Drug use as potential protection against pathogens:

Tobacco consumption vs. helminth load in Aka foragers

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Major risk factors for disease
Developed countries top 10
Two scientific paradigms for investigating the effects of recreational plant drugs are in conflict.

Evolutionary biology (Ultimate level)

Neurobiology (Proximate level)
The *reward* model of drug use
(proximate level)
The mesolimbic dopamine system

Reward! This explains initial seeking and use (not addiction).
The punishment model of drug origins
(ultimate level)
Plants produce sugar for their own growth and development
Heterotrophs (herbivores) have a negative impact on autotrophs (plants)
In defense, plants produce numerous toxins, many that severely disrupt neuronal signaling.
Nicotine

Lots of research on this commercially important, socially burdensome cholinergic neurotoxin
Defensive action of nicotine

Acetylcholine (neurotransmitter)

Nicotine (plant neurotoxin that mimics acetylcholine)

Wild tobacco (*Nicotiana attenuata*)

Acetylcholine receptors at neuromuscular junction
Most 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>Nicotiana, Duboisia</td>
<td>Nicotine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Acetylcholine</td>
<td>Nicotinic receptor</td>
</tr>
<tr>
<td>Betel nut</td>
<td>Areca catechu</td>
<td>Arecoline&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Acetylcholine</td>
<td>Muscarinic receptor</td>
</tr>
<tr>
<td>Coca</td>
<td>Erythroxylum</td>
<td>Cocaine&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Norepinephrine, epinephrine</td>
<td>Adrenergic receptors</td>
</tr>
<tr>
<td>Khat</td>
<td>Catha edulis</td>
<td>Ephedrine&lt;sup&gt;e&lt;/sup&gt;, cathinone&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>Norepinephrine, epinephrine</td>
<td>Adrenergic receptors</td>
</tr>
<tr>
<td>Cactus</td>
<td>Lophophora</td>
<td>Mescaline</td>
<td>Serotonin</td>
<td>Serotonin receptor</td>
</tr>
<tr>
<td>Coca</td>
<td>Erythroxylum</td>
<td>Cocaine&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Dopamine</td>
<td>Dopamine receptor</td>
</tr>
<tr>
<td>Khat</td>
<td>Catha edulis</td>
<td>Cathinone&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>Dopamine</td>
<td>Dopamine receptor</td>
</tr>
<tr>
<td>Coffee, Cola nut</td>
<td>Coffea, Cola nitida</td>
<td>Caffeine&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Adenosine</td>
<td>Adenosine receptor</td>
</tr>
<tr>
<td>Tea</td>
<td>Camellia sinensis</td>
<td>Caffeine&lt;sup&gt;b&lt;/sup&gt;, theophylline&lt;sup&gt;b&lt;/sup&gt;, theobromine&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Adenosine</td>
<td>Adenosine receptor</td>
</tr>
<tr>
<td>Chocolate</td>
<td>Theobromine cacao</td>
<td>Theobromine&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Adenosine</td>
<td>Adenosine receptor</td>
</tr>
<tr>
<td>Opium</td>
<td>Papaver somniferum</td>
<td>Codeine&lt;sup&gt;a&lt;/sup&gt;, morphine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Endorphins</td>
<td>Opioid receptor</td>
</tr>
<tr>
<td>Cannabis</td>
<td>Cannabis sativa</td>
<td>Δ9-THC&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Anandamide</td>
<td>Cannabinoid receptor</td>
</tr>
</tbody>
</table>

<sup>a</sup>receptor agonist, <sup>b</sup>receptor antagonist, <sup>c</sup>reuptake inhibitor
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.*
Deepening the paradox
Nicotine is extremely toxic to humans

1. Smokers absorb relatively large doses of a potent neurotoxin.

2. There must be robust mechanisms preventing overdoses: despite ~1 billion users worldwide smoking 15 billion cigarettes daily, mortality from acute nicotine poisoning is very low (mostly from nicotine-based insecticides).
Aversion circuits deeply involved in neurobiology of nicotine

Laviolette and van der Kooy 2004
The paradox in neurobiological terms

Why don’t aversion and aversive learning prevent repeated consumption of the plant neurotoxins used as drugs?
One potential resolution of the paradox:

Humans have an evolved propensity to use neurotoxins for the purposes for which they were designed…
Animal & plant pathogens are basically the same

- Viruses
- Bacteria
- Nematodes
- Arthropods

Did animals evolve to take advantage of 400+ million years of pharmacological ‘R&D’ by plants?
Hypothesis

• Psychoactive compounds are attractive because they manifestly interfere with neural signaling in the herbivore, and hence might harm those herbivore pathogens with nervous systems.

