Cyfip2 plays an important role in nicotine reward in mice

M. Imad Damaj[1], Michael F. Miles[1], Sean Deats[2] and Vivek Kumar[2]

Mouse substrains can be a powerful source for discovery of genes and pathways regulating complex behavior. In this study, we report that C57BL/6J (B6J) and C57BL/6NCrl (B6N) substrains, differ significantly in nicotine pharmacology after acute and repeated administration. We characterized behavioral and pharmacological responses to nicotine male adult B6J and B6N mice in a battery of tests. We measured nicotine's acute effects (antinociception and hypothermia), repeated (locomotor sensitization) and reward using the conditioned place preference (CPP) test. In general, B6N mice were less sensitive than B6J mice to nicotine's acute effects and nicotine CPP. In contrast, we found that B6N has a higher sensitized locomotor response to nicotine than B6J. However, nicotine metabolism and levels did not differ between the two substrains after acute administration. We tested whether the *Cyfip2* (S968F) mutation that is known to regulate psychostimulant response could also contribute to the differences seen in nicotine reward. For that, we evaluated nicotine CPP in B6J mice that were genetically engineered via CRISPR/Cas9-edited gene knockin and bred to contain two copies of the *Cyfip2N/N* mutation on a completely isogenic B6J background. Surprisingly, these mice were less sensitive to nicotine CPP. Furthermore, nicotine CPP developed in B6N mice carrying *Cyfip2J/J* allele (correction of the mutation on an isogenic B6N background) similarly to the B6J mice. These results show that the *Cyfip2 S968F* missense mutation is a causal genetic factor underlying nicotine reward differences seen in B6 substrains. These results suggest that these substrains may be useful for future genetic studies on nicotine behaviors.

[1]Department of Pharmacology and Toxicology, Medical College of Virginia Campus, Virginia Commonwealth University, 1217 E Marshall St, Richmond, VA 23298, USA; [2]Jackson Laboratory, Bar Harbor, ME 04609, USA

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