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Nicotine Metabolism Genetics in C57BL/6J and NOD/ShiLtJ mouse strains

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Variability in nicotine metabolism gene sequence and expression can influence nicotine addiction susceptibility. This genetic variability can be modeled in rodent systems. Mice metabolize nicotine similarly to humans and are therefore an ideal model system to use for these studies. Preliminary data suggest that there are differences in nicotine metabolism between two inbred mouse strains, C57BL/6J and NOD/ShiLtJ. Nicotine metabolism was assessed in male C57BL/6J and NOD/ShiLtJ mice by collecting serum after acute nicotine treatment (1 mg/kg). Nicotine metabolites were quantified using liquid chromatography-mass spectrometry (LC-MS). To identify possible genetic factors mediating nicotine metabolism differences, genetic variants in 24 nicotine metabolism-related genes were compared using the Sanger Institute Mouse Genomes Project database. Cyp2a5, Cyp2a4, and Aox1 expression levels were measured by qPCR in liver tissue from both strains. NOD/ShiLtJ mice had higher serum levels of cotinine [$F(1,44) = 4.377$, $p<0.05$] and lower levels of hydroxycotinine [$F(1,44) = 23.844$, $p<0.01$] 1-2 hours after nicotine treatment. NOD/ShiLtJ mice showed reduced liver expression of Cyp2a5 and Cyp2a4, genes that are important for nicotine metabolism in mice ($p<0.05$). NOD/ShiLtJ mice had increased expression of Aox1, another nicotine metabolism-related gene ($p<0.05$). Non-synonymous polymorphisms were found in 3 of the 24 examined gene sequences: Cyp2f2, Aox1, and Cyp3a44. These data demonstrate differences in nicotine metabolism between two mouse strains. This sets a foundation for future studies to explore the influence of genetic variants differentiating C57BL/6J and NOD/ShiLtJ mice on addiction-relevant behaviors.