Drug use as potential protection against pathogens:

Tobacco consumption vs. helminth load in Aka foragers

Edward H. Hagen[1], Casey Roulette[1], Barry S. Hewlett[1], Roger J. Sullivan[2], Rémi Laganier[3]

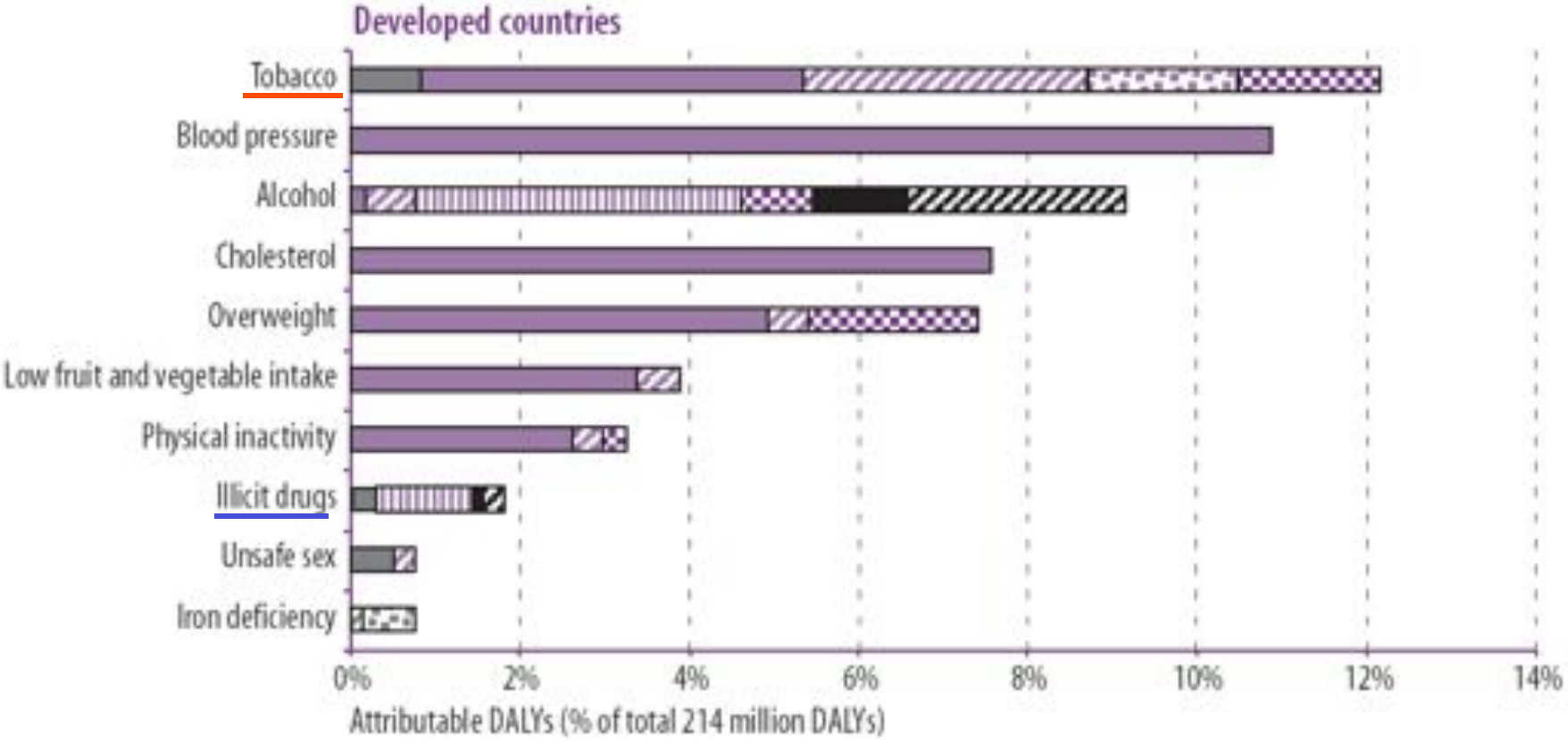
[1]Washington State University, Vancouver

