The evolutionary significance of drug toxicity over reward

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Drug reward is an evolutionary conundrum. It is not surprising that neural circuitry evolved to reward or reinforce behaviors leading to the essentials of survival and reproduction, like food, water, and sex. Why, though, would these same circuits reward and reinforce the consumption of drugs of abuse, which is often harmful? Here we briefly review the history of reward-based learning, which resulted in a widely accepted evolutionary account of drug reward that we term the *hijack hypothesis*. We then critique the evolutionary bases of the hijack hypothesis. We conclude by sketching an alternative evolutionary model of human drug use grounded in drug toxicity. Specifically, avoidance of toxic drugs is a compelling hypothesis for the low use of drugs by children and women relative to men. In addition, the regulated ingestion of small quantities of toxins might have provided important medicinal and other benefits to humans and non-human animals over the course of their evolution.

Neurobiological theories of drug use are deeply intertwined with those of reward-based learning. The main idea was captured in Thorndike's *law of effect*: "Of several responses made to the same situation, those which are accompanied or closely

followed by satisfaction to the animal will, other things being equal, be more firmly connected with the situation, so that, when it recurs, they will be more likely to recur" (Thorndike 1911). The related concept of *reinforcement* refers to the ability of certain stimuli, such as food, to strengthen learned stimulus-response associations. Relief from aversive stimuli could similarly “negatively reinforce" stimulus-response associations.

Early animal studies of drug addiction found evidence for both negative and positive reinforcement. In animals addicted to, e.g., morphine, relief from aversive withdrawal symptoms reinforced stimuli associated with obtaining the drug, but morphine’s hedonic or euphoric effects also positively reinforced drug use (Spragg 1940; Beach 1957).

The neurobiological story of reward-based learning began with Olds and Milner’s observation that rats will self-administer an electrical current to the septal region of the brain. They concluded that such intracranial stimulation was possibly the most potent reward ever used in animal experimentation to that date (Olds and Milner 1954). Its resemblance to drug addiction was immediately evident (Milner 1991).

More than two decades of experiments ensued to identify the precise neurons and neurotransmitters mediating the reinforcing effects of self-stimulation, in conjunction with work invested in understanding drug reward in its own right. The neurons critical for both septal self-stimulation and the reinforcing properties of at least some drugs turned out to be dopamine neurons in the midbrain, commonly referred to as the *mesolimbic dopamine system* (MDS). Thus were born two

intimately intertwined theories, the dopamine theory of reinforcement learning and the dopamine theory of substance use and addiction, each deeply rooted in the stimulus-response paradigm at the core of behaviorism.

The hijack hypothesis

Drug reward requires an evolutionary explanation: unlike food, sex, and other natural rewards, drugs, at first glance, do not make an obvious contribution to an animal's survival or reproduction. In fact, chronic drug use is often harmful. Hence, it seems the brain should have evolved circuits to prevent drug use, rather than to reinforce it. One possibility is that drugs, like wires in the brain, are evolutionarily novel and their rewarding properties are artificial. Indeed, neurobiologists came to view drugs in the same way as intracranial electrodes, that is, as evolutionarily novel laboratory instruments to selectively activate or deactivate specific neural circuits (Wise 1996). After noting that "intravenous drug rewards establish and maintain response habits similar to those established and maintained by natural rewards" Wise (1996, 320) goes on to say that: "This should not be surprising; the brain mechanisms that make animals susceptible to brain stimulation reward evolved long before the human inventions that made intracranial self-stimulation or drug addiction possible." These human inventions include "e.g. the use of fire, pipes, and cigarette papers; the use of the hypodermic syringe and needle; agricultural skills for the harvesting and curing of tobacco; the ability to synthesize or purify

drugs; the ability to concentrate, store, and transport alcoholic beverages" (Wise 1996, p. 320).

Subsequent highly cited review articles on the neurobiology of drug use endorsed the notion that brains are susceptible to drugs of abuse because they are evolutionarily novel and are consumed in a novel fashion. Natural rewards such as food and sex "activate" the reward system, whereas drug rewards "hijack," "usurp," "co-opt," or artificially stimulate it (for references, see Hagen, Roulette, and Sullivan 2013). Kelley and Berridge (2002, 3306), for instance, open their review with:

> Addictive drugs act on brain reward systems, although the brain evolved to respond not to drugs but to natural rewards, such as food and sex. Appropriate responses to natural rewards were evolutionarily important for survival, reproduction, and fitness. In a quirk of evolutionary fate, humans discovered how to stimulate this system artificially with drugs.

In another example, Hyman (2005, 1414) leads into a section titled "A Hijacking of Neural Systems Related to the Pursuit of Rewards" with:

> [A]ddiction represents a pathological usurpation of the neural mechanisms of learning and memory that under normal circumstances serve to shape survival behaviors related to the pursuit of rewards and the cues that predict them.

According to the hijack hypothesis, then, drugs of abuse, like intracranial electrodes, (1) are evolutionarily novel, especially in their purity or concentration, (2) are consumed in a novel fashion, and (3) provided no evolutionary fitness benefit. There are reasons to be skeptical of each proposition. (Skepticism of the hijack hypothesis is also increasing within neurobiology because most laboratory animals, when given

a choice between an intravenous drug dose and a non-drug reward, choose the non-drug reward; see, e.g., Ahmed et al. 2013).

The evolution of drugs of abuse and other pesticides

All living organisms, including all humans, are the latest members of unbroken lineages of organisms extending back to the origin of life, over 3 billion years ago. Today, almost all organisms acquire their energy directly or indirectly from oxygenic photosynthesis, which uses sunlight to reduce carbon dioxide to organic carbon, and stores chemical energy in the form of sugars and other carbohydrates. These then provide the building blocks and fuel for the growth and reproduction of the photosynthetic organisms, termed *autotrophs*. The first single-celled oxygenic photosynthetic autotrophs evolved about 2.4 billion years ago (Hohmann-Marriott and Blankenship 2011).

Unfortunately for these autotrophs, *heterotrophs* evolved that feed on them, sparking an evolutionary arms race (Dawkins and Krebs 1979) that continues to this day: heterotrophs evolved to exploit autotroph tissues and energy stores; autotrophs, in turn, evolved numerous defenses; heterotrophs then co-evolved countermeasures, and so forth.[1] Key events in this arms race include the evolution of marine animals more than 600 million years ago (Knoll and Carroll 1999), and the evolution of terrestrial plants ~ 400 million years ago, along with the terrestrial

[1] Autotrophs and heterotrophs have also undergone mutually beneficial coevolution. See discussion in Hagen et al. (2009).

bacterial, fungal, nematode, invertebrate and vertebrate herbivores that feed on them (Herrera and Pellmyr 2009).

