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Impact of poor inhibitory control and atomoxetine treatment on brain reward function in response to nicotine and nicotine withdrawal in rats

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Inhibitory control deficit, a form of motor impulsivity, has been implicated in tobacco smoking. Both nicotine dependence and impulsivity have been linked to decreased norepinephrine (NE) neurotransmission. The present work investigated whether trait impulsivity may influence sensitivity to the reward enhancing effects of nicotine and/or affective aspects of nicotine withdrawal. We also investigated whether atomoxetine, a NE reuptake blocker that increases NE transmission and decreases impulsivity, reverses the affective and somatic aspects of nicotine withdrawal in rats with different impulsivity levels. Rats were selected from the top and bottom 25% of the population for high (HI) and low (LI) levels of inhibitory control, as measured by premature responses in the 5-choice serial reaction time task. Brain reward function in HI and LI rats were assessed using the intracranial self-stimulation procedure. Threshold lowering reflects an enhancement in the reward value of the stimulation during nicotine exposure. Threshold elevations, a measure of reward deficits, reflect a decrease in the reward value of the stimulation during nicotine withdrawal. Acute nicotine induced threshold lowering in HI rats to a lesser extent than in LI rats, and decreased responding during timeout period in HI, but not LI rats. The threshold elevations and increased number of somatic signs during nicotine withdrawal were diminished in HI compared to LI rats. Chronic atomoxetine prevented the development of affective and somatic aspects of nicotine withdrawal in HI and LI rats. The results suggest that poor inhibitory control results in diminished sensitivity to nicotine-induced reward enhancement and reward deficits during nicotine withdrawal. Acute nicotine improved inhibitory control in HI rats. Diminished responsiveness to the effects of nicotine and nicotine withdrawal and beneficial effects of nicotine on efficiency of task performance may promote nicotine dependence in smokers with poor inhibitory control. Pharmacological treatments that increase NE transmission may be effective antismoking aids in all smokers independent of impulsivity levels.

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Mice null for the metabotropic glutamate receptor 7 (mGluR7) exhibit attenuated brain reward deficits induced by cocaine and nicotine withdrawal and decreased somatic signs of nicotine withdrawal

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Glutamatergic neurotransmission is critically involved in the reinforcing effects of nicotine and cocaine. However, little is known about the involvement of the metabotropic glutamate receptor 7 (mGluR7) in nicotine and cocaine dependence and withdrawal. mGluR7s negatively modulate glutamate transmission as inhibitory autoreceptors on glutamatergic neuron. The present

study aimed to assess the role of mGluR7 in the anhedonic aspects of the nicotine and cocaine withdrawal syndromes and somatic signs of nicotine withdrawal using mGluR7 knockout (mGluR7^{-/-}) and wildtype (mGluR7^{+/+}) mice. The anhedonic aspects of withdrawal were assessed with brain reward thresholds derived from the intracranial self-stimulation (ICSS) procedure. Brain reward thresholds and somatic signs were assessed after the induction of withdrawal by cessation of administration of 90 mg/kg/day cocaine (salt)/saline administration for 3 days (IP) or 40 mg/kg/day nicotine (base)/saline administration for 39 days (SC) delivered via osmotic minipumps. Cocaine-withdrawing mGluR7^{-/-} mice demonstrated similar threshold elevations as mGluR7^{+/+} mice 3–12 h post-pump removal. At 24 h post-pump removal, thresholds of cocaine-withdrawing mGluR7^{-/-} mice returned to baseline levels, while thresholds of mGluR7^{+/+} mice remained significantly elevated compared to thresholds of saline-treated mGluR7^{+/+} mice until 100 h post-pump removal. A similar pattern of threshold elevations and return to baseline levels was seen during early nicotine withdrawal for the mGluR7^{-/-} and mGluR7^{+/+} mice. Specifically, the magnitude of threshold elevations was similar in nicotine-withdrawing mGluR7^{-/-} and mGluR7^{+/+} mice 3–12 h post-pump removal. At 24 h post-pump removal, thresholds of nicotine-withdrawing mGluR7^{+/+} were still elevated compared to thresholds of saline-treated mGluR7^{+/+} mice, whereas thresholds of mGluR7^{-/-} mice returned to baseline levels. Increases in somatic signs were attenuated at 24 h post-pump removal in nicotine-withdrawing mGluR7^{-/-} compared to mGluR7^{+/+} mice. These results demonstrated that the anhedonic aspects of the cocaine and nicotine withdrawal syndromes, as well as the somatic aspects of nicotine withdrawal, were attenuated in mGluR7^{-/-} mice compared to wildtype mice. This attenuation of withdrawal signs in mGluR7^{-/-} mice may result from the lack of adaptations in mGluR7 function that cocaine/nicotine administration may induce in mGluR7^{+/+} mice. Thus, these data suggest an involvement of mGluR7 in the development of nicotine and cocaine dependence, and the anhedonic and somatic signs of cocaine and nicotine withdrawal.

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Hippocampal Class I Major Histocompatibility Complex genes are differentially expressed in schizophrenic smokersMelissa L. Sinkus^{1,*}, Sharon Mexal², Ralph Berger¹, Sherry Leonard^{1,3}¹ University of Colorado at Denver, Aurora, CO, USA² Ambry Genetics, Aliso Viejo, CA, USA³ Veterans Affairs Medical Research Service, Denver, CO, USA

There is evidence that genes believed to belong to immune function also have other functions specific to the brain. The Class I Major Histocompatibility Complex (MHCI) is necessary for remodeling of dendritic trees during development, and a necessary component for long term potentiation. These processes are aberrant in schizophrenia. In addition, three genome-wide association studies have linked the extended MHC gene region to schizophrenia. The $\alpha 7$ nicotinic acetylcholine receptor ($\alpha 7$ nAChR) is essential for down regulating immune activation and nicotine suppresses the immune response. The expression of this receptor is decreased in schizophrenia, and there is a non-specific over-activation of the immune system in this disorder. The prevalence of smoking is high in schizophrenia. To date, there have been no reports of