[2]California State University, Sacramento

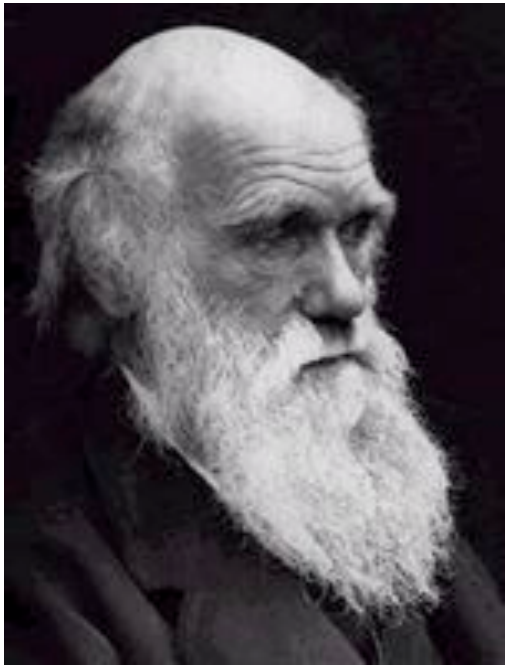
[3]Institut Pasteur de Bangui, CAR

WASHINGTON STATE UNIVERSITY VANCOUVER

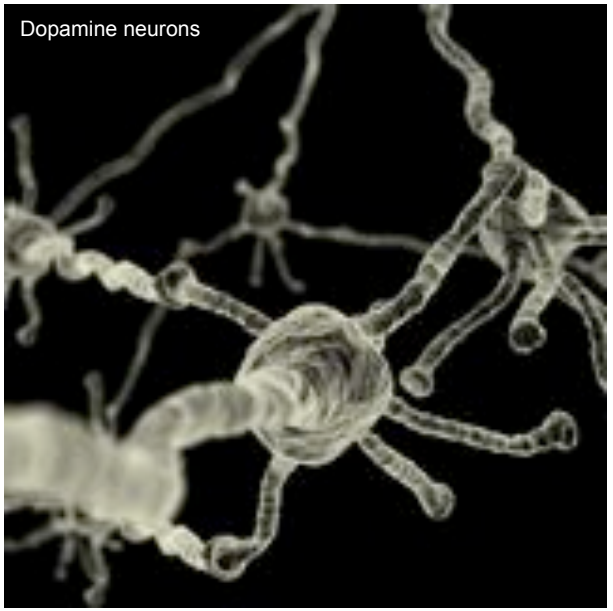
Major risk factors for disease
Developed countries top 10



Two scientific paradigms for investigating the effects of recreational plant drugs are in conflict



Evolutionary biology
(Ultimate level)

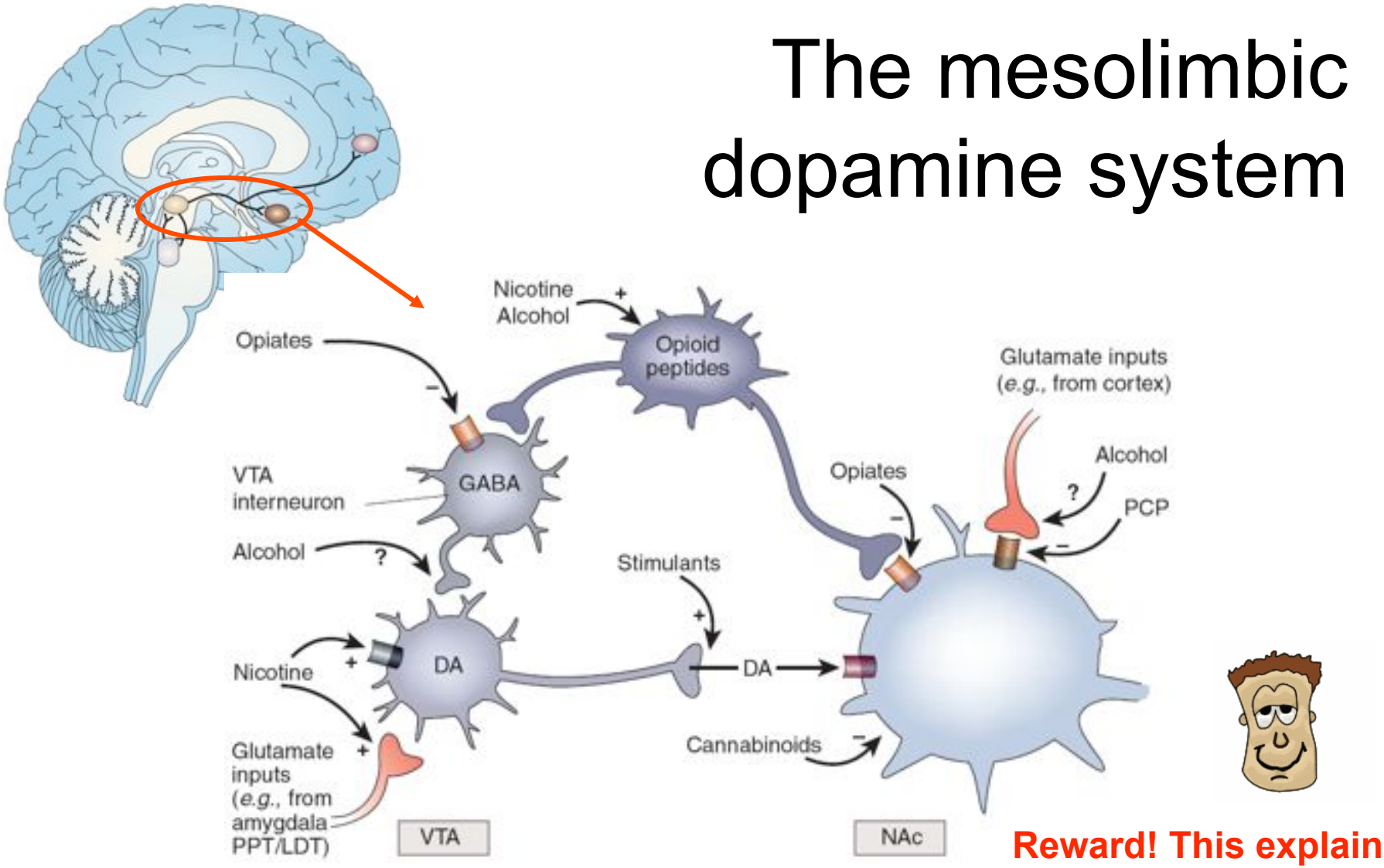


Neurobiology
(Proximate level)

The reward model of drug use

(proximate level)

The mesolimbic dopamine system



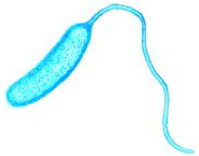
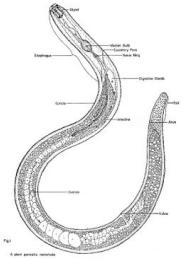
Reward! This explains initial seeking and use (not addiction).