Central to our account of human drug use are the chemical defenses that evolved in marine, and later, terrestrial autotrophs (plants). Some chemical defenses, such as tannins and other phenolics, have relatively non-specific effects on a wide range of molecular targets in the herbivore, for example binding to proteins and changing their conformation, thereby impairing their function. Other chemical defenses – neurotoxins – evolved to interfere specifically with signaling in the central nervous system (CNS) and peripheral nervous system. Various plant neurotoxins interfere with nearly every step in neuronal signaling, including (1) neurotransmitter synthesis, storage, release, binding, and re-uptake (2) receptor activation and function; and (3) key enzymes involved in signal transduction. Plant neurotoxins have these effects, in many cases, because they have evolved to resemble endogenous neurotransmitters. Disruption of nervous system function by such toxins serves as a potent deterrent to herbivores (Wink 2011).

Because plant drugs, almost by definition, interfere with signaling in the CNS and elsewhere, they are widely believed to have evolved as plant defenses (Wink 2011). Nevertheless, among the popular plant drugs, only nicotine, which we discuss next, has been conclusively shown to serve plant defense.

Nicotine

In what follows we will often rely on studies of tobacco and nicotine because, for our purposes, tobacco is an ideal model drug. First, it is globally popular and highly addictive. Second, nicotine's role in plant defense is well documented: numerous studies of tobacco demonstrate that nicotine reduces leaf loss and plant mortality and increases production of viable seed by deterring, harming and killing herbivores (Baldwin 2001; Steppuhn et al. 2004). Third, we can draw on the extensive research on the nervous system effects of nicotine. Fourth, although the two domesticated tobacco species were probably artificially selected to increase their nicotine content, several of the more than 60 wild tobacco species have nicotine content comparable to or exceeding the domesticated species (Sisson and Severson 1990), and both wild and domesticated species were widely used by pre-Columbian Native Americans (Tushingham and Eerkens 2016). This indicates that consumption of nicotine-rich tobacco is not simply a modern phenomenon. Finally, tobacco is usually consumed by chewing or smoking, and it is conceivable that humans chewed, or even smoked, various toxic and psychoactive plants for much of our recent evolution (Sullivan and Hagen 2002; Hardy et al. 2012).

Nicotine is a dangerous neurotoxin. In humans, oral ingestion of 4-8 mg of nicotine causes burning of the mouth and throat, nausea, vomiting, and diarrhea. Higher doses result in dizziness, weakness, and confusion, progressing to convulsions, hypertension and coma. Ingestion of concentrated nicotine pesticides can cause death within 5 minutes, usually from respiratory failure (Landoni 1991).

A single cigarette typically contains 10–20 mg of nicotine, enough to seriously endanger a young child and cause acute toxic symptoms in an adult. When a cigarette is smoked, much of its nicotine is burned, however, and smokers ultimately absorb 0.5–2 mg per cigarette. Tobacco chewers absorb up to 4.5 mg per "wad" (Hukkanen, Jacob, and Benowitz 2005), a dose that is often sufficient to cause severe acute toxicity in naive users.

Despite its acute toxicity, nicotine is not thought to be directly responsible for the chronic diseases caused by smoking (but see Grando 2014). Thus, its toxicity, which explains why it is present in tobacco leaves in the first place, plays little role in research on tobacco use and addiction. In the framework we develop here, however, drug toxicity plays a central role.

Although the data are not yet as conclusive as they are for nicotine, a defensive role will probably be established for most other plant drugs, such as cocaine, morphine, codeine, THC, and caffeine (reviewed in Hagen et al. 2009). Like nicotine, most plant drugs are acutely toxic for humans, and the typical quantities consumed by drug abusers are often surprisingly close to the lethal dose (Gable 2004; Lachenmeier and Rehm 2015). For these reasons, in the remainder of the chapter we will often refer to recreational drugs as neurotoxic plant pesticides, which better describes their evolved function.

We will also draw on the extensive research on pharmaceuticals because these are frequently derived from plant toxins (e.g., nicotine, which has therapeutic

applications and is also widely used as a pesticide), chemically resemble plant toxins, or have neurophysiological effects analogous to those of plant toxins.

Human toxin defense mechanisms

Human capabilities to detect, avoid, and neutralize plant toxins evolved over the course of our billion year evolutionary arms race with autotroph defenses. During the final phase of this arms race, the human lineage was a lineage of primates, which diverged from other mammals roughly 65 million years ago, and which subsist mostly on plants and insects (Fleagle 2013). As many insect species sequester plant toxins to deter predators, both elements of the primate diet required effective defenses against plant toxins. Primate toxin defense mechanisms, inherited from mammalian and vertebrate ancestors, would therefore have been continuously maintained and 'tuned' by natural selection. When human and chimpanzee ancestors diverged, probably more than 6 million years ago, the human lineage inherited a robust suite of toxin defense mechanisms. There is substantial evidence that these defense mechanisms correctly recognize all drugs of abuse as toxic (Sullivan, Hagen, and Hammerstein 2008; Hagen et al. 2009).

Taste receptors

Basic human anatomy prioritizes toxin defense, and taste buds are on the front lines. Taste is responsible for evaluating the nutritious content of food and preventing the ingestion of toxic substances. The sweet and umami taste receptors, which identify

two key nutrients — sugars and amino acids — belong to a small, three-member family of genes, the T1Rs, that are expressed in taste receptor cells in the tongue (Chandrashekar et al. 2006).

Bitter taste, in contrast, must prevent the ingestion of tens of thousands of structurally diverse toxins. Not surprisingly, bitter taste is mediated by a large repertoire of about 25 receptor genes, the T2Rs (Chandrashekar et al. 2006). All common recreational plant drugs taste bitter. Thus, these receptors properly recognize common psychoactive plant drugs as toxic.

In addition to their expression in tongue and palate epithelium, the sweet, umami, and bitter taste receptors are also expressed in other tissues exposed to nutrients and toxins, such as the respiratory system, gastrointestinal tract, testes, and brain (Behrens and Meyerhof 2010).

Barrier defenses

If a toxic plant substance is ingested it then encounters a “barrier defense." The body can be conceptualized as a set of compartments, such as the intestines and lungs, that are typically separated by tissue barriers comprising epithelial or endothelial cells linked together with special proteins forming “tight junctions." These tissue barriers include our skin, gastrointestinal (GI) tract, respiratory tract, and the blood brain barrier (BBB). The barriers have several functions, such as allowing an influx of essential chemicals like sugar and oxygen into a compartment, and simultaneously preventing an influx of microorganisms and toxins (Mullin et al.

