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. © 2009 IBRO. Published by Elsevier Ltd. All rights reserved.

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.

Contents

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

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
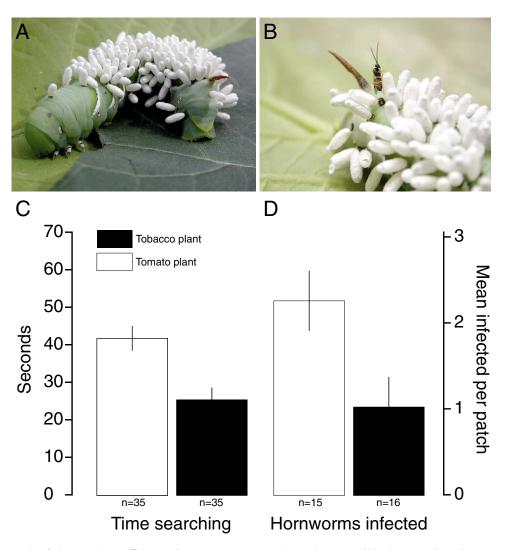
Fig. 1. Possible example of pharmacophagy. Tobacco diet appears to protect tobacco hornworm (*Manduca sexta*), a tobacco specialist herbivore, from infection by a tomato-plant-adapted sub-population of the parasitoid wasp *Cotesia congregata* (but not from a tobacco-plant-adapted sub-population). (A) Hornworm infected with larva of the parasitoid wasp. (B) Adult wasp emerging from cocoon. (C) Parasitoids from a tomato-adapted sub-population spent less time searching for hornworms on disks of tobacco leaf (more toxic) than tomato leaf (less toxic). Females used in this experiment had no prior exposure to plants. (D) Early in the season, fewer hornworms feeding on tobacco plants were infected by tomato-adapted parasitoids than hornworms feeding on tomato plants (tobacco-adapted parasitoids, in contrast, equally attacked hornworms feeding on tobacco or tomato plants). This difference disappeared late in the season, perhaps due to learning by the parasitoids. Each bar represents the least squares mean±SE. Charts redrawn from Kester and Barbosa (1994). Photographs c. Galveston County Master Gardener Association, Inc.

There have been a number of recent, comprehensive reviews of the roles of the mesolimbic dopamine system (MDS) and reward-related learning in drug seeking and use (Everitt and Robbins, 2005; Kalivas and Volkow, 2005; Koob and Le Moal, 2005; Lüscher and Ungless, 2006; Nestler, 2005; Schultz, 2007). We therefore only briefly describe DA cell activity and influential models of the functional role of DA.

DA neurons giving rise to the MDS play a central role in reward processing. These neurons are located in the midbrain structures of the ventral tegmental area (VTA) and substantia nigra pars compacta (SNc) and project to the nucleus accumbens (NAc) and dorsal striatum, composed of the caudate and putamen. In a number of mammals, including rats and monkeys, electrophysiological re-

cordings revealed transient increases in the activity of the VTA DA neurons when the organism encountered reward-related stimuli (Kelley and Berridge, 2002). The rise in activity of these dopaminergic projections increases the levels of extracellular DA in the NAc, mediating functional behavioral responses to reward-related stimuli (Koob and Le Moal, 2005; Nestler, 2005).

Addictive drugs modulate dopaminergic circuitry

Reward models of drug use are based on the observation that, despite their diverse effects on the CNS and PNS, all addictive drugs modulate DA activity in the MDS (Di Chiara and Imperato, 1988; Balfour, 2002; Fagen et al., 2003; Hyman et al., 2006; Nestler, 2005). Via disinhibition, exci-

tation, or uptake blockade, each drug causes DA to increase in the NAc. The elevation in NAc DA levels affects normal reward processing mechanisms to enhance drug seeking and consumption.

Nicotine. To illustrate a few of the mechanisms by which an addictive drug elevates DA levels in the NAc, we focus on nicotine. Nicotine activates nAChRs, which are abundant in the CNS, PNS, as well as non-neuronal cells (Gotti and Clementi, 2004). We will concentrate on nAChRs located on (1) DA cells, (2) targets of the DA neurons (e.g. NAc, Fig. 2), and (3) inputs to the DA neurons. Nicotinic AChRs are ionic channels, which have direct impact on the neuron's membrane potential. Binding of nicotine to neuronal nAChRs causes depolarization. Those nAChRs located on the cell bodies of DA neurons immediately enhance excitation, and nAChRs on DA neuron nerve terminals increase release of DA in the target structures (Mansvelder et al., 2003; Rice and Cragg, 2004).

The duration of the nicotinic effect is determined by receptor desensitization, which depends, among other things, on the receptor subtype (Laviolette and van der Kooy, 2004). Although nicotine excites both excitatory and inhibitory inputs to the VTA DA neurons, differences in desensitization time courses of receptors cause a net increase in DA cell activity lasting for several minutes (Mansvelder et al., 2002). Furthermore, nicotine may also affect the fine temporal structure of DA signaling (Mameli-Engvall et al., 2006). Zhang and Sulzer (2004) elegantly demonstrated a differential desensitization of baseline vs. transient activity of DA neurons, effectively increasing prominence of the response (or enhancing the signal/noise ratio). On a longer time scale, the nicotine-induced increase in activity of the excitatory inputs leads to long-term poten-
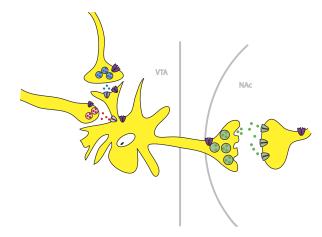
tiation (LTP) in this pathway (Mansvelder and McGehee, 2000).

The picture sketched here is unique to nicotine. Other drugs manipulate the MDS via different routes. We now describe the functional meaning of changes in DA neuron activity.

Functional roles of DA

There is widespread agreement about the importance of DA neurons to drug use, as well as for responses to beneficial stimuli, yet debate continues about their precise role in these behaviors. In an early interpretation of DA function in the MDS, dopaminergic systems were thought to directly mediate the rewarding or primary motivational characteristics of natural stimuli such as food, water, and sex, as well as the conditioned pleasure produced by stimuli previously associated with reward (e.g. Wise et al., 1978; Wise and Rompre, 1989), a hypothesis sometimes referred to as the *hedonia* hypothesis. Under this hypothesis, the DA increase caused by addictive drugs induces hedonic experiences.

Drug use, however, often does not produce hedonic or euphoric effects. Moreover, manipulation of DA transmission has a powerful impact on behavior without changing hedonic reactions. It has therefore been argued that "wanting" is distinct neurologically, psychologically, and conceptually from "liking," and that the MDS mediates wanting, not liking (i.e. not hedonia). In other words, DA assigns motivation to stimuli (Berridge, 2007), a hypothesis termed *incentive-salience* (Robinson and Berridge, 1993; Berridge and Robinson, 1998). Under this hypothesis, drug-induced DA release labels the drug as a "wanted" stimulus.

DA neurons fail to respond when animals receive an *anticipated* reward. This finding is in line with a computational reinforcement learning model (Montague et al., 1996; Schultz et al., 1997), suggesting that the response of midbrain dopaminergic neurons encode reward prediction errors, rather than absolute reward. Reward prediction errors are defined as the difference between the predicted and the actual reward. Thus, unpredicted rewards elicit activation of midbrain dopaminergic neurons (positive-prediction error), fully predicted rewards elicit no response, and the omission of predicted rewards induces a depression (negative-prediction error) (Montague et al., 1996; Schultz et al., 1997; Morris et al., 2004, 2006; Pan et al., 2005; Schultz, 2007). This reward prediction error signal is crucial for learning about reward-related stimuli in a family of computationally powerful reinforcement learning mechanisms. Under this hypothesis, the DA release following drug intake strongly reinforces the drug-taking behavior.

In summary, despite debate on the exact role of DA, there is agreement that DA plays a major role in the processing of reward-related stimuli and that drug-induced DA release is central to drug use phenomena. All of these DA hypotheses therefore raise the paradox of drug reward.

Fig. 2. Sites of action of nicotine in the MDS. Nicotinic receptors are located pre-synaptically on afferents to DA neurons. Their activation increases the amount of released neurotransmitter. On the post-synaptic site in the VTA they directly act on the DA neuron. In the target structures (NAc, striatum, frontal cortex) nicotinic receptors are mainly pre-synaptic, enhancing DA release. The natural ligand for these receptors is acetylcholine. In the VTA and SNc acetylcholine is secreted by projections from the brain-stem pedunculopontine tegmental nucleus (PPTg), whereas in the NAc and striatum it is released by local interneurons.

PARADOX OF DRUG REWARD

To recapitulate our findings so far: Neurobiologists have developed a strong case that several plant neurotoxins stimulate reward and reinforcement circuitry in humans and other mammals. Theirs is a "proximate-level" model, one grounded in physiological facts. Phytobiologists, on the other hand, have developed a strong case that many plant secondary metabolites, including psychoactive compounds, are best explained by their ability to *punish*, not reward, herbivores. From the "ultimate-level," evolutionary biological perspective, it is therefore in the fitness interests of both plant and herbivore that the herbivore is averse to the plant's defensive toxins. Specifically, plants should not have evolved defensive chemicals that easily trigger reward or reinforcement in consumers, and consumers should not have evolved neural mechanisms that readily reward or reinforce consumption of neurotoxins. Framed in the ultimate-level, evolutionary model of drug origins, drug reward is paradoxical (Sullivan et al., 2008).

Is drug reward an "accident"?