The punishment model of drug origins

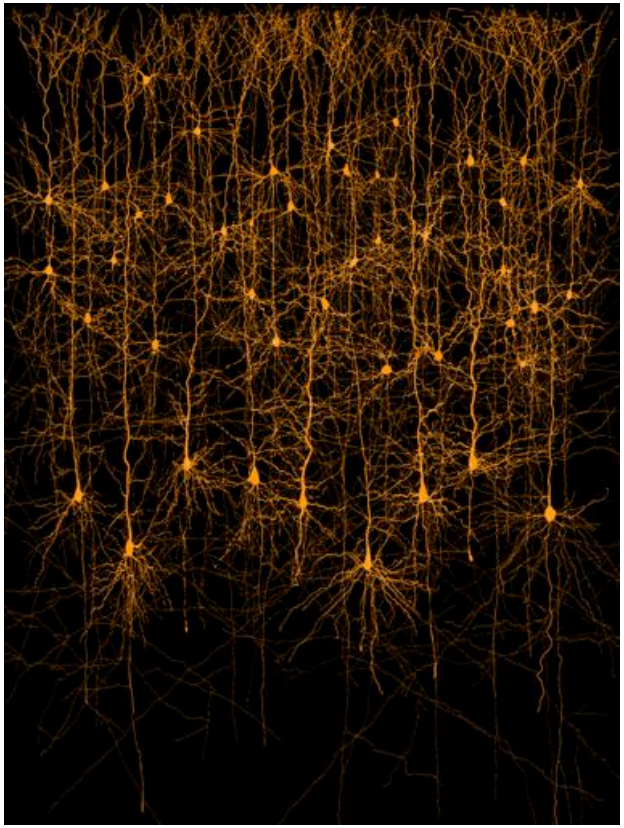
(ultimate level)

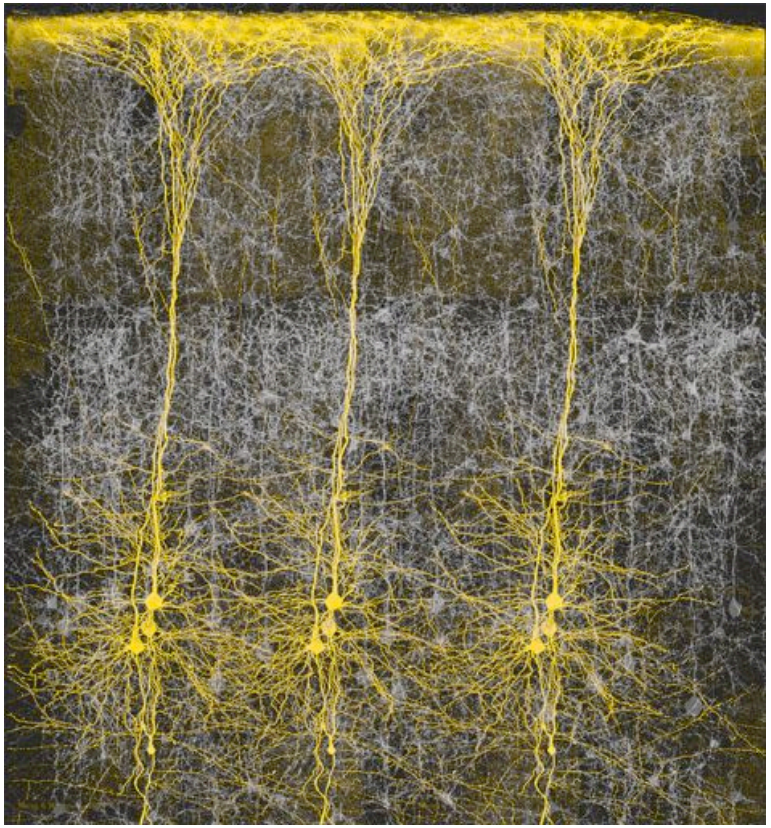
Plants produce sugar for their *own* growth and development

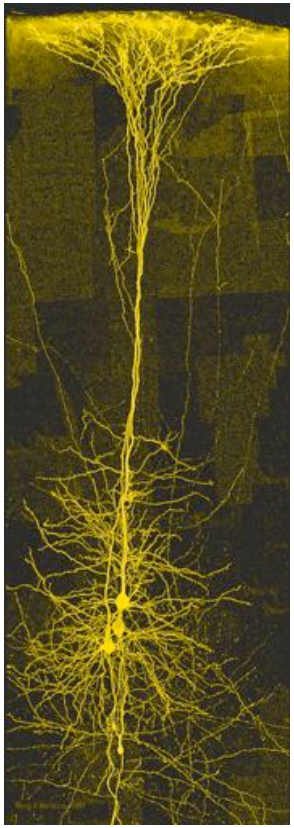
Heterotrophs (herbivores) have a negative impact on autotrophs (plants)

