Neuroscience and Biobehavioral Reviews 56 (2015) 50–61

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

A proposed resolution to the paradox of drug reward: Dopamine's evolution from an aversive signal to a facilitator of drug reward via negative reinforcement

Ryan Ting-A-Kee[a,b,*], Andrew Heinmiller[a], Derek van der Kooy[a,b]

[a] Neurobiology Research Group, University of Toronto, Terrence Donnelly Centre for Cellular and Biomolecular Research, Toronto, Ontario, Canada M5S 3E1
[b] Institute of Medical Science, University of Toronto, Terrence Donnelly Centre for Cellular and Biomolecular Research, Toronto, Ontario, Canada M5S 3E1

ARTICLE INFO

Article history:
Received 20 June 2014
Received in revised form 9 June 2015
Accepted 19 June 2015
Available online 24 June 2015

Keywords:
Neurotoxins
Dopamine
Aversion
Reward
Nicotine
Ventral tegmental area
Evolution
Rostromedial tegmentum
Tegmental pedunculopontine nucleus
GABA
Negative reinforcement

ABSTRACT

The mystery surrounding how plant neurotoxins came to possess reinforcing properties is termed the paradox of drug reward. Here we propose a resolution to this paradox whereby dopamine – which has traditionally been viewed as a signal of reward – initially signaled aversion and encouraged escape. We suggest that after being consumed, plant neurotoxins such as nicotine activated an aversive dopaminergic pathway, thereby deterring predatory herbivores. Later evolutionary events – including the development of a GABAergic system capable of modulating dopaminergic activity – led to the ability to down-regulate and 'control' this dopamine-based aversion. We speculate that this negative reinforcement system evolved so that animals could suppress aversive states such as hunger in order to attend to other internal drives (such as mating and shelter) that would result in improved organismal fitness.

Contents

* Corresponding author at: Institute of Medical Science, University of Toronto, Terrence Donnelly Centre for Cellular and Biomolecular Research, Toronto, Ontario, Canada M5S 3E1. Tel.: +1 416 978 4539; fax: +1 416 978 2666.
E-mail addresses: ryan.ting.a.kee@utoronto.ca (R. Ting-A-Kee), andrewheinmiller@gmail.com (A. Heinmiller), derek.van.der.kooy@utoronto.ca (D. van der Kooy).

http://dx.doi.org/10.1016/j.neubiorev.2015.06.016
0149-7634/

1. Introduction

In their struggle with the animals that feed on them, many plants have evolved chemicals to help improve their survival. For example, caffeine acts as an adenosine receptor antagonist to enhance the memory of pollinators, thereby boosting plant reproduction (Wright et al., 2013). On the other hand, other chemicals act as bitter-tasting defensive toxins, reducing plant consumption by predatory herbivores and disrupting multiple levels of neurotransmitter signaling (Wink and Roberts, 1998; Wink et al., 1998). The curious thing about these latter chemicals is that in humans and other animals – including non-human primates, rodents, crayfish and bees – these same toxins act on the central nervous system to paradoxically induce reward and approach behavior (Imeh-Nathaniel et al., 2014; Singaravelan et al., 2005; Wise, 2004). While nicotine is the best-studied example, other plant toxins that possess rewarding properties include cannabis, cocaine and caffeine (Ettenberg, 2004; Nehlig, 1999; Panlilio et al., 2010; Wise, 1996). Indeed, many neurotoxins/drugs of abuse possess both strong aversive and rewarding properties in animals and humans (Hunt and Amit, 1987; Wise, 1996). For example, pairing these chemicals with drinking solutions results in an aversion to these solutions and yet, they also support self-administration behavior (Hunt and Amit, 1987; Verendeev and Riley, 2012). Herein lies the *paradox of drug reward*, described by Sullivan et al. as the incompatibility between neurobiology's reward model and evolutionary biology's punishment model (Hagen et al., 2009; Sullivan et al., 2008). Plant neurotoxins evolved to deter predation and yet, some species possess motivational systems (such as those involving dopamine) which can be activated by the consumption of these same molecules, thereby *encouraging* further drug-seeking behavior. How did the defensive chemicals produced by plants come to trigger reward in their animal predators?

2. The paradox of nicotine reward

Due to its widespread prevalence and the vast amount of research that has been conducted on it, the North American tobacco plant *Nicotiana attenuata* is the best example of this paradox. It is metabolized into nicotine and regulates its biosynthesis according to which of its tissues are most valuable and/or damaged, increasing nicotine production in the areas under attack by herbivores (Baldwin, 2001). Similarly, tobacco plants engineered to have increased nicotine production show reduced leaf loss to herbivores such as the tobacco hornworm *Manduca sexta*, which conversely shows lower survivorship and growth on these modified plants as compared to those with normal nicotine production (Steppuhn et al., 2004).

Nicotine activates nicotinic acetylcholine receptors (Zevin et al., 1998) and acts in mammals at the neuromuscular junction to facilitate muscle contraction (Hirsch, 2007), and in the central nervous system to aid in processes such as attention, learning, and memory (Corrigall et al., 1994; Wolf and Heberlein, 2003). The most common nicotine receptors in the brain (with subunits $\alpha4\beta2$) have a higher affinity for nicotine than those at the neuromuscular junction due to their stronger binding interactions (a result of key structural differences between the receptor types) (Xiu et al., 2009). Re-expression of β2-subunit nicotinic receptors into the ventral tegmental area (a part of the brain associated with reward processing) of $\beta2^{-/-}$ mice restores nicotine self-administration behavior (Maskos et al., 2005; Picciotto et al., 1997). These data show that while nicotine does possess aversive properties, its actions at central receptors are responsible for its rewarding effects in mammals (Benowitz, 1996).

2.1. The paradox of cocaine, caffeine and opiate reward

While nicotine is the best example, other chemicals produced by plants also act as deterrents to predatory herbivores. Although far less-well characterized, evidence suggests that other plant alkaloids such as cocaine, caffeine, and morphine are toxic to their predators (Furstenberg-Hagg et al., 2013; Hodgson, 2012; Howe and Jander, 2008; Iason and Villalba, 2006; Sorensen and Dearing, 2003). For example, cocaine produces toxic effects in insects by potentiating chemical neurotransmission (Nathanson et al., 1993). Additionally, caffeine sprays prevent the consumption of plants by slugs and snails (Hollingsworth et al., 2002). While it is not clear what mechanism underlies this effect (increased duration of action potentials has been proposed as one explanation) (Ahmed et al., 1997), recent evidence suggests that enhanced dopaminergic activity may be a possibility (which we will discuss in more detail later on), potentially indicating a role for dopamine in aversive behavior (Sturgess et al., 2010).

Despite these toxic effects, these same neurotoxins possess well-established rewarding properties in humans and other animals (Levens and Akins, 2001; Risinger and Oakes, 1995; Schroeder and Riters, 2006; Sullivan et al., 2008; Wise, 1996) by acting on specific receptors (e.g., opioid receptors, adenosine receptors) and specific neurotransmitter pathways, including those utilizing dopamine (Lupica et al., 2004; Pettit et al., 1984; Wise, 1989). These examples provide further evidence for the paradox of drug reward, demonstrating that plant toxins that are meant to deter predators also are capable of producing reward.

2.2. How do we explain the paradox of drug reward?

Perhaps the simplest resolution to this problem is to propose that the reward systems in question evolved independently of plant neurotoxin exposure. For example, it is possible that plants and humans were less likely to share direct interactions than plants and other animals. This might be the case if humans were introduced to an environment after the indigenous plant life had already evolved to deal with the threat of other animal predators. In this situation, plant chemicals geared toward discouraging herbivore predation might not have been 'designed' for humans and consequently, insufficient time has elapsed to allow for a human counter-adaptation to these substances (Sullivan et al., 2008).

However, this view is contradicted by evidence from human cytochrome P450 enzymes, which play important roles in metabolizing foreign toxins (Lewis, 2001; Sullivan et al., 2008), and from drug transporter adaptations that remove these toxins (Petzinger and Geyer, 2006). Sullivan et al. cite their presence as evidence *against* the argument that plant neurotoxins are an evolutionary novelty, as these enzymes would have been lost had animals not been exposed to their substrates previously. In humans, there are a wide variety of CYP2A6 isozymes (an enzyme which metabolizes nicotine), suggesting that differences in nicotine metabolism may be reflective of our species' differing environmental surroundings over time (Mwenifumbo and Tyndale, 2007). Additionally, taste receptors may have evolved to help animals detect and avoid toxic substances such as nicotine (Behrens and Meyerhof, 2009; Glendinning, 1994; Liscia and Solari, 2000). Indeed, blockade of rat tongue nicotine receptors reduces the aversive response to nicotine-containing water (an example of acute aversion due to taste) and increased the overall relative preference for nicotine vs. water (Oliveira-Maia et al., 2009). This is different from the aversion produced by the chronic, withdrawal-inducing psychoactive effects of a drug, which are mediated by brain nicotine receptors (Maskos et al., 2005).

If we reject the notion that plant neurotoxins and animal reward systems evolved independently, what else can explain the paradox

of drug reward? One proposed solution to this problem states that plant compounds act both on systems that produce toxic effects in potential predators (for example, cocaine acts as an insecticide by potentiating the neurotransmitter octopamine) but also, on the dopaminergic system, producing parallel rewarding effects in these predators due to chance mutation (Barron et al., 2009; Nathanson et al., 1993). Conversely, Sullivan et al. have suggested that humans consume plant neurotoxins because they act as an effective defense against parasites (Hagen et al., 2009; Sullivan et al., 2008). Indeed, evidence indicates that animals have used plant toxins as a form of self-medication against, for example, gastrointestinal parasites (Billing and Sherman, 1998; Hagen et al., 2013). As the proponents of this hypothesis point out, nicotine, arecoline (betel nut), and THC (tetrahydrocannabinol) – three of the more popular psychoactive substances used today – are effective against some parasitic organisms (Hagen et al., 2013). This suggests that despite their toxic effects, these plant neurotoxins may possess benefits for the organisms that consume them.

This proposal is an intriguing one, challenging the idea that drugs of abuse utilize the reward systems of consuming organisms to produce addictive, drug-seeking behavior (Hagen et al., 2013). However, an explanation of parasitic defense is not the only one that can explain these data. Indeed, we wish to suggest another idea which may complement this theory. We suggest that the evolution of the mammalian brain motivational system – of which dopamine plays an integral part – plays an important role in why toxic plant chemicals produce approach behavior. We suggest that approach behavior evolved after the inhibition of the aversive dopamine signal associated with toxic chemicals, via the evolution of a GABAergic modulatory system. This idea complements the previous 'parasite defense' theory as it more precisely specifies the potential conditions for when consumption of toxic chemicals may be beneficial. By suppressing the aversive nature of these plant chemicals, organisms are able to consume nutritive (but normally aversive) plant matter in times of extreme need (such as starvation). Our theory does not suggest that drug consumption is important for organismal growth per se but rather, we suggest that suppression of the toxic effects of these drugs can provide a 'window' for organisms to pursue other resources that may lead to increased fitness and future growth opportunities.

