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Effects of Adolescent Nicotine Exposure on Nicotine and Cocaine Reward in Mice: Impact of Genetic Background

Significance: Despite the decline in cigarette use, the surge of other nicotine-containing products such as e-cigarettes and vapes has offset this trend, particularly among adolescents. Most individuals with nicotine addiction report their first use during adolescence, a period linked to an increased vulnerability to later substance use disorders, including cocaine. However, the genetic factors underlying this co-dependence have yet to be elucidated.

Methods: Five inbred mouse strains (129S1/SvImJ, C57BL/6J, A/J, DBA/2J, NOD ShILtJ from Jackson Lab) were tested. Beginning at post-natal day (PND) 28, male adolescent mice received nicotine (0.5 mg/kg, s.c.) or vehicle (saline) twice daily through PND 34. After maturation in a drug free state into adulthood (PND 70), mice were tested for nicotine (0.5 mg/kg) or cocaine (10 mg/kg) reward in the conditioned place preference (CPP) test.

Results: The 129S1/SvImJ, C57BL/6J, and NOD ShILtJ mouse strains developed significant CPP for both nicotine and cocaine. Adolescent nicotine exposure enhanced cocaine CPP in 129S1/SvImJ and C57BL/6J strains, whereas it strengthened nicotine CPP only in C57BL/6J and NOD/ShILtJ mice. While A/J mice did not exhibit a baseline CPP for either nicotine or cocaine, adolescent nicotine pretreatment attenuated later nicotine preference and potentiated cocaine preference in adulthood. The DBA/2J strain only formed cocaine CPP and there was no effect of adolescent nicotine pretreatment.

Conclusions: Our results show that adolescent nicotine exposure causes strain-dependent alterations to adult drug reward, indicating that genetic factors play an important role in susceptibility to long-term neuroadaptations. These findings highlight the importance of using diverse genetic backgrounds in studies to clarify how early nicotine use influences adult vulnerability to polysubstance use.

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