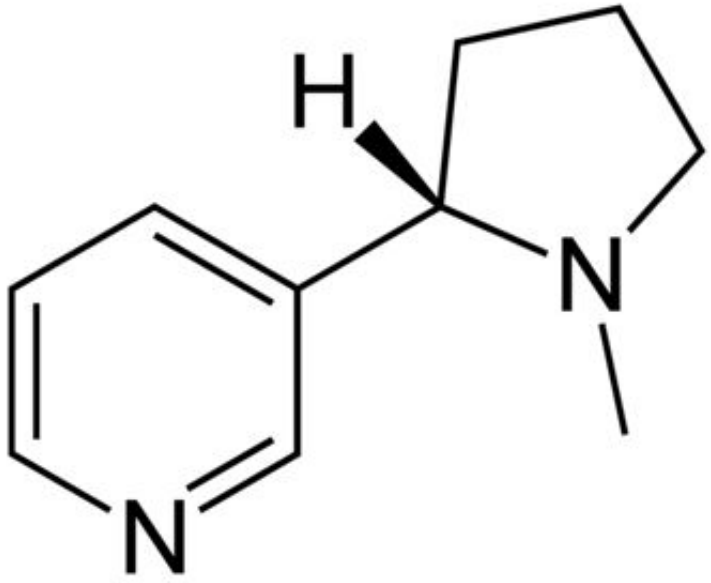




In defense, plants produce numerous toxins, many that severely disrupt neuronal signaling









Nicotine

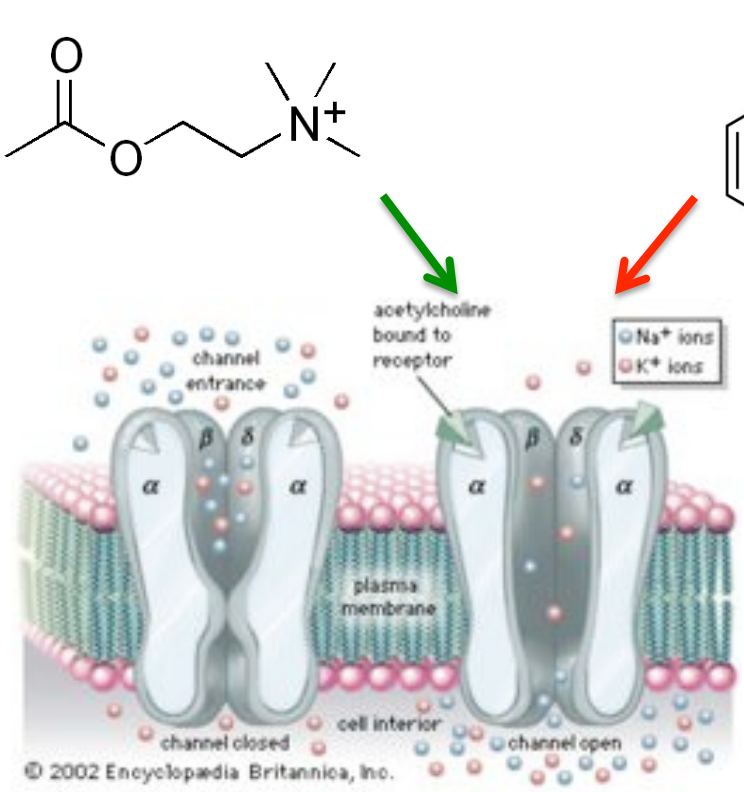
Nicotiana attenuata

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

Defensive action of nicotine

Acetylcholine
(neurotransmitter)

Nicotine
(plant neurotoxin that mimics acetylcholine)



Acetylcholine receptors at neuromuscular junction

Wild tobacco *(Nicotiana attenuata)*

Most drugs are plant neurotoxins

Relationships between plant neurotoxins commonly used as drugs and CNS receptors.

Drug	Plant	Toxin	Neurotransmitter	Receptor
Tobacco, Pituri	*Nicotiana, Duboisia*	Nicotine[a]	Acetylcholine	Nicotinic receptor
Betel nut	*Areca catechu*	Arecoline[a]	Acetylcholine	Muscarinic receptor
Coca	*Erythroxylum*	Cocaine[c]	Norepinephrine, epinephrine	Adrenergic receptors
Khat	*Catha edulis*	Ephedrine[c], cathinone[a,c]	Norepinephrine, epinephrine	Adrenergic receptors
Cactus	*Lophophora*	Mescaline	Serotonin	Serotonin receptor
Coca	*Erythroxylum*	Cocaine[c]	Dopamine	Dopamine receptor
Khat	*Catha edulis*	Cathinone[a,c]	Dopamine	Dopamine receptor
Coffee, Cola nut	*Coffea, Cola nitida*	Caffeine[b]	Adenosine	Adenosine receptor
Tea	*Camellia sinensis*	Caffeine[b], theophylline[b], theobromine[b]	Adenosine	Adenosine receptor
Chocolate	*Theobromine cacao*	Theobromine[b]	Adenosine	Adenosine receptor
Opium	*Papaver somniferum*	Codeine[a], morphine[a]	Endorphins	Opioid receptor
Cannabis	*Cannabis sativa*	Δ9-THC[a]	Anandamide	Cannabinoid receptor

[a]receptor agonist, [b]receptor antagonist, [c]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.