• Tobacco use reduces helminth load.
Helminths

• Est. 2 billion people infected with soil-transmitted helminths and schistosomes.

• Health consequences
  – Malnutrition
  – Impaired growth and development
  – Iron deficiency anemia
  – Decreased physical fitness and work capacity
  – Impaired cognitive function

• Global burden of disease = 43.5 million life years lost
  – Tuberculosis = 46.5 million
  – Malaria = 34.5 million

C. G. Nicholas Mascie-Taylor and Enamul Karim 2003
Efficacy of nicotine against helminths

- Many commercial anthelmintics (e.g., levamisole, pyrantel) attack same neuroreceptor system as nicotine.
- 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.
Study population: Aka foragers of the Central African Republic

Aka camp

Study site rationale: The Aka have high levels of intestinal parasites, smoke a lot, and have almost no access to commercial anthelmintics.
Study population: Aka foragers of the Central African Republic

N=39

20 females
19 males

Ages are rough estimates

Sample age distribution (N=34)
Predictor variables

• Smoker status (self report)
  – Indexes chronic nicotine exposure

• Salivary cotinine
  – Nicotine metabolite with half life ~18 hrs (nicotine half life ~ 2 hrs)
  – Indexes intensity of recent nicotine exposure

Barry Hewlett and Casey Roulette interviewing Aka about tobacco use

Saliva collection tube
Outcome variable

Helminth load

- Appreciable levels of three species
  - Hookworm *Ancylostoma duodenale*, *Necator americanus*
  - Ascaris *lumbricoides*
  - Whipworm *Trichuris trichiura*
- 0-3 point scale for egg counts of each species (none, low, moderate, high)
- Total score: 0-9
Predictions

1. Self-reported smokers have lower helminth load

2. Salivary cotinine (an index of the intensity of recent nicotine exposure) is inversely correlated with helminth load
Summary stats: Self-reported smoker

<table>
<thead>
<tr>
<th></th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-reported smoker</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>5</td>
<td>18</td>
</tr>
</tbody>
</table>
Summary stats: Cotinine

<table>
<thead>
<tr>
<th>Self-reported smoker</th>
<th>Cotinine &lt; 15 ng/ml</th>
<th>Cotinine &gt; 80 ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Yes</td>
<td>5</td>
<td>16</td>
</tr>
</tbody>
</table>

4 of 5 female smokers had not recently smoked, whereas only 1 of 18 male smokers had not recently smoked.
Summary stats (outcome)

Only one participant had no evidence of intestinal parasites

Ascaris: 38%
Whipworm: 47%
Hookworm: 94%
Testing predictions

1. Self-reported smokers have lower helminth load

2. Salivary cotinine is inversely correlated with helminth load
Challenge

• Essentially no variation in male self-reported smoker status (only 1 male non-smoker).
• Hence, can only test prediction #1 in women.
Result

- Smoker mean helminth load = 2.2
- Non-smoker mean helminth load = 3.5
- \( t = 1.8, \; d = 0.72, \; p = 0.04 \)

- Women only
Testing predictions

1. [Female] smokers have lower helminth load (d = 0.72, p = 0.04)

2. Salivary cotinine (an index of the intensity of recent nicotine exposure) is inversely correlated with helminth load.
Challenge

• Recent smoking status is confounded with sex, self-reported smoker status

• Strategy: restrict analysis to recent smokers group
Result

Recent smokers only

$r = -0.50, p = 0.035$

$r_s = -0.51, p = 0.031$

Males only:

$r = -0.48, p = 0.047$
Testing predictions

1. [Female] self-reported smokers have lower helminth load ($d = 0.72, p = 0.04$)

2. [Male recent smoker] salivary cotinine is inversely correlated with helminth load ($r = -0.48, p = 0.047$).
Limitations

• Correlation ≠ causation
  – Maybe healthier people smoke more

• Some variable might confound smoking and helminth load
  – Maybe richer Aka are healthier and also buy more cigarettes
  – Maybe smoking decreases helminth egg expulsion independent of infection levels.

• Small sample size
  – Could only test self-reported smoker vs. helminths in women
  – Could only test salivary cotinine vs. helminths in male recent smokers
Conclusions

- There is an incompatibility between the evolutionary biological account of drug origins, which views drugs as neurotoxic plant defenses, and the neurobiological account of drug seeking and use, which emphasizes the rewarding properties of drugs (the paradox).

- Animals, including humans, might have evolved to counter-exploit plant toxins to kill pathogens: plant neurotoxins are bad for us but worse for our pathogens.

- In support, we found self-reported smokers have significantly lower helminth load than non-smokers (women only).

- We also found cotinine levels (an index of recent nicotine exposure) are negatively correlated with helminth load (male recent smokers only).