3. A new resolution to the drug reward paradox: dopamine originally signaled aversive and not rewarding events

Our new proposed model involves three steps (Fig. 1). First, we suggest that earlier animals utilized dopamine as an aversive 'escape' signal (Fig. 1, step 1**)** (Horvitz, 2000; Riemensperger et al., 2005; Salamone, 1994; Vergoz et al., 2007). According to our model, nicotine activates this aversive system by acting on nicotine receptors located on ventral tegmental area (VTA) dopamine cells (Fig. 1, step 1). We speculate that stressful conditions which signaled reduced fitness – for example, states of hunger or starvation – also utilized this aversive system (Carr, 2002; Salamone, 1994).

Second, we propose that the development of a controlling mechanism allowing for the regulation of this aversive dopaminergic signal was selected for (Fig. 1, step 2). Ventral tegmental area or rostromedial tegmentum (RMTg) GABAergic neurons that reduce mesolimbic dopaminergic activity are two potential examples of such a regulatory system (Balcita-Pedicino et al., 2011; Gysling and Wang, 1983; Jhou et al., 2009; Johnson and North, 1992; Omelchenko and Sesack, 2009). The reduction in an aversive dopaminergic signal could then result in increased approach behavior via the process of negative reinforcement: the encouragement of approach behavior (e.g., drug consumption) by the removal of negative events or circumstances. In the case of nicotine, by acting on nicotinic receptors located on GABAergic cells projecting to VTA dopamine cells, nicotine is able to dampen an aversive dopaminergic signal even in the presence of the aversive stimulus itself (Laviolette and van der Kooy, 2004). Similarly, in the case of toxic plants, the removal of their aversiveness makes it more likely that an organism will investigate (and consume) them further, particularly given their now 'unmasked' attractive properties (e.g., their nutritional value).

Inhibition of an aversive situation makes it more likely that an organism will demonstrate increased exploratory behavior for other important resources, some of which may lead to a solution to their aversive state. For example, when their hunger is suppressed, organisms are more likely to (and more capable of) seek out other resources such as shelter, prospective mates, and food. It should be noted that inhibition of the aversive dopaminergic signal does *not* actually reduce the *toxicity* of the plants themselves – this is unaffected. Rather, GABAergic inhibition of this signal merely reduces the natural *avoidance* one may exhibit for them. The plants themselves remain toxic.

In the final part of our model, we suggest that this same GABAergic regulatory system became linked to dopamine-independent primary reward, via a projection from the VTA to the brainstem tegmental pedunculopontine nucleus (TPP) (Fig. 1, step 3) (Bechara et al., 1992; Hnasko et al., 2005; Olmstead et al., 1998). This primary reward pathway is activated by nicotine (Laviolette et al., 2002) as well as other stimuli (Bechara and van der Kooy, 1992). Additionally, we suggest that alternative positive reinforcing mechanisms (including dopaminergic signaling) also evolved.

In short, we propose that plants evolved defensive toxins that initially tapped into the aversive dopaminergic system of its predators but over time, in more complex organisms, a GABAergic 'control' system evolved to regulate this dopaminergic system and thereby mediate approach behavior via negative reinforcement. Later on, a reward system evolved from the same upstream origin, to further reinforce the continued repetition of beneficial behaviors. We hypothesize that these changes occurred because they provided organisms with a selective advantage, allowing them the time to either address a specific need (e.g., hunger) or the ability to delay pursuit of this need in order to pursue other more-readily available resources (e.g., a prospective mate) – even when confronted by unfavorable environmental circumstances. We propose that the inhibition of an aversive state provides an organism with more time to evaluate, plan, and execute actions beneficial to their survival. Furthermore, we suggest that GABAergic modulation of dopaminergic signaling is a key system responsible for enabling how these changes took place. This GABAergic system likely evolved due to crucial chance mutations in the ventral tegmental area.

4. The many roles of dopamine

The search for brain 'reward centers' has been prominent ever since Olds' and Milner's finding that electrical stimulation of the brain could produce motivated behavior (Olds and Milner, 1954). To this end, the mammalian mesolimbic dopaminergic system has received a great deal of attention (Wise, 1996). Increased activity of this system – consisting of VTA dopamine cells and their projections to the nucleus accumbens (NAc) – has been correlated with the administration or consumption of natural reinforcers, psychostimulants, and brain stimulation (Apicella et al., 1991; Fibiger et al., 1987; Heffner et al., 1980; Pettit and Justice, 1989). Indeed, direct optogenetic stimulation of VTA dopamine neurons alone can produce behavioral conditioning (Tsai et al., 2009) and dopamine receptor antagonists or dopaminergic cell lesions reduce responding or approach behavior for many drugs of abuse (Beninger et al., 1987; Di Chiara and Imperato, 1985; Rolls et al., 1974; Spyraki et al.,

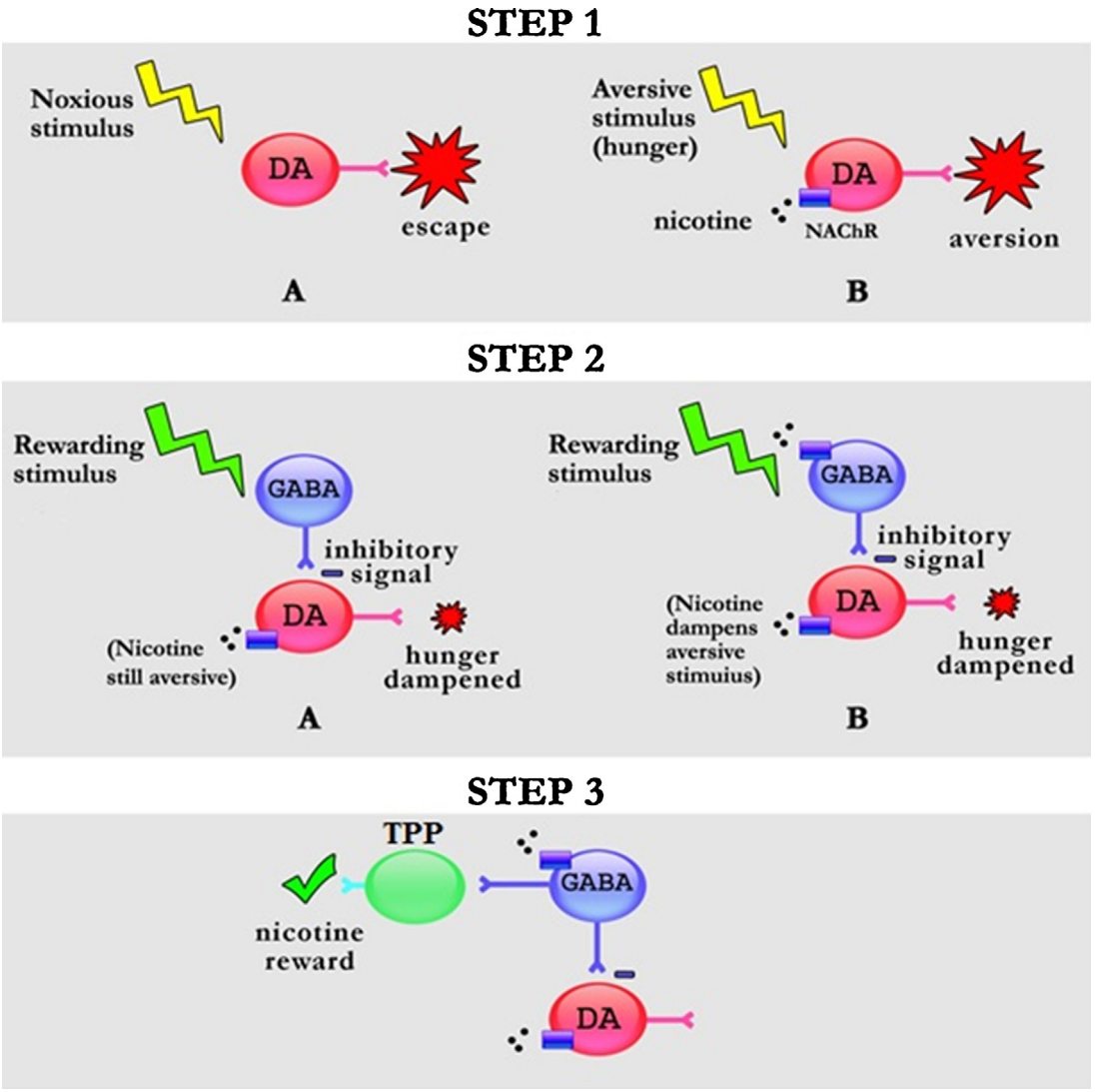

Fig. 1. A three-step model for the evolution of drug motivational systems in animals. *Step 1*: Initially, noxious stimuli stimulate dopamine neurons which provoke locomotion and perhaps, escape in early animals (A). This later evolves to incorporate aversive stimuli such as hunger into a general aversive response. Nicotine taps into this system by activating excitatory nicotinic acetylcholine receptors on the dopamine neurons, producing aversion (B). *Step 2*: Later, GABA neurons within the ventral tegmental area (VTA) (or the RMTg), with an inhibitory influence on the dopamine system, evolve (A). At this stage, 'rewarding' stimuli act to inhibit the aversive dopaminergic signal whereas nicotine continues to be aversive by activating dopamine neurons. With the evolution of nicotinic receptors on the GABA neuron, nicotine now effectively dampens the aversive dopamine response to aversive stimuli such as hunger (B). Thus, 'reward' is actually brought about by negative reinforcement – the absence of an aversive signal even in the presence of an aversive stimulus such as hunger or nicotine itself. It is possible that multiple subpopulations of dopamine neurons – with differing inputs and outputs – exist. *Step 3*: Later still, the same GABA cells come to code for dopamine-independent primary reward through a projection from the VTA to the tegmental pedunculopontine nucleus (TPP). This primary reward pathway is also activated by nicotine. The system is resistant to adaptive changes in the tobacco plant because it would be difficult for the plant to evolve a chemical that is selective for only one cell type within the same anatomical region. While the details concerning other drugs/plant neurotoxins will differ, we speculate that the general principles are similar.

