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Bidirectional Effects of a *Taar1* SNP Conversion on Methamphetamine Traits

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Methamphetamine (MA) is a substrate for the trace amine-associated receptor 1 (TAAR1). Growing evidence supports a role for TAAR1 in susceptibility to MA and other drug intake and indicates that greater TAAR1 function reduces drug self-administration. A single nucleotide polymorphism (SNP) in the *Taar1* gene predicts a conformational change in the receptor and has functional consequences; cells expressing the mutant *Taar1*^{m1J} allele do not exhibit a cAMP response to TAAR1 agonists seen in cells expressing the *Taar1*$^{+}$ allele. Mice with the *Taar1*$^{m1J/m1J}$ genotype exhibit increased MA intake and reduced sensitivity to hypothermic and aversive effects of MA, compared to *Taar1*$^{+/+}$ mice. We used CRISPR-Cas9 to excise the *Taar1*$^{+}$ allele and replace it with the *Taar1*^{m1J} allele or to excise the *Taar1*^{m1J} allele and replace it with the *Taar1*$^{+}$ allele in mice bred for high MA intake or in their DBA/2J and C57BL/6J progenitors. Profound changes in MA intake and sensitivity to the hypothermic and conditioned aversive effects of MA occurred that were not dependent on genetic background, supporting a role for *Taar1* in these MA traits. Future studies will examine the effects of a TAAR1 agonist in comparison to MA and will employ electrophysiology and chemogenetics to examine brain circuitry and mechanisms underlying TAAR1-mediated effects on MA intake and sensitivity. A focus will be on lateral habenula (LHb) to ventral tegmental area and dorsal raphe projections, which are aversion circuits hypothesized to be regulated by MA. Support: U01DA041579 (TP); P50DA039841 (EC), P50DA018165 (TP); R01DA046081 (TP), Department of Veterans Affairs (TP)