It is tempting to conclude, for several reasons, that drug reward might be an accident, and, if so, that this would resolve the paradox. First, it is unlikely that plant defensive chemicals evolved to deter herbivory by humans because a plant species' defensive compounds should deter its principal herbivores, which could include various bacteria, fungi, nematodes, arthropods, and vertebrates. Plants also appear to have evolved compounds to inhibit the growth and reproduction of competing plants (caffeine, for instance, is an autotoxin, i.e. it is toxic to other coffee and tea plants; Singh et al., 1999). If plant drugs evolved primarily to deter non-mammalian herbivores (perhaps even a single specialist herbivore) or to inhibit the growth and reproduction of competing plants, their effects on mammals, and humans in particular, need not necessarily be toxic or aversive. Indeed, because the insect aversive system employs DA (see next section), which underlies the reward system in mammals, a plant targeting dopaminergic systems in insects might inadvertently trigger reward or reinforcement in mammals.

Second, a plant defensive compound might have evolved to target one system in herbivores but accidentally activates other systems at the same time. In an experiment with honeybees, Barron et al. (2009) found that treatment with a low dose of cocaine increased the likelihood and rate of bees dancing after foraging, consistent with the hypothesis that cocaine caused forager bees to overestimate the value of the floral resources they collected, and hence that cocaine has effects on reward processing in honeybees similar to those seen in mammals. Barron et al. (2009) argue that the reinforcing properties of low doses of cocaine in honeybees and other herbivores occur as a "side effect" of cocaine's evolved role as a potent disrupter of the biogenic amine neuromodulator systems regulating motor control in insects and mammals. Such disruption occurs when cocaine is consumed in the high doses found in coca leaves.

Third, if certain plant drugs evolved to perform strictly non-defensive functions then, for that drug, some (but not all) arguments for the paradox are lost. Indeed, it is known that a variety of plant compounds manipulate animals in ways other than punishment and deterrence. Many plants, for example, provide important benefits to animals, such as fruit and nectar, in order to obtain important services, such as pollen or seed dispersal. Tobacco and other plants emit scents that attract such pollinators and seed dispersers (Kessler et al., 2008). During and after attack by feeding insect larvae, many plants also increase emissions of volatile organic compounds, which attract predators of the larvae (Kessler and Baldwin, 2001). It is therefore at least conceivable that, to increase plant fitness, some plant drugs did not evolve to punish herbivores but instead to "manipulate" animals, microbes, or even other plants, in unknown ways (see section on aposematism below). It is also possible some drugs serve a purely internal function for the plant. To resolve the paradox for a particular drug, its precise ecological role will therefore have to be identified. (We hasten to add that although, conceivably, some drugs might not serve plant defense, the evidence supporting a defensive function for nicotine in tobacco is overwhelming, and it is a potent repellent to herbivores, pollinators, and nectar robbers; Kessler et al., 2008.)

Finally, among the over 29,000 identified plant alkaloids (Wink, 2003) and other defensive compounds, humans might have simply discovered precisely those very few that, despite their toxicity to the target organisms, accidentally trigger human reward or reinforcement mechanisms (Nesse, 2002).

At present, we cannot assess the likelihood of an accidental activation of the human midbrain DA system by some plant compounds. It is crucial to note, however, that the accident hypothesis (even if true) does not necessarily solve the paradox of drug reward. The (possibly) accidental elevation of NAc DA by plant compounds could provide a resolution of the paradox at the proximate level (i.e. one based on physiological rather than evolutionary considerations). Yet if the human nervous system and other elements of our physiology correctly identify drugs as toxins, an ultimate, evolutionary puzzle remains: why did we not evolve to avoid consuming recognizably toxic compounds, such as nicotine, despite any incidental rewarding or reinforcing effects?

Seeking an ultimate resolution of the paradox, we next briefly review the neurobiology of aversion and aversive learning, finding that drugs *are* recognized as toxins. We then discuss the interaction of appetitive and aversive learning in section. Finally, we propose and evaluate potential resolutions of the paradox in section.

AVERSION AND AVERSIVE LEARNING

Consumption of poisonous compounds should invoke neurobiological processes involved with aversion and deterrence. Exposure to psychoactive drugs typically triggers two responses: along with the drug-specific "rewarding" or reinforcing effects, there is indeed an aversive reaction, as

expected for toxins. Nicotine and cocaine, for example, can have both rewarding and aversive effects, including nausea, dizziness, headache and digestive malaise (Shoaib, 1998; Ettenberg, 2004; Risinger and Oakes, 1995; Eissenberg and Balster, 2000; Laviolette and van der Kooy, 2003a; DiFranza et al., 2004). Thus, physiologically, most drugs are correctly identified as toxic.

Encounter with aversive stimuli usually elicits a form of learning known as *aversive learning*, the ultimate goal of which is reduction in the behavior that is associated with the aversive reaction. Aversive learning has been demonstrated in many species, from sea-slugs (Walters et al., 1981, 1979), nematodes (Nuttley et al., 2001), and insects (Vergoz et al., 2007; Unoki et al., 2006, 2005; Riemensperger et al., 2005; Glanzman, 2005; Schwaerzel et al., 2003) to rodents (Guimaraes et al., 1993; Nader et al., 2000; Wang et al., 2005; Wilensky et al., 2006; Fanselow and Gale, 2003; Boatman and Kim, 2006; Lee and Kim, 2004; Davis, 1992; Maren and Quirk, 2004), rabbits (Frey et al., 1976), non-human primates (Paton et al., 2006), and humans (Seymour et al., 2007b; Delgado et al., 2006). Aversive learning is a core feature of behavior.

Intake of highly toxic drugs is limited

Drug consumption is limited, probably by aversion and aversive learning. Typical quantities consumed by drug abusers are often worryingly close to the lethal dose. For 20 abused substances, Gable (2004) computed the "safety ratio," the ratio of the acute lethal dose to the dose most commonly used for non-medical purposes. Several plant drugs had surprisingly small safety ratios: heroin (intravenous)=6, cocaine (intranasal)=15, and codeine (oral)=20. Although Gable did not examine nicotine, the lethal dose for an adult is estimated to be 30–60 mg (Gosselin et al., 1984). Because smokers typically absorb 0.5–2 mg per cigarette, and chewers up to 4.5 mg per "wad" (Hukkanen et al., 2005), the safety ratio for nicotine is roughly 20–40 (Room, 2006), on par with cocaine and codeine.

Worldwide, an estimated 15 billion cigarettes are smoked every day, and 1.3 billion adults, or 1/3 of the world's adult population, are tobacco users (Guindon and Boisclair, 2003). Given these numbers, it is remarkable that there are almost no deaths from acute nicotine poisoning via smoking or chewing tobacco (Gable, 2004), although deaths from other types of nicotine poisoning are well known (e.g. from harvesting and processing tobacco, exposure to nicotine-based insecticides, or ingestion of cigarettes, cigars, or nicotine gum by children; de Landoni, 1991). Morbidity and mortality from chronic tobacco use, of course, is unquestionably high.

It seems, therefore, that humans have evolved a superbly efficient protective system against plant neurotoxins that helps to maintain a surprisingly low mortality rate. In neurobiological terms, the paradox of drug reward could therefore be rephrased: Why do aversion and aversive learning systems fail to prevent repeated consumption of certain plant neurotoxins?

Neurobiology of aversive learning

Despite many similarities between the underlying principles of appetitive (reward) and aversive associative learning, cumulative evidence seems to point to different, although converging, neuronal pathways signaling the different components of the association process. In mammals, a number of brain structures have been implicated with the signaling of aversive stimuli and with aversive learning: the dorsolateral amygdala (Nitschke et al., 2006; Fanselow and Gale, 2003; Maren, 2003; Nader et al., 2000; Zald and Pardo, 2002), anterior insula (Nitschke et al., 2006), anterior cingulate cortex (Nitschke et al., 2006; Johansen and Fields, 2004; Blair et al., 2006), and dorsolateral prefrontal cortex (Dunsmoor et al., 2008; Nitschke et al., 2006). The dorsolateral amygdala, in particular, seems to be activated in response to unpleasant stimuli in a wide range of modalities, possibly mediating the pavlovian response (Fendt and Fanselow, 1999; Seymour et al., 2007b).

The VTA, a component of reward processing as we discussed earlier, might also play a role in aversive learning. A VTA non-dopaminergic subpopulation is actually excited by aversive stimuli; furthermore, DA neurons in the VTA pause during aversive stimuli (Ungless et al., 2004). The DA pause during aversive stimuli could be an important signaling factor in aversive learning. It has also been proposed that DA signals aversive events via a non-phasic firing mode (Horvitz, 2000). Obviously, the precise role, or roles, of DA in the MDS, including reward, reinforcement, and aversion, bears strongly on understanding how a drug-induced increase in DA impacts drug use behavior.

Whereas there is a near-consensus on the role of midbrain DA in appetitive learning in mammals (Schultz, 2007; Ungless, 2004; but see also Berridge, 2007), the counterpart to this role in aversive learning has not yet been clearly identified. A theoretical study has implicated 5-HT (Daw et al., 2002), but empiric evidence is lacking.

Insects' reward and aversive systems, in contrast, have both been identified (Schroll et al., 2006; Giurfa, 2006). Interestingly, aversive learning in insects employs the dopaminergic system (Riemensperger et al., 2005; Vergoz et al., 2007), whereas appetitive learning is mediated by the octopaminergic system (Unoki et al., 2005). General features of insect aversive learning are similar to the mammalian DA reward learning system: the insect system has the ability to learn to predict future punishments and develops a response that is in accordance with a punishment prediction error (Riemensperger et al., 2005).