1982; Yokel and Wise, 1975). Further evidence also suggests that the nigrostriatal dopaminergic pathway, which originates in the substantia nigra and is generally more-studied for its role in movement disorders, may also be important for reward processing (Wise, 2009).

More recent research has led to modified theories regarding dopamine's actual role in motivated behavior. For example, one prominent theory suggests that dopamine is not important for mediating reward per se but rather, *incentive salience*: the 'wanting' or intense aberrant *desire* for an object, which is fundamentally distinct and separate from 'liking' or the *inherent* rewarding properties of the object itself (Berridge and Robinson, 1998). Another theory is that dopamine plays a crucial role in 'error prediction', as research by Schultz and colleagues suggests that dopamine neurons predict and detect rewards and signal motivating events (Schultz, 1998). Their work indicates that dopamine cells shift their response firing patterns – from rewarding stimuli, to predictive cues instead – but respond with a *decrease* in firing if the reward is unexpectedly omitted (Apicella et al., 1991; Schultz et al., 1993). Clearly, whatever its true role (and it may have many), dopaminergic signaling is important for a wide-range of reward-related functions (Wise, 2004, 2009).

However, in contrast to this view of dopamine as a 'reward' molecule, there is considerable evidence suggesting that mesolimbic dopaminergic activity is observed in response to both rewarding *and* aversive events (Berton et al., 2006; Brischoux et al., 2009; Horvitz, 2000; Kimura et al., 2010; Lebestky et al., 2009; Salamone, 1994). Indeed, dopamine neurons have been observed to fire in response to a variety of aversive stimuli, including foot shock (Sorg and Kalivas, 1991), tail shock (Abercrombie et al., 1989), and tail pinch (Louilot et al., 1986). This effect is also observed with other forms of stress including restraint stress (Weiss et al.,

1997) and drug injection-induced anxiogenic stress (McCullough and Salamone, 1992).

Furthermore, dopamine has been shown to be critical for aversive learning in both invertebrates (Riemensperger et al., 2005; Vergoz et al., 2007) and other mammals (Horvitz, 2000; Pezze and Feldon, 2004; Sellings et al., 2008; Weitemier and Murphy, 2009). For example, the roundworm *Caenorhabditis elegans* is normally attracted to sodium (Bargmann and Horvitz, 1991). However, if the sodium has been paired with starvation (associative conditioning), *C. elegans* will avoid it. This avoidant behavior is blocked in mutants with reduced dopaminergic signaling, suggesting that dopamine is critical for the display of this negative association (Hukema et al., 2008). Similarly, inhibiting dopaminergic transmission (by blocking tyrosine hydroxylase production using mutant fly strains) can block the formation of an aversive conditioned response to electric shock in fruit flies (*Drosophila melanogaster*) (Schwaerzel et al., 2003). Conversely, these same mutant strains were shown to be capable of both learning *and* demonstrating a conditioned approach to sugar, an appetitive stimulus. This is an important example because it illustrates that aversive and rewarding behaviors may indeed be subserved by different biological pathways and that dopamine may actually be *more* important for aversive stimuli, and not necessary for reward.

The complex role of dopamine in motivated behavior can be illustrated by considering the example of nicotine. Although its rewarding properties are well established, dopamine's role in mediating these effects is not entirely clear. While some research suggests that nicotine's rewarding effects are mediated by increased dopaminergic signaling in the NAc [see (Di Chiara, 2000; Paterson, 2009) and references therein], other studies link mesolimbic dopaminergic activity with the *aversive* effects of the drug (Laviolette and van der Kooy, 2003; Sellings et al., 2008; Tan et al., 2009). For example, pharmacological blockade of dopaminergic receptors changed the behavior of rats injected with a dose of nicotine they normally found aversive. Instead of demonstrating a conditioned avoidance of an environment paired with this nicotine dose, the animals instead *approached* this environment (Laviolette and van der Kooy, 2003). This suggests that the animals now found it rewarding due to a reduction in the aversive dopamine-dependent properties of the drug.

One alternative explanation for these data are that this pursuit of nicotine is due to a homeostatic need to return dopamine to its 'normal' level. However, we argue against this interpretation for a number of reasons. For one, in the experiment cited above, dopamine receptor antagonism switched an aversive dose of nicotine to a rewarding dose (Laviolette and van der Kooy, 2003). This suggests that the subjects are not simply compensating for low dopamine levels. As well, dopamine receptor antagonism had no effect on responding when using higher, rewarding nicotine doses, further underlining this point (Laviolette and van der Kooy, 2003). Additionally, research into dopamine receptor knockout animals suggests that a lack of dopamine does not necessarily lead to increased drug-seeking behavior (Hnasko et al., 2005). Last, in place conditioning experiments using dopaminergic receptor antagonists, these receptors are blocked only during the 'training phase' and *not* during the testing component. In other words, the animals possess 'normal' dopaminergic levels during testing and yet *still* exhibit increased drug-seeking behavior. This suggests that the animals are not seeking out the drugs to correct an inherent physiological imbalance per se and that dopamine levels may not be the strongest predictor of drug-seeking behavior. Instead, the tegmental pedunculopontine nucleus appears to be a critical neural substrate for nicotine reward (Laviolette et al., 2002), although dopamine has certainly been shown to be important for nicotine reward in various circumstances, such as in animals chronically administered nicotine (Grieder et al., 2012).

Rewarding and aversive nicotine doses produce distinctly different cellular firing patterns in the NAc (Sun and Laviolette, 2014) and it has been suggested that the treatment of patients with schizophrenia (who possess excess dopaminergic activity) by using dopamine receptor antagonists might even be partly responsible for their higher-than-normal smoking rates (Laviolette and van der Kooy, 2003; McEvoy et al., 1995). Instead of people smoking more because they are seeking out reward, they may instead be more motivated because nicotine is *less* aversive. We have argued that dopamine is responsible for signaling the aversive properties of nicotine; therefore, dopamine receptor blockade might facilitate increased nicotine consumption. This interpretation makes it unsurprising that dopamine receptor antagonists might potentiate smoking behavior, and fits within our model of negative reinforcement. That said, other arguments to explain this phenomena have been proposed, including the 'self-medication' hypothesis which argues that schizophrenic patients smoke more in order to overcome the effects of neuroleptics or treat psychotic actions (although, it has been shown that smoking actually worsens these neuroleptic side effects and psychotic symptoms) (Dalack et al., 1998; Laviolette and van der Kooy, 2003).

While their rewarding effects are more well-known, other drugs of abuse also possess well-characterized aversive effects. For example, caffeine doses that are clearly aversive in rats can be converted into rewarding doses after blocking dopaminergic transmission (via dopamine receptor antagonists or by using dopamine receptor knockout animals) (Sturgess et al., 2010). Cocaine and morphine (along with many other drugs of abuse) also possess strong aversive properties as demonstrated by what is known as the conditioned taste aversion paradigm (King and Riley, 2013; Serafine et al., 2012). In this assay, drug injections are paired with flavored solutions and over time, animal subjects change their consumption habits to avoid drinking from the drug-paired (but not drug-unpaired) solution. The presentation of these aversive cues produce changes (suppression) in dopamine release in certain parts of the brain, underlining the fact that drugs of abuse possess both rewarding and aversive components and that dopamine may be important for either (Verendeev and Riley, 2012).

Taken together, the evidence suggests that the role of dopamine in motivated behavior is a complex one and is not only limited to the pursuit of reward. Indeed, dopamine has even been suggested to mediate behavioral flexibility, and dopaminergic activity has been reported to mediate goal-directed strategy-shifting (Haluk and Floresco, 2009; Pezze et al., 2007; Ragozzino, 2002). D1 dopamine receptors have been suggested to mediate more 'complex' forms of flexibility (e.g., the ability to switch strategies) whereas D2 dopamine receptor activity appears to impair more 'basic' stimulus-reward associations (Haluk and Floresco, 2009). Overall, this suggests that not only does dopamine play a complex behavioral role but also, that this role may have evolved over time in order to encourage or eliminate behaviors that promote or reduce survival, respectively (Agnoli et al., 2012).

4.1. The evolution of dopaminergic signaling

The many functions of dopaminergic signaling suggest that its role may have changed and evolved over time. Dopaminergic neurons date back at least 600 million years to a common ancestor of the Cnidaria (which includes hydra and jellyfish) and Bilateria (bilaterally symmetric animals constituting most present-day animals) (Anctil et al., 2002; Bouchard et al., 2003). Its biosynthesis by the unicellular protozoan *Tetrahymena pyriformis* suggests that it may have represented an early intercellular signal within colonies of ancient single-celled organisms (Goldman et al., 1981; Le Roith and Roth, 1984; Le Roith et al., 1983).

Dopamine possesses a prominent role in the regulation of locomotion. For example, dopamine modulates motor neurons in lobsters (Bucher et al., 2003), and both reductions and increases in dopaminergic transmission stimulate locomotor activity in *C. elegans* (Gaglia and Kenyon, 2009). Further evidence supporting the importance of dopamine in locomotion can be found in organisms such as honeybees (*Apis mellifera*), where dopamine appears to regulate mating activities and general locomotion (Akasaka et al., 2010), as well as in fruit flies (Riemensperger et al., 2005; Van Swinderen and Andretic, 2011). It also has been shown to play a crucial role in the locomotion of rats (Ahlenius et al., 1987), birds (Levens and Akins, 2001), and monkeys (Dill et al., 1979), and in humans, it plays a central role in motor diseases such as Parkinson's (Barbeau, 1970). As dopamine has remained a key transmitter integral to motoric activity in such a wide variety of organisms, it is plausible that one of its important roles early on and throughout evolution has been to act as a *motor signal* (Vidal-Gadea and Pierce-Shimomura, 2012). In less complex organisms, perhaps this initially took the form of mediating an escape-type response when encountering noxious stimuli, similar to the cockroach (*Periplaneta americana*) escape reflex. Here, thoracic interneurons (whose activity is modulated by dopamine) are involved in integrating sensory information necessary for orienting the animal during escape (Casagrand and Ritzmann, 1992; Ritzmann and Pollack, 1990; Ritzmann et al., 1991). Similarly, dopamine has been identified in alga as an anti-herbivore defense against sea urchins (Van Alstyne et al., 2006).