2005). The barriers achieve these effects by limiting or enhancing passive diffusion across the cells and tight junctions, and also by active mechanisms that transport essential chemicals into a compartment, and that neutralize and transport toxins out of a compartment.

Figure 1 illustrates the basic anatomical and cellular components of the barrier defenses against toxins and other xenobiotics. A plant toxin (represented as a pharmaceutical) comes into contact with a barrier, such as the skin, airways, lung, or intestine. If the toxin manages to enter a cell, such as an enterocyte, it then activates a complex network of proteins that neutralize and remove it in a four-phase process.

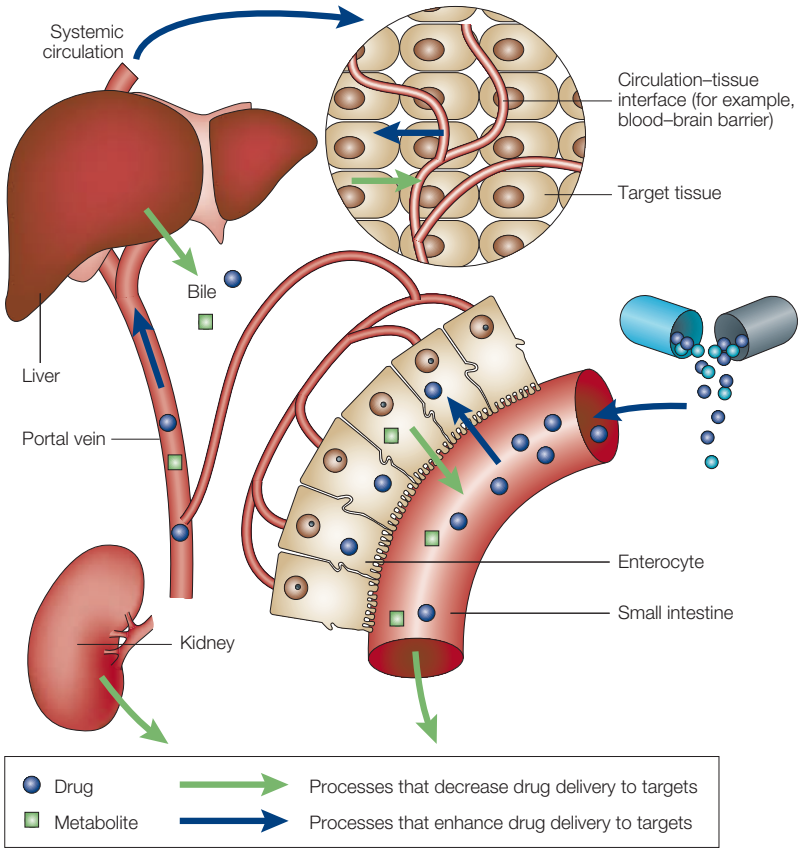

Figure 1: Toxin defense mechanisms of the gut "barrier," and first pass elimination. Many toxic substances (represented here as a pharmacuetical drug) entering the gastrointestinal tract are first metabolized by enzymes in the gut wall, or are transported back into the intestine. The remaining absorbed fraction enters the portal vein and is immediately routed through the liver, the principal organ of detoxification, before entering systemic circulation where it encounters other barrier defenses, such as the blood-brain barrier. Figure from Roden and George Jr (2002).

Phase 0 involves transporters — special proteins that span cell membranes and move chemicals into and out of cells using passive and active mechanisms. Efflux transporters generally remove toxins and waste products from the cell, and are

typically members of the ATP binding cassette (ABC) super family. Humans have 48 ABC transporter genes, about 20 of which are efflux transporters. In Phase 0, a xenobiotic enters the cell, and an ABC transporter pumps it back out.

In Phase I, any xenobiotic remaining in the cell is chemically altered by enzymes to reduce toxicity and increase water solubility to facilitate excretion. Typically, this involves oxidation by one or more cytochrome P450 (CYP) enzymes. Humans have 57 CYP genes, about 25 of which are involved in xenobiotic metabolism (Sullivan, Hagen, and Hammerstein 2008).

In Phase II, diverse families of enzymes conjugate charged species with xenobiotic metabolites, further reducing toxicity[2] and increasing water solubility. Phase I and II xenobiotic metabolizing enzymes are most highly expressed in the liver, but are also expressed in most other tissue barriers, including skin, intestine, lung, placenta, and brain (Gundert-Remy et al. 2014). Xenobiotics can also bind to xenosensing nuclear receptors that then up-regulate expression of metabolic and transport proteins, accelerating elimination of the xenobiotic.

In Phase III, metabolites are pumped out of the cell by a transporter for renal or biliary elimination. For details on Phase 0-III, see Tóth et al. (2015), and references therein.

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[2] Occasionally, Phase I and Phase II metabolites are more toxic than the parent compound.

Nausea, vomiting, and conditioned taste aversion

Most nutrients, toxins, and other xenobiotics are processed in the gut, where many toxins are partially or completely neutralized and eliminated as just described. In addition, the gut is richly innervated, with large quantities of information conveyed from the GI tract to the CNS via the afferent vagal nerve. The *area postrema*, in particular, is a chemosensitive part of the brain that is outside the BBB, and therefore is also exposed to chemicals in systemic circulation. Together, these circuits can respond to toxins in the gut and blood with nausea, vomiting, and learned aversions and avoidances (Babic and Browning 2014).

Toxins that are not expelled from, or metabolized by, the gut enter the bloodstream and are then immediately routed through the liver, the principal detoxification organ, which further metabolizes and eliminates them. Any remaining toxin enters systemic circulation where it encounters other barrier tissues, such as the BBB, and further metabolism (Figure 1).

Psychoactive drugs like nicotine are neurotoxins, some portions of which evade all such defenses, successfully entering the brain and interfering with CNS function.

Evaluating the hijack hypothesis in light of evolved xenobiotic defenses

The multiple layers of toxin defenses involving scores of receptor, metabolic and transporter genes, numerous distinct tissue barriers, complex neural circuits,

organs like the liver and kidneys, and the basic organization of the circulatory system, all demonstrate that human ancestors were regularly exposed to a large variety of dangerous xenobiotic toxins that entered the body via the skin, GI tract, and respiratory tract. These toxins often gained access to systemic circulation and, as evidenced by an extremely robust BBB that prevents most drugs from entering the brain (Pardridge 2012), many posed a substantial threat to CNS function, i.e., were psychoactive. Exposure to psychoactive plant compounds is not evolutionarily novel.

