Drugs are bad...for pathogens

Testing an alternative to the reward model of recreational drug use and its implications for smoking cessation.

Edward H. Hagen¹, Casey Roulette¹, Mark Remiker¹, Jennifer Wilcox¹, Roger J. Sullivan², Didier Monchy³

¹Washington State University, Vancouver
²California State University, Sacramento
³Institut Pasteur de Bangui, CAR
Most recreational drugs are plant neurotoxins

<table>
<thead>
<tr>
<th>Drug</th>
<th>Plant</th>
<th>Toxin</th>
<th>Neurotransmitter</th>
<th>Receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco, Pituri</td>
<td><em>Nicotiana, Duboisia</em></td>
<td>Nicotine(^a)</td>
<td>Acetylcholine</td>
<td>Nicotinic receptor</td>
</tr>
<tr>
<td>Betel nut</td>
<td><em>Areca catechu</em></td>
<td>Arecoline(^a)</td>
<td>Acetylcholine</td>
<td>Muscarinic receptor</td>
</tr>
<tr>
<td>Coca</td>
<td><em>Erythroxyllum</em></td>
<td>Cocaine(^c)</td>
<td>Norepinephrine, epinephrine</td>
<td>Adrenergic receptors</td>
</tr>
<tr>
<td>Khat</td>
<td><em>Catha edulis</em></td>
<td>Ephedrine(^{e, c}),</td>
<td>Norepinephrine, epinephrine</td>
<td>Adrenergic receptors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cathinone(^{a, c})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cactus</td>
<td><em>Lophophora</em></td>
<td>Mescaline</td>
<td>Serotonin</td>
<td>Serotonin receptor</td>
</tr>
<tr>
<td>Coca</td>
<td><em>Erythroxyllum</em></td>
<td>Cocaine(^c)</td>
<td>Dopamine</td>
<td>Dopamine receptor</td>
</tr>
<tr>
<td>Khat</td>
<td><em>Catha edulis</em></td>
<td>Cathinone(^{a, c})</td>
<td>Dopamine</td>
<td>Dopamine receptor</td>
</tr>
<tr>
<td>Coffee, Cola nut</td>
<td><em>Coffeea, Cola nitida</em></td>
<td>Caffeine(^b)</td>
<td>Adenosine</td>
<td>Adenosine receptor</td>
</tr>
<tr>
<td>Tea</td>
<td><em>Camellia sinensis</em></td>
<td>Caffeine(^b),</td>
<td>Adenosine</td>
<td>Adenosine receptor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>theophylline(^b),</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>theobromine(^b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chocolate</td>
<td><em>Theobromine cacao</em></td>
<td>Theobromine(^b)</td>
<td>Adenosine</td>
<td>Adenosine receptor</td>
</tr>
<tr>
<td>Opium</td>
<td><em>Papaver somniferum</em></td>
<td>Codeine(^a),</td>
<td>Endorphins</td>
<td>Opioid receptor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>morphine(^a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cannabis</td>
<td><em>Cannabis sativa</em></td>
<td>Δ9-THC(^a)</td>
<td>Anandamide</td>
<td>Cannabinoid receptor</td>
</tr>
</tbody>
</table>

\(^a\)receptor agonist, \(^b\)receptor antagonist, \(^c\)reuptake inhibitor
The reward model

Drugs of abuse stimulate reward circuitry in the brain.
The paradox of drug reward

Nicotine, caffeine, and other drugs only exist because they deterred herbivores, not rewarded them.

Herbivores, in turn, have evolved to avoid, expel, and neutralize toxins – reactions to toxins should generally be aversive, not be rewarding.

Hagen et al. 2009 Neuroscience.
Nicotine is extremely toxic to humans

<table>
<thead>
<tr>
<th>Toxin</th>
<th>Recreational dose</th>
<th>Lethal dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrogen cyanide</td>
<td>50 mg</td>
<td></td>
</tr>
<tr>
<td>Nicotine</td>
<td>1-4 mg</td>
<td>30-60 mg</td>
</tr>
</tbody>
</table>

But, this acute toxicity plays almost no role in mainstream drug use theory

(Nicotine is not a carcinogen)
Why no nicotine overdoses?

~ 1 billion tobacco users
~15 billion cigarettes smoked every day

Acute mortality from recreational tobacco use is essentially non-existent

Why?
Nicotine activates many toxin defense mechanisms

• Bitter taste receptors
• Gastrointestinal “taste” receptors
• Xenobiotic-sensing nuclear receptors
• Xenobiotic metabolizing enzymes
• Aversion circuitry in the CNS
Is the brain regulating exposure to plant neurotoxins?
The pharmacophagy model

Psychoactivity is a reliably cue of neurotoxicity, and although neurotoxins are bad for us they might be worse for pathogens with nervous systems.