It therefore seems possible that neurotoxins targeting the insect aversive DA system could accidentally trigger the mammalian reward DA system. However, many plant drugs elevate DA in mammals via multiple signal cascades. A model in which these effects are transferred from the insect aversive system to the mammalian reward system would require important similarities in the neuroanatomical, pharmacological and physiological structure of the dopaminergic system in insects and mammals. There is currently little evidence for this. At least one study, for

example, found the toxic effects of cocaine in insects to involve potentiation of octopamine neurotransmission, not DA reuptake (Nathanson et al., 1993). Furthermore, in contrast to the idea that drugs will have opposite effects on insects and mammals, it has been argued that there are instead many similarities (e.g. Barron et al., 2009), such as an increase in locomotor activity for certain nicotine dosages (Wolf and Heberlein, 2003). Finally, although differences in neurotransmitter systems among herbivore species pose a problem to plants in developing general chemical defense mechanisms, there probably has been selection on most plants to produce toxins that successfully deter a range of invertebrate and vertebrate herbivores. Nicotine, for instance, is extremely toxic to both invertebrates and vertebrates (de Landoni, 1991).

Conditioned taste-aversion (CTA)

Because we are interested in detection of, and responses to, dietary toxins by animals, we focus on results from an experimental paradigm based on oral consumption and taste.

Taste information is rapidly conveyed to the CNS through taste receptors located in the oral cavity. In the CNS, two neural pathways are activated by these inputs. Cortical gustatory regions code the quantitative and qualitative aspects of the tasted substance. In parallel, affective properties of the taste are processed in the insular cortex, amygdala and the VTA. These areas project to the feeding center in the lateral hypothalamus, thus controlling feeding behavior (Yamamoto, 2006).

Aversive learning following the consistent pairing of an artificially induced illness with oral consumption of a previously neutral, or even pleasant, substance is termed CTA (Revusky and Bedarf, 1967; Revusky, 1968). Such aversive learning results in a decline in the consumption of the substance. It is important to note, however, that aversions are also readily formed to substances which the subject has tasted without ingesting, and in the absence of any consummatory response (Dickinson and Mackintosh, 1978).

CTA exhibits properties known from other forms of associative learning (for a review, see Klosterhalfen and Klosterhalfen, 1985). It is dependent on reliable presentations demonstrating the association of the conditioned stimulus (CS, taste) to the unconditioned stimulus (US, sickness) (McLaren and Dickinson, 1990), and is impeded by uncorrelated presentations of both, by repeated presentations of one stimulus and not the other, by non-causal presentations, and by total predictability of the US by other CS. Importantly, and similar to appetitive learning, CTA is sensitive to motivational modulation. Devaluation of the US, e.g. by habituation following aversive conditioning, reduces the magnitude of the avoidance response subsequently elicited by the CS (Rescorla, 1973).

Several features of CTA distinguish it from most forms of appetitive learning, however, highlighting the evolutionary importance of avoiding toxins. First, similar to other types of aversive learning, learning often occurs with a single pairing of CS and US (Barber et al., 1998). Second,

conditioning can occur even when there are extremely long intervals between stimulus presentation and the sickness (McLaren and Dickinson, 1990). However, an inverse relation between the time delay and strength of learning still exists. Finally, animals seem disposed to readily associate illness or nausea with taste but not with other stimuli (Klosterhalfen and Klosterhalfen, 1985). Because most classes of psychoactive drugs can induce CTA (Cappell et al., 1973; Hunt and Amit, 1987), each of these features renders the failure to successfully acquire a distaste to drug consumption all the more puzzling. In summary, many psychoactive drugs seem to have the surprising property of being able to induce both aversive and rewarding effects (Hunt and Amit, 1987; Parker, 1995; Wise et al., 1976).

Nicotine. Nicotine is one of the psychoactive drugs that induce CTA. In rodents, for example, consumption of saccharin solution followed by s.c. injection of nicotine reduces future saccharin solution consumption (Korkosz et al., 2006; Castane et al., 2006). Direct injections of nicotine in the NAc can also produce CTA (Shoaib, 1998). In humans, nicotine injections induce aversive responses, especially in non-smokers (Eissenberg and Balster, 2000). The neural machinery that identifies nicotine as a toxin therefore exists and is functional.

Interaction of appetitive and aversive learning

In natural situations, appetitive and aversive learning mechanisms interact to achieve adaptive decision-making by comparing a behavior's expected rewards (benefits) with expected punishments (costs). Therefore, an architecture must exist in which the two opposing motivational mechanisms, the aversive and appetitive ones, competitively interact and a decision is reached (Dickinson and Dearing, 1979; Seymour et al., 2007b). It has been long known, for instance, that pairing a CS with reward will suppress subsequent aversive learning to the same CS. Similarly, an appetitive CS will suppress aversive motivated behavior (Pearce and Dickinson, 1975; Dickinson and Mackintosh, 1978).

In mammals, a number of (not necessarily mutually exclusive) brain structures have been proposed to serve as the site of an interaction between appetitive and aversive learning: different regions in the striatum (Seymour et al., 2007a), the amygdala (Balleine and Killcross, 2006; Paton et al., 2006), and the orbitofrontal cortex (Hosokawa et al., 2007). We suggest that the interaction of appetitive and aversion mechanisms, and their corresponding learning systems, is fundamental to the neurobiology of drug use, a point we illustrate with the complex interactions between the aversive and rewarding effects of nicotine.

Nicotine. Rewarding and aversive effects of nicotine administered to the VTA of rats were illustrated through place preference/avoidance paradigms (Laviolette et al., 2002; Laviolette and van der Kooy, 2003a,b). The value assigned to intra-VTA or systemic nicotine administration was dose dependent; high doses appeared to be rewarding whereas low doses caused aversion. Aversion was

reversed to reward after blocking DA D2 receptors in the NAc. Note, however, that the D2 receptors, acting as autoreceptors on dopaminergic terminals in the NAc, downregulate DA release and upregulate DA reuptake (Wu et al., 2002). Thus it may be that the net effect of blocking these receptors resulted in an increase in the NAc DA level (Pucak and Grace, 1994).

Interaction of aversion and reward can also be mediated by different nAChR subtypes. In the NAc, they seem to differentially trigger aversion or reward in response to intra-VTA nicotine infusion. Specifically, the $\alpha7$ subunit–containing receptors are those that seem to mediate the rewarding effect of nicotine (Laviolette and van der Kooy, 2003b).

These and other findings indicate that besides reward and reinforcement effects, drugs of abuse exhibit aversive effects, and some interaction occurs in the VTA and NAc regions. From our ecological perspective, aversion and aversive learning, not reward and reinforcement, are the expected responses to neurotoxins. These results therefore suggest that an important next step in understanding the neurobiology of drug use will be to much more systematically investigate the interaction of appetitive and aversion mechanisms in response to drug exposure. In addition to reward-related and other effects, toxicity and aversion will probably be central components in future neurobiological models of initial acute drug exposure, a point also made by others (e.g. Freeman et al., 2008; and references therein). Such proximate-level models cannot resolve the paradox because they do not explain why these systems evolved to behave the way they do. Drug reward and reinforcement, in particular, remains a puzzle.

Aposematism: advertising toxicity

Neurobiological research on the effects of drugs on the CNS has focused on reward learning mechanisms, and to a lesser extent on aversive ones. However, other changes in the CNS due to drug consumption are well documented. Ecological concepts might shed light on some effects of drugs beyond reward and aversion.

Toxic animal species, like hornets, commonly evolve signals, such as distinctive colorizing, to advertise their toxicity to predators, a phenomenon termed *aposematism* (Wallace, 1867, 1889; for some of the theoretical complexities, see Mallet and Joron, 1999; Mappes et al., 2005). These signals help predators to quickly and reliably learn to avoid this toxic prey. Although much less studied, aposematism in toxic plants also seems to have evolved, in the form of colors or odors (e.g. Harper, 1977; Eisner and Grant, 1981; Lev-Yadun and Gould, 2007).

We are interested in the possibility of selection on plants to send neurochemical aposematic signals to herbivores—an example of what ecologists variously refer to as *semiochemicals*, *infochemicals*, or *allelochemicals* (Law and Regnier, 1971; Nordlund and Lewis, 1976; Dicke and Sabelis, 1988)—and selection of herbivores to evolve neural machinery to detect such signals.

Cocaine, for example, alters the content of brain 5-HT and norepinephrine (Filip et al., 2005; Hall et al., 2004;

Hnasko et al., 2007). ACh levels are also altered following cocaine use (Fink-Jensen et al., 2003), and it is likely that cholinergic neurons participate in the rewarding effects of other drugs of abuse (Smith et al., 2004). Much effort has been devoted to study the eventual funneling of these effects to modulation of NAc DA levels (for review, see Lüscher and Ungless, 2006). Because alterations in brain NE, 5-HT and ACh levels are associated with differences in arousal levels, memory and attention (Dani, 2001; Arnsten and Li, 2005; Corbetta et al., 2008; Everitt and Robbins, 1997; Reuter et al., 2007; Sarnyai et al., 2000), they might be facets of plant–herbivore signaling.

To signal toxicity, we suggest that plants could have evolved compounds to manipulate elements of herbivore nervous systems by passing through the blood–brain barrier to directly trigger attention, aversion, and other learning mechanisms in the CNS. Aspects of plant chemical cocktails could be the neurochemical equivalents of the hornet's distinctive black and yellow bands. Moreover, the triggering of aversion and aversive learning after neurotoxin administration might not only be a physiological reaction to the toxic elements of the plant, but could also be directly stimulated by plants to advertise their toxicity.

