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The Missing Lynx: The Role of Lynx2 in Nicotine Relapse

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Nicotine addiction and nicotine-related diseases continue to be the leading cause of preventable death worldwide. Despite the availability of pharmaceutical and behavioral interventions, few individuals are successful in achieving long-term nicotine cessation. This thereby emphasizes the need to explore the neurobiological mechanisms underlying nicotine-related behaviors. Of interest, endogenous allosteric modulators acting on the nicotinic acetylcholine receptor (nAChR) have recently emerged as a novel target for drug development. Lynx2 is a negative allosteric modulator of the nAChR and has been shown to significantly decrease nAChR activity in the presence of an agonist, impacting downstream nAChR-mediated behaviors. In these studies, we assessed the global and region-specific impact of lynx2 in incubation of nicotine craving following nicotine self-administration and nicotine abstinence in mice. First, *lynx2* knockout mice and their wildtype littermates were assessed for alterations in nicotine seeking with the incubation of craving protocol following abstinence. Thereafter, wildtype mice were examined following viral mediated knockdown of *lynx2* or a scrambled vector into the medial prefrontal cortex (mPFC). Our data suggest that global knockout of lynx2 prevents the incubation of nicotine craving, which is the increase in nicotine seeking following abstinence. However, region-specific knockdown of lynx2 in the mPFC increases the magnitude of nicotine seeking compared to scrambled vector control mice. Together, these findings illustrate lynx2's dynamic role in nicotine relapse related behaviors and lay the foundation for our understanding of nAChR allosteric modulators in mediating drug seeking behaviors.

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