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Reduced Intake When Drugs Make You Cold

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Mice selectively bred for high methamphetamine (MA) drinking (MAHDR) exhibit greater sensitivity to MA reward and are insensitive to aversive and hypothermic effects of MA, whereas mice bred for low MA drinking (MALDR) exhibit the opposite MA phenotypes. To determine if their differential sensitivity to MA-induced hypothermia extends to drugs of similar and different classes, we examined sensitivity to the hypothermic effect of the stimulant cocaine, the amphetamine-like substance 3,4-methylenedioxymethamphetamine (MDMA), and the opioid morphine in these lines. The lines did not differ in thermal response to cocaine, only MALDR mice exhibited a hypothermic response to 3,4-methylenedioxymethamphetamine (MDMA), and MAHDR mice were more sensitive to the hypothermic effect of morphine than MALDR mice. Previous work identified the trace amine-associated receptor 1 gene (*Taar1*) as a quantitative trait gene for MA intake. The MAHDR line is homozygous for the mutant $Taar1^{m1J}$ allele, whereas the MALDR line possesses at least one copy of the reference $Taar1^{+}$ allele. We genotyped the mice tested for morphine-induced hypothermia and report genetic linkage between *Taar1* and the mu-opioid receptor gene (*Oprm1*), such that the MAHDR line more often inherits the $Oprm1^{D2}$ allele and the MALDR line more often inherits the $Oprm1^{B6}$ allele. We also present data from a family of recombinant inbred mouse strains supporting the influence of *Oprm1* genotype, but not *Taar1* genotype, on thermal response to morphine. These results nominate *Oprm1* as a genetic risk factor for morphine-induced hypothermia, and provide additional evidence for a connection between drug preference and drug thermal response.