In more complex organisms, mechanisms allowing for the detection of (and escape from) noxious stimuli also are likely to have been strongly selected for by evolution. In animals with sufficient access to food sources, predation is an unnecessary risk and avoiding danger is of paramount importance: while the failure to escape a threat can be lethal, the failure to find a positive reward is generally less serious (assuming, of course, that the animal can afford to wait while it searches for valuable resources). For example, guppies will avoid an area containing food if there is a danger of predation, choosing instead to stay in a safe environment containing adequate resources (Abrahams and Dill, 1989). However, in situations where certain valuable resources (i.e., food) are plentiful, animals will accept a certain level of risk and forage in areas where predation is a danger (Abrahams and Dill, 1989; Stephens, 2008).

Over time, other stimuli indicative of reduced fitness may have come to activate the dopamine 'escape' response, which may have evolved to mediate a general aversive signal in times of stress. We speculate that eventually, the dopaminergic system grew to encompass the avoidance *and* approach behavior that comprises the concept of motivation itself.

4.2. GABAergic modulation of dopamine-dependent aversion

In mammalian organisms, mesolimbic dopaminergic neurons are subject to modulation by various cellular inputs. For example, activation of upstream GABA cells (both within the VTA and from the more caudal RMTg) inhibits VTA dopamine neuron firing (Jhou et al., 2009; Johnson and North, 1992; Omelchenko et al., 2009; Omelchenko and Sesack, 2009; van Zessen et al., 2012). This ability to inhibit the dopaminergic signal of aversion – that is, the electrophysiological dopaminergic 'firing pattern' that occurs when an organism encounters an aversive (as opposed to a rewarding) stimuli – might confer a selective, evolutionary advantage, particularly when conflicts between competing drives occur. For example, without this ability, a hungry animal might always be forced to search for food in order to satisfy its hunger. It would not be able to consume a wide variety of plants due to their protective neurotoxins. However, the ability to temporarily down-regulate the dopaminergic aversion produced by these plants (for example, via GABAergic regulation) would allow a hungry animal to 'manage' its hunger long enough to pursue other valuable, survival-enhancing resources (such as the pursuit of a prospective mate) or possibly, adapt to the situation at hand in order to 'escape' or satisfy its hunger. This ability to 'delay' an aversive/stressful state – so as to escape from/satiate it – would only be possible in animals capable of overcoming the natural aversiveness of plant compounds such as nicotine. This 'escape' might result in the unintended consequence of a strong reward-seeking drive that could promote survival. Indeed, early consumption of psychotropics (e.g., the betel nut plant, which was not regarded as a 'drug' per se by the populace) helped indigenous populations to stave off aversive states such as hunger in order to increase their chances of survival (Sullivan and Hagen, 2002).

In our hypothetical model, dopamine first signals an aversive state (Fig. 1, step 1). GABA neurons act as a negative reinforcement signal by turning down the aversive dopaminergic 'deprivation' signal (Fig. 1, step 2). With the aversion (caused by a stressor of some sort) temporarily lifted, the organism is free to deal with the source of the aversive signal either immediately, or after some period of time (Fig. 1, step 3). The ability to delay immediate action would allow for the more careful deployment of a particular strategy, or the development and refinement of more complex behaviors. Instead of needing to immediately 'escape' their predicament, animals might be able to cope with their stress long enough to formulate a plan to deal with it. Work by de Ridder et al. (2014) suggests that people who are hungry may actually perform better on a task where subjects have the option to select larger but delayed rewards (the correct response) over smaller, immediate rewards. Research also suggests that injections of benzodiazepines (which are agonists at GABA receptors) in pigeons results in improved performances on this same "delay discounting" task (Eppolito et al., 2011). Conversely, drugs which increase dopaminergic signaling can result in the incorrect selection of the smaller, more immediate reward (Roesch et al., 2007), although this effect is not always consistent and likely depends on a variety of factors such as the assay, animal strain, and drug dose (Huskinson and Anderson, 2012).

It is possible that extreme states of stress, such as severe food deprivation, may encourage organisms to take more risks. Indeed, food deprivation can result in increased drug-seeking behavior (Carr, 2002), which itself has long been associated with impulsivity and risk taking (Jentsch et al., 2014). While this risk taking can be potentially beneficial, there is also the possibility that it will not be. For example, drug use may facilitate a cycle of risky behavior that is not necessarily survival-increasing. However, while an accumulation of negative factors (e.g., low blood sugar, injuries, etc.) will prevent the optimal performance of an organism, we propose that a certain level of stress (e.g., non-debilitating hunger) may actually be beneficial, similar to the optimal arousal theory proposed by Hebb (1955). This idea suggests that organisms perform best at a certain level of arousal (not too much and not too little) and that therefore, a certain level of stress and risk taking may be a good thing.

According to our hypothesis, the intersection of how a GABAergic system came to modulate an aversive dopaminergic signaling system is a key event explaining why aversive plant compounds also are found to be rewarding by other organisms. Therefore, the evolution of this GABAergic signal is of great interest. GABA plays an important signaling role in the neural systems of many organisms including insects (Anthony et al., 1993; Busto et al., 2010; Sattelle et al., 1991), turtles (Chen and Chesler, 1991) and chickens (Jonaidi and Noori, 2012). In experiments using fruit flies, where odors were paired with electric shocks, it was suggested that dopaminergic signaling is responsible for relaying information regarding negative cues to the fly's mushroom body neurons (Davis, 2005), although it is possible that dopamine is simply transmitting a

general signal of aversive learning. Both this aversive olfactory learning (mediated by dopamine neurotransmission), as well as appetitive olfactory learning (mediated by octopamine neurotransmission), are modulated by GABAergic inputs (Busto et al., 2010). Conversely, dopamine and GABA play opposing roles in promoting and inhibiting fruit fly mating behavior (Crickmore and Vosshall, 2013), and GABA has been reported to modulate dopamine-dependent locomotor feeding in *aplysia*, a commonly-used model organism better known as a sea slug (Diaz-Rios and Miller, 2005). The existence of GABA modulatory systems in less complex organisms – prior to an established role for dopamine in appetitive behaviors (octopamine generally occupies this role in insects) (Perry and Barron, 2013) – suggests that this system may have been in place prior to the development of a dopamine-dependent 'reward' system.

It has been difficult to fully parse out the evolutionary role of GABA within the context of this theory. GABA appears to have been an integral component of multiple species' motivational systems for a long time, although the source of the GABAergic input to dopamine cells (e.g., VTA, RMTg, etc.) may differ. What is clear, however, is that distinct GABAergic systems exist in many species and that this modulatory system exerts a crucial level of control over dopaminergic signaling, allowing for approach behavior via negative reinforcement (Fig. 1, step 2).

4.3. Dopamine signaling and reward

In addition to its role in movement and aversion, dopamine signaling also provides reward-relevant information in mammals and other organisms. Even today, the precise nature of this information is still under some debate. As discussed previously, dopamine signaling has been reported to mediate incentive salience (Robinson and Berridge, 1993) and the prediction of both rewarding and aversive events (Matsumoto and Hikosaka, 2009; Schultz, 1998), as well as a number of other reward-related processes (Wise, 2004). In turn, this dopaminergic signaling is subject to a variety of cellular controls.

GABA inhibition of VTA dopamine neurons attenuates sucrose and ethanol seeking (Eiler and June, 2007; van Zessen et al., 2012), and increases in RMTg GABA neuron activity have been observed in response to some aversive stimuli, resulting in *decreased* midbrain dopaminergic activity (conversely, decreases in RMTg activity have been observed in response to reward-predictive stimuli) (Barrot et al., 2013; Jhou et al., 2009). VTA glutamate cells also likely play a part in this modulatory system as, in addition to making local connections with VTA dopamine neurons, RMTg GABA neurons are themselves modified by glutamatergic inputs from the lateral habenula (Balcita-Pedicino et al., 2010; Dobi et al., 2010; Omelchenko and Sesack, 2007; Yamaguchi et al., 2007), an area of the brain located near the thalamus and implicated in the motivational control of behavior (Hikosaka et al., 2008).

The interplay between glutamate and dopamine may be a key component of motivated behavior. Indeed, work by Kalivas and colleagues suggests that glutamate may play a fundamental role in the process of drug addiction (Kalivas, 2009). According to the Glutamate Homeostasis Hypothesis of addiction, while dopamine still acts as the primary signaling mechanism of reward information, addiction itself is thought to be the product of "aberrant response inhibition": a failure to make the 'right' decision and cease the maladaptive cycle of drug-seeking and drug-taking. Neuroimaging studies support the idea of dysregulation in the brain of drug users (Goldstein and Volkow, 2002). According to proponents of the glutamate hypothesis, this dysregulation is thought to be the result of a glutamate imbalance in drug-dependent subjects (Kalivas, 2009; Kalivas et al., 2009). A number of studies support the idea that glutamatergic signaling is necessary for the development of drug dependence (Harris and Aston-Jones, 2003; McFarland et al., 2003; Melendez et al., 2005; Schenk et al., 1993) and one line of supporting evidence comes from work demonstrating that pretreatment with a glutamate receptor antagonist inhibits the locomotor sensitization to amphetamine and cocaine that normally accompanies their usage (Kalivas and Alesdatter, 1993; Karler et al., 1989). It is clear that the area of dopamine-dependent reward is a complex one that is subject to a great degree of control.

Complementing this mammalian dopamine-dependent reward system, further evidence suggests the concurrent existence of a dopamine-independent reward system. Strong evidence in support of this comes (in part) from studies utilizing the associative paradigm known as place conditioning, where the approach to drug-paired environments is taken as an index of the conditioned rewarding properties of a stimulus (as well as an indirect measure of primary reward) (Tzschentke, 2007). In dopamine knockout mice, a lack of dopamine did not impair their learning, memory recall, or demonstration of a morphine place preference, suggesting that dopamine is not always critical for these processes (although these mice showed locomotor and morphine analgesia abnormalities) (Hnasko et al., 2005). As these mice are clearly capable of demonstrating drug-seeking behavior, it suggests that while dopamine certainly plays a critical role in some forms of reward processing, alternative 'reward systems' must also exist.

One example of this is the brainstem structure known as the TPP. Using a place conditioning assay, it was demonstrated that the TPP was required for either well-fed or drug-naive animals to demonstrate food or morphine place preferences, respectively (Bechara and van der Kooy, 1992; Olmstead et al., 1998). The TPP is anatomically connected with a large number of brain regions important for various functions such as movement, arousal, and motivation (Steckler et al., 1994) and is located at the caudal end of the medial forebrain bundle, a set of axons linked to reward processing (Hernandez et al., 2006). It contains a number of neurotransmitters including GABA, glutamate, and acetylcholine (Bevan and Bolam, 1995; Ford et al., 1995), but it is unclear which of these (if any) are important for reward. While there is limited information on the comparative anatomy of the TPP between species, it has been suggested that in most complex organisms (e.g., cats, rats, non-human primates, humans), it functions in a similar manner (Alam et al., 2011). In summary, while dopamine clearly plays an important role in reward processing, other dopamine-independent mechanisms also exist and occupy key roles in the process of motivation (Fig. 1, step 3).

