLA) with implications for post-traumatic stress disorder (PTSD).

**Methods**. Male and female mice had either global conditional OCT3 KO (amphetamine studies) or OCT3 or SERT depleted from 5-HT neurons. In vivo high-speed chronoamperometry, intravenous self-administration (IVSA) or fear conditioning approaches were used. Sample sizes were 6-12 and analyzed by ANOVA with relevant post-hoc tests.

**Results**. OCT3 KO markedly attenuated amphetamine-evoked DA release in dorsal striatum, and dramatically diminished IVSA. 5-HT clearance in BLA was slowed at low but not high extracellular concentrations and the SSRI fluvoxamine was without effect in mice with SERT KO compared to controls. In OCT3 KO mice, 5-HT clearance was slowed both at low and high extracellular concentrations. Behaviorally, fear learning was unaffected by SERT or OCT3 KO on 5-HT neurons. In OCT3 KO mice, however, freezing was reduced during context recall 4 days later. Preliminary results suggest SERT KO mice display reduced freezing in cued recall.

**Discussion**. These data suggest that 1) OCT3 may be an attractive target for development of novel therapeutics to treat amphetamine-type stimulant use disorders for which no treatments currently exist; 2) Both SERT and OCT3 are important players in 5-HT uptake in BLA and suggest that OCT3 may contribute more extensively to 5-HT uptake than previously appreciated; and 3) SERT and OCT3 play an active role in fear memory recall and open the possibility that pharmacotherapeutics that target OCT3 and SERT concurrently may result in a greater therapeutic response as opposed to SSRIs alone for treatment of PTSD and related disorders.