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REVIEW

ECOLOGY AND NEUROBIOLOGY OF TOXIN AVOIDANCE AND THE PARADOX OF DRUG REWARD

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Abstract—Current neurobiological theory of drug use is based on the observation that all addictive drugs induce changes in activity of dopaminergic circuitry, interfering with reward processing, and thus enhancing drug seeking and consumption behaviors. Current theory of drug origins, in contrast, views almost all major drugs of abuse, including nicotine, cocaine and opiates, as plant neurotoxins that evolved to punish and deter herbivores. According to this latter view, plants should not have evolved compounds that reward or reinforce plant consumption. Mammals, in turn, should not have evolved reinforcement mechanisms easily triggered by toxic substances. Situated in an ecological context, therefore, drug reward is a paradox. In an attempt to resolve the paradox, we review the neurobiology of aversive learning and toxin avoidance and their relationships to appetitive learning. We seek to answer the question: why does aversive learning not prevent the repeated use of plant drugs? We conclude by proposing alternative models of drug seeking and use. Specifically, we suggest that humans, like other animals, might have evolved to counter-exploit plant neurotoxins.

Key words: pharmacophagy, reward learning, aversive learning, nicotine, dopamine, psychoactive substance use.

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Abbreviations: CS, conditioned stimulus; CTA, conditioned taste-aversion; DA, dopamine; MDS, mesocorticolimbic dopamine system; NAc, nucleus accumbens; nAChR, nicotinic acetylcholine receptor; PNS, peripheral nervous system; SNc, substantia nigra pars compacta; THC, delta-9-tetrahydrocannabinol; US, unconditioned stimulus; VTA, ventral tegmental area.

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INTRODUCTION

Almost all major recreational drugs, including caffeine, nicotine, delta-9-tetrahydrocannabinol (THC, the active ingredient in cannabis), cocaine, amphetamines, and heroin (but excepting alcohol) are plant neurotoxins or, in the case of several synthetic drugs, their close chemical analogs. (Neurotoxins are defined by their ability to cause structural damage or functional disturbance of nervous tissues upon application of relatively small amounts.) These drugs acquire their psychoactive effects by interfering with neuronal signaling in the CNS, for example by

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binding to neurotransmitter receptors, or interfering with neurotransmitter transport mechanisms (Wink, 2000). Many of the components of neuron signaling targeted by these toxins are ancient, and are found in most animals. For instance, the nicotinic acetylcholine receptor (nAChR), targeted by the neurotoxin nicotine, has an evolutionary history extending back about 1 billion years (Novere and Changeux, 1995). The nAChR mediates the CNS effects of nicotine by changing the levels of dopamine (DA), which is involved in reward processing. Crucial aspects of DA function, such as the dopaminergic neuromodulation of glutamatergic synapses, appear to be conserved across the eumetazoan clades (insects, vertebrates, mollusks, and nematodes) (Hills, 2006). The DA system is directly targeted by cocaine and, as we discuss later, is also heavily involved in the CNS effects of nicotine and other addictive drugs.

Here we show that the two scientific traditions specializing in the physiological effects of plant neurotoxins are largely incompatible. The first tradition comprises phytobiologists, ecologists, and pharmacologists studying plants, plant–herbivore interactions, and plant secondary compounds. According to this tradition, many secondary compounds evolved to deter herbivores.

The second tradition focuses on the neurobiology of drug use and addiction in humans. This tradition emphasizes the important role of DA in reward-related behavior and explains addiction as the result of drug interference with natural reward systems. According to neurobiologists, drugs such as nicotine, cocaine, opium, and THC activate neural circuits involved in reward processing, thus encouraging consumption. In seeming contradiction, plant biologists argue that such drugs evolved precisely because they successfully punished and deterred consumption. This apparent contradiction has been termed the *paradox of drug reward* (Sullivan and Hagen, 2002; Sullivan et al., 2008).

After describing the two perspectives in depth, we then take steps to address the paradox by reviewing the neurobiology of aversive learning and toxin avoidance and their relationships to appetitive learning. We seek an answer to the question: Why does aversive learning not prevent the repeated use of those plant neurotoxins commonly used as drugs? We examine the possibility that drug exposure is an evolutionary novelty, and we propose alternative "ultimate" models of drug seeking and use, according to which humans might have evolved to counter-exploit plant toxins in various ways.

ECOLOGY: PUNISHMENT MODEL OF DRUG ORIGINS

There is a 300–400 million year history of antagonistic co-evolution between terrestrial plants, which photosynthesize chemical forms of energy for their own reproduction, and the bacterial, fungal, nematode, invertebrate and vertebrate herbivores that exploit plant tissues and energy stores for food and other nutrients, often severely damaging a plant's ability to reproduce. To limit such damage, most plant species have evolved aggressive defense strategies to punish herbivores that feed on them. These strategies include mechanical defenses, such as thorns, as well as chemical defenses, such as toxins that interfere with herbivore growth, development, fecundity and other aspects of functioning (Karban and Baldwin, 1997).

Plant chemical defenses against herbivores

One broad category of chemical defenses includes compounds with relatively nonspecific effects on a wide range of molecular targets in the herbivore. Tannins and other phenolics, for instance, can form multiple hydrogen and ionic bonds with numerous proteins, changing their conformation and impairing their function (Wink, 2003).

Another broad category of defensive compounds interferes with specific aspects of herbivore physiology. Of central interest to us are those compounds that have evolved to interfere with signaling in the CNS and peripheral nervous system (PNS). Psychoactive plant-based drugs fall into this category. It is striking that different plant compounds 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 (Wink, 2000). In many cases, plant compounds achieve these effects because they have evolved to resemble endogenous neurotransmitters. Many plant drugs are alkaloids, secondary metabolites containing nitrogen. Several alkaloids form a quaternary nitrogen configuration under physiological conditions, a structural motif present in most neurotransmitters (Wink, 2006).

The punishment model has successfully explained the function of many plant secondary metabolites (Swain, 1977; Wink, 1998). Even so, the precise evolved functions of most plant secondary compounds are still unknown, and among the popular plant drugs only nicotine, which we discuss next, has been conclusively shown to serve plant defense.

Nicotine. The defensive functions of nicotine are particularly well documented. We use nicotine examples throughout this article because, unlike other plant drugs, nicotine has been extensively studied from both ecological and neurobiological perspectives, and it is one of the world's most popular plant drugs, behind only caffeine and chocolate. Furthermore, smoking is estimated to account for 12% of global adult mortality (Ezzati and Lopez, 2004), which makes tobacco consumption one of the scientific community's most urgent, unsolved problems.

Nicotiana attenuata, a wild North American tobacco plant used by Native Americans, is an important model species for the analysis of plant–herbivore interactions involving nicotine. It is attacked by over 20 different herbivores, ranging from mammalian browsers to intracellular-feeding insects. These attacks induce defensive responses, including production of nicotine, which, because it is costly for the plant, is allocated to tissues that are vital to plant fitness, and/or are likely to be eaten by herbivores (Baldwin, 2001). Studies in which nicotine production in