4.4. Drug deprivation and dopamine

Changes in an organism's surroundings can have a profound impact on their own internal biology. This idea is summed up in the Opponent Process theory of motivation (Solomon and Corbit, 1974) which states that for every change to an organism's *status quo* – for example, feeling pain – there is an opposing process that works to counteract this change: in this case, a physiological response (release of natural endorphins) geared toward counteracting this painful experience. This idea was later expanded upon by others, who suggested that all organisms have a 'homeostatic balance point' (Koob and Le Moal, 2005, 2001). In particular, this viewpoint was adopted to explain the problem of drug abuse: of how an initially rewarding substance gradually became less and less pleasurable, to the extent of inducing a state of deprivation and withdrawal (Koob and Le Moal, 2001, 2008). This withdrawal, in turn, motivated further drug-seeking behavior, producing a cycle of negative reinforcement. This updated version of the Opponent Process theory is known as the Allostasis model (George et al., 2012; Koob and Le Moal, 2001) and incorporates the general idea that

previous drug experience can have a considerable influence on the effects of subsequent drug exposure (LeBlanc and Cappell, 1974).

Our proposed model shares many similarities with that of Koob and Le Moal (2005, 2001). For example, the ability of complex organisms to inhibit an aversive signal (perhaps via GABAergic modulation of dopamine signaling) may feed into the process of addiction by disabling the natural 'opponent process' response. Instead of being able to delay the pursuit of such basic necessities as food, drug users may instead end up foregoing its pursuit altogether and completely substituting drug-seeking behavior instead – to the detriment of their own health.

However, our theory differs from the Opponent Process theory in a few key ways. For one, we suggest that dopamine is responsible for signaling the aversive properties of stimuli, a novel idea in the context of Opponent Process theory. Furthermore, our model goes on to postulate that the blockade of this aversive state in turn leads to approach behavior ('reward') – in other words, the 'opponent' process itself. Additionally, our model incorporates a role for dopamine-independent reward mechanisms, such as those mediated by the TPP.

Like the allostasis model, we suggest that the degree of an organism's prior drug exposure can determine the mechanisms which control drug reward (Bechara and van der Kooy, 1992). Chronic drug use can lead to a 'drug-deprived' state characterized experimentally by withdrawal symptoms and/or the avoidance of places associated with withdrawal. The alleviation of these withdrawal symptoms by further drug intake is an example of negative reinforcement (Fig. 1, step 2). When animals are in a non-deprived, drug-naive (or food-stated) state, morphine, nicotine, and food place preferences are blocked by excitotoxic lesions of the TPP (Bechara and van der Kooy, 1992; Laviolette et al., 2002; Olmstead et al., 1998), but not by dopamine receptor antagonists. These place preferences are thought to be motivated by the inherent rewarding properties of the stimuli themselves (Bechara and van der Kooy, 1992). Conversely, in animals who have experienced chronic morphine or nicotine exposure (or are in a state of food deprivation), lesions of the TPP have no effect on these place preferences; instead, disruption of dopaminergic signaling is able to completely attenuate them. These place preferences are thought to be due to the alleviation of a withdrawal state because the animals avoid the withdrawal-paired environment much more strongly than they approach the drug-paired environment (Bechara and van der Kooy, 1992). These experiments double-dissociate the mechanisms critical for reward when animals are in non-deprived and deprived states.

The idea that an organism's 'motivational state' can determine the part of the brain important for reward-seeking behavior can be used to resolve the paradox of drug reward. While more complex organisms may normally avoid a neurotoxin-producing plant – finding it aversive when in the non-deprived state – they may choose to consume it when in a deprived, highly stressed state, such as a state of withdrawal (Koob, 2008; Koob and Le Moal, 2001). In essence, this search for more risky rewards (and risk-taking in general) is a consequence of stressful conditions (such as starvation) in the first place. This risky reward-seeking behavior may confer survival benefits to the organism and lead to future scenarios where risk-taking is more acceptable. In other words, the removal of 'risk inhibition' (aversion) may produce a strong desire for future reward-seeking behavior.

Under this model, there might be insufficient selective pressure on plants to become more toxic since their toxins actually would work for much of the time. Conversely, there might be insufficient pressure on animals to evolve counter-adaptations since, once satiated, they would no longer wish to consume these plants. The ability to pursue a potential benefit (e.g., nutrients critical for survival) by temporarily 'overriding' its toxic downside can be viewed as an adaptive mechanism of sorts (Hagen et al., 2009), albeit one that may come with drawbacks should an organism fail to recognize that it cannot put off essential needs (e.g., seeking out food) indefinitely.

Furthermore, even though a plant neurotoxin specifically targeting dopamine neurons in the VTA might be effective, it is difficult to imagine that such a specific toxin would evolve without also having a similar effect at the modulatory GABA neurons. For example, nicotine receptors are found on both VTA GABA and dopamine neurons and therefore, nicotine might be less effective as a deterrent since it might act on both cell types to produce opposing results (Fig. 1, step 3). Both direct activation of dopamine neurons, as well as indirect activation (caused by binding to presynaptic nicotine receptors which would increase excitatory input onto dopamine cells) would result in increased dopaminergic activity whereas direct activation of GABA neurons would reduce dopaminergic activity (although this may lead to desensitization of the nicotinic receptors on GABA cells and a resulting rebound excitation of dopamine cells) (Laviolette and van der Kooy, 2004; Yin and French, 2000).

Similar to the Opponent Process Theory, our model suggests that the drug history of an organism appears to be a crucial factor governing the brain mechanisms responsible for drug motivation. These changes in brain mechanisms may be useful in helping to explain the paradox of drug reward.

5. Conclusion

Toxic plant compounds prevent plant consumption and yet also instigate reward-seeking behavior in predators. This is known as the paradox of drug reward (Hagen et al., 2009). Here, we propose a potential resolution to this paradox. We suggest that originally, dopamine was most critical for movement, locomotion, and mediating escape. However, over time, dopamine came to be associated with aversion (Giurfa, 2006; Riemensperger et al., 2005; Schwaerzel et al., 2003). We argue that neurotoxic plant compounds originally *did* induce a state of aversion in predatory organisms, as mediated by dopaminergic signaling (Fig. 1, step 1). However, mutational changes allowed for the evolution of a GABAergic system that could inhibit this dopaminergic signal and allow predators to circumvent this aversive state. This ability to cope with stressful circumstances such as hunger – in order to pursue other resources or seek out better solutions to the problem of hunger itself – provided organisms with a selective advantage. Due to the suppression of these negative conditions (but not an actual change in the toxicity of neurotoxic plants themselves), we suggest that organisms increased their approach behavior toward various resources of interest, via the process of negative reinforcement (Fig. 1, step 2). The inhibition of dopaminergic signaling enabled organisms to ingest otherwise toxic and harmful plants for the purpose of survival. The further evolution of dopaminergic signaling led to its own ability to instigate reward seeking. Additionally, non-dopamine-dependent mechanisms of reward seeking (such

Table 1
Remaining questions.

- How does the timing of dopamine release affect reward and aversion? What precise role does learning and memory play in this process?
- What role do other (and more recently evolved) structures such as the prefrontal cortex play in reward and aversion?
- Why do many mammals (which have very similar reward/aversion neurobiology) avoid noxious plant species in the wild, whereas humans cultivate and consume them? How has human culture shaped the consumption of plant neurotoxins?
- Why are some psychoactive plant neurotoxins addictive (nicotine) whereas others are not (psilocybin), despite the fact that they are both consumed recreationally?

Table 2
Plant neurotoxins.

Plant	Psychoactive compound	Neuronal target	Human consumption	Primary herbivores
Coca (*Erythroxylum coca*)	Cocaine	Dopamine reuptake inhibitor	Chewed by South American indigenous peoples for over 1000 years	Cutie ant; Ulo butterfly larva; Mounga (burrowing insect)
Tobacco (*Nicotiana tabacum*)	Nicotine	Agonist of nicotinic acetylcholine receptors	Used in the Americas in conjunction with religious ceremonies prior to the arrival of Europeans	Aphids; Tobacco budworm; Tobacco hornworm; Stinkbug; Vegetable Weevil; Whitefringed beetle
Opium poppy (*Papaver somniferum*)	Opiates (ex. Morphine, Heroin)	Agonist at (primarily μ) opioid receptors	First grown in western Mediterranean probably for food. Cultivated by Sumerians 3400 BCE for euphoric effects	Root Weevil; Aphids; Thrips; Sawfly; Head gall fly; Capsule weevil; Capsule borer
Cannabis (*Cannabis sativa*)	Tetrahydrocannabinol	Agonist at cannabinoid receptors	Ancient spiritual use dates back to 2200 BCE around what is now Afghanistan and Pakistan and in Indian culture as far back as 3000 BCE	Aphids; Whiteflies; Leafhoppers; Mealybugs

as those dependent upon the TPP) also developed (Fig. 1, step 3). This allowed organisms to demonstrate approach behavior without having to first experience aversive states of withdrawal.

As there are now many diverse processes which require dopaminergic signaling – e.g., learning, memory, locomotion, reward, and aversion – this suggests that the dopaminergic system has indeed undergone considerable evolutionary change over the years. That said, it is unclear exactly when the transition from an 'aversive' dopaminergic system, to one concerned with (among other things) reward, occurred. It is possible that this change was already beginning to take place sometime before invertebrate and vertebrate organisms 'branched off' from one another, as both show evidence of dopamine-dependent aversive and appetitive behaviors (Waddell, 2013). However, further research into this question will be required in order to make a definitive statement.

Despite these gaps in our knowledge and a number of other questions (Table 1), this hypothesis provides an evolutionary explanation for the paradox of reward. We suggest that the consumption of neurotoxin-producing plants occurs primarily in situations when an animal is in a stressful, deprived state, where it is forced to prioritize survival. This hypothesis also explains why no counter-adaptation has arisen: the plant toxins *do* work initially, before animals become 'tolerant' to their effects via GABAergic modulation and the aversiveness of the toxin is lessened. Additionally, the more recent evolution of a TPP-dependent reward system might provide sufficient 'evolutionary novelty' to help further explain the paradox of drug reward.

