MA intake and sensitization in mice with a non-functional trace amine-associated receptor 1

T.J. Phillips[1,2], H. Baba[2], J. Erk [2], C. Reed [2], O. Iancu[2], R. Hitzemann[1,2]

[1]Veterans Affairs Portland Health Care System and [2]Oregon Health & Science University, Portland, OR, 97239 USA

The intermittent administration of central stimulants induces behavioral sensitization. Although the molecular mechanisms related to robust sensitization have been determined in some detail, unknown is why some genotypes are more prone and how magnitude of sensitization relates to voluntary drug intake. We have focused on heritable genetic mechanisms via a selective breeding strategy using a heterogeneous mouse stock (HS) derived from the 8 founders of the collaborative cross (CC). The HS-CC captures more than 90% of the genetic diversity available in *Mus musculus*; however, one extensively studied inbred strain is not among those included - the DBA/2J (D2) strain. The D2 possesses a unique spontaneously arising SNP in the trace amine-associated receptor 1 (*Taar1*) gene that results in a non-functional receptor and increases methamphetamine (MA) intake. However, the impact of the *Taar1* SNP on MA intake is variable in crosses of the D2 and C57BL/6J strains. Our focus was on this individual variation and the role of this SNP in MA-induced sensitization. First, the D2 strain was crossed into the HS-CC. Next, selective breeding was initiated from a population of HS-CC in which all individuals possessed the *Taar1* SNP; a randomly bred control line of individuals with the alternative allele was also maintained. There was considerable variation in MA intake in the HS-CCxD2 F2 population (mean=4.4±0.3 mg/kg; range=0.1-17.0 mg/kg). Furthermore, acute MA stimulation and magnitude of sensitization were significantly greater in F2 mice that possessed the *Taar1* SNP. Offspring from the S1 selection generation for high *vs* low MA intake differed by 0.6 mg/kg for voluntary MA intake (5.1±0.4 *vs* 4.5±0.3). Control line S1 offspring consumed 0.7±0.1 mg/kg MA. Further response to selection will indicate that additional genes in the HS-CC impact MA intake. Alternatively, epigenetic factors may impact sensitivity and resistance to the effects of the *Taar1* SNP.

Supported by the Department of Veterans Affairs I01BX002106, NIH NIDA U01 DA041579, NIH NIDA P50DA018165, and NIH NIAAA R24AA020245.