Selective overexpression of EAAT3 in midbrain dopamine neurons leads to increased OCD-like behaviors

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Objectives. Obsessive compulsive disorder (OCD) is a severe, chronic condition that affects 2-3% of the population. Genetic findings have pointed to *SLC1A1*, encoding the neuronal glutamate transporter EAAT3/EAAC1, with evidence suggesting increased expression may contribute to risk. We previously reported that a loss of *Slc1a1* in mice leads to decreased amphetamine (AMPH)-induced dopamine (DA) release, locomotion, and stereotypic movements, as well as decreased SKF-38393 (D1-agonist)-induced grooming behavior. Viral rescue of midbrain *Slc1a1* expression partially restored the behavioral response to AMPH, suggesting an impact on DA neuron function. Here, to test more directly the developmental impact of DA neuron EAAT3 overexpression on compulsive-like behaviors, we generated mice with DA neuron-selective overexpression of EAAT3. We hypothesized that increased expression in DA neurons will lead to increased OCD-like behaviors.

Methods. We used the Flexible Accelerated STOP Tetracycline Operator-knockin (FAST) system to generate tTA-mediated overexpression of EAAT3. tetO-*Slc1a1* homozygous mice were crossed with TH-tTA heterozygous mice to generate TH-tTA+//tetO-*Slc1a1* and TH-tTA-//tetO-*Slc1a1*(control) offspring. Doxycline-supplemented chow was used to regulate tetO-driven EAAT3 expression. Mice were evaluated for AMPH-induced locomotion and for AMPH and SKF-38393-induced preservative behaviors.

Results. TH-tTA+//tetO-*Slc1a1* mice displayed increased AMPH-induced locomotion (3.0 mg/kg dose, curve–fit analysis, $F(4, 370) = 16.33$, $P < 0.0001$, n = 10-11), and stereotypic behavior (8.0 mg/kg dose, 2-way RM ANOVA; genotype $F(1, 19) = 7.088$, $P = 0.0154$, n = 10-11). No significant effect on SKF-38393-induced grooming behavior was observed. Normalizing DA neuron EAAT3 expression in the same mice diminished the AMPH-induced locomotion ($F(4, 370) = 2.105$, $P = 0.0796$, n = 10-11) and stereotypic ($F(1, 19) = 0.02466$, $P = 0.8769$, n = 10-11) response.

Discussion. Our findings indicate that changes in EAAT3 expression can dynamically alter neurotransmission in DA neurons to modulate compulsive-like behaviors. Ongoing studies are examining the impact of EAAT3 overexpression on DA neuronal activity and release during compulsive-like behaviors.