While hypotheses about the evolutionary history of any trait are difficult to test experimentally, modern organisms of potentially evolutionarily ancient origin can be used to support these suggestions. For example, the fact that simple organisms such as *C. elegans* and *D. melanogaster* show evidence of an early role of dopamine in aversion is supportive of these ideas (Dexter et al., 2012; Riemensperger et al., 2005; Van Swinderen and Andretic, 2011). Furthermore, one might take the example of herbivorous insects that feed on plants commonly known to produce neurotoxins (Table 2). For example, the tobacco hornworm appears to be affected by high nicotine levels in tobacco plants; therefore, experiments involving the blockade of dopamine in these animals may help to refute or support our suggestions. Similarly, expanding on the alga research concerning dopamine's role as an aversive signal mentioned previously might help to test this model (Van Alstyne et al., 2006).

While we cannot necessarily refute other hypotheses attempting to explain the paradox of drug reward, our model compliments the idea that plant neurotoxins may be consumed because this can lead to rewarding consequences. These may include improved parasitic defenses or perhaps, the idea that neurotoxic plants still have nutritive value that can make their consumption worthwhile (at least in certain circumstances). Furthermore, this model might be of particular interest to the study of addiction as it suggests that a focus on dopamine-dependent reward mechanisms may not be enough to fully understand and treat this disease. Drug-seeking behavior may be dependent on a number of other factors, including withdrawal-induced negative reinforcement and dopamine-independent mechanisms of reward. Therefore, the study of other important systems (such as GABAergic and glutamatergic regulation of dopamine signaling) may be of particular importance.

It would appear, then, that the ongoing evolution of plants and the animals that consume them is far from over. While it remains unclear when (evolutionarily speaking) organisms began to find these plant toxins rewarding, the fact that many plants with direct psychoactive effects are now cultivated by humans all over the world might instead suggest the current establishment of a new equilibrium.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

Funded by the Canadian Institutes of Health Research (CIHR) and a Natural Sciences and Engineering Research Council of Canada (NSERC) graduate training award.

References

Abercrombie, E., Keefe, K., DiFrischia, D., Zigmond, M., 1989. Differential effect of stress on in vivo dopamine release in striatum, nucleus accumbens, and medial frontal cortex. J. Neurochem. 52, 1655–1658.
Abrahams, M.V., Dill, L.M., 1989. A determination of the energetic equivalence of the risk of predation. Ecology 70, 999–1007.
Agnoli, L., Mainolfi, P., Invernizzi, R.W., Carli, M., 2012. Dopamine D1-like and D2-like receptors in the dorsal striatum control different aspects of attentional performance in the five-choice serial reaction time task under a condition of increased activity of corticostriatal inputs. Neuropsychopharmacology 38, 701–714.
Ahlenius, S., Hillegaart, V., Thorell, G., Magnusson, O., Fowler, C., 1987. Suppression of exploratory locomotor activity and increase in dopamine turnover following the local application of cis-flupenthixol into limbic projection areas of the rat striatum. Brain Res. 402, 131–138.
Ahmed, I.A., Hopkins, P.M., Winlow, W., 1997. Low concentrations of caffeine raise intracellular calcium concentration only in the presence of extracellular calcium in cultured molluscan neurons. Gen. Pharmacol. 28, 245–250.
Akasaka, S., Sasaki, K., Harano, K., Nagao, T., 2010. Dopamine enhances locomotor activity for mating in male honeybees (*Apis mellifera* L.). J. Insect. Physiol. 56, 1160–1166.

Alam, M., Schwabe, K., Krauss, J.K., 2011. The pedunculopontine nucleus area: critical evaluation of interspecies differences relevant for its use as a target for deep brain stimulation. Brain 134, 11–23.
Anctil, M., Hurtubise, P., Gillis, M., 2002. Tyrosine hydroxylase and dopamine-beta-hydroxylase immunoreactivities in the cnidarian *Renilla koellikeri*. Cell Tissue Res. 310, 109–117.
Anthony, N.M., Harrison, J.B., Sattelle, D.B., 1993. GABA receptor molecules of insects. EXS 63, 172–209.
Apicella, P., Ljungberg, T., Scarnati, E., Schultz, W., 1991. Responses to reward in monkey dorsal and ventral striatum. Exp. Brain Res. 85, 491–500.
Balcita-Pedicino, J.J., Omelchenko, N., Bell, R., Sesack, S.R., 2010. The inhibitory influence of the lateral habenula on midbrain dopamine cells: ultrastructural evidence for indirect mediation via the rostromedial mesopontine tegmental nucleus. J. Comp. Neurol. 519, 1143–1164.
Balcita-Pedicino, J.J., Omelchenko, N., Bell, R., Sesack, S.R., 2011. The inhibitory influence of the lateral habenula on midbrain dopamine cells: ultrastructural evidence for indirect mediation via the rostromedial mesopontine tegmental nucleus. J. Comp. Neurol. 519, 1143–1164.
Baldwin, I., 2001. An ecologically motivated analysis of plant-herbivore interactions in native tobacco. Plant Physiol. 127, 1449–1458.
Barbeau, A., 1970. Dopamine and disease. Can. Med. Assoc. J. 103, 824–832.
Bargmann, C.I., Horvitz, H.R., 1991. Chemosensory neurons with overlapping functions direct chemotaxis to multiple chemicals in *C. elegans*. Neuron 7, 729–742.
Barron, A.B., Maleszka, R., Helliwell, P.G., Robinson, G.E., 2009. Effects of cocaine on honey bee dance behaviour. J. Exp. Biol. 212, 163–168.
Barrot, M., Sesack, S.R., Georges, F., Pistis, M., Hong, S., Jhou, T.C., 2013. Braking dopamine systems: a new GABA master structure for mesolimbic and nigrostriatal functions. J. Neurosci. 32, 14094–14101.
Bechara, A., van der Kooy, D., 1992. A single brain stem substrate mediates the motivational effects of both opiates and food in nondeprived rats but not in deprived rats. Behav. Neurosci. 106, 351–363.
Bechara, A., Harrington, F., Nader, K., van der Kooy, D., 1992. Neurobiology of motivation: double dissociation of two motivational mechanisms mediating opiate reward in drug-naive versus drug-dependent animals. Behav. Neurosci. 106, 798–807.
Behrens, M., Meyerhof, W., 2009. Mammalian Bitter Taste Perception. Results and Problems in Cell Differentiation, vol. 47., pp. 203–220.
Beninger, R., Cheng, M., Hahn, B., Hoffman, D., Mazurski, E., Morency, M., Ramm, P., Stewart, R., 1987. Effects of extinction, pimozide, SCH 23390, and metoclopramide on food-rewarded operant responding of rats. Psychopharmacology 92, 343–349.
Benowitz, N.L., 1996. Pharmacology of nicotine: addiction and therapeutics. Ann. Rev. Pharmacol. Toxicol. 36, 597–613.
Berridge, K., Robinson, T., 1998. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? Brain Res. Rev. 28, 309–369.
Berton, O., McClung, C.A., DiLeone, R.J., Krishnan, V., Renthal, W., Russo, S.J., Graham, D., Tsankova, N.M., Bolanos, C.A., Rios, M., Monteggia, L.M., Self, D.W., Nestler, E.J., 2006. Essential role of BDNF in the mesolimbic dopamine pathway in social defeat stress. Science 311, 864–868.
Bevan, M.D., Bolam, J.P., 1995. Cholinergic, gabaergic, and glutamate-enriched inputs from the mesopontine tegmentum to the subthalamic nucleus in the rat. J. Neurosci. 15, 7105–7120.
Billing, J., Sherman, P.W., 1998. Antimicrobial functions of spices: why some like it hot. Q. Rev. Biol. 73, 3–49.
Bouchard, C., Ribeiro, P., Dubé, F., Anctil, M., 2003. A new g protein-coupled receptor from a primitive metazoan shows homology with vertebrate aminergic receptors and displays constitutive activity in mammalian cells. J. Neurochem. 86, 1149–1161.
Brischoux, F., Chakraborty, S., Brierley, D.I., Ungless, M.A., 2009. Phasic excitation of dopamine neurons in the ventral VTA by noxious stimuli. Proc. Natl. Acad. Sci. U. S. A. 106, 4894–4899.
Bucher, D., Thirumalai, V., Marder, E., 2003. Axonal dopamine receptors activate peripheral spike initiation in a stomatogastric motor neuron. J. Neurosci. 23, 6866–6875.
Busto, G.U., Cervantes-Sandoval, I., Davis, R.L., 2010. Olfactory learning in drosophila. Physiology (Bethesda) 25, 338–346.
Carr, K.D., 2002. Augmentation of drug reward by chronic food restriction: behavioral evidence and underlying mechanisms. Physiol. Behav. 76, 353–364.
Casagrand, J., Ritzmann, R., 1992. Biogenic amines modulate synaptic transmission between identified giant interneurons and thoracic interneurons in the escape system of the cockroach. J. Neurobiol. 23, 644–655.
Chen, J.C., Chesler, M., 1991. Extracellular alkalinization evoked by GABA and its relationship to activity-dependent ph shifts in turtle cerebellum. J. Physiol. 442, 431–446.
Corrigall, W., Coen, K., Adamson, K., 1994. Self-administered nicotine activates the mesolimbic dopamine system through the ventral tegmental area. Brain Res. 653, 278–284.
Crickmore, M.A., Vosshall, L.B., 2013. Opposing dopaminergic and GABAergic neurons control the duration and persistence of copulation in Drosophila. Cell 155, 881–893.
Dalack, G.W., Healy, D.J., Meador-Woodruff, J.H., 1998. Nicotine dependence in schizophrenia: clinical phenomena and laboratory findings. Am. J. Psychiatry 155, 1490–1501.
Davis, R.L., 2005. Olfactory memory formation in Drosophila: from molecular to systems neuroscience. Annu. Rev. Neurosci. 28, 275–302.
de Ridder, D., Kroese, F., Adriaanse, M., Evers, C., 2014. Always gamble on an empty stomach: hunger is associated with advantageous decision making. PLOS ONE 9, e111081.
Dexter, P.M., Caldwell, K.A., Caldwell, G.A., 2012. A predictable worm: application of *Caenorhabditis elegans* for mechanistic investigation of movement disorders. Neurotherapeutics 9, 393–404.
Di Chiara, G., Imperato, A., 1985. Ethanol preferentially stimulates dopamine release in the nucleus accumbens of freely moving rats. Eur. J. Pharmacol. 115, 131–132.
Di Chiara, G., 2000. Role of dopamine in the behavioural actions of nicotine related to addiction. Eur. J. Pharmacol. 393, 295–314.
Diaz-Rios, M., Miller, M.W., 2005. Rapid dopaminergic signaling by interneurons that contain markers for catecholamines and GABA in the feeding circuitry of aplysia. J. Neurophysiol. 93, 2142–2156.
Dill, R.E., Jones, D.L., Gillin, J.C., Murphy, G., 1979. Comparison of behavioral effects of systemic L-DOPA and intracranial dopamine in mesolimbic forebrain of nonhuman primates. Pharmacol. Biochem. Behav. 10, 711–716.
Dobi, A., Margolis, E.B., Wang, H.L., Harvey, B.K., Morales, M., 2010. Glutamatergic and nonglutamatergic neurons of the ventral tegmental area establish local synaptic contacts with dopaminergic and nondopaminergic neurons. J. Neurosci. 30, 218–229.
Eiler, I.I., June, W.J.A.H.L., 2007. Blockade of GABA-A receptors within the extended amygdala attenuates D2 regulation of alcohol-motivated behaviors in the ventral tegmental area of alcohol-preferring (p) rats. Neuropharmacology 52, 1570–1579.
Eppolito, A.K., France, C.P., Gerak, L.R., 2011. Effects of acute and chronic flunitrazepam on delay discounting in pigeons. J. Exp. Anal. Behav. 95, 163–174.
Ettenberg, A., 2004. Opponent process properties of self-administered cocaine. Neurosci. Behav. Rev. 27, 721–728.
Fibiger, H.C., LePiane, F.G., Jakubovic, A., Phillips, A.G., 1987. The role of dopamine in intracranial self-stimulation of the ventral tegmental area. J. Neurosci. 7, 3888–3896.
Ford, B., Holmes, C.J., Mainville, L., Jones, B.E., 1995. Gabaergic neurons in the rat pontomesencephalic tegmentum: codistribution with cholinergic and other tegmental neurons projecting to the posterior lateral hypothalamus. J. Comp. Neurol. 363, 177–196.
Furstenberg-Hagg, J., Zagrobelny, M., Bak, S., 2013. Plant defense against insect herbivores. Int. J. Mol. Sci. 14, 10242–10297.
Gaglia, M.M., Kenyon, C., 2009. Stimulation of movement in a quiescent, hibernation-like form of *Caenorhabditis elegans* by dopamine signaling. J. Neurosci. 29, 7302–7314.
George, O., Le Moal, M., Koob, G.F., 2012. Allostasis and addiction: role of the dopamine and corticotropin-releasing factor systems. Physiol. Behav. 106, 58–64.
Giurfa, M., 2006. Associative learning: the instructive function of biogenic amines. Curr. Biol. 16, R892–R895.
Glendinning, J., 1994. Is the bitter rejection response always adaptive? Physiol. Behav. 56, 1217–1227.
Goldman, M., Gundersen, R., Erickson, C., Thompson, G.J., 1981. High performance liquid chromatographic analysis of catecholamines in growing and non-growing *Tetrahymena pyriformis*. Biochim. Biophys. Acta 676, 221–225.
Goldstein, R.Z., Volkow, N.D., 2002. Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. Am. J. Psychiatry 159, 1642–1652.
Grieder, T.E., George, O., Tan, H., George, S.R., Le Foll, B., Laviolette, S.R., van der Kooy, D., 2012. Phasic D1 and tonic D2 dopamine receptor signaling double dissociate the motivational effects of acute nicotine and chronic nicotine withdrawal. Proc. Natl. Acad. Sci. U. S. A. 109, 3101–3106.
Gysling, K., Wang, R.Y., 1983. Morphine-induced activation of a10 dopamine neurons in the rat. Brain Res. 277, 119–127.
Hagen, E., Sullivan, R., Schmidt, R., Morris, G., Kempter, R., Hammerstein, P., 2009. Ecology and neurobiology of toxin avoidance and the paradox of drug reward. Neuroscience 160, 69–84.
Hagen, E.H., Roulette, C.J., Sullivan, R.J., 2013. Explaining human recreational use of 'pesticides': the neurotoxin regulation model of substance use vs. the hijack model and implications for age and sex differences in drug consumption. Front. Psychiatry 4, 142.
Haluk, D.M., Floresco, S.B., 2009. Ventral striatal dopamine modulation of different forms of behavioral flexibility. Neuropsychopharmacology 34, 2041–2052.
Harris, G.C., Aston-Jones, G., 2003. Critical role for ventral tegmental glutamate in preference for a cocaine-conditioned environment. Neuropsychopharmacology 28, 73–76.
Hebb, D.O., 1955. Drives and the c.N.S. (conceptual nervous system). Psychol. Rev. 62, 243–254.
Heffner, T.G., Hartman, J.A., Seiden, L.S., 1980. Feeding increases dopamine metabolism in the rat brain. Science 208, 1168–1170.
Hernandez, G., Hamdani, S., Rajabi, H., Conover, K., Stewart, J., Arvanitogiannis, A., Shizgal, P., 2006. Prolonged rewarding stimulation of the rat medial forebrain bundle: neurochemical and behavioral consequences. Behav. Neurosci. 120, 888–904.
Hikosaka, O., Sesack, S.R., Lecourtier, L., Shepard, P.D., 2008. Habenula: crossroad between the basal ganglia and the limbic system. J. Neurosci. 28, 11825–11829.
Hirsch, N.P., 2007. Neuromuscular junction in health and disease. Br. J. Anaesth. 99, 132–138.