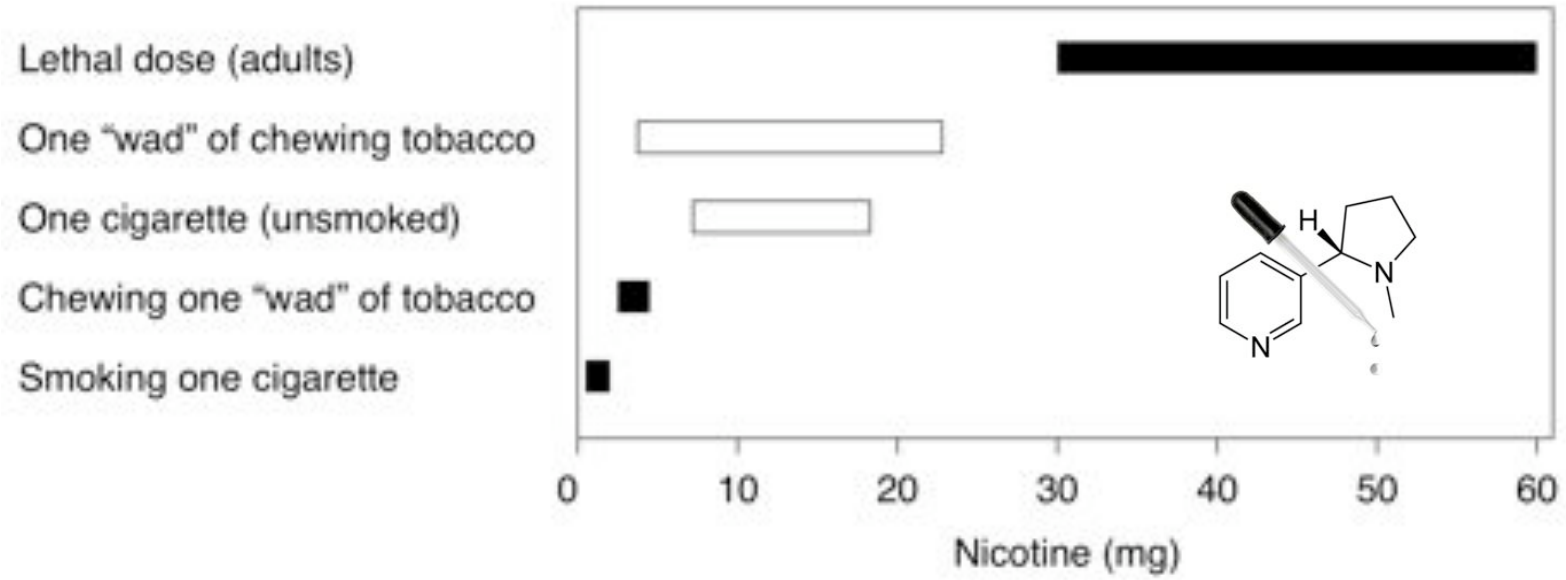
Sullivan et al. 2008 *Proc R Soc*.
Hagen et al. 2009 *Neuroscience*.