Even if this speculation were true, it would not resolve the paradox of drug reward. But such aposematic signaling could illuminate the interaction between certain plant neurotoxins and various systems in the PNS and CNS other than reward and reinforcement, e.g. those systems involved with attention to, and learning about, features of the local environment, especially dangerous features. We briefly discuss the cognitive benefits of some plant drugs below.

TOWARDS RESOLVING THE PARADOX

We now explore three avenues towards resolving the paradox of drug reward: evolutionary novelty, non-defensive functions of secondary compounds, and counter-exploitation.

Is drug exposure an evolutionary novelty?

Nesse and Berridge (1997) proposed that current patterns of drug exposure are an evolutionary novelty, and therefore drugs, at least in their pure form, were probably not a selection pressure on human neurophysiology. If true, our brains might not be adapted to recognize psychoactive drugs as toxic, and reward circuits might inadvertently be triggered when such drugs are consumed.

Although particular drugs, and their ready availability, are probably evolutionarily novel (e.g. nicotine from the New World tobacco plant, commercially produced and marketed on a global scale), we note that psychoactive drug use (1) primarily involves plant toxins, compounds that have been an important part of animal diets for hundreds of millions of years; (2) does trigger toxin avoidance mechanisms in most individuals, including aversive reactions to evolutionarily novel compounds such as nicotine, even in pure form; (3) is a pan-human phenomenon, involving similar substances and concentrations across a

diverse array of cultures; and (4) is geographically wide-spread in the archaeological record, at least for much of the later Holocene (Sullivan and Hagen, 2002; Sullivan et al., 2008). Moreover, humans, like other animals, have evolved several layers of protection against plant toxins, including receptors for detecting, and enzymes for metabolizing, plant neurotoxins and other xenobiotics. Evidence of conserved function, stabilizing selection, and population-specific selection of at least some human bitter taste receptors (Soranzo et al., 2005; but see Wang et al., 2004) and xenobiotic metabolizing cytochrome P450 genes indicates a long evolutionary exposure to plant toxins as a class, albeit at reduced levels relative to other primates (Sullivan et al., 2008). Aversion and aversive learning (reviewed above), xenobiotic transporter proteins, and the blood–brain barrier, which provide protection mechanisms against many plant toxins, are additional evidence that mammalian evolution has been shaped by exposure to plant defensive compounds.

Nesse and Berridge (1997) also argued that novel routes of drug administration bypass adaptive information processing systems to act directly on mechanisms controlling emotion and behavior. This might be true for some drugs (e.g. injecting heroin), but for others (e.g. chewing coca or tobacco leaves) it is not. Even so, injection of pure drugs can still cause aversive reactions in most individuals (for such data on s.c. injections of pure nicotine in humans, see Foulds et al., 1997).

Tobacco, marijuana, areca palm, opium poppy, coca, coffee, tea, and cacao are domesticates. This means that in the last several thousand years their profile of secondary compounds has likely been tailored by artificial selection to fit human preferences. Hence, the precise recipes of these drug cocktails are evolutionarily novel. Nevertheless, at least when it comes to nicotine, the level of drug in commercially marketed products is similar to that in the tobacco and other nicotine-containing plants (wild and domestic) long used by indigenous peoples (Sullivan and Hagen, 2002). Domestication also implies significant interaction between humans and the wild progenitor species, presumably to obtain access to the same psychoactive substances. We therefore conclude that, despite these complications, exposure to potent psychoactive plant toxins as a class is probably not an evolutionary novelty for humans.

Counter-exploitation of plant neurotoxins

As an alternative to the preceding hypotheses, we propose that attraction to toxic plant compounds might have actively evolved because of benefits accruing from their consumption. We have argued for the existence of superbly well-functioning neurobiological mechanisms for toxin defense, and that interactions between appetite and aversion clearly play a central role in drug use patterns. In light of this conclusion, the inability of the latter defense mechanisms to completely prevent any use of tobacco, cocaine, opiates, and other psychoactive drugs raises the possibility that during the evolution of the human lineage there were

biological fitness benefits associated with regulated consumption of these substances.

Costly signaling. Diamond (1992) proposed that drug use could be a costly signal, or handicap (Spence, 1973; Zahavi, 1975), one solution to the paradoxical propensity of humans to consume toxins. Just as the large, bright tail of the male peacock is a signal to females that the male is probably fit and healthy—because only then could he afford such a costly ornament—consuming a potent neurotoxin with few ill effects could also signal health and fitness to potential mates (see also Hill and Chow, 2002). We think drug use as a costly signal is an intriguing avenue to explore, and hope to see this hypothesis developed further. One challenge for future theorizing is that the costly signaling hypothesis requires individuals to minimize negative effects on overall system functioning after consuming neurotoxins, yet the aim of many drug users is to distort perception (i.e. to increase rather than minimize costs). Perhaps the fitness signal is a function of dose vs. effect, or even includes the ability to fully recover from, rather than simply minimize, the consequences of toxin consumption. Finally, many users consume drugs to enhance cognitive performance (Sahakian and Morein-Zamir, 2007), which is a benefit rather than a cost.

Pharmacophagy: exploiting plant "research and development" against parasites. Terrestrial plants account for about 50% of net primary production, and represent over 99% of primary producer biomass (Field et al., 1998). Excluding a large class of decomposers (organisms that consume dead plant and animal tissue), a substantial fraction of the world's viruses, bacteria, fungi, nematodes and arthropods feed off living plants. Hence, an enormous quantity of pharmaceutical "research and development" against these parasites has been, and continues to be, conducted by naturally evolving plant species. The same major categories of parasites also attack humans and other animals. It has been demonstrated, for example, that bacterial pathogens of plants and animals employ similar infectious strategies (e.g. type III secretion systems), which has selected for convergent defenses in plants and animals (Schultz, 2002).

Animals counter-exploit plant toxins against parasites. To inhibit and kill their own parasites, some animals might have evolved to counter-exploit the products of hundreds of millions of years of "research" by plants (Villalba and Provenza, 2007). As we noted earlier, there is evidence that a number of herbivores evolved to subsist on a mixed diet of palatable and toxic plants, in effect trading off diet quality (and thus growth) for what is termed *enemy-reduced* or *enemy-free space* (e.g. Singer and Stireman, 2003). Even more intriguing is evidence that some herbivores contingently vary the toxicity of their diet in response to infection. In one study, for example, unparasitized caterpillars (*Platyprepia virginalis*) were more likely to survive on a diet of lupin (low toxicity), whereas caterpillars parasitized by a tachnid parasitoid (*Thelaira americana*) were more likely to survive on poison hemlock. When offered a choice of both plants in field tests, parasitized caterpillars

were more likely to choose hemlock, and unparasitized caterpillars were more likely to choose lupin (Karban and English-Loeb, 1997). For a recent review of this field, see Ode (2006).

Primates, too, appear to engage in pharmacophagy (Johns, 1990; Huffman, 1997, 2007). In humans, it has been proposed that toxins in fava beans and cassava might be effective against *Plasmodium falciparum* infections, explaining geographic use patterns of these plants and genetic polymorphisms (Jackson, 1990, 1996); and the ubiquitous use of spices could be an adaptation to exploit plant toxins to combat bacterial infections of food (Billing and Sherman, 1998). Sullivan and Hagen (2002) hypothesized that hominins may have exploited plant toxins to overcome nutritional and energetic constraints on CNS signaling.

Nicotine and other popular plant drugs fight parasites. Intriguingly, some recreational drugs are remarkably effective treatments for mammalian pathogens (Rodriguez et al., 1982). For example, nicotine, arecoline (the principal psychoactive component of betel nut, widely chewed in Asia and the Pacific), and THC, three of the world's most popular plant drugs, are potent anthelmintics. Nicotine, arecoline, and their close chemical relatives have been widely used to de-worm livestock (Hammond et al., 1997; World Health Organization, 1981; Iqbal et al., 2006; Msolla et al., 1987; Kabelik et al., 1960; Kohler, 2001; Tomizawa and Casida, 2005); cannabis is toxic to plant-parasitic nematodes (Grewal, 1989; McPartland, 1997; McPartland and Glass, 2001). These compounds are also frequently mentioned as anthelmintics in the enthnomedical literature (e.g. Fabricant and Farnsworth, 2001; McPartland and Glass, 2001).

Thus, speculatively, the widespread recreational use of tobacco, betel nut, and cannabis could be a form of human pharmacophagy, an evolved response to chronic infections of helminths, or other parasites with nicotinic or muscarinic receptors, in ancestral human populations (the source of the nematocidal effects of cannabis is currently unknown; McPartland and Glass, 2001). We doubt, however, there was selection for use of these plant drugs specifically; instead, there could have been selection to seek out and use plants rich in cholinergic agents (there are a number of cholinergic plant toxins; Wink and Schimmer, 1999) and other toxins of various types. Psychoactive plant substances could be especially valued because these clearly interfere with neuronal signaling in humans and hence might be expected to also interfere with the nervous systems of pathogens such as helminths and arthropods.

Other potential benefits.   Neurotoxins have other effects that may be beneficial under certain conditions: cannabis and opiates are powerful analgesics; caffeine and nicotine can act as cognitive enhancers (Basbaum and Fields, 1978; Chaperon and Thiebot, 1999; Ignelzi and Atkinson, 1980; Lieberman, 2003; Rezvani and Levin, 2001). These effects are related to the fact that plant drugs chemically mimic endogenous signaling molecules.