Hnasko, T.S., Sotak, B.N., Palmiter, R.D., 2005. Morphine reward in dopamine-deficient mice. Nature 438, 854–857.
Hodgson, E., 2012. Toxins and venoms. Prog. Mol. Biol. Transl. Sci. 112, 373–415.
Hollingsworth, R.G., Armstrong, J.W., Campbell, E., 2002. Caffeine as a repellent for slugs and snails. Nature 417, 915–916.
Horvitz, J., 2000. Mesolimbocortical and nigrostriatal dopamine responses to salient non-reward events. Neuroscience 96, 651–656.
Howe, G.A., Jander, G., 2008. Plant immunity to insect herbivores. Annu. Rev. Plant Biol. 59, 41–66.
Hukema, R., Rademakers, S., Jansen, G., 2008. Gustatory plasticity in *C. elegans* involves integration of negative cues and NaCl taste mediated by serotonin, dopamine, and glutamate. Learn. Mem. 15, 829–836.
Hunt, T., Amit, Z., 1987. Conditioned taste aversion induced by self-administered drugs: paradox revisited. Neurosci. Biobehav. Rev. 11, 107–130.
Huskinson, S.L., Anderson, K.G., 2012. Effects of acute and chronic administration of diazepam on delay discounting in Lewis and Fischer 344 rats. Behav. Pharmacol. 23, 315–330.
Iason, G.R., Villalba, J.J., 2006. Behavioral strategies of mammal herbivores against plant secondary metabolites: the avoidance-tolerance continuum. J. Chem. Ecol. 32, 1115–1132.
Imeh-Nathaniel, A., Okon, M., Huber, R., Nathaniel, T.I., 2014. Exploratory behavior and withdrawal signs in crayfish: chronic central morphine injections and termination effects. Behav. Brain Res. 264, 181–187.
Jentsch, J.D., Ashenhurst, J.R., Cervantes, M.C., Groman, S.M., James, A.S., Pennington, Z.T., 2014. Dissecting impulsivity and its relationships to drug addictions. Ann. N. Y. Acad. Sci. 1327, 1–26.
Jhou, T.C., Fields, H.L., Baxter, M.G., Saper, C.B., Holland, P.C., 2009. The rostromedial tegmental nucleus (RMTG), a gabaergic afferent to midbrain dopamine neurons, encodes aversive stimuli and inhibits motor responses. Neuron 61, 786–800.
Johnson, S.W., North, R.A., 1992. Opioids excite dopamine neurons by hyperpolarization of local interneurons. J. Neurosci. 12, 483–488.
Jonaidi, H., Noori, Z., 2012. Neuropeptide *y*-induced feeding is dependent on GABAA receptors in neonatal chicks. J. Comp. Physiol. A Neuroethol. Sens. Neural. Behav. Physiol. 198, 827–832.
Kalivas, P.W., Alesdatter, J.E., 1993. Involvement of n-methyl-D-aspartate receptor stimulation in the ventral tegmental area and amygdala in behavioral sensitization to cocaine. J. Pharmacol. Exp. Ther. 267, 486–495.
Kalivas, P.W., Lalumiere, R.T., Knackstedt, L., Shen, H., 2009. Glutamate transmission in addiction. Neuropharmacology 56 (Suppl. 1), 169–173.
Kalivas, P.W., 2009. The glutamate homeostasis hypothesis of addiction. Nat. Rev. Neurosci. 10, 561–572.
Karler, R., Calder, L.D., Chaudhry, I.A., Turkanis, S.A., 1989. Blockade of "reverse tolerance" to cocaine and amphetamine by MK-801. Life Sci. 45, 599–606.
Kimura, K.D., Fujita, K., Katsura, I., 2010. Enhancement of odor avoidance regulated by dopamine signaling in *Caenorhabditis elegans*. J. Neurosci. 30, 16365–16375.
King, H.E., Riley, A.L., 2013. A history of morphine-induced taste aversion learning fails to affect morphine-induced place preference conditioning in rats. Learn. Behav. 41, 433–442.
Koob, G., Le Moal, M., 2005. Plasticity of reward neurocircuitry and the 'dark side' of drug addiction. Nat. Neurosci. 8, 1442–1444.
Koob, G.F., Le Moal, M., 2001. Drug addiction, dysregulation of reward, and allostasis. Neuropsychopharmacology 24, 97–129.
Koob, G.F., Le Moal, M., 2008. Addiction and the brain antireward system. Annu. Rev. Psychol. 59, 29–53.
Koob, G.F., 2008. A role for brain stress systems in addiction. Neuron 59, 11–34.
Laviolette, S., Alexson, T., 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, 8653–8660.
Laviolette, S., van der Kooy, D., 2003. Blockade of mesolimbic dopamine transmission dramatically increases sensitivity to the rewarding effects of nicotine in the ventral tegmental area. Mol. Psychiatr. 8 (50-59), 59.
Laviolette, S., van der Kooy, D., 2004. The neurobiology of nicotine addiction: bridging the gap from molecules to behaviour. Nat. Rev. Neurosci. 5, 55–65.
Le Roith, D., Shiloach, J., Berelowitz, M., Frohman, L., Liotta, A., Krieger, D., Roth, J., 1983. Are messenger molecules in microbes the ancestors of the vertebrate hormones and tissue factors? Fed. Proc. 42, 2602–2607.
Le Roith, D., Roth, J., 1984. Vertebrate hormones and neuropeptides in microbes: evolutionary origin of intercellular communication. Front. Neuroendocrinol. 8, 1–25.
Lebestky, T., Chang J.-S.C., Dankert, H., Zelnik, L., Kim, Y.-C., Han, K.-A., Wolf, F.W., Perona, P., Anderson, D.J., 2009. Two different forms of arousal in Drosophila are oppositely regulated by the dopamine D1 receptor ortholog DopR via distinct neural circuits. Neuron 64, 522–536.
LeBlanc, A.E., Cappell, H., 1974. Attenuation of punishing effects of morphine and amphetamine by chronic prior treatment. J. Comp. Physiol. Psychol. 87, 691–698.
Levens, N., Akins, C.K., 2001. Cocaine induces conditioned place preference and increases locomotor activity in male Japanese quail. Pharmacol. Biochem. Behav. 68, 71–80.
Lewis, D., 2001. Guide to Cytochromes p450: Structure and Function. Taylor and Francis, London, UK.
Liscia, A., Solari, P., 2000. Bitter taste recognition in the blowfly: electrophysiological and behavioral evidence. Physiol. Behav. 70, 61–65.
Louilot, A., Le Moal, M., Simon, H., 1986. Differential reactivity of dopaminergic neurons in the nucleus accumbens in response to different behavioral situations. An in vivo voltammetric study in free moving rats. Brain Res. 397, 395–400.
Lupica, C.R., Riegel, A.C., Hoffman, A.F., 2004. Marijuana and cannabinoid regulation of brain reward circuits. Br. J. Pharmacol. 143, 227–234.
Maskos, U., Molles, B., Pons, S., Besson, M., Guiard, B., Guilloux, J., Evrard, A., Cazala, P., Cormier, A., Mameli-Engvall, M., Dufour, N., Cloëz-Tayarani, I., Bemelmans, A., Mallet, J., Gardier, A., David, V., Faure, P., Granon, S., Changeux, J., 2005. Nicotine reinforcement and cognition restored by targeted expression of nicotinic receptors. Nature 436, 103–107.
Matsumoto, M., Hikosaka, O., 2009. Two types of dopamine neuron distinctly convey positive and negative motivational signals. Nature 459, 837–842.
McCullough, L.D., Salamone, J.D., 1992. Anxiogenic drugs beta-CCE and FG 7142 increase extracellular dopamine levels in nucleus accumbens. Psychopharmacology (Berl) 109, 379–382.
McEvoy, J.P., Freudenreich, O., Levin, E.D., Rose, J.E., 1995. Haloperidol increases smoking in patients with schizophrenia. Psychopharmacology (Berl) 119, 124–126.
McFarland, K., Lapish, C.C., Kalivas, P.W., 2003. Prefrontal glutamate release into the core of the nucleus accumbens mediates cocaine-induced reinstatement of drug-seeking behavior. J. Neurosci. 23, 3531–3537.
Melendez, R.I., Hicks, M.P., Cagle, S.S., Kalivas, P.W., 2005. Ethanol exposure decreases glutamate uptake in the nucleus accumbens. Alcohol Clin. Exp. Res. 29, 326–333.
Mwenifumbo, J.C., Tyndale, R.F., 2007. Genetic variability in CYP2A6 and the pharmacokinetics of nicotine. Pharmacogenomics 8, 1385–1402.
Nathanson, J.A., Hunnicutt, E.J., Kantham, L., Scavone, C., 1993. Cocaine as a naturally occurring insecticide. Proc. Natl. Acad. Sci. U. S. A. 90, 9645–9648.
Nehlig, A., 1999. Are we dependent upon coffee and caffeine? A review on human and animal data. Neurosci. Biobehav. Rev. 23, 563–576.
Olds, J., Milner, P., 1954. Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. J. Comp. Physiol. Psychol. 47, 419–427.
Oliveira-Maia, A., Stapleton-Kotloski, J., Lyall, V., Phan, T., Mummalaneni, S., Melone, P., Desimone, J., Nicolelis, M., Simon, S., 2009. Nicotine activates TRPM5-dependent and independent taste pathways. Neuroscience 106, 1596–1601.
Olmstead, M.C., Munn, E.M., Franklin, K.B., Wise, R.A., 1998. Effects of pedunculopontine tegmental nucleus lesions on responding for intravenous heroin under different schedules of reinforcement. J. Neurosci. 18, 5035–5044.
Omelchenko, N., Sesack, S.R., 2007. Glutamate synaptic inputs to ventral tegmental area neurons in the rat derive primarily from subcortical sources. Neuroscience 146, 1259–1274.
Omelchenko, N., Bell, R., Sesack, S.R., 2009. Lateral habenula projections to dopamine and GABA neurons in the rat ventral tegmental area. Eur. J. Neurosci. 30, 1239–1250.
Omelchenko, N., Sesack, S.R., 2009. Ultrastructural analysis of local collaterals of rat ventral tegmental area neurons: GABA phenotype and synapses onto dopamine and GABA cells. Synapse 63, 895–906.
Panlilio, L.V., Justinova, Z., Goldberg, S.R., 2010. Animal models of cannabinoid reward. Br. J. Pharmacol. 160, 499–510.
Paterson, N., 2009. The neuropharmacological substrates of nicotine reward: reinforcing versus reinforcement-enhancing effects of nicotine. Behav. Pharmacol. 20, 211–225.
Perry, C.J., Barron, A.B., 2013. Neural mechanisms of reward in insects. Annu. Rev. Entomol. 58, 543–562.
Pettit, H.O., Ettenberg, A., Bloom, F.E., Koob, G.F., 1984. Destruction of dopamine in the nucleus accumbens selectively attenuates cocaine but not heroin self-administration in rats. Psychopharmacology (Berl) 84, 167–173.
Pettit, H.O., Justice, J.B., 1989. Dopamine in the nucleus accumbens during cocaine self-administration as studied by in vivo microdialysis. Pharmacol. Biochem. Behav. 34, 899–904.
Petzinger, E., Geyer, J., 2006. Drug transporters in pharmacokinetics. Naunyn. Schmied. Arch. Pharmacol. 372, 465–475.
Pezze, M., Feldon, J., 2004. Mesolimbic dopaminergic pathways in fear conditioning. Prog. Neurobiol. 74, 301–320.
Pezze, M.A., Dalley, J.W., Robbins, T.W., 2007. Differential roles of dopamine D1 and D2 receptors in the nucleus accumbens in attentional performance on the five-choice serial reaction time task. Neuropsychopharmacology 32, 273–283.
Picciotto, M., Zoli, M., Zachariou, V., Changeux, J., 1997. Contribution of nicotinic acetylcholine receptors containing the beta 2-subunit to the behavioural effects of nicotine. Biochem. Soc. Trans. 25, 824–829.
Ragozzino, M.E., 2002. The effects of dopamine d(1) receptor blockade in the prelimbic-infralimbic areas on behavioral flexibility. Learn. Mem. 9, 18–28.
Riemensperger, T., Völler, T., Stock, P., Buchner, E., Fiala, A., 2005. Punishment prediction by dopaminergic neurons in Drosophila. Curr. Biol. 15, 1953–1960.
Risinger, F.O., Oakes, R.A., 1995. Nicotine-induced conditioned place preference and conditioned place aversion in mice. Pharmacol. Biochem. Behav. 51, 457–461.
Ritzmann, R., Pollack, A., 1990. Parallel motor pathways from thoracic interneurons of the ventral giant interneuron system of the cockroach, *Periplaneta americana*. J. Neurobiol. 21, 1219–1235.
Ritzmann, R., Pollack, A., Hudson, S., Hyvonen, A., 1991. Convergence of multi-modal sensory signals at thoracic interneurons of the escape system of the cockroach, *Periplaneta americana*. Brain Res. 563, 175–183.
Robinson, T.E., Berridge, K.C., 1993. The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res. Rev. 18, 247–291.