Tobacco Hornworm *Manduca sexta*

Deepening the paradox

Nicotine is extremely toxic to humans

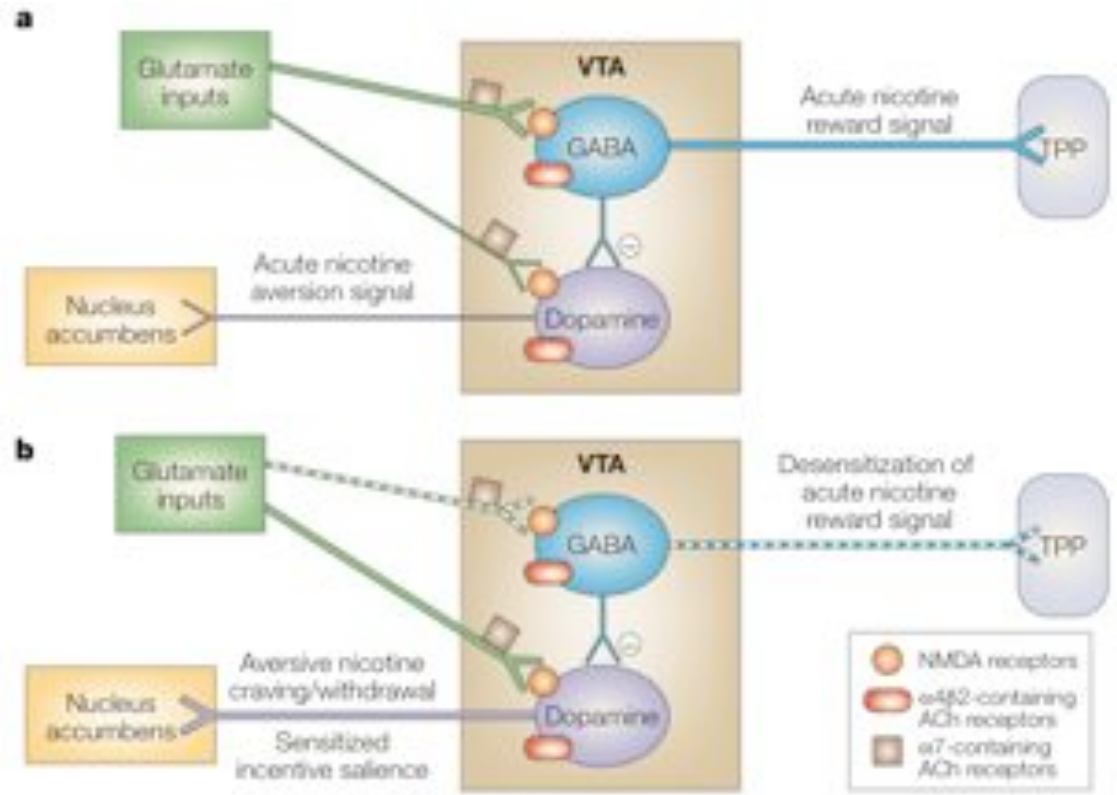
CDC, American Cancer Society



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

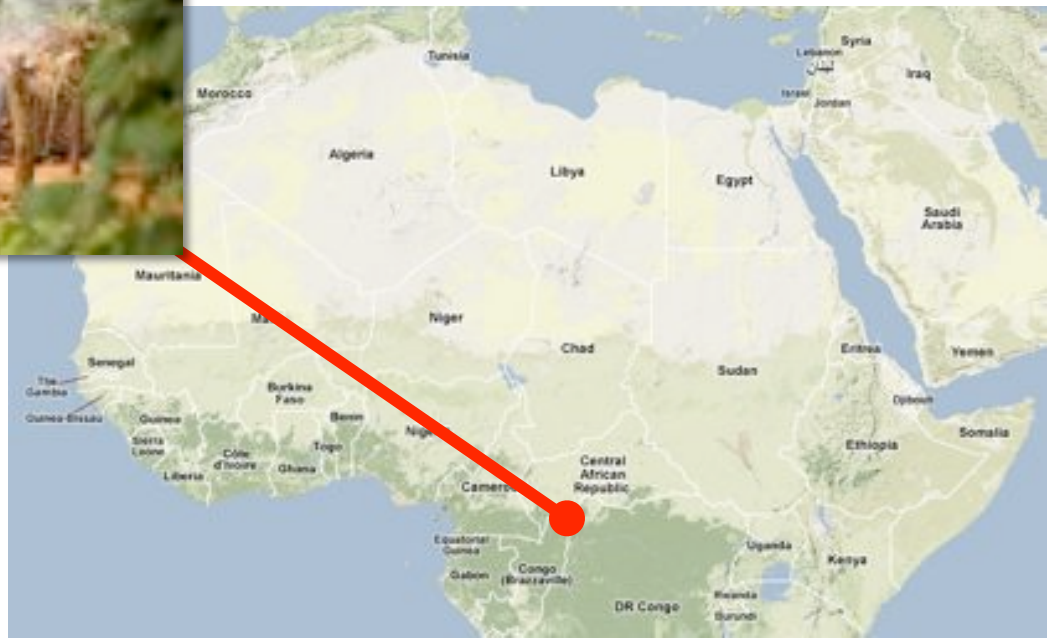
Efficacy of nicotine against helminths

- 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.