Evolutionarily novel levels of drug purity do not appear to be a general explanation for drug use and addiction either. Pure nicotine is not abused by humans, and most smokers do not prefer nicotine spray to placebo; nicotine and nicotinic receptor agonists only slightly improve smoking cessation rates; and other constituents of tobacco smoke, such as acetaldehyde, norharman and harman (MAO inhibitors) appear to potentiate the addictive properties of nicotine (Small et al. 2010). E-cigarettes, which deliver nicotine and flavorants, may be as or less addictive than nicotine gums, which themselves are not very addictive (Etter and Eissenberg 2015).

Evolutionarily novel methods of administration are also unlikely to explain recreational drug use and dependence, as chewing tobacco is addictive (US Department of Health and Human Services, 1986) but chewing plants is not evolutionarily novel. Inhalation of toxic smoke was also probably common during human evolution. Our hominoid and hominin ancestors evolved in forest and

savannah environments that regularly experienced wildfires, and our lineage might have achieved control of fire by 1 million years ago (Parker et al. 2016). It is therefore likely that human ancestors were frequently exposed to vaporized plant toxins, which probably helps explain the presence of robust xenobiotic defenses in our respiratory tract.[3] Furthermore, indigenous drug use often incorporates cultural techniques to "free base" psychoactive neurotoxins and to utilize physiology to avoid first-pass metabolism. For example, both betel nut (SE Asia) and coca (American Andes) is commonly mixed with a base (e.g. lime) and is chewed in the buccal cavity where the free alkaloids can cross directly into the blood stream and into the CNS (Sullivan and Hagen 2002).

Thus, psychoactive compounds are not evolutionarily novel; they can be found in plants in concentrations similar to globally popular drugs (e.g., several wild tobacco species); evolutionarily novel purity does not explain their addictiveness (at least for nicotine); and they regularly entered systemic circulation via ingestion, contact with the skin, and inhalation, just as recreational drugs do today. Exposure to psychoactive compounds is as 'natural' as exposure to sugars and starches.

Moreover, nicotine and other popular recreational plant drugs activate most known toxin defense mechanisms, including bitter taste (Wiener et al. 2012), xenobiotic

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[3] Even hypodermic injection is not an evolutionarily novel mode of exposure to psychoactive toxins. Although we have emphasized plant neurotoxins, numerous vertebrates and invertebrates produce potent neurotoxins that they inject into predators and prey with stingers and fangs. There is increasing evidence that humans have an innate fear of spiders and snakes, probably because many of these species are venomous and frequently attacked human ancestors with fangs (Öhman and Mineka, 2001). Even today, snakebite is a major cause of morbidity and mortality in much of the world (Gutiérrez et al., 2013). The dangers of bites and stings might also explain an apparent innate fear of needles (Hamilton, 1995).

nuclear receptors (Lamba 2004), xenobiotic metabolism (Sullivan, Hagen, and Hammerstein 2008), nausea and vomiting (Wishart et al. 2015), and conditioned avoidances and aversions (Lin, Arthurs, and Reilly 2016 and references therein). Human neurophysiology correctly recognizes drugs of abuse as the toxic pesticides that they are.

In summary, drug researchers correctly realized that the rewarding and reinforcing properties of toxic and harmful substances required an evolutionary explanation, but, on very scant evidence, wrongly concluded that drugs and their routes of administration were evolutionarily novel, and that this provided an adequate evolutionary account of human drug use. Plants are under strong selection to evolve compounds that 'hijack' herbivore nervous systems, but for precisely the opposite effects: to punish and deter plant consumption, not reward or reinforce it.

Without considerable further evidence, it is not possible to accept that neurotoxic pesticides like nicotine are able to 'hijack' reward circuits because they are evolutionarily novel, or are consumed in a novel fashion. The hijack hypothesis can only be rescued with more convincing evolutionary arguments and much stronger empirical evidence. As we explain next, the correct evolutionary account of human drug use is not yet clear.

The paradox of drug reward

The widespread recreational use of, and addiction to, several neurotoxic plant pesticides is extremely puzzling, to say the least. The reigning neurobiological

paradigm of drug use, grounded in the rewarding or reinforcing effects of drugs in humans and other laboratory animals, is obviously in conflict with the reigning evolutionary biological paradigm of drug origins, grounded in the punishing effects of nicotine and other plant-based drugs on herbivores. Specifically, plants should not have evolved compounds that reward or reinforce plant consumption by herbivores, nor should herbivores have evolved neurological systems that reward or reinforce ingestion of potent plant neurotoxins. This contradiction has been termed the paradox of drug reward (Sullivan, Hagen, and Hammerstein 2008; Hagen et al. 2009; see also Sullivan and Hagen 2002).

Drug researchers have long recognized that drugs are toxins and have aversive effects, and that drug toxicity and aversiveness is at odds with drug reward (for review, see Verendeev and Riley 2012). Pavlov himself related experiments in which dogs learned to associate the toxic effects of morphine injections with stimuli. In the most striking cases, vomiting and other symptoms could be caused simply by the dog seeing the experimenter (Pavlov 1927). Unfortunately, drug aversion has had little influence on drug use theory (Verendeev and Riley 2012).

In the remainder of this chapter, we propose that drug toxicity explains dramatic age and sex differences in drug use. We also explore possible resolutions of the paradox of drug reward that are grounded in the neurotoxic properties of common recreational drugs.

Explaining the dramatic age difference in drug use

Users of popular neurotoxic pesticides report little-to-no use prior to the age of 10 (Figure 2). This is remarkable. Why are children so resistant to drug use? Although many researchers focus on the rapid adolescent transition to neurotoxic pesticide use, so far as we can tell there is essentially no investigation of the striking *lack* of child neurotoxic pesticide use. Perhaps drug researchers simply assume that parental and societal restrictions prevent child use.

This assumption seems reasonable for tobacco, as the US spends about $500 million each year on tobacco control efforts (WHO 2013). It is much less reasonable for caffeine, a bitter-tasting defensive neurotoxin that is found in 13 orders of the plant kingdom (Ashihara and Suzuki, 2004), and that shows promise as a pesticide and repellant for slugs, snails, birds and insects (e.g., Hollingsworth et al. 2002, Avery et al. 2005). Like nicotine, caffeine is a rewarding psychostimulant that strongly interacts with the central dopaminergic systems (Ferré 2008). Unlike nicotine, caffeine faces few social restrictions against use — it is listed by the US Food and Drug Administration as "GRAS [generally recognized as safe] for use in cola-type beverages at levels not to exceed 200 parts per million (ppm) (0.02%)" (Rosenfeld et al. 2014, p. 26). This level corresponds to 71 mg of caffeine in a 12-oz serving (although most colas contain about half that amount). For comparison, a 1 oz shot of espresso contains about 64 mg of caffeine, an 8 oz cup of coffee might contain 145 mg of caffeine, energy drinks typically contain 17-224 mg of caffeine per serving, and chocolate candy contains 11-115 mg caffeine per oz (Rosenfeld et al. 2014).

