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Long-term Effects of Adolescent Nicotine Exposure on Sensitivity and Cotinine in the Diversity Outbred Mouse Population

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Exposure to drugs of abuse during adolescence is a critical predictor for nicotine dependence. Nicotine use is a complex disease with Gene x Environment interactions. The Diversity Outbred (DO) population allows assessment of genetic components underlying addiction-related traits. We examined long-term effects of adolescent nicotine exposure on adult nicotine. DO mice were exposed to 24 mg/kg/day of nicotine or saline continuously for 12 days during adolescence. After long abstinence, adult mice were assessed on nicotine-induced locomotor activity as a measure of sensitivity to nicotine. We administered an acute dose of nicotine (0.81 mg/kg) and after testing, blood collections were done to analyze cotinine levels. A generalized linear mixed model was used for assessing treatment and sex differences in locomotor activity. Sex differences were seen with males having lower nicotine-induced locomotion compared to females. Adolescent nicotine treatment decreased the effects of an acute nicotine dose on adult locomotion. Cotinine metabolism had sexual dimorphic effects: females had higher levels of cotinine compared to sex counterparts. In males, adolescent exposure resulted in lower levels of cotinine. We conclude that sex contributes to variability in nicotine-induced changes in locomotion and cotinine metabolism. Altogether, adolescent nicotine results in long-lasting, sex-specific changes in nicotine sensitivity and nicotine metabolism in the DO population. Future studies are examining the genetic architecture of these phenotypes.