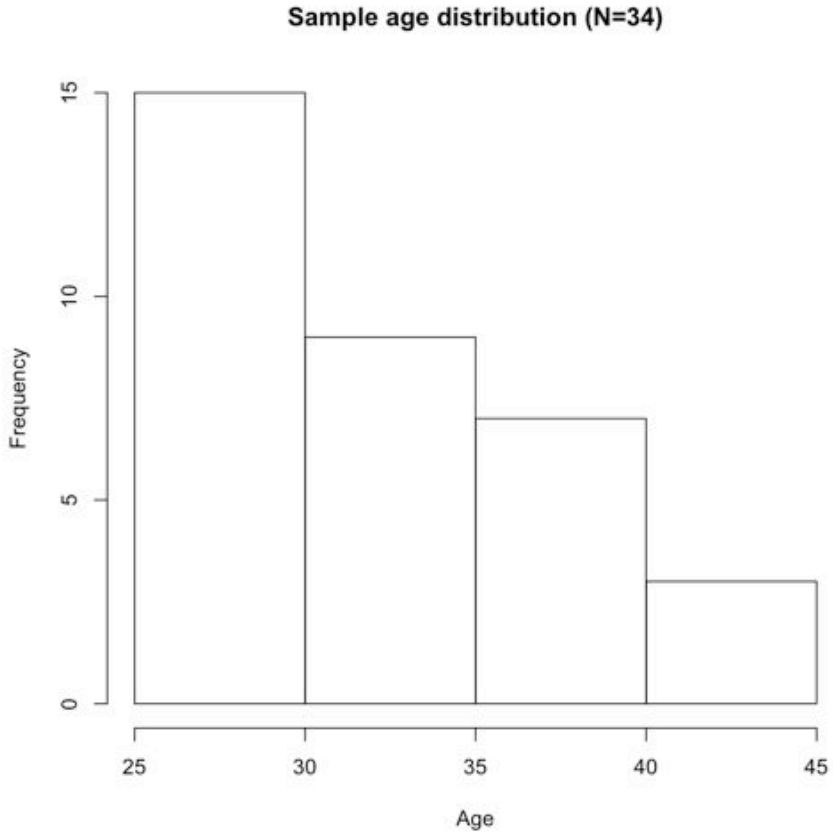


Study population: Aka foragers of the Central African Republic

N=39

20 females
19 males

Ages are rough estimates



Predictor variables

- Smoker status (self report)
  - Indexes chronic nicotine exposure

Barry Hewlett and Casey Roulette interviewing
Aka about tobacco use

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

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

Stool collection kit
Formalin/PVA

Predictions

1. Self-reported smokers have lower helminth load

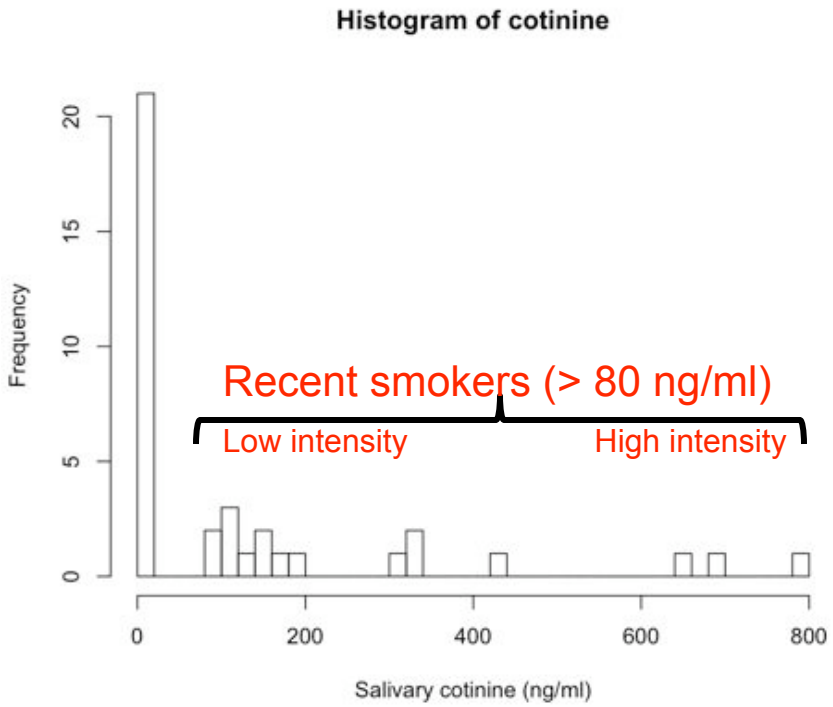
2. Salivary cotinine (an index of the intensity of recent nicotine exposure) is inversely correlated with helminth load

Summary stats: Self-reported smoker

	Female	Male
Self-reported smoker		
No	15	1
Yes	5	18

Smoker status (self-report) vs. Sex

Summary stats: Cotinine



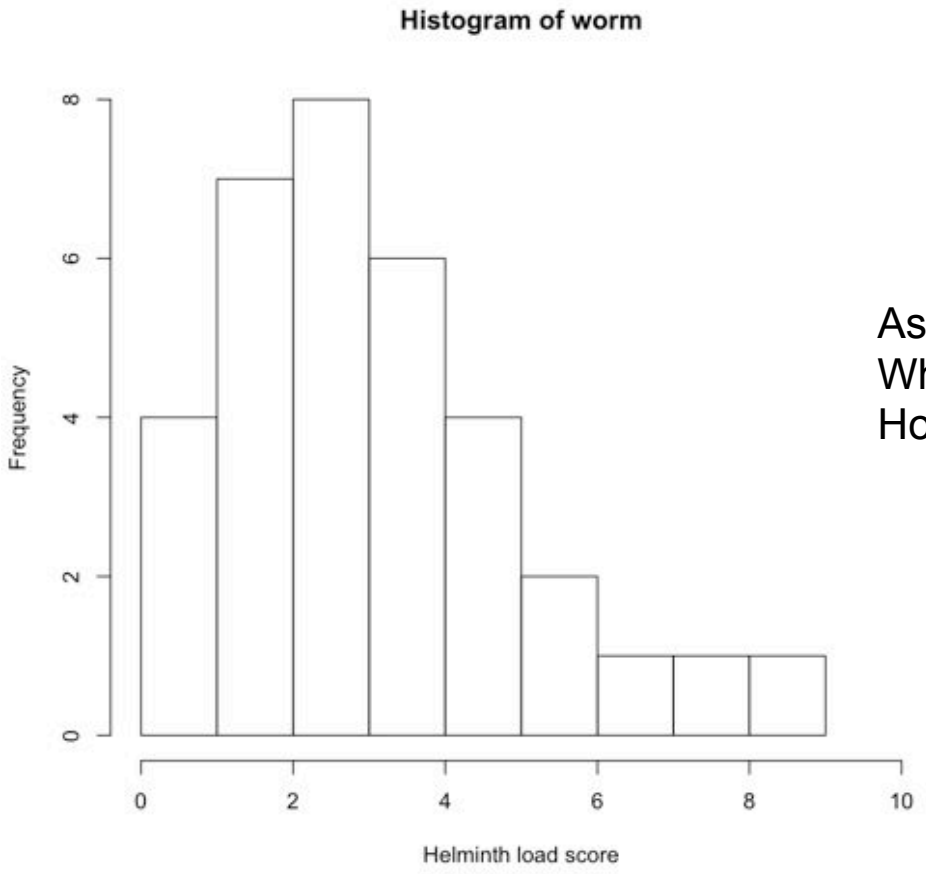
	Cotinine < 15 ng/ml	Cotinine > 80 ng/ml
Self-reported smoker		
No	16	0
Yes	5	16

Smoker status (self-report) vs. cotinine conc.