The brain is regulating exposure to psychoactive substances as a form of:

- Chemoprophylaxis: recreational drug use deters infection by pathogens with nervous systems
- Chemotherapy: recreational drug use treats infection by pathogens with nervous systems

Psychoactive drugs
Hypothesis

Recreational tobacco use is an (unconscious) form of self-medication against helminths.
Efficacy of nicotine against helminths

- Many commercial anthelmintics (e.g., levamisole, pyrantel) attack same neuroreceptor system as nicotine (nAChRs).
- Nicotine sulfate was widely used to de-worm livestock.
- Aqueous tobacco extracts still used in developing world to de-worm livestock.
- Tobacco widely reported as an anthelmintic in the ethnomedical literature.
Testing the chemotherapy hypothesis with a randomized control trial
Predictions

Infection with helminths should increase smoking

Elimination of helminths should decrease smoking
Study population: Aka foragers of the Central African Republic

Aka camp

Study site rationale

• High levels of intestinal parasites
• Heavy tobacco use
• Almost no access to commercial anthelmintics.
Study population

- Three neighboring populations of Aka
- 191 males (most Aka women do not smoke)
Worm burden

Measure **worm burden**

- Appreciable levels of 3 (4) species
  - **Hookworm** Ancylostoma duodenale, Necator americanus (99%)
  - **Ascaris lumbricoides** (57%)
  - **Whipworm** Trichuris trichiura (56%)

- Semi-quantified **total egg count** of all species

![Stool collection kit](Formalin/PVA)
Randomize into treatment and placebo control groups (double-blind)

400 mg albendazole

Placebo
Outcome variable

Measure salivary cotinine

- Nicotine metabolite
- Half life ~ 18 hrs (nicotine half life ~ 2 hrs)
- Indexes intensity of recent nicotine exposure
Randomized control trial

Administer 400 mg albendazole or placebo (double-blind)
Prediction

Albendazole treatment group will have reduced salivary cotinine relative to placebo control group
Manipulation check

Worm burden

\[ t = 7.0537, \text{ df } = 86.781, \text{ p-value } = 2.001 \times 10^{-10} \]

95 percent confidence interval:

7.78 \quad \text{Inf}

sample estimates:

mean in group control mean in group treatment

13.66 \quad 3.47
Distribution of $\Delta$cotinine/cotinine in treatment vs control groups

$\Delta$cotinine = post-treatment cotinine conc. - pretreatment cotinine conc.
Means not significantly different

\[ \Delta \text{cotinine/cotinine} \]

- Mean in group control: 0.16
- Mean in group treatment: 0.04

p-value = 0.17
Distributions are significantly different

Two-sample Kolmogorov-Smirnov test

\[ D^- = 0.32, \ p\text{-value} = 0.019 \]

Treatment group is significantly more

- Positively skewed (1.2 vs. 0.24)
- Leptokurtotic (1.8 vs. -1.0)
Self-reported *cannabis* use

<table>
<thead>
<tr>
<th></th>
<th>Chisq</th>
<th>Df</th>
<th>RobustF</th>
<th>Pr(F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>region</td>
<td>5.96</td>
<td>2</td>
<td>0.013 *</td>
<td></td>
</tr>
<tr>
<td>albendazole</td>
<td>0.50</td>
<td>1</td>
<td>0.472</td>
<td></td>
</tr>
<tr>
<td>cannabis</td>
<td>2.14</td>
<td>1</td>
<td>0.136</td>
<td></td>
</tr>
<tr>
<td>albendazole:cannabis</td>
<td>4.17</td>
<td>1</td>
<td>0.038 *</td>
<td></td>
</tr>
</tbody>
</table>
Adding age to the model

<table>
<thead>
<tr>
<th></th>
<th>Chisq</th>
<th>Df</th>
<th>RobustF</th>
<th>Pr(F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>region</td>
<td>2</td>
<td>5.34</td>
<td>0.019</td>
<td>*</td>
</tr>
<tr>
<td>albendazole</td>
<td>1</td>
<td>0.59</td>
<td>0.43</td>
<td></td>
</tr>
<tr>
<td>cannabis</td>
<td>1</td>
<td>9.50</td>
<td>0.002</td>
<td>**</td>
</tr>
<tr>
<td>age</td>
<td>1</td>
<td>0.07</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>albendazole:age</td>
<td>1</td>
<td>4.85</td>
<td>0.025</td>
<td>*</td>
</tr>
</tbody>
</table>
Limitations: Altered behavior or altered metabolism?

- Cotinine biomarker conflates smoking behavior and nicotine metabolism
- Drugs, including albendazole, induce & inhibit metabolic enzymes
  - Nicotine largely metabolized by CYP2A6
  - No evidence that albendazole induces or inhibits CYP2A6 (?)
  - Post-treatment saliva collected ~ 2 weeks after treatment
- Infections & inflammation alter xenobiotic metabolism (usually down-regulate)
Conclusions

• Hypothesis
  – Humans might have an evolved (but unconscious) propensity to consume plant neurotoxins to kill pathogens: plant neurotoxins are bad for us but worse for our pathogens.
  – If so, treating helminths might decrease smoking behavior

• In support, we found
  – Albendazole treatment skewed Δcotinine to lower values relative to placebo.
  – Significant mean effect of treatment depended on self-reported cannabis use and/or age

• Limitation
  – Study design cannot disentangle behavioral changes from metabolic changes
Acknowledgements

Thanks to the WSU Alcohol and Drug Abuse Research Program for funding, and to our research assistants: Nicaise, and Mesmin.