Despite the light regulation of caffeine compared to tobacco and nicotine, and its ready availability in colas, chocolate candies, and other child food products, child consumption of caffeine is low (Figure 3a,b,c), suggesting that low child use of putatively “rewarding" neurotoxic pesticides is not explained solely by parental or societal controls. What, then, does explain the dramatic lack of child neurotoxic pesticide use, and the equally dramatic, ‘switch-like’ transition to neurotoxic pesticide use during adolescence?

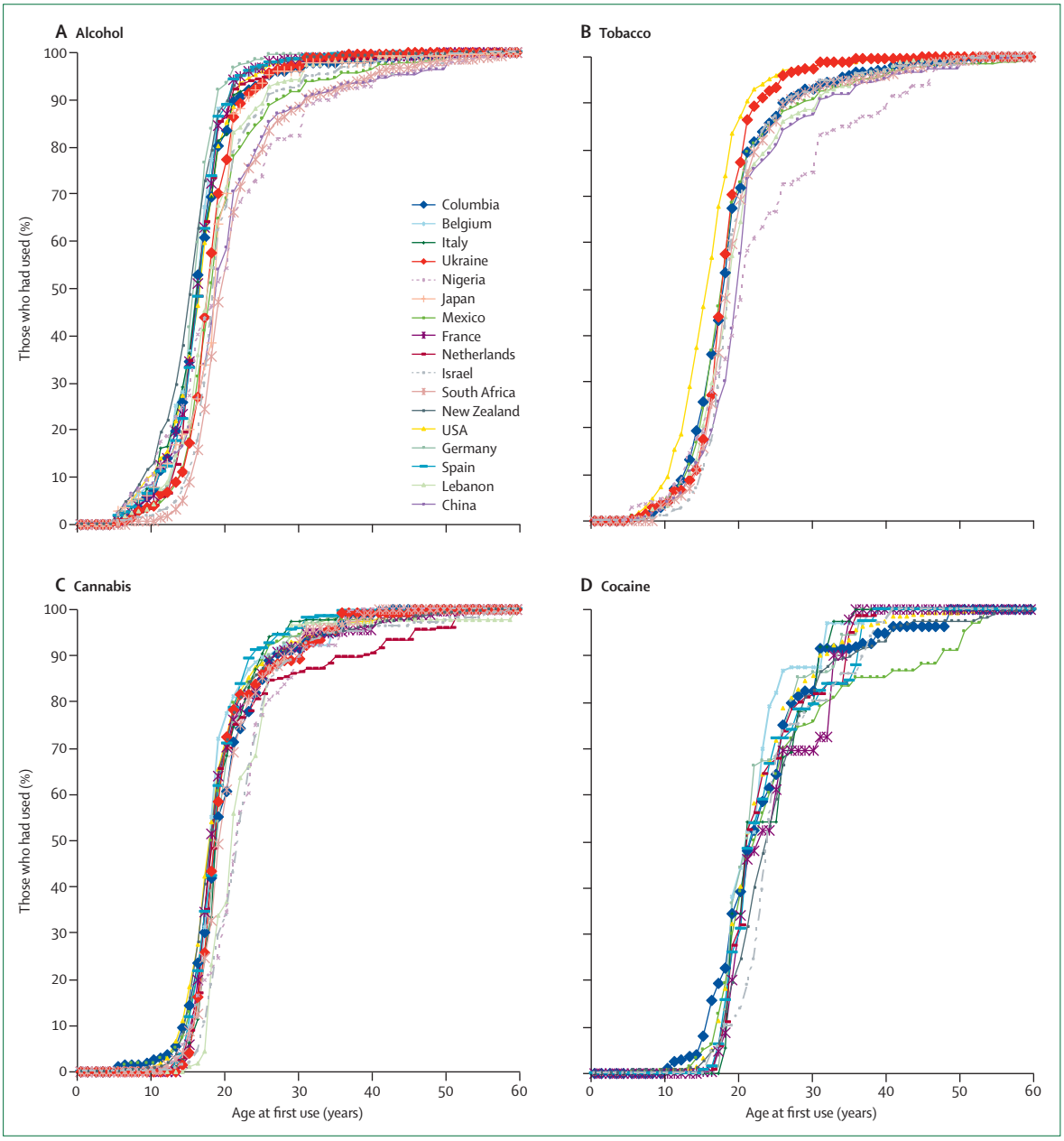

Figure 2: Cumulative distribution of self-reported age of first use of alcohol, tobacco, cannabis, and cocaine in a large (N=85,052) cross-national sample of users of these substances. These patterns suggest the existence of a developmental 'switch' to drug use during adolescence. Figure from Degenhardt et al. (2016).