The question is, if it is possible to enhance performance by ingesting compounds that chemically resemble endogenous signaling molecules, why did natural selection not simply increase production of the endogenous signaling molecules? There are a variety of potential answers involving evolutionary constraints, tradeoffs, and the like. Sullivan and Hagen (2002) suggested that although levels of endogenous signaling molecules are probably close to optimal in healthy individuals under normal circumstances, internal signaling functions would occasionally become compromised, perhaps due to deficiencies in dietary precursors in marginal environments, excess utilization of signaling molecules (e.g. as a consequence of chronic high stress), or disease. In such cases, limited doses of some plant secondary compounds might have been able to partially compensate for impaired functionality. It is also possible, in humans at least, that cultural evolution or even rational thought could identify benefits from plant compounds that offset the costs of exposure. This is obviously the case in modern medicine, which often exploits plant-derived compounds for clinical applications: one third of the current top 20 drugs on the market are plant derived (Howitz and Sinclair, 2008).

Cholinergic brain systems play important roles in attention and memory, for example, and also have been implicated in Alzheimer's disease, schizophrenia and other mental illnesses. Nicotine and other nicotinic agonists correspondingly improve performance on attention and memory tasks, and clinical studies have shown nicotine to be an effective treatment for some of the cognitive deficits associated with the aforementioned diseases (Rezvani and Levin, 2001).

Thus, in principle, drug-seeking behavior, and its neurophysiological basis, could have evolved because of beneficial effects of neurotoxins. We do not doubt that these neurotoxins constitute serious health hazards. Rather, these health hazards, which often appear only at high doses or later in life, may have been offset by immediate benefits, resulting in a net increase in biological fitness.

Counter-exploitation mediated by the MDS?.   Drug effects on the CNS are currently interpreted in terms of two general, and largely distinct, proximate mechanisms: one related to reward, centered on the MDS, and the other to aversion; these systems, however, do interact (reviewed above). One hypothesis is that if humans and other mammals did evolve to counter-exploit plant neurotoxins, then the interaction of appetitive and aversive mechanisms effectively regulates exposure to neurotoxins. According to this conjecture, the benefits of exposure lead to the evolution of mechanisms in which useful neurotoxins activate reward and reinforcement to counterbalance pre-existing aversion and aversive learning mechanisms. This predicts, for example, that for any animal which has evolved to counter-exploit a plant toxin, reward and reinforcement mechanisms in that animal will activate when the animal is exposed to the counter-exploited toxin or close chemical analogs. Conversely, unexploited toxins will not activate reward and reinforcement mechanisms.

Because plants have a well-demonstrated ability to subvert herbivore nervous systems, a fully developed toxin counter-exploitation model would also have to consider that co-evolving plants, to deter consumption, will attempt to subvert reward, reinforcement and aversion mechanisms.

CONCLUSION

Neurobiological research has confirmed that DA plays a major role in the processing of reward-related stimuli in the CNS, that drug-induced DA release is central to drug use phenomena, and that drugs of abuse can also cause aversive effects. Although we see no easy resolution to the paradox that plant drugs—compounds which probably evolved to defend plants from herbivores—reinforce their own consumption in laboratory animals and humans, an ecological perspective indicates some future directions for neurobiological research on drug use.

First, exposure to potent psychoactive substances is unlikely to be an evolutionary novelty, but more data on the domestication of drug plants could yield important insights into this issue. Second, drugs should, and do, trigger aversion and aversive learning circuitry. Examining the relationship between drugs and signaling pathways downstream from chemoreceptors could therefore yield interesting results. More generally, aversion and aversive learning, and their interactions with reward and reinforcement, are likely to play central roles in proximate neurobiological models of drug use. A pure reward and reinforcement model of initial acute drug exposure is therefore problematic.

Third, it is unlikely that early human populations were a significant selection pressure on plants. Instead, plants evolved to defend themselves from their principal invertebrate and vertebrate herbivores. We therefore propose further investigations on differences and similarities in the effect of neurotoxic drugs on the dopaminergic systems of invertebrate and vertebrate herbivores. For example, an important study would be to measure the activity of DA and octopamine neurons in insect herbivores upon exposure to different concentrations of drugs. Fourth, plant drugs could be components of plant–animal signaling. This means that in addition to their toxic effects, plant chemical cocktails might have evolved to trigger PNS and CNS systems in herbivores involved with attention to, and learning about, features of the local environment, especially dangerous features.

Fifth, because some drugs are so toxic, the relative absence of overdoses suggests the mechanisms mediating drug use are regulatory. The challenge, then, is to understand why the human brain appears to be regulating, rather than eliminating, exposure to certain neurotoxins. We speculate that consumption of some drugs might once have provided a benefit that offset the costs, perhaps as costly signals of fitness, protection against parasites, or a means to adaptively modulate endogenous signaling systems. If so, only such counter-exploited neurotoxins or their close chemical analogs should reinforce their own use.

REFERENCES

Arnsten AFT, Li BM (2005) Neurobiology of executive functions: catecholamine influences on prefrontal cortical functions. Biol Psychiatry 57(11):1377–1384.

Baldwin IT (2001) An ecologically motivated analysis of plant–herbivore interactions in native tobacco. Plant Physiol 127(4):1449–1458.

Balfour DJK (2002) Neuroplasticity within the mesoaccumbens dopamine system and its role in tobacco dependence. Curr Drug Targets CNS Neurol Disord 1(4):413–421.

Balleine BW, Killcross S (2006) Parallel incentive processing: an integrated view of amygdala function. Trends Neurosci 29(5):272–279.

Barber TA, Klunk AM, Howorth PD, Pearlman MF, Patrick KE (1998) A new look at an old task: advantages and uses of sickness-conditioned learning in day-old chicks. Pharmacol Biochem Behav 60(2):423–430.

Barbosa P, Gross P, Kemper J (1991) Influence of plant allelochemicals on the tobacco hornworm and its parasitoid Cotesia congregata. Ecology 72(5):1567–1575.

Barbosa P, Saunders JA, Kemper J, Trumbule R, Olechno J, Martinat P (1986) Plant allelochemicals and insect parasitoids: effects of nicotine on *Cotesia congregata* (Say) (*Hymenoptera*: *Braconidae*) and Hyposoter *annulipes* (Cresson) (*Hymenoptera*: *Ichneumonidae*). J Chem Ecol 12(6):1319–1328.

Barron AB, Maleszka R, Helliwell PG, Robinson GE (2009) Effects of cocaine on honey bee dance behaviour. J Exp Biol 212(2):163–168.

Basbaum AI, Fields HL (1978) Endogenous pain control mechanisms: review and hypothesis. Ann Neurol 4:451–462.

Berridge KC (2007) The debate over dopamine's role in reward: the case for incentive salience. Psychopharmacology (Berl) 191(3):391–431.

Berridge KC, Robinson TE (1998) What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? Brain Res Brain Res Rev 28(3):309–369.

Billing J, Sherman PW (1998) Antimicrobial functions of spices: why some like it hot. Q Rev Biol 73(1):3–49.

Blair K, Marsh AA, Morton J, Vythilingam M, Jones M, Mondillo K, Pine DC, Drevets WC, Blair JR (2006) Choosing the lesser of two evils, the better of two goods: specifying the roles of ventromedial prefrontal cortex and dorsal anterior cingulate in object choice. J Neurol Sci 26(44):11379–11386.

Boatman JA, Kim JJ (2006) A thalamo-cortico-amygdala pathway mediates auditory fear conditioning in the intact brain. Eur J Neurosci 24(3):894–900.

Boppré M (1984) Redefining "pharmacophagy." J Chem Ecol 10(7):1151–1154.

Cappell H, LeBlanc AE, Endrenyi L (1973) Aversive conditioning by psychoactive drugs: effects of morphine, alcohol and chlordiazepoxide. Psychopharmacology 29(3):239–246.

Castane A, Soria G, Ledent C, Maldonado R, Valverde O (2006) Attenuation of nicotine-induced rewarding effects in A2A knockout mice. Neuropharmacology 51(3):631–640.

Chaperon F, Thiebot MH (1999) Behavioral effects of cannabinoid agents in animals. Crit Rev Neurobiol 13(3):243–281.

Corbetta M, Patel G, Shulman GL (2008) The reorienting system of the human brain: from environment to theory of mind. Neuron 58: 306–324.

Daly JW, Kaneko T, Wilham J, Garraffo HM, Spande TF, Espinosa A, Donnelly MA (2002) Bioactive alkaloids of frog skin: combinatorial bioprospecting reveals that pumiliotoxins have an arthropod source. Proc Natl Acad Sci U S A 99(22):13996–14001.

Dani JA (2001) Overview of nicotinic receptors and their roles in the central nervous system. Biol Psychiatry 49(3):166–174.

Davis M (1992) The role of the amygdala in fear and anxiety. Annu Rev Neurosci 15:353–375.

Daw ND, Kakade S, Dayan P (2002) Opponent interactions between serotonin and dopamine. Neural Netw 15(4–6):603–616.

de Landoni JH (1991) Nicotine. Poisons information monographs. International Programme on Chemical Safety. Last accessed March 6, 2009. http://www.inchem.org/documents/pims/chemical/nicotine.htm.

Delgado MR, Olsson A, Phelps EA (2006) Extending animal models of fear conditioning to humans. Biol Psychiatry 73(1):39–48.

Diamond JM (1992) The third chimpanzee. HarperCollins.

Di Chiara G, Imperato A (1988) Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc Natl Acad Sci U S A 85(14): 5274–5278.

Dicke M, Sabelis MW (1988) Infochemical terminology: based on cost-benefit analysis rather than origin of compounds? Funct Ecol 2(2):131–139.

Dickinson A, Dearing MF (1979) Appetitive-aversive interactions and inhibitory processes, pp 203–231. Hillsdale, NJ: Erlbaum.

Dickinson A, Mackintosh NJ (1978) Classical conditioning in animals. Annu Rev Psychol 29(1):587–612.

