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Effects of opioid receptor blockade on nicotine-taking and seeking behavior in rats: Clinical implications for smoking cessation medication

Statement of the Problem: Brain opioidergic neurotransmission has been implicated in reinforcement-related processes for several drugs of abuse. However, it remains not fully understood whether activation of opioid receptors plays a role in the reinforcing/motivational effects of nicotine and its associated environmental cues. The present work examined effects of pharmacological antagonism of opioid receptors on nicotine primary reinforcement and conditioned motivation by nicotine cues.

Methodology & Theoretical Orientation: Male Sprague-Dawley rats were trained to press a lever for intravenous self-administration of nicotine (0.03 mg/kg/infusion, free base). Nicotine conditioned stimuli (cues) were established via pairing sensory stimuli with each nicotine injection. In subsequent extinction test sessions, lever responses produced neither nicotine injection nor its associated cues. In relapse test sessions performed after extinction, lever responses resulted in re-presentation of the cues without nicotine injection. Opioid antagonists were administered prior to the test sessions.

Findings: Pretreatment with the non-selective opioid antagonist naltrexone (0, 0.25, 1, 2 mg/kg) effectively attenuated lever responses supported by nicotine cues. In contrast, naltrexone (both acute and chronic treatment) did not change lever responses for nicotine self-administration. However, further tests revealed that pretreatment with antagonists selective for μ receptors (Naloxanazine: 0, 5, 15 mg/kg) but not δ-receptors (Naltrindole: 0, 0.5, 5 mg/kg), or κ receptors (GNTI: 0, 0.25, 1 mg/kg) suppressed nicotine self-administration.

Conclusions & Significance: These results suggest a clinical potential of the non-selective opioid antagonists for preventing cue-triggered tobacco craving. Moreover, the results indicate that the μ rather than δ or κ subtype of opioid receptors plays a role in mediating the primary reinforcement of nicotine, suggesting that opioid neurotransmission via the μ receptors would be a promising target for the development of opioid ligands for curbing nicotine intake and stopping tobacco smoking.

Biography

Xiu Liu has received his MD and PhD in China and completed Postdoctoral training at the Scripps Research Institute in USA. He is a Professor and the Associate Director of the Graduate Program in Pathology at the University of Mississippi Medical Center. He has a two-decade track record of studying drug addiction, particularly nicotine and alcohol addictive behavior in animal models. His research has been funded by USA National Institute of Health and Food and Drug Administration grants and the State of California Tobacco-Related Disease Research Program grants. He has published 60 research papers, 6 book chapters and more than 80 research abstracts. He has served as a Member of Grant Review Panel for international and national research funding agencies and an Editorial Board Member of more than a dozen reputed journals.

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