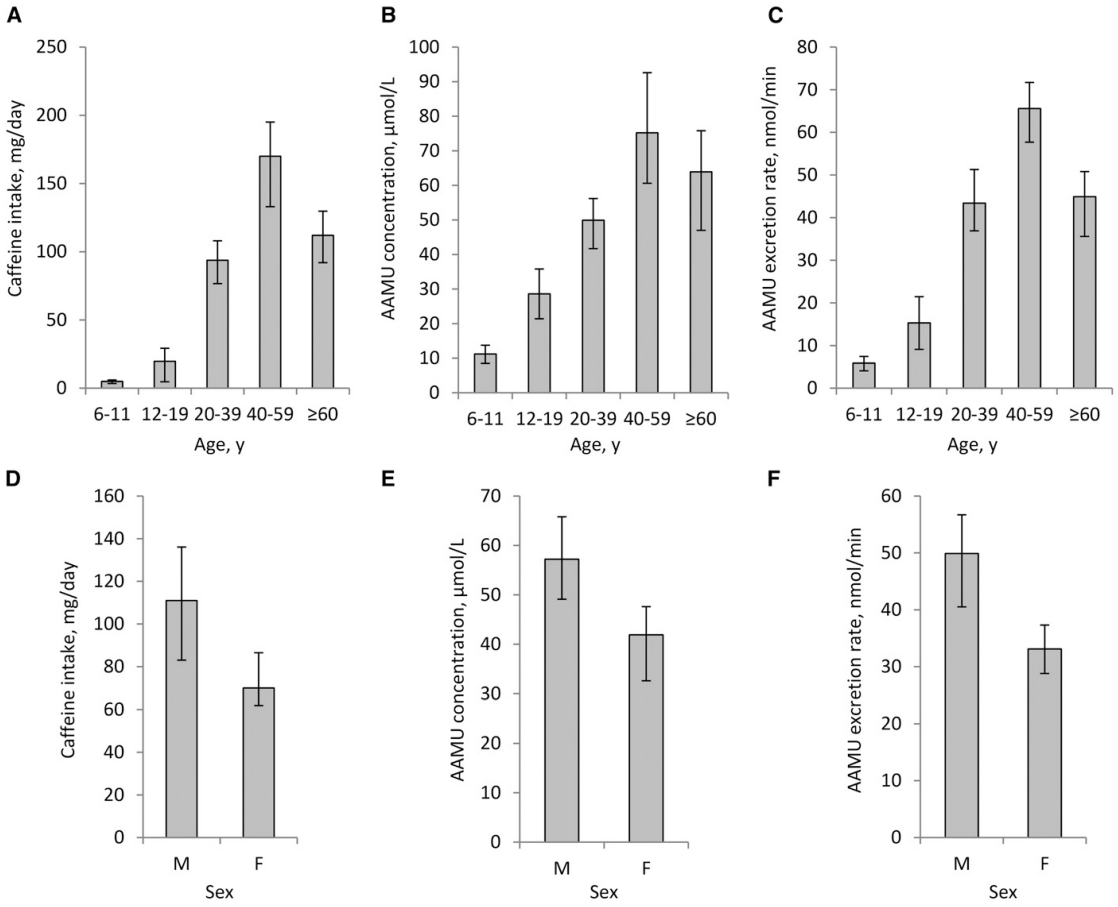

Figure 3: Age and sex vs. caffeine intake from dietary recall and urinary caffeine metabolite 5-acetylamino-6-amino-3-methyluracil (AAMU) in a representative sample of the US population (n = 2466). Figure from Rybak et al. (2015).

Plant defensive pesticides are often teratogenic, disrupting development and permanently impairing functionality. Nicotine is a teratogen that interferes with acetylcholine signaling, which has a unique trophic role in brain development. Nicotine exposure can disrupt all phases of brain assembly (Dwyer, Broide, and Leslie 2008).

Consistent with the risk that plant toxins pose to child development, there is considerable evidence for heightened toxin defenses during infancy and childhood. Although infants recognize that plants are sources of food, they are more reluctant to touch novel plants compared to other types of novel artifacts and natural objects of similar appearance, which might reflect an evolved psychological defense against plant toxins (Wertz and Wynn 2014). Neophobic food rejection occurs primarily due to visual cues. Foods that do not 'look right' – green vegetables for example, or foods that resemble known bitter foods – are rejected without being placed in the mouth. Food neophobia peaks between 2 and 6, and then decreases with age, becoming relatively stable in adulthood, a developmental trajectory widely interpreted to reflect an evolved defense against plant teratogens. Children also have a higher density of taste buds on the tip of the tongue than adults and are more sensitive to bitter tastes. High bitter taste sensitivity leads to reduced consumption of bitter vegetables, especially in children. For review, see Hagen, Roulette, and Sullivan (2013).

As a starting point for future research on low child drug use, we propose a model with three elements. First, to prevent ingestion of teratogens, children are innately neophobic, picky, and have heightened bitter sensitivity. Consequently, they find most neurotoxic pesticides to be especially unpalatable.

Second, social learning plays an especially important role in toxin avoidance. Whereas learning about toxic substances via individual trial-and-error comes with the potentially high cost of ingesting a toxin, one can socially learn to avoid toxic

substances from knowledgeable others “for free” (Boyd and Richerson 1985; Rogers 1988). Children should therefore be particularly attentive to information from parents and other adults that certain substances are dangerous, poisonous, or do not taste good, and assiduously avoid those substances (Cashdan 1994). In contrast, we expect considerable child resistance to parents’ efforts to restrict access to candy and other sugary foods, which, from an evolutionary perspective, are nearly pure beneficial nutrients.

Third, in adolescence brain and other organ development is nearing completion. We propose that adolescent onset of neurotoxic pesticide use is partly related to the reduced risk of developmental disruption and consequent reduced aversion to plant toxins, which also serves to broaden diet. See Figure 4.

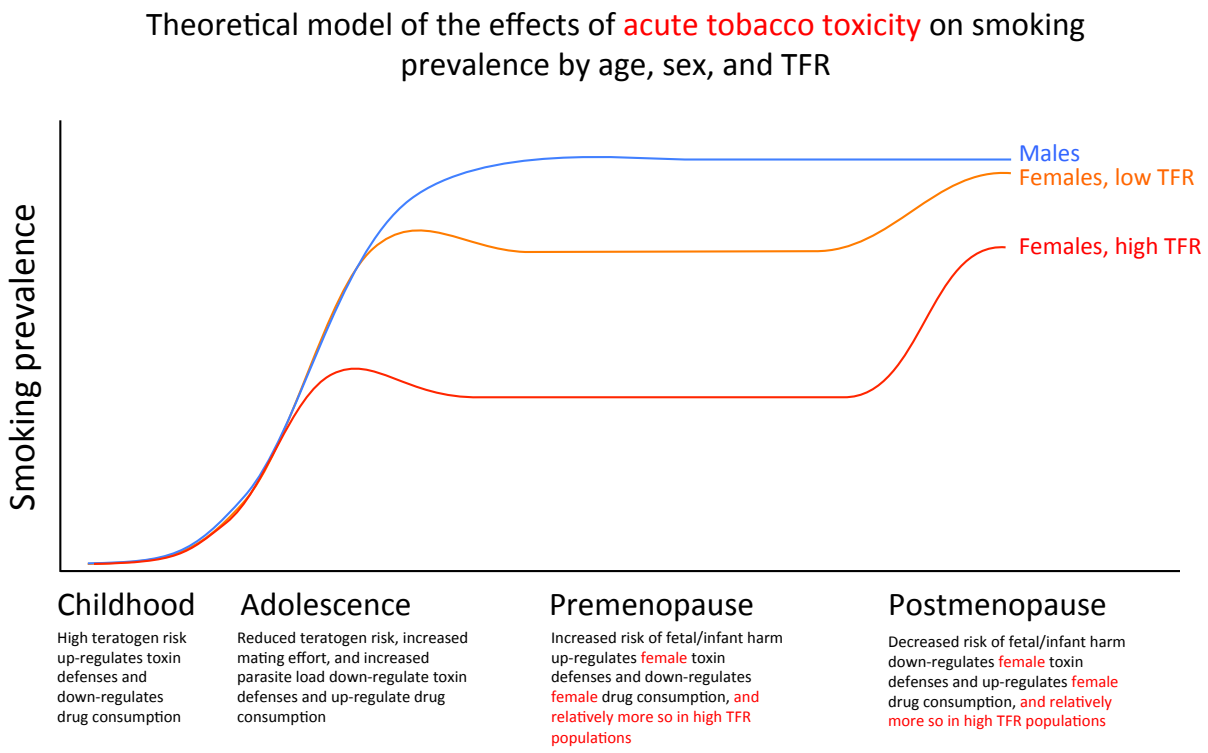

Figure 4: Theoretical model of age and sex differences in use of tobacco and other plant drugs. TFR: Total fertility rate. Figure from Hagen, Garfield, and Sullivan (2016).