DiFranza JR, Savageau JA, Fletcher K, Ockene JK, Rigotti NA, McNeill AD, Coleman M, Wood C (2004) Recollections and repercussions of the first inhaled cigarette. Addict Behav 29(2):261–272.

Dunsmoor JE, Bandettini PA, Knight DC (2008) Neural correlates of unconditioned response diminution during pavlovian conditioning. Neuroimage 40:811–817.

Eisner T, Grant R (1981) Toxicity, odor aversion, and olfactory aposematism. Science 213(4506):476.

Eissenberg T, Balster RL (2000) Initial tobacco use episodes in children and adolescents: current knowledge, future directions. Drug Alcohol Depend 59(1):S41–S60.

El-Heneidy AH, Barbosa P, Gross P (1988) Influence of dietary nicotine on the fall armyworm, Spodoptera frugiperda and its parasitoid, the ichneumonid wasp Hyposoter annulipes. Entomol Exp Applicata 46(3):227–232.

Ettenberg A (2004) Opponent process properties of self-administered cocaine. Neurosci Biobehav Rev 27(8):721–728.

Everitt BJ, Robbins TW (1997) Central cholinergic systems and cognition. Annu Rev Int Psychol 48(1):649–684.

Everitt BJ, Robbins TW (2005) Neural systems of reward for drug addiction: from actions to habits to compulsion. Nat Neurosci 8: 1481–1489.

Ezzati M, Lopez AD (2004) Smoking and oral tobacco use. In: Comparative quantification of health risks: global and regional burden of disease attributable to selected major risk factors (Ezzati M, Lopez AD, Rogers A, Murray CJL, eds), pp 883–957. Geneva: WHO.

Fabricant DS, Farnsworth NR (2001) The value of plants used in traditional medicine for drug discovery. Environ Health Perspect 109 (Suppl 1):69–75.

Fagen ZM, Mansvelder HD, Keath JR, McGehee DS (2003) Short- and long-term modulation of synaptic inputs to brain reward areas by nicotine. Ann N Y Acad Sci 1003:185–195.

Fanselow EE, Gale GD (2003) The amygdala, fear, and memory. Ann N Y Acad Sci 985:125–134.

Fendt M, Fanselow MS (1999) The neuroanatomical and neurochemical basis of conditioned fear. Neurosci Biobehav Rev 23(5): 743–760.

Field CB, Behrenfeld MJ, Randerson JT, Falkowski P (1998) Primary production of the biosphere: integrating terrestrial and oceanic components. Science 281(5374):237–240.

Filip M, Frankowska M, Zaniewska M, Golda A, Przegalinski E (2005) The serotonergic system and its role in cocaine addiction. Pharmacol Rep 57(6):685–700.

Fink-Jensen A, Fedorova I, Wörtwein G, Woldbye DPD, Rasmussen T, Thomsen M, Bolwig TG, Knitowski KM, McKinzie DL, Yamada M, Wess J, Basile A (2003) Role for m5 muscarinic acetylcholine receptors in cocaine addiction. J Neurosci Res 74:91–96.

Foulds J, Stapleton JA, Bell N, Swettenham J, Jarvis MJ, Russell MAH (1997) Mood and physiological effects of subcutaneous nicotine in smokers and never-smokers. Drug Alcohol Depend 44(2–3): 105–115.

Freeman KB, Verendeev A, Riley AL (2008) Noradrenergic antagonism enhances the conditioned aversive effects of cocaine. Pharmacol Biochem Behav 88(4):523–532.

Frey PW, Maisiak R, Dugue G (1976) Unconditional stimulus characteristics in rabbit eyelid conditioning. J Expert Psychol Anim Biobehav Proc 2(2):175–190.

Gable RS (2004) Comparison of acute lethal toxicity of commonly abused psychoactive substances. Addiction 99(6):686–696.

Giurfa M (2006) Associative learning: the instructive function of biogenic amines. Curr Biol 16(20):892–895.

Glanzman DL (2005) Associative learning: Hebbian flies. Curr Biol 15(11):R416–R419.

Gosselin RE, Smith RP, Hodge HC (1984) Of commercial products. Clinical toxicology II, 5th ed. Baltimore, MD: Williams & Wilkins.

Gotti C, Clementi F (2004) Neuronal nicotinic receptors: from structure to pathology. Prog Neurobiol 74(6):363–396.

Grewal PS (1989) Nematicidal effects of some plant-extracts to Aphelenchoides composticola (Nematoda) infesting mushroom, Agaricus bisporus. Rev Nématol 12(3):317–322.

Guimaraes FS, DelBel EA, Padovan CM, Netto SM, de Almeida RT (1993) Hippocampal 5-ht receptors and consolidation of stressful memories. Behav Brain Res 58(1–2):133–139.

Guindon GE, Boisclair D (2003) Past, current and future trends in tobacco use. Economics of Tobacco Control Discussion Papers.

Hall FS, Sora I, Drgonova J, Li XFEI, Goeb M, Uhl GR (2004) Molecular mechanisms underlying the rewarding effects of cocaine. Ann N Y Acad Sci 1025:47–56.

Hammond JA, Fielding D, Bishop SC (1997) Prospects for plant anthelmintics in tropical veterinary medicine. Vet Res Commun 21:213–228.

Harper JL (1977) Population biology of plants. London: Academic Press.

Hill EM, Chow K (2002) Life-history theory and risky drinking. Addiction 97(4):401–413.

Hills T (2006) Animal foraging and the evolution of goal-directed cognition. Cogn Sci 30:3–41.

Hnasko TS, Sotak BN, Palmiter RD (2007) Cocaine-conditioned place preference by dopamine-deficient mice is mediated by serotonin. J Neurol Sci 27(46):12484–12488.

Hollingsworth RG, Armstrong JW, Campbell E (2003) Caffeine as a novel toxicant for slugs and snails. Ann Appl Biol 142(1):91–97.

Horvitz JC (2000) Mesolimbocortical and nigrostriatal dopamine responses to salient non-reward events. Neuroscience 96(4):651–656.

Hosokawa T, Kato K, Inoue M, Mikami A (2007) Neurons in the macaque orbitofrontal cortex code relative preference of both rewarding and aversive outcomes. Neurosci Res 57(3):434–445.

Howitz KT, Sinclair DA (2008) Xenohormesis: sensing the chemical cues of other species. Cell 133:387–391.

Huffman MA (1997) Current evidence for self-medication in primates: A multidisciplinary perspective. Am J Phys Anthropol 104(S25): 171–200.

Huffman MA (2007) Primate self-medication. In: Primates in perspective (Campbell C, Fuentes A, MacKinnon K, Panger M, Bearder S, eds), pp 677–690. Oxford: University of Oxford Press.

Hukkanen J, Jacob P, Benowitz NL (2005) Metabolism and disposition kinetics of nicotine. Pharmacol Rev 57(1):79–115.

Hunt T, Amit Z (1987) Conditioned taste aversion induced by self-administered drugs: paradox revisited. Neurosci Biobehav Rev 11(1):107–130.

Hyman SE, Malenka RC, Nestler EJ (2006) Neural mechanisms of addiction: the role of reward-related learning and memory. Annu Rev Neurosci 29:565–598.

Ignelzi RJ, Atkinson JH (1980) Pain and its modulation. Part 2. Efferent mechanisms. Neurosurgery 6:584–590.

Iqbal Z, Lateef M, Jabbar A, Ghayur MN, Gilani AH (2006) In vitro and in vivo anthelmintic activity of Nicotiana tabacum L. leaves against gastrointestinal nematodes of sheep. Phytother Res 20(1):46–48.

Jackson FLC (1990) Two evolutionary models for the interactions of dietary organic cyanogens, hemoglobins, and falciparum malaria. Am J Hum Biol 2:521–532.

Jackson FLC (1996) The coevolutionary relationship of humans and domesticated plants. Yearbook Phys Anthropol 39:161–176.

Johansen JP, Fields HL (2004) Glutamatergic activation of anterior cingulate cortex produces an aversive teaching signal. Nat Neurosci 7(4):398–403.

Johns T (1990) With bitter herbs they shall eat it: chemical ecology and the origins of human diet and medicine. Tucson: University of Arizona Press.

Kabelik J, Krejei Z, Santavy F (1960) Cannabis as a medicament. Bull Narc 12:5–23.

Kalivas PW, Volkow ND (2005) The neural basis of addiction: A pathology of motivation and choice. Am J Psychiatry 162:1403–1413.

Karban R, Agrawal AA (2002) Herbivore offense. Annu Rev Ecol Syst 33:641–664.

Karban R, Baldwin IT (1997) Induced responses to herbivory. Chicago University Press.

Karban R, English-Loeb G (1997) Tachinid parasitoids affect host plant choice by caterpillars to increase caterpillar survival. Ecology 78(2):603–611.

Kelley AE, Berridge KC (2002) The neuroscience of natural rewards: relevance to addictive drugs. J Neurol Sci 22(9):3306–3311.

Kessler A, Baldwin IT (2001) Defensive function of herbivore-induced plant volatile emissions in nature. Science 291(5511):2141–2144.

Kessler D, Gase K, Baldwin IT (2008) Field experiments with transformed plants reveal the sense of floral scents. Science 321 (5893):1200–1202.

Kester KM, Barbosa P (1994) Behavioral responses to host foodplants of two populations of the insect parasitoid Cotesia congregata (Say). Oecologia 99(1):151–157.

Klosterhalfen S, Klosterhalfen W (1985) Conditioned taste aversion and traditional learning. Psychol Res 47(2):71–94.

