2.27

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

Athina Markou, David T. Hubbard, Svetlana Semenova*

Department of Psychiatry, School of Medicine, University of California, San Diego, La Jolla, CA, USA

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.

Acknowledgments: This work was supported by the Tobacco-Related Disease Research Program (TRDRP) from the State of California grant #18KT-0022 to SS.

doi:10.1016/j.bcp.2011.07.058

2.28

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

Astrid K. Stoker*, Athina Markou

Department of Psychiatry, School of Medicine, University of California San Diego, La Jolla, CA, USA

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.

Acknowledgments: This work was supported by NIH grant R01DA023209 to AM.

doi:10.1016/j.bcp.2011.07.059

2.29

Hippocampal Class I Major Histocompatibility Complex genes are differentially expressed in schizophrenic smokers

Melissa L. Sinkus[1,*], Sharon Mexal[2], Ralph Berger[1], Sherry Leonard[1,3]

[1] *University of Colorado at Denver, Aurora, CO, USA*
[2] *Ambry Genetics, Aliso Viejo, CA, USA*
[3] *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 α7 nicotinic acetylcholine receptor (α7 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

how smoking affects immune dysregulation in schizophrenia. We compared immune gene expression in human postmortem hippocampus of schizophrenic and control smokers and non-smokers. QRT-PCR was employed to quantify gene activity. Immune response gene expression was generally decreased in hippocampi of all smokers. Decreases were seen in HLA-G, adrenomedullin, NFκB, lymphocyte antigen 6 complex, nuclear factor of activated T-cells, and integrin β1. A set of immune genes was differentially regulated in schizophrenic smokers. mRNA levels of four transcripts were significantly elevated in schizophrenic nonsmokers compared to all other groups. These included the interleukin-10 receptor, allograft inflammatory factor 1, HLA-A (an MHCI gene), and β2-microglobulin, an MHCI co-subunit. In situ hybridization was used to visualize the expression HLA-A, and immunofluorescent double labeling for cell-type specific markers was used to identify cells that express HLA-A in the hippocampus. Expression of HLA-A was seen in the follicular cells and polymorphic later of the dentate gyrus, and in cells in the stratum pyramidale of the CA1-CA4 regions of the hippocampus. HLA-A mRNA was detected in glutamatergic and GABAergic cells but not in glia. Immune genes tended to be upregulated in the hippocampi of schizophrenic subjects compared to controls and smoking appears to reverse this phenomenon, suggesting that nicotinic receptors modulate their expression in the brain. MHCI may be involved in modulating neuron–neuron connections rather than neuron–glial interactions. Upregulated MHCI and its associated protein, β2-microglobulin may be part of the etiology of decreased LTP and dendritic spine density found in schizophrenia. Further studies are needed to determine whether these effects are specific to the α7nAChR.

doi:10.1016/j.bcp.2011.07.060