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Role of the lateral habenula-dorsal raphe circuit in methamphetamine-induced aversion

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Keywords

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Abstract

Strong initial sensitivity to aversive drug effects likely results in drug avoidance and reduces the probability of addiction. The activation of glutamatergic lateral habenula (LHb) afferents projecting to dorsal raphe (DR) serotonin (5-HT) and GABA interneurons is implicated in the perception of aversion induced by several stimuli. Specifically, inhibition of DR 5-HT neurons is associated with the perception of aversion, whereas activation of these neurons is associated with reward. Our research was designed to test the role of this circuit in methamphetamine (MA)-induced aversion using mice selectively bred for differential genetic risk for voluntary MA consumption. Mice bred for low MA intake (MALDR) exhibit high sensitivity to the aversive effects of MA and low sensitivity to MA reward, whereas mice bred for high MA intake (MAHDR) have opposite MA aversion and reward phenotypes. MA is a full trace amine-associated receptor 1 (TAAR1) agonist and studies from our lab have found TAAR1 functionality is critical for sensitivity to the aversive effects of MA. MALDR mice possess functional TAAR1, whereas MAHDR mice possess a mutation, resulting in the loss of TAAR1 function. We performed research to determine whether MA-induced activation of the LHb and the effect of MA on DR 5-HT neuron firing differs between the MALDR and MAHDR lines. Acute MA induced significantly greater neural activation, measured by cFos expression, in the LHb of MALDR mice, compared to MAHDR mice. Using ex-vivo electrophysiology, we found that MA affects firing frequency in DR 5-HT neurons of MAHDR mice but not of MALDR mice. Greater MA-induced neural activation in the LHb of MALDR mice may be related to their high sensitivity to MA-induced aversion, whereas effects of MA in the DR of MAHDR mice may be related to their sensitivity to the rewarding effects of MA, which are not found in MALDR mice.