Kohler P (2001) The biochemical basis of anthelmintic action and resistance. Int J Parasitol 31(4):336–345.

Koob GF, Le Moal M (2005) Plasticity of reward neurocircuitry and the "dark side" of drug addiction. Nat Neurosci 8:1442–1444.

Korkosz A, Scinska A, Taracha E, Plaznik A, Kukwa A, Kostowski W, Bienkowski P (2006) Nicotine-induced conditioned taste aversion in the rat: effects of ethanol. Eur J Pharmacol 537(1–3):99–105.

Laurent P, Braekman J-C, Daloze D (2005) Insect chemical defense. Top Curr Chem 240:167–229.

Laviolette SR, Alexson TO, van der Kooy D (2002) Lesions of the tegmental pedunculopontine nucleus block the rewarding effects and reveal the aversive effects of nicotine in the ventral tegmental area. J Neurosci 22(19):8653–8660.

Laviolette SR, van der Kooy D (2003a) Blockade of mesolimbic dopamine transmission dramatically increases sensitivity to the rewarding effects of nicotine in the ventral tegmental area. Mol Psychiatry 8(1):50–59.

Laviolette SR, van der Kooy D (2003b) The motivational valence of nicotine in the rat ventral tegmental area is switched from rewarding to aversive following blockade of the alpha7-subunit-containing nicotinic acetylcholine receptor. Psychopharmacology (Berl) 166(3):306–313.

Laviolette SR, van der Kooy D (2004) The neurobiology of nicotine addiction: bridging the gap from molecules to behaviour. Nat Rev Neurosci 5(1):55–65.

Law JH, Regnier FE (1971) Pheromones. Annu Rev Biochem 40(1): 533–548.

Lee T, Kim JJ (2004) Differential effects of cerebellar, amygdalar, and hippocampal lesions on classical eyeblink conditioning in rats. J Neurol Sci 24(13):3242–3250.

Lev-Yadun S, Gould KS (2007) What do red and yellow autumn leaves signal? Bot Rev 73(4):279–289.

Lieberman HR (2003) Nutrition, brain function and cognitive performance. Appetite 40(3):245–254.

Lüscher C, Ungless MA (2006) The mechanistic classification of addictive drugs. PLoS Med 3:2005–2010.

Mallet J, Joron M (1999) Evolution of diversity in warning color and mimicry: polymorphisms, shifting balance, and speciation. Annu Rev Int Ecol Syst 30(1):201–233.

Mameli-Engvall M, Evrard A, Pons S, Maskos U, Svensson TH, Changeux J-P, Faure P (2006) Hierarchical control of dopamine neuron-firing patterns by nicotinic receptors [comparative study]. Neuron 50(6):911–921.

Mansvelder HD, De Rover M, McGehee DS, Brussaard AB (2003) Cholinergic modulation of dopaminergic reward areas: upstream and downstream targets of nicotine addiction. Eur J Pharmacol 480(1–3):117–123.

Mansvelder HD, Keath JR, McGehee DS (2002) Synaptic mechanisms underlie nicotine-induced excitability of brain reward areas. Neuron 33(6):905–919.

Mansvelder HD, McGehee DS (2000) Long-term potentiation of excitatory inputs to brain reward areas by nicotine. Neuron 27(2): 349–357.

Mappes J, Marples N, Endler JA (2005) The complex business of survival by aposematism. Trends Ecol Evol 20(11):598–603.

Maren S (2003) What the amygdala does and doesn't do in aversive learning. Learn Mem 10(5):306–308.

Maren S, Quirk GJ (2004) Neuronal signalling of fear memory. Nat Rev Neurosci 5(11):844–852.

Mayr E (1961) Cause and effect in biology. Science 134:1501–1506.

McLaren IPL, Dickinson A (1990) The conditioning connection. Philos Trans Biol Sci 329(1253):179–186.

McPartland JM (1997) Cannabis as repellent and pesticide. J Int Hemp Assoc 4(2):89–94.

McPartland JM, Glass M (2001) Nematicidal effects of hemp (Cannabis sativa) may not be mediated by cannabinoid receptors. N Z J Crop Hort Sci 29:301–307.

Montague PR, Dayan P, Sejnowski TJ (1996) A framework for mesencephalic dopamine systems based on predictive hebbian learning [comparative study]. J Neurol Sci 16(5):1936–1947.

Morris G, Arkadir D, Nevet A, Vaadia E, Bergman H (2004) Coincident but distinct messages of midbrain dopamine and striatal tonically active neurons. Neuron 43(1):133–143.

Morris G, Nevet A, Arkadir D, Vaadia E, Bergman H (2006) Midbrain dopamine neurons encode decisions for future action. Nat Neurosci 9(8):1057–1063.

Msolla P, Mmbuji WE, Kasuku AA (1987) Field control of bovine parasitic otitis. Trop Anim Health Prod 19(3):179–183.

Nader K, Schafe GE, Le Doux JE (2000) Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. Nature 406(6797):722–726.

Nathanson JA, Hunnicutt EJ, Kantham L, Scavone C (1993) Cocaine as a naturally occurring insecticide. Proc Natl Acad Sci U S A 90(20):9645–9648.

Nesse RM (2002) Evolution and addiction. Addiction 97(4):470–471.

Nesse RM, Berridge KC (1997) Psychoactive drug use in evolutionary perspective. Science 278:63–66.

Nestler EJ (2005) Is there a common molecular pathway for addiction? Nat Neurosci 8:1445–1449.

Nitschke JB, Sarinopoulos I, Mackiewicz KL, Schaefer HS, Davidson RJ (2006a) Functional neuroanatomy of aversion and its anticipation. Neuroimage 29(1):106–116.

Nitschke JB, Sarinopoulos I, Mackiewicz KL, Schaefer HS, Davidson RJ (2006b) Functional neuroanatomy of aversion and its anticipation. Neuroimage 29(1):106–116.

Nordlund DA, Lewis WJ (1976) Terminology of chemical releasing stimuli in intraspecific and interspecific interactions. J Chem Ecol 2(2):211–220.

Novere N, Changeux JP (1995) Molecular evolution of the nicotinic acetylcholine receptor: an example of multigene family in excitable cells. J Mol Evol 40(2):155–172.

Nuttley WM, Harbinder S, van der Kooy D (2001) Regulation of distinct attractive and aversive mechanisms mediating benzaldehyde chemotaxis in Caenorhabditis elegans. Learn Mem 8(3):170–181.

Ode PJ (2006) Plant chemistry and natural enemy fitness: effects on herbivore and natural enemy interactions. Annu Rev Entomol 51:163–185.

Pan W-X, Schmidt R, Wickens JR, Hyland BI (2005) Dopamine cells respond to predicted events during classical conditioning: evidence for eligibility traces in the reward-learning network. J Neurol Sci 25(26):6235–6242.

Parker LA (1995) Rewarding drugs produce taste avoidance, but not taste aversion. Neurosci Biobehav Rev 19(1):143–151.

Paton JJ, Belova MA, Morrison SE, Salzman CD (2006) The primate amygdala represents the positive and negative value of visual stimuli during learning. Nature 439(7078):865–870.

Pearce JM, Dickinson A (1975) Pavlovian counterconditioning: changing the suppressive properties of shock by association with food. J Expert Psychol Anim Biobehav Proc 1(2):170–177.

Petzinger E, Geyer J (2006) Drug transporters in pharmacokinetics. Naunyn Schmiedebergs Arch Pharmacol 372(6):465–475.

Price PW, Bouton CE, Gross P, McPheron BA, Thompson JN, Weis AE (1980) Interactions among three trophic levels: influence of plants on interactions between insect herbivores and natural enemies. Annu Rev Ecol Syst 11(1):41–65.

Pucak ML, Grace AA (1994) Evidence that systemically administered dopamine antagonists activate dopamine neuron firing primarily by blockade of somatodendritic autoreceptors. J Pharmacol Exp Ther 271:1181–1192.

Rao FV, Andersen OA, Vora KA, DeMartino JA, van Aalten DMF (2005) Methylxanthine drugs are chitinase inhibitors: investigation of inhibition and binding modes. Chem Biol 12(9):973–980.

Rescorla RA (1973) Effect of us habituation following conditioning. J Comp Physiol Psychol 82(1):137–143.

Reuter M, Ott U, Vaitl D, Hennig J (2007) Impaired executive control is associated with a variation in the promoter region of the tryptophan hydroxylase 2 gene. J Cogn Neurosci 19(3):401–408.

Revusky SH (1968) Aversion to sucrose produced by contingent x-irradiation: temporal and dosage parameters. J Comp Physiol Psychol 65(1):17–22.

Revusky SH, Bedarf EW (1967) Association of illness with prior ingestion of novel foods. Science 155(759):219–220.

Rezvani AH, Levin ED (2001) Cognitive effects of nicotine. Biol Psychiatry 49(3):258–267.

Rice ME, Cragg SJ (2004) Nicotine amplifies reward-related dopamine signals in striatum. Nat Neurosci 7(6):583–584.

Riemensperger T, Voller T, Stock P, Buchner E, Fiala A (2005) Punishment prediction by dopaminergic neurons in Drosophila [comparative study]. Curr Biol 15(21):1953–1960.

Risinger FO, Oakes RA (1995) Nicotine-induced conditioned place preference and conditioned place aversion in mice. Pharmacol Biochem Behav 51(2–3):457–461.

Robinson TE, Berridge KC (1993) The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res Rev 18(3):247–291.

Rodriguez E, Cavin JC, West JE (1982) The possible role of Amazonian psychoactive plants in the chemotherapy of parasitic worms-a hypothesis. J Ethnopharmacol 6(3):303–309.

