Published in final edited form as:
Neuron. 2013 August 7; 79(3): 406–407. doi:10.1016/j.neuron.2013.07.018.

Alcohol and Tobacco: How Smoking May Promote Excessive Drinking

Jonathan P. Britt[1] and **Antonello Bonci**[1,2,*]

[1]National Institute on Drug Abuse, Intramural Research Program, Cellular Neurobiology Research Branch, Baltimore, MD 21224, USA

[2]Solomon H. Snyder Neuroscience Institute, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA

Abstract

Cigarette smokers tend to drink more alcohol than their nonsmoking peers. In this issue of *Neuron*, Doyon et al. (2013) found that nicotine-induced increases in stress hormones can augment ethanol self-administration in rats, suggesting that a drug interaction may contribute to this phenomenon.

Smokers drink twice as much alcohol as nonsmokers, and alcoholism is at least four times more prevalent among those who smoke (Grant et al., 2004; Larsson and Engel, 2004). One potential explanation for these alarming facts is that tobacco and alcohol consumption may both correlate with specific personality traits. A second idea is that drinking alcohol encourages smoking, since people tend to find tobacco more satisfying when they drink (Rose et al., 2004). A third possibility, however, one brought to light through animal research, is that tobacco use promotes excessive alcohol consumption. There have been several studies, in fact, showing that exposure to nicotine can increase subsequent ethanol self-administration (Larsson and Engel, 2004; Smith et al., 1999).

The implications of this kind of drug interaction are significant, potentially impacting tobacco awareness programs as well as the treatment of alcohol abuse disorders. For example, should alcoholics be advised to abstain from tobacco as a means to reduce their drinking? Perhaps a pharmaceutical intervention could discourage excessive drinking among smokers.

In pursuit of these ideas, in this issue of *Neuron*, Doyon et al. (2013) seek to uncover the mechanism by which tobacco use promotes alcohol consumption. They show that a single exposure to nicotine can cause drugnaive rats to self-administer more ethanol over 4 subsequent days than they otherwise would. Doyon et al. (2013) then carefully track down the mechanism underlying this effect and find the culprit to be nicotine-induced increases in stress hormones acting in the ventral tegmental area.

*Correspondence: antonello.bonci@nih.gov.

Dopamine Neuron Reactivity

At the center of this study is the regulation of synaptic inputs to dopamine neurons in the midbrain. First, Doyon et al. (2013) confirmed that nicotine and ethanol are both capable of augmenting dopamine levels in the nucleus accumbens. They also found that when administered together, the drugs produced additive effects on dopamine levels, consistent with their somewhat divergent mechanisms of regulating dopamine neuron activity (Fagen et al., 2003; Söderpalm and Ericson, 2013). When nicotine was administered first, however, 3–40 hr prior, ethanol-induced increases in dopamine levels were significantly attenuated. Importantly, nicotine pretreatment did not alter dopaminergic responses to subsequent nicotine injections, indicating that this dopaminergic circuitry is generally capable of responding to drugs in a consistent manner. The extended time window during which these nicotine-ethanol interactions were observed, when dopaminergic responses to ethanol were blunted, coincided with the period when nicotine-exposed animals increased their ethanol intake.

This connection is somewhat counterintuitive, that ethanol self-administration rates would rise precisely when dopamine neurons exhibit a muted response to ethanol. However, a blunted dopamine system has previously been associated with increased susceptibility to alcohol abuse (Martinez et al., 2005). There is also evidence that animals self-administer drugs of abuse at a frequency necessary to maintain a specific elevated level of dopamine (Ranaldi et al., 1999), suggesting that the nicotine-pretreated rats may have increased their drinking to compensate for the diminished potency of ethanol on dopaminergic signaling.

Ethanol is believed to augment dopamine levels in the nucleus accumbens by increasing the firing rate of ventral tegmental area dopamine neurons. Using brain slice electrophysiology, Doyon et al. (2013) confirmed that bath application of ethanol increases the excitatory drive onto midbrain dopamine neurons, as well as their average firing rate. In nicotine-pretreated animals, however, ethanol caused a marked increase in both inhibitory and excitatory drive onto these neurons. The enhanced inhibitory input seemed to neutralize the excitatory drive, as firing rates of dopamine neurons were largely insensitive to bath-applied ethanol in tissue from nicotine-pretreated rats. Consistent with this observation, $GABA_A$ receptor blockade in brain slices eliminated the differential effect of ethanol on dopamine neuron firing rates between saline- and nicotine-pretreated animals. Together, these data indicate that exposure to nicotine can sensitize GABAergic transmission to the effects of ethanol.

Stress Hormones Intervene

Nicotinic receptors are extremely diverse and widely expressed, so uncovering how they alter GABAergic signaling in response to ethanol is a daunting task. Fortunately, Doyon et al. (2013) focused their attention on neuroendocrine signals, with the rationale that stress-related hormones are known to cause long-term alterations in dopamine and GABA transmission (Joëls and Baram, 2009; Sparta et al., 2013). Furthermore, nicotine can potently activate the hypothalamicpituitary-adrenal axis and increase plasma levels of corticosterone, the principle glucocorticoid in rodents (Caggiula et al., 1998).

To test whether glucocorticoid receptors were involved in the interaction between nicotine and ethanol, Doyon et al. (2013) pretreated animals with the glucocorticoid receptor antagonist RU486 prior to the nicotine exposure. This pretreatment completely blocked the interaction between nicotine and ethanol on both dopamine neuron physiology and ethanol self-administration. When RU486 was on board during the nicotine pretreatment, GABAergic transmission onto dopamine neurons was not sensitized to the effects of ethanol. Furthermore, ethanol-induced increases in dopamine levels in these animals were just as robust as they were in naive animals, not blunted as was observed in animals pretreated with nicotine alone. Remarkably, this restoration of dopamine neuron reactivity correlated with a moderation of ethanol self-administration, restoring it to the levels typical of saline-pretreated animals.

