1. No.
   2021T006

2. Title
   Analysis of Nicotine Dependence and Behavioral Addictions Using Genetically Modified Mice in the Dopamine Nerve System

3. Period
   2021-2025

4. Summary
   We investigated neural mechanisms underlying nicotine-related reward behavior and behavioral addiction using lateral hypothalamic intracranial self-stimulation (lhICSS). In wild-type mice, low-dose nicotine showed a trend toward increasing ICSS but did not reach statistical significance. By contrast, in dopamine transporter knockout (DAT-KO) mice, low-dose nicotine facilitated ICSS, and this facilitation was dose-dependently suppressed by ifenprodil. In a two-bottle choice test, an acute and transient reduction in nicotine preference by ifenprodil was also observed in wild-type mice. Furthermore, dopamine-deficient (DD) mice acquired and maintained ICSS, suggesting the presence of a dopamine-independent component in hedonic reward. Under a progressive procedure in which the number of responses required to obtain reward increases in a variable and uncertain manner (progressive variable ratio; PVR), DAT-KO mice exhibited enhanced response maintenance (persistence), and opioid antagonists did not alter this persistence, pointing to a non-opioid modulatory mechanism. Taken together, these findings indicate that dopamine can amplify motivation under uncertainty, whereas non-dopaminergic systems may tune or constrain such persistence.