Room R (2006) Room with a view: the dangerousness of drugs. Addiction 101:166–168.

Sahakian B, Morein-Zamir S (2007) Professor's little helper. Nature 450(7173):1157–1159.

Sarnyai Z, Sibille EL, Pavlides C, Fenster RJ, McEwen BS, Toth M (2000) Impaired hippocampal-dependent learning and functional abnormalities in the hippocampus in mice lacking serotonin (1a) receptors. Proc Natl Acad Sci U S A 97(26):14731–14736.

Schroll C, Riemensperger T, Bucher D, Ehmer J, Voller T, Erbguth K, Gerber B, Hendel T, Nagel G, Buchner E, Fiala A (2006) Light-induced activation of distinct modulatory neurons triggers appetitive or aversive learning in Drosophila larvae. Curr Biol 16(17):1741–1747.

Schultz JC (2002) Shared signals and the potential for phylogenetic espionage between plants and animals. Integr Comp Biol 42(3):454–462.

Schultz W (2004) Neural coding of basic reward terms of animal learning theory, game theory, microeconomics and behavioural ecology. Curr Opin Neurobiol 14(2):139–147.

Schultz W (2007) Behavioral dopamine signals. Trends Neurosci 30(5):203–210.

Schultz W, Dayan P, Montague PR (1997) A neural substrate of prediction and reward. Science 275(5306):1593–1599.

Schwaerzel M, Monastirioti M, Scholz H, Friggi-Grelin F, Birman S, Heisenberg M (2003) Dopamine and octopamine differentiate between aversive and appetitive olfactory memories in Drosophila. J Neurol Sci 23(33):10495–10502.

Seymour B, Daw N, Dayan P, Singer T, Dolan R (2007a) Differential encoding of losses and gains in the human striatum. J Neurol Sci 27(18):4826–4831.

Seymour B, Singer T, Dolan R (2007b) The neurobiology of punishment. Nat Rev Neurosci 8(4):300–311.

Shoaib M (1998) Is dopamine important in nicotine dependence? J Physiol Paris 92(3–4):229–233.

Singer MS, Stireman JO (2003) Does anti-parasitoid defense explain host-plant selection by a polyphagous caterpillar? Oikos 100(3):554–562.

Singh HP, Batish DR, Kohli RK (1999) Autotoxicity: concept, organisms, and ecological significance. Crit Rev Plant Sci 18(6):757–772.

Smiley JT, Horn JM, Rank NE (1985) Ecological effects of salicin at three trophic levels: new problems from old adaptations. Science 229(4714):649–651.

Smith JE, Co C, Yin X, Sizemore GM, Liguori A, Johnson WE, Martin TJ (2004) Involvement of cholinergic neuronal systems in intravenous cocaine self-administration. Neurosci Biobehav Rev 27(8):841–850.

Soranzo N, Bufe B, Sabeti PC, Wilson JF, Weale ME, Marguerie R, Meyerhof W, Goldstein DB (2005) Positive selection on a high-sensitivity allele of the human bitter-taste receptor TAS2R16. Curr Biol 15(14):1257–1265.

Spence M (1973) Job market signaling. Q J Econ 87(3):355–374.

Steppuhn A, Gase K, Krock B, Halitschke R, Baldwin IT (2004) Nicotine's defensive function in nature. PLoS Biol 2:1074–1080.

Sullivan RJ, Hagen EH (2002) Psychotropic substance-seeking: evolutionary pathology or adaptation? Addiction 97:389–400.

Sullivan RJ, Hagen EH, Hammerstein P (2008) Revealing the paradox of drug reward in human evolution. Proc R Soc B 275:1231–1241.

Swain T (1977) Secondary compounds as protective agents. Annu Rev 28:479–501.

Thorpe KW, Barbosa P (1986) Effects of consumption of high and low nicotine tobacco by *Manduca sexta* (*Lepidoptera*: *Sphingidae*) on survival of gregarious endoparasitoid *Cotesia congregata* (*Hymenoptera*: *Braconidae*). J Chem Ecol 12(6):1329–1337.

Thurston R, Fox PM (1972) Inhibition by nicotine of emergence of *Apanteles congregatus* from its host, the tobacco hornworm. Ann Entomol Soc Am 65:547–550.

Tomizawa M, Casida JE (2005) Neonicotinoid insecticide toxicology: mechanisms of selective action. Annu Rev Pharmacol Toxicol 45:247–268.

Ungless MA (2004) Dopamine: the salient issue. Trends Neurosci 27(12):702–706.

Ungless MA, Magill PJ, Bolam JP (2004) Uniform inhibition of dopamine neurons in the ventral tegmental area by aversive stimuli. Science 303(5666):2040–2042.

Unoki S, Matsumoto Y, Mizunami M (2005) Participation of octopaminergic reward system and dopaminergic punishment system in insect olfactory learning revealed by pharmacological study. Eur J Neurosci 22(6):1409–1416.

Unoki S, Matsumoto Y, Mizunami M (2006) Roles of octopaminergic and dopaminergic neurons in mediating reward and punishment signals in insect visual learning. Eur J Neurosci 24(7):2031–2038.

Vergoz V, Roussel E, Sandoz JC, Giurfa M (2007) Aversive learning in honeybees revealed by the olfactory conditioning of the sting extension reflex. PLoS ONE 2:e288.

Vet LEM, Dicke M (1992) Ecology of infochemical by natural enemies in a tritrophic context. Annu Rev Entomol 37:141–172.

Villalba JJ, Provenza FD (2007) Self-medication and homeostatic behaviour in herbivores: learning about the benefits of nature's pharmacy. Animals 1(09):1360–1370.

Wallace AR (1867) Proceedings of the Entomological Society of London. Volume 4, pages IXXX–IXXXi.

Wallace AR (1889) Darwinism: an exposition of the theory of natural selection with some of its applications. London: Macmillan.

Walters ET, Carew TJ, Kandel ER (1979) Classical conditioning in *Aplysia californica*. Proc Natl Acad Sci U S A 76(12):6675–6679.

Walters ET, Carew TJ, Kandel ER (1981) Associative learning in *Aplysia*: evidence for conditioned fear in an invertebrate. Science 211(4481):504–506.

Wang SH, Ostlund SB, Nader K, Balleine BW (2005) Consolidation and reconsolidation of incentive learning in the amygdala. J Neurol Sci 25(4):830–835.

Wang X, Thomas SD, Zhang J (2004) Relaxation of selective constraint and loss of function in the evolution of human bitter taste receptor genes. Hum Mol Genet 13(21):2671–2678.

West R (2001) Theories of addiction. Addiction 96(1):3–13.

Wilensky AE, Schafe GE, Kristensen MP, LeDoux JE (2006) Rethinking the fear circuit: the central nucleus of the amygdala is required for the acquisition, consolidation, and expression of pavlovian fear conditioning. J Neurol Sci 26(48):12387–12396.

Wink M (1998) Chemical ecology of alkaloids. In: Alkaloids: biochemistry, ecology, and medicinal applications (Roberts MF, Wink M, eds), pp 265–300. New York: Plenum Press.

Wink M (2000) Interference of alkaloids with neuroreceptors and ion channels. Stud Natl Prod Chem 21:3–122.

Wink M (2003) Evolution of secondary metabolites from an ecological and molecular phylogenetic perspective. Phytochemistry 64(1): 3–19.

Wink M (2006) Importance of plant secondary metabolites for protection against insects and microbial infections. In: Naturally occurring bioactive compounds (Rai M, Carpinella MC, eds), pp 251–268. Elsevier.

Wink M, Schimmer O (1999) Modes of action of defensive secondary metabolites. In: Functions of plant secondary metabolites and their exploitation in biotechnology, Vol. 3. Annual plant reviews (Wink M, ed), pp 17–133. Blackwell.

Wink M, Schmeller T, Latz-Brüning B (1998) Modes of action of allelochemical alkaloids: interaction with neuroreceptors, DNA, and other molecular targets. J Chem Ecol 24(11):1881–1937.

Wise RA, Rompre PP (1989) Brain dopamine and reward. Annu Rev Psychol 40:191–225.

Wise RA, Spindler J, deWit H, Gerberg GJ (1978) Neuroleptic-induced "anhedonia" in rats: pimozide blocks reward quality of food. Science 201(4352):262–264.

Wise RA, Yokel RA, DeWit H (1976) Both positive reinforcement and conditioned aversion from amphetamine and from apomorphine in rats. Science 191(4233):1273–1275.

Wolf FW, Heberlein U (2003) Invertebrate models of drug abuse. J Neurobiol 54(1):161–178.

World Health Organization (1981) Guidelines for surveillance, prevention and control of echinococcosis/hydatidosis. In: Echinococcosis-hydatidosis surveillance, prevention and control (Eckert J, Gemmell MA, Souslby EJL, eds), p 147. FAO/UNEP/WHO.

Wu Q, Reith MEA, Walker QD, Kuhn CM, Carroll FI, Garris PA (2002) Concurrent autoreceptor-mediated control of dopamine release and uptake during neurotransmission: an in vivo voltammetric study. J Neurol Sci 22(14):6272–6281.

Yamamoto T (2006) Neural substrates for the processing of cognitive and affective aspects of taste in the brain. Arch Histol Cytol 69(4):243–255.

Zahavi A (1975) Mate selection-a selection for a handicap. J Theor Biol 53:205–214.

Zald DH, Pardo JV (2002) The neural correlates of aversive auditory stimulation. Neuroimage 16 (3 Pt 1):746–753.

Zhang H, Sulzer D (2004) Frequency-dependent modulation of dopamine release by nicotine. Nat Neurosci 7(6):581–582.