Evidence for an epistatic effect of *Oprm1* and *Taar1* in risk for methamphetamine consumption

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Purpose: *Taar1* impacts risk for methamphetamine (MA) intake and *Oprm1* is regulated by the top-ranked transcription factor network underlying risk. The current studies sought to further establish *Taar1* as a quantitative trait gene for MA intake and to examine the combined effects of different *Oprm1* and *Taar1* allele types on MA intake. **Methods:** In Experiment 1, DBA/2 mice that originated from a common ancestral population, but are housed and distributed by different suppliers, were tested for MA intake in a two-bottle choice test (water vs 20 mg/L MA for 4 days and then water vs 40 mg/L MA for 4 days; MA was offered for 18h/day, but water and food were available at all times) and genotyped for a single nucleotide *Taar1* polymorphism that defines whether the translated receptor (TAAR1) is functional or non-functional. In Experiment 2, C57BL/6J (B6) x DBA/2J (D2) recombinant inbred strains (BXD RI) were genotyped for their strain-specific *Oprm1* and *Taar1* alleles, and strains of 4 possible genotype classes (*Oprm1*-*Taar1*: B6-B6, B6-D2/J, D2-B6, D2-D2/J; 4 strains of each type) were tested for MA intake. **Results:** DBA/2 (D2/J) mice supplied by The Jackson Laboratory consumed significantly more MA and exhibited higher levels of methamphetamine preference in a two-bottle choice procedure, compared to DBA/2 mice from Charles River, Taconic or Harlan-Sprague Dawley. Only D2/J mice possess a *Taar1* single nucleotide polymorphism that negates TAAR1 function and corresponded with higher MA intake; these mice are homozygously fixed for this mutation. All BXD RI strains with the B6-*Taar1* allele consumed less than 1 mg/kg MA on average (range of strain means= 0-0.7 mg/kg/18h for 40 mg/L MA). BXD RI strains with the D2/J-*Taar1* allele consumed significantly more MA (range of strain means = 2.7-6.7 mg/kg/18h for 40 mg/L MA). There was a significant *Oprm1* allele x *Taar1* allele interaction for consumption of MA from the 40 mg/L MA solution ($F[1,169]=8.9$, $p=.01$) with mice that were D2-*Oprm1*/D2/J-*Taar1* consuming more MA than mice that were B6-*Oprm1*/D2/J-*Taar1*. The correlation between *Taar1* genotype and MA intake for individual animals across all strains (DBA/2 and RI; N=221) was $r=0.85$ ($p<1x10^{-5}$), indicating that *Taar1* genotype accounted for 72% of the phenotypic variance in MA intake. The interaction was not significant for MA consumption from the lower, 20 mg/L MA concentration solution. **Conclusions:** The current data lend additional support for *Taar1* as a quantitative trait gene on mouse chromosome 10 that impacts risk for MA intake. Furthermore, its impact may interact with *Oprm1* genotype. A large proportion of the phenotypic variance is accounted for by *Taar1* genotype alone. Data are needed in humans to determine if *TAAR1* polymorphisms could serve as markers for MA use disorders and if knowledge of *OPRM1* genotype enhances risk assessment.

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