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

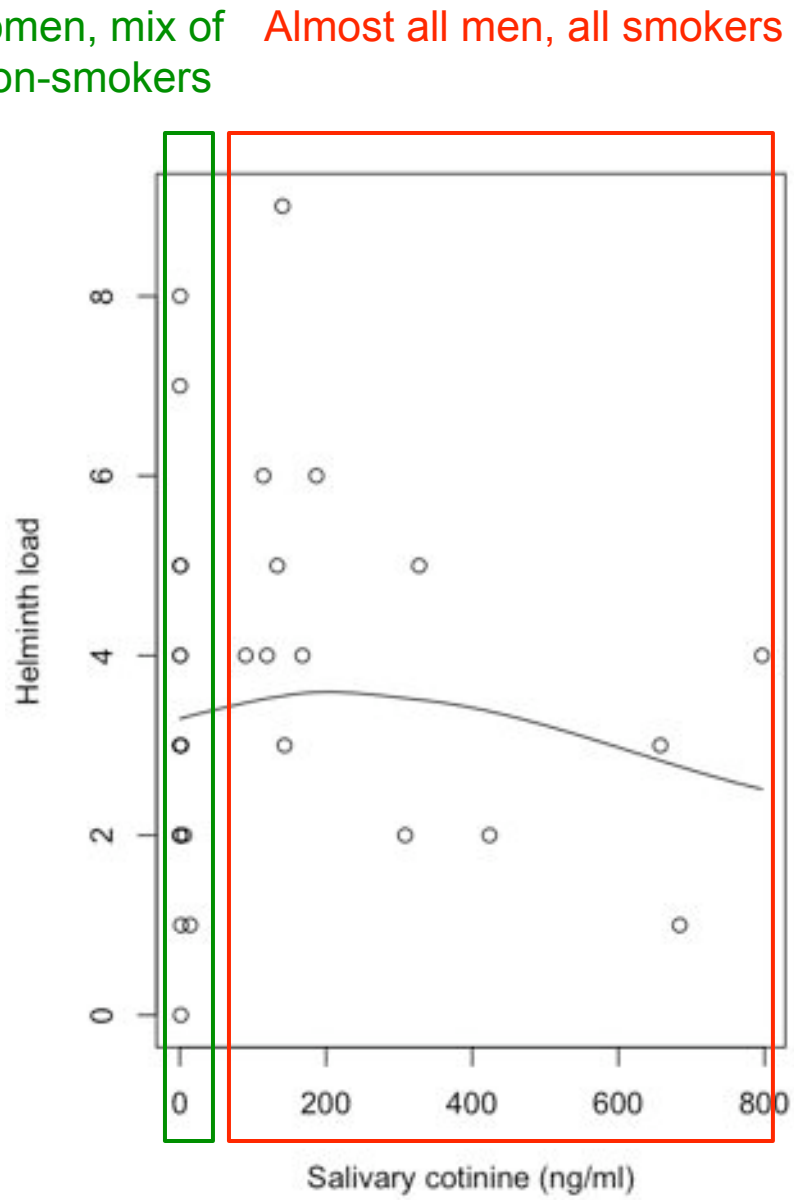
Testing predictions

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

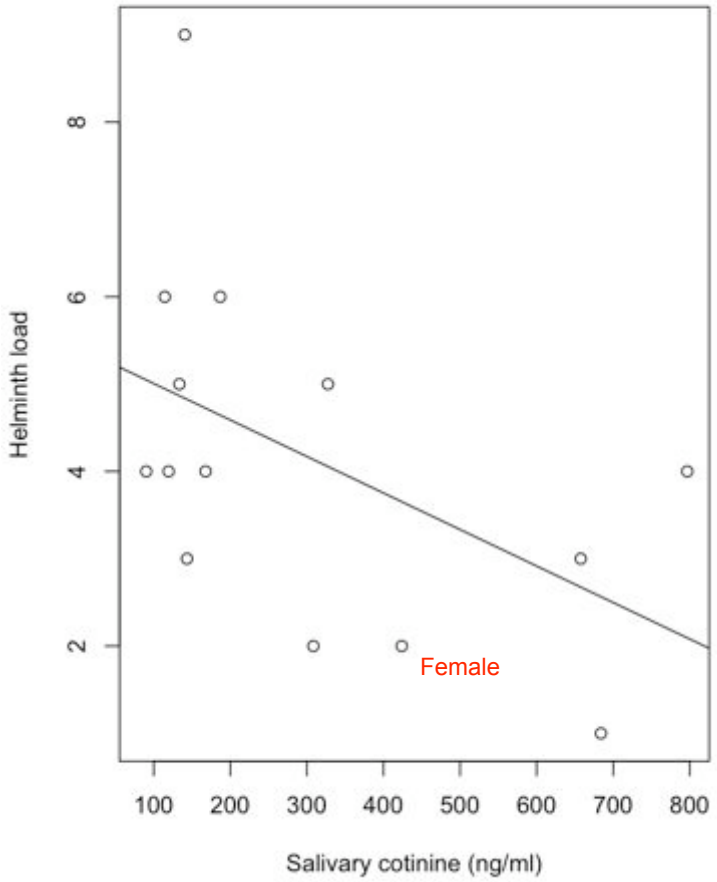
2. Salivary cotinine (an index of the intensity of recent nicotine exposure) is inversely correlated with helminth load.

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:

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

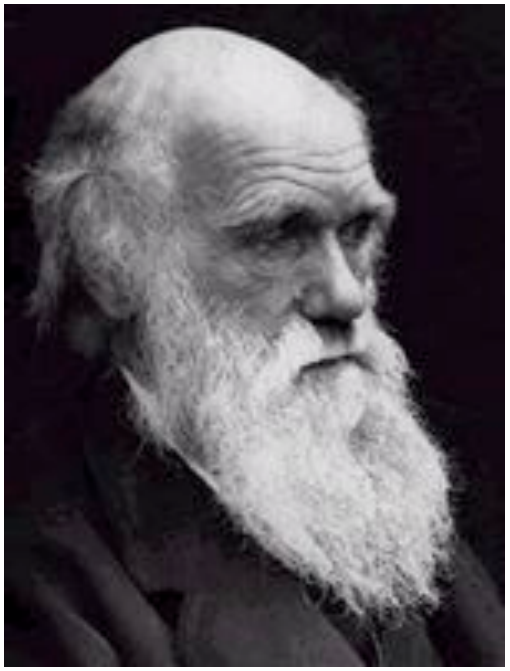
Testing predictions

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).