How Generalizable Are These Effects?

In human users, the interactions between tobacco and alcohol are bound to be complex and multifaceted. The present study cleverly took advantage of naive animals and controlled environments to provide insight into the cellular mechanisms by which these drugs interact. In doing so, it has provided an intriguing potential explanation for why smokers drink more alcohol than their peers. It also offers potential targets for pharmaceutical interventions designed to attenuate heavy drinking in people codependent on alcoholic and tobacco. Key questions regarding the interaction between nicotine and ethanol remain to be answered, however. For example, how would more naturalistic exposure to nicotine alter drinking behavior? Doyon et al. (2013) administered nicotine via both intraperitoneal and intravenous methods, but it is not clear how well that relates to the intermittent smoking and drinking patterns observed in people. How does repeated, fluctuating use of tobacco and alcohol interact with dopamine signaling and affect future drug consumption?

An intriguing part of these data is that nicotine-induced glucocorticoid receptor signaling altered the sensitivity of GABAergic transmission to ethanol. It will be important to determine whether glucocorticoid receptor signaling is sufficient for these effects or whether the nicotine trigger is essential. It will also be necessary to determine how specific this phenomenon is to ethanol, a drug that has numerous and complex interactions with several neurotransmitter systems (Söderpalm and Ericson, 2013). Doyon et al. (2013) began to pursue this line of investigation by asking whether $GABA_A$ receptors had a central role, since they are one of the primary targets of ethanol. To test this, Doyon et al. (2013) replaced ethanol with Diazepam, a benzodiazepine that positively modulates $GABA_A$ receptors. As was observed with ethanol in brain slices, this compound became markedly more potent in augmenting GABAergic transmission when animals were pretreated with nicotine. This suggests that nicotine-induced glucocorticoid receptor signaling selectively primes $GABA_A$ receptors, but what specifically is altered in these receptors or in GABAergic transmission in general is not clear from this study. This will be an important area of future research, as the interaction between nicotine and benzodiazepines may be highly significant in terms of clinical and societal impact.

Another intriguing question that arises from this data is whether the sensitivity of GABAergic inputs to nicotine-ethanol interactions depends on where the fibers originate

from or where they project to (Britt and Bonci, 2013). Doyon et al. (2013) only focused on the specific population of GABAergic fibers that synapse onto midbrain dopamine neurons. In follow-up studies, it will be important to determine whether GABA or glutamate transmission elsewhere in the brain is similarly affected by nicotine-induced glucocorticoid signaling.

Uncovering the full extent of the interactions between alcohol and tobacco, two of the top causes of preventable death in the United States, could have immense benefit to society. A basic question raised by this research is whether alcoholics seeking treatment should prioritize smoking cessation on their road to recovery. Similarly, does abstaining from tobacco significantly reduce an individual's risk of becoming an alcoholic? A warning that smoking increases one's risk of developing alcoholism may resonate particularly well with children that have an alcoholic parent. Further research in this area is essential to ultimately uncover the links between nicotine, alcohol, and glucocorticoid receptor signaling that may be targeted to help treat alcohol abuse disorders.

Acknowledgments

This work was supported by the Intramural Research Program of the National Institute of Health, National Institute on Drug Abuse.

References

Britt, JP.; Bonci, A. Curr Opin Neurobiol. 2013. Published online January 30, 2013. http://dx.doi.org/10.1016/j.conb.2013.01.010

Caggiula AR, Donny EC, Epstein LH, Sved AF, Knopf S, Rose C, McAllister CG, Antelman SM, Perkins KA. Psychoneuroendocrinology. 1998; 23:143–159. [PubMed: 9621395]

Doyon WM, Dong Y, Ostroumov A, Thomas AM, Zhang TA, Dani JA. Neuron. 2013; 79(this issue): 530–540. [PubMed: 23871233]

Fagen ZM, Mansvelder HD, Keath JR, McGehee DS. Ann N Y Acad Sci. 2003; 1003:185–195. [PubMed: 14684446]

Grant BF, Hasin DS, Chou SP, Stinson FS, Dawson DA. Arch Gen Psychiatry. 2004; 61:1107–1115. [PubMed: 15520358]

Joëls M, Baram TZ. Nat Rev Neurosci. 2009; 10:459–466. [PubMed: 19339973]

Larsson A, Engel JA. Neurosci Biobehav Rev. 2004; 27:713–720. [PubMed: 15019421]

Martinez D, Gil R, Slifstein M, Hwang DR, Huang Y, Perez A, Kegeles L, Talbot P, Evans S, Krystal J, et al. Biol Psychiatry. 2005; 58:779–786. [PubMed: 16018986]

Ranaldi R, Pocock D, Zereik R, Wise RA. J Neurosci. 1999; 19:4102–4109. [PubMed: 10234038]

Rose JE, Brauer LH, Behm FM, Cramblett M, Calkins K, Lawhon D. Nicotine Tob Res. 2004; 6:133–144. [PubMed: 14982697]

Smith BR, Horan JT, Gaskin S, Amit Z. Psychopharmacology (Berl). 1999; 142:408–412. [PubMed: 10229066]

Söderpalm B, Ericson M. Curr Top Behav Neurosci. 2013; 13:127–161. [PubMed: 22094880]

Sparta, DR.; Hopf, FW.; Gibb, SL.; Cho, SL.; Stuber, GD.; Messing, RO.; Ron, D.; Bonci, A. Alcohol Clin Exp Res. 2013. Published online June 13, 2013. http://dx.doi.org/10.1111/acer.12153