Explaining the large sex difference in drug use

More men regularly use neurotoxic pesticides (and alcohol) than women, though the extent of the male bias varies by nation, substance, age, birth cohort, and other factors. Male prevalence of smoking is almost always greater than female prevalence, for instance, albeit with considerable variation across nations (Fig. 5). In the US there is even a male bias in caffeine intake (Fig. 3).

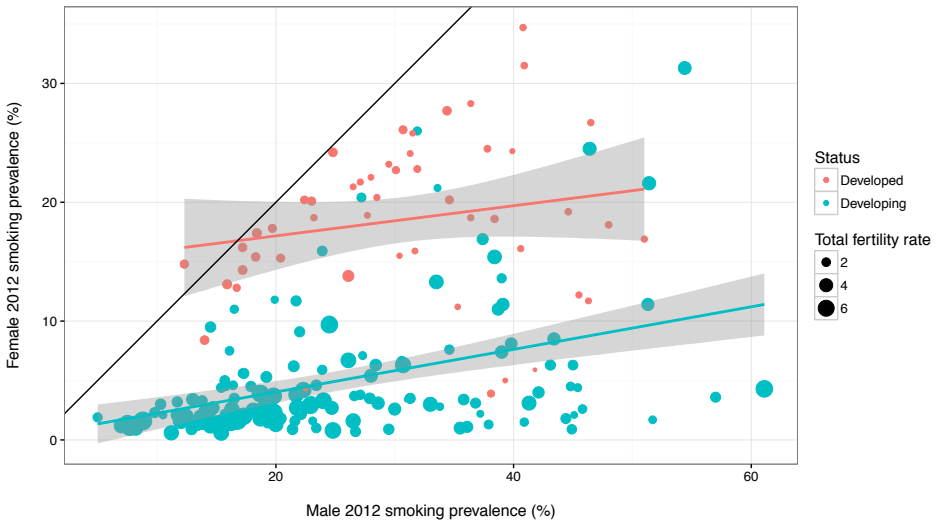

Figure 5: Female vs. male smoking prevalence across nations. Each dot is one country. The solid diagonal line represents equal prevalence. Figure from Hagen, Garfield, and Sullivan (2016).

The global male bias is narrower in younger cohorts, especially for the legal drugs tobacco and alcohol, and in recent years US adolescent girls (12-17) were more likely than adolescent boys to use alcohol and be non-medical users of psychotherapeutic drugs. In the US population as a whole, however, men were more likely than women to be users of all categories of drugs, including psychotherapeutic drugs and alcohol. For review, see Hagen, Roulette, and Sullivan (2013).

Over human evolution, ingestion of neurotoxic pesticides would probably have posed similar threats to men and women, but women of childbearing age faced the additional risk of disrupted fetal and infant development. Ancestral women were pregnant or lactating for much of their late teens to their late thirties. At the age that young women in Western societies might begin regular use of plant drugs (and

regular use of birth control), with their first pregnancy often years in the future, most women in ancestral environments were beginning about two decades of pregnancy and lactation. This could have selected for an increased ability to detect and avoid plant teratogens that would be harmful to fetuses and nursing infants, resulting in lower female use of neurotoxic pesticides that is evident even today.

There is considerable evidence for sex differences in toxin detection and disposition. Less clear is whether these differences are a consequence of greater toxin defenses in women, particularly pregnant women, or instead are byproducts of, e.g., sex differences in body size and composition.

Women have more taste buds than men and, according to most studies, are able to detect lower concentrations of bitter substances. High bitter sensitivity, in turn, generally predicts reduced vegetable intake in both women and men. Most studies indicate that women also have higher toxin metabolism rates. During pregnancy, heightened food aversions appear to help prevent ingestion of toxic plants, including coffee and tobacco, that might pose a risk to the developing fetus, especially during organogenesis. Women smokers, for example, commonly report new olfactory and gustatory aversions to tobacco during pregnancy, and the olfactory aversions are associated with women smoking less (Pletsch et al. 2008). Nicotine metabolism is accelerated in pregnancy, and activities of many xenobiotic-metabolizing enzymes are increased several-fold. For references and further discussion, see Hagen, Roulette, and Sullivan (2013).

In countries where women are pregnant and lactating more often (i.e., those with higher total fertility rates), there are fewer women smokers, even after accounting for gender inequality (Hagen, Garfield, and Sullivan 2016). The diminishing sex differences in use of some substances in younger cohorts might therefore partially reflect the global fertility transition over the last several decades that involves increased use of birth control, later age at marriage, delay of first birth, and lower total fertility, all of which would allow women, especially younger women, to increase drug intake while limiting fetal and infant exposure (Hagen, Roulette, and Sullivan 2013). We propose that social learning also plays an important role in women's decisions to use or avoid toxic plant substances (Placek and Hagen 2015; under review). See figure 4.

Possible explanations for regulated neurotoxic pesticide intake: an evolved 'taste' for drugs?

Drug toxicity would seem to predict no use whatsoever by individuals of any age or sex, contrary to the global popularity of smoking and other drug use.

Drug reward might be an accident. Over 100,000 plant defensive compounds have been identified (Wink 2011), and perhaps humans simply discovered a very few that, despite their toxicity to insects and other herbivores, accidentally trigger reward or reinforcement mechanisms (Hagen et al. 2009). This hypothesis faces a 'Goldilocks' problem, though: recreational plant pesticides must be accidentally rewarding or reinforcing enough to overcome their aversive properties, yet because

they are often highly toxic, they cannot be so rewarding or reinforcing for most users that they lead to immediate overdoses and death. The accidental effects of these compounds must be 'just right.' Hence, for each drug, the accident hypothesis involves not just one rare accident, but two.

