Nicotine Decreases Ethanol-induced Dopamine Signaling and Increases Self-administration via Steroid Hormones

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Most Costly to Society and Humanity

**Tobacco** kills nearly 6 million people worldwide each year. One billion smokers, and up to half of its users will die from tobacco-associated disease.

**Tobacco** caused 100 million deaths in the 20th century. If current trends continue, it may cause one billion deaths in the 21st century.

**Alcohol** is the most commonly used and widely abused psychoactive drug in the world.

**Alcohol** is a causal factor in more than 200 disease and injury conditions. Worldwide, over 3 million people die every year due to harmful use of alcohol, and this represents 5.9 % of all deaths.
People dependent on alcohol are 3X more likely to smoke, and people dependent on tobacco are 4X more likely to be dependent on alcohol.

Alcohol and tobacco use may lead to major health risks when used alone and especially when used together. When combined, alcohol and tobacco dramatically increase the risk of certain cancers.

The link between alcohol and tobacco so significant that statistics indicate more alcoholics die of tobacco-related illness than die of alcohol-related problems.
Microdialysis for Dopamine in NAc

Microdialysis/HPLC Measures DA
Microdialysis
Ethanol and Nicotine

% of Basal [DA]

Time (min)

Nic+Ethanol
Nicotine
Ethanol

Area-Under-Curve

Ethanol
Nicotine
Nic+Ethanol
Nicotine Pretreatment Attenuates Ethanol-induced DA Release

Saline or Nicotine

3 hours

[DA] assay every 5 min

Nic or Sal 3 hrs Prior

% of Basal [DA]

0 20 40 60

Time (min)
Nicotine Pretreatment Attenuates Ethanol-induced DA Release

Saline or Nicotine

EtOH

15 hours

[DA] assay every 5 min

Nic or Sal 3 hrs Prior

Nic or Sal 15 hrs Prior

% of Basal [DA]

Time (min)

Nic 3hr

Sal 3hr

Nic 15hr

Sal 15hr

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Nicotine Pretreatment Attenuates Ethanol-induced DA Release

Saline or Nicotine assay every 5 min

40 hours [DA] assay every 5 min

Nicotine Pretreatment Attenuates Ethanol-induced DA Release

Nic or Sal 3 hrs Prior

Nic or Sal 15 hrs Prior

Nic or Sal 40 hrs Prior

% of Basal [DA]

Time (min)

Ethanol

Sal 3hr

Nic 3hr *

Sal 15hr

Nic 15hr **

Ethanol

Sal 40hr

Nic 40hr # #
Acute Nicotine Pretreatment Increases Ethanol Self-administration

Operant Training

3 hours

Saline or Nicotine

Operant EtOH Self-administration

Day 1

Day 2

......

Day 7

Ethanol Intake Per Session (g/kg)

Sal 3hr

Nic 3hr

Control

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[Graph showing increased ethanol intake after nicotine pretreatment]
Chronic Nicotine Pretreatment Decreases Ethanol-induced DA Release
Chronic Nicotine Pretreatment Increases Ethanol Self-administration
Nicotinic Receptors Mediate EtOH-induced Effect

- Nic 15hr + DHβE 5.0 mg/kg
- Nic 15hr
- Sal 15hr / DHβE Control

β2 nAChRs

- Nic 15hr + MLA 5.0 mg/kg
- Sal 15hr

α7 nAChRs
Does Nicotine Pretreatment alter DA Release for all Addictive Drugs?
Ethanol induces DA Signal by Increasing DA Neuron Firing

Neurobiotin TH
Lateral VTA

Sal 15hr (Control)
Basal Ethanol

10 mV
0.5 s

VTA In Vitro Slice
Ethanol induces DA Signal by Increasing DA Neuron Firing

VTA In Vitro Slice

Effect of EtOH

DA

GABA (-)

Glutamate (+)

NAc
Ethanol Increases EPSCs to Increase DA Neuron Firing
Ethanol Increases EPSCs to Increase DA Neuron Firing

Nicotine Pretreatment does Not change EPSCs onto DA Neurons
After Nicotine Pretreatment, Ethanol Does Not Increase DA Neuron Firing
Does Nicotine Pretreatment alter DA Release for all Addictive Drugs?
Ethanol induces Slight Increase in GABAergic IPSCs
After Nicotine Pretreatment, Ethanol Induces Greater Increase in GABAergic IPSCs
After Nicotine Pretreatment, Ethanol Induces Greater Increase in GABAergic IPSCs
After Nicotine Pretreatment, GABAergic Paired-pulse Ratio Decreases

Suggests Higher Probability of GABA Release in response to EtOH after Nicotine Pretreatment

Normalized Paired-pulse Evoked IPSCs After Ethanol Application

Control  Nic -15hr

![Graph showing paired-pulse ratio for saline and nicotine pretreatment after ethanol application.](image-url)
Nicotine Pretreatment Effect Mediated by GABAergic Activity

The overall results indicate that nicotine pretreatment alters ethanol’s action via GABAergic signaling.
Stress Hormones Influence DA Transmission and Alcohol Use

Stress hormones, such as glucocorticoids, have a profound influence on neural function and modulate DA transmission. Long-term alterations in glucocorticoid systems are linked to alcohol use disorders. Given that nicotine activates the HPA axis, it follows that the stress hormone signals mediated by nicotine could alter subsequent alcohol consumption.

(Adinoff et al., 2003; Barrot et al., 2000; Butts et al., 2011; Joels and Baram, 2009; Jose et al., 2000; Koob and Volkow, 2010; Kulka, 1990; Prager and Johnson, 2009; Sinha et al., 2011; Vendruscolo et al., 2012)
Systemic Inhibition of Glucocorticoids Prevents Nicotine Pretreatment Effect over EtOH-induced DA Release

**Systemic Injection**

![Graph showing percentage of basal DA over time with different treatment conditions.](image1)

![Graph showing corticosterone levels over time with nicotine treatment.](image2)
Local VTA Microinfusion of Glucocorticoid Inhibitor, RU486
Local VTA Inhibition of Glucocorticoids Prevents Nicotine Pretreatment Effect over EtOH-induced DA Release
Inhibition of Glucocorticoids also Prevents Nicotine Pretreatment’s Enhancement of EtOH Self-administration
Inhibition of Glucocorticoids also Prevents Nicotine Pretreatment’s Influence of GABAergic Activity
Inhibition of Glucocorticoids also Prevents Nicotine Pretreatment’s Influence of GABAergic Activity
Nicotine Decreases Ethanol-induced Dopamine Signaling
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A simplified schematic of the major dopaminergic, glutamatergic and GABAergic connections to and from the ventral tegmental area (VTA) and nucleus accumbens (NAc) in the rodent brain.