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The role of Lateral Habenula inputs onto Dorsal Raphe serotonin neurons in regulating methamphetamine induced aversion.

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Abstract

The CDC reports that 52.9% of people who used MA in the last year have a MA use disorder. Quantitative trait locus mapping in selectively bred high and low MA drinking (MADR) mouse lines identified a single nucleotide polymorphism (SNP) that accounts for 60% of the genetically determined differences in MA intake in the MADR lines. This nonsynonymous substitution mutation within the trace amine-associated receptor 1 (Taar1) gene alters the protein amino acid sequence and results in the expression of a nonfunctional TAAR1 receptor. MA is a full TAAR1 agonist, and homozygosity for this mutation (Taar1m1J) segregates with high MA drinking and low sensitivity with MA-induced aversion. MA-induced potentiation of NMDA-mediated excitatory postsynaptic currents (EPSCs) is dependent on TAAR1 in midbrain dopamine neurons and is observed in MALDR mice but not MAHDR mice. These results suggest that increased activation of NMDA receptors is important for aversive effects of MA. Since the lateral habenula-dorsal raphe (DR) circuitry, specifically serotonin (5-HT) neurons in the DR, regulate aversive behaviors, we also measured the effects of MA on EPSCs in DR brain slices from C57BL/6J mice, one of the two progenitor strains of the MADR lines. MA potentiates NMDA EPSCs in larger neurons (putative 5-HT neurons), but not smaller cells. Post-hoc immunohistochemistry will confirm cell type. Future studies will compare the MADR lines. Sensitivity to MA-induced aversion via TAAR1 signaling may play an important protective role against developing MA use disorders.