Alternatively, *regulated* toxin intake might have produced fitness benefits in certain circumstances. Because wild plant foods are infused with defensive chemicals, plant consumers, including human ancestors, should have evolved some type of regulatory mechanism that balances intake of nutrients vs. toxins so as to avoid poisoning (Torregrossa and Dearing 2009). See Figure 6. But regulated toxin intake occurs even in the absence of a nutrient signal. Laboratory animals regulate their self-administration of drugs at a fairly constant and stable level regardless of the dose per injection or number of lever presses requires (Yokel and Wise 1976). Human cigarette smokers similarly alter their smoking behavior in response to changes in nicotine content so as to maintain a relatively constant blood concentration of nicotine (Scherer and Lee 2014). These are clues that special mechanisms might have evolved to carefully regulate plant toxin intake (Hagen et al. 2009; Hagen, Roulette, and Sullivan 2013).

There are many possible fitness benefits of regulated ingestion of neurotoxic plant pesticides, most of which reconceptualize these compounds as valuable medicines rather than hijackers (Sullivan and Hagen 2002; Sullivan, Hagen, and Hammerstein 2008; Hagen et al. 2009; Hagen, Roulette, and Sullivan 2013). Neurotoxic pesticides achieve their effects because they evolved to manipulate cellular signaling. Nicotine,

for instance, mimics acetylcholine, a neurotransmitter involved in neuromuscular communication and many other important functions. In large doses, nicotine kills. In small, highly regulated doses, though, such as the ~ 1 mg delivered by smoking a cigarette, it might provide a number of immediate benefits. (The long-term health costs of smoking are indisputable, however.)

One possible benefit is defense against parasites. Many heterotrophic species evolved to co-opt plant toxins for prophylactic or therapeutic effects against pathogens, i.e., self-medication, also known as pharmacophagy or zoopharmacognosy. All popular recreational drugs are toxic to parasitic worms (helminths). It is not out of the questions that humans and other animals evolved to seek out and ingest small quantities of neurotoxic pesticides to help combat helminths and other parasites (Sullivan, Hagen, and Hammerstein 2008; Hagen et al. 2009; Hagen, Roulette, and Sullivan 2013; Roulette et al. 2014). If the pharmacophagy hypothesis is correct, then the toxicity of drugs to parasites provides the ultimate explanation for their use by humans. See Figure 6.

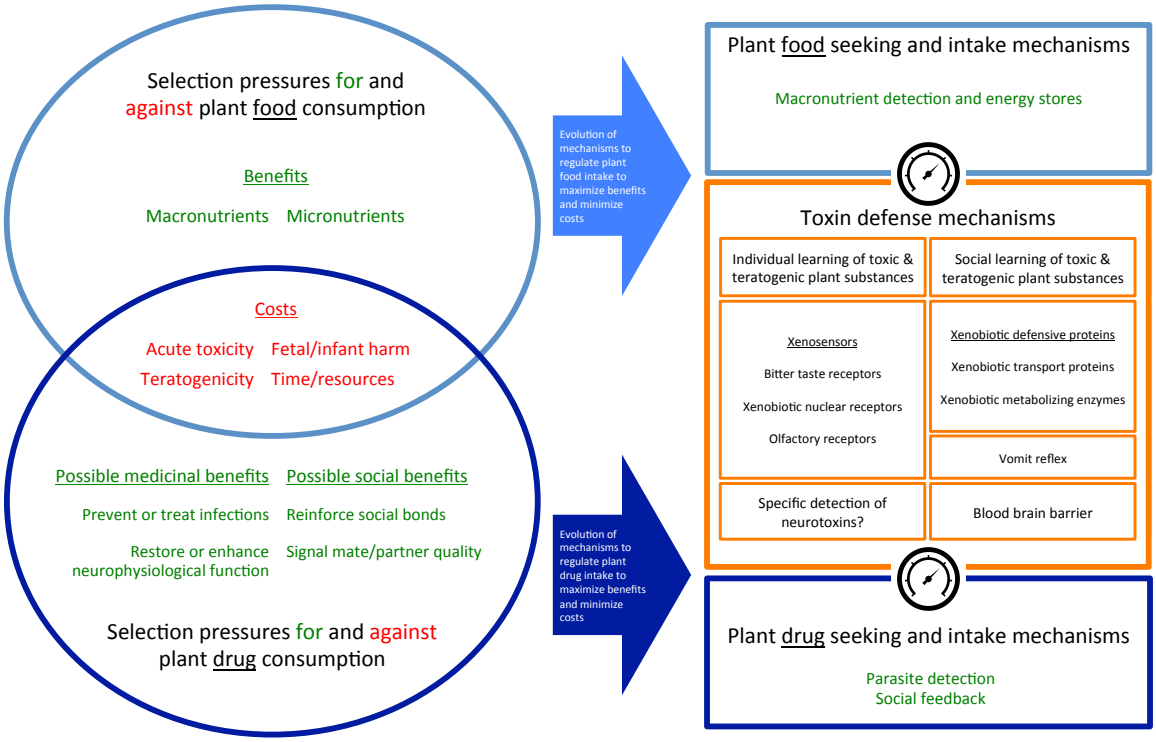

Figure 6: *The neurotoxin regulation model* of the evolution of "recreational" drug use. Benefits are in green; costs are in red. Figure modified from Hagen, Garfield, and Sullivan (2016).

Salt intake provides a useful analogy: there are complex neuronal and endocrine mechanisms, including special salty taste receptors on the tongue, that regulate intake of milligrams of this valuable environmental chemical to maintain sodium homeostasis (Geerling and Loewy 2008), even though there is no conscious awareness of its biological benefits. Similarly, bitter taste receptors and other xenosensors, in conjunction with neuronal, immunological, and other mechanisms, might regulate intake of milligrams of neurotoxins for their medicinal or social benefits without any conscious awareness of these benefits.

In conclusion, popular recreational drugs are neurotoxic pesticides, varieties of which have infused the diets of human ancestors for hundreds of millions of years. These and other xenobiotics selected for a sophisticated, multilayered toxin defense system that correctly identifies all drugs of abuse as toxins. In this light, it is doubtful that recreational drugs are best characterized as evolutionarily novel hijackers of reward circuitry. Although the correct evolutionary account of recreational drug use is not yet clear, our neurotoxin regulation hypothesis (Fig. 6) provides a compelling hypothesis for the very low use of recreational drugs by children, the low use by women of reproductive age relative to men, and the careful titration of drug intake by humans and non-human animals. The increasing evidence that non-human animals ingest plant toxins to help defend against pathogens and provide other fitness benefits should inspire similar hypotheses for human drug use.

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