Roesch, M.R., Takahashi, Y., Gugsa, N., Bissonette, G.B., Schoenbaum, G., 2007. Previous cocaine exposure makes rats hypersensitive to both delay and reward magnitude. J. Neurosci. 27, 245–250.
Rolls, E.T., Rolls, B.J., Kelly, P.H., Shaw, S.G., Wood, R.J., Dale, R., 1974. The relative attenuation of self-stimulation, eating and drinking produced by dopamine-receptor blockade. Psychopharmacology 38, 219–230.
Salamone, J.D., 1994. The involvement of nucleus accumbens dopamine in appetitive and aversive motivation. Behav. Brain Res. 61, 117–133.
Sattelle, D.B., Lummis, S.C., Wong, J.F., Rauh, J.J., 1991. Pharmacology of insect GABA receptors. Neurochem. Res. 16, 363–374.
Schenk, S., Valadez, A., Worley, C.M., McNamara, C., 1993. Blockade of the acquisition of cocaine self-administration by the NMDA antagonist MK-801 (dizocilpine). Behav. Pharmacol. 4, 652–659.
Schroeder, M.B., Riters, L.V., 2006. Pharmacological manipulations of dopamine and opioids have differential effects on sexually motivated song in male European starlings. Physiol. Behav. 88, 575–584.
Schultz, W., Apicella, P., Ljungberg, T., 1993. Responses of monkey dopamine neurons to reward and conditioned stimuli during successive steps of learning a delayed response task. J. Neurosci. 13, 900–913.
Schultz, W., 1998. Predictive reward signal of dopamine neurons. J. Neurophysiol. 80, 1–27.
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. Neurosci. 23, 10495–10502.
Sellings, L., Baharnouri, G., McQuade, L., Clarke, P., 2008. Rewarding and aversive effects of nicotine are segregated within the nucleus accumbens. Eur. J. Neurosci. 28, 342–352.
Serafine, K.M., Briscione, M.A., Rice, K.C., Riley, A.L., 2012. Dopamine mediates cocaine-induced conditioned taste aversions as demonstrated with cross-drug preexposure to GBR 12909. Pharmacol. Biochem. Behav. 102, 269–274.
Singaravelan, N., Nee'man, G., Inbar, M., Izhaki, I., 2005. Feeding responses of free-flying honeybees to secondary compounds mimicking floral nectars. J. Chem. Ecol. 31, 2791–2804.
Solomon, R.L., Corbit, J.D., 1974. An opponent-process theory of motivation. I. Temporal dynamics of affect. Psychol. Rev. 81, 119–145.
Sorensen, J.S., Dearing, M.D., 2003. Elimination of plant toxins by herbivorous woodrats: revisiting an explanation for dietary specialization in mammalian herbivores. Oecologia 134, 88–94.
Sorg, B.A., Kalivas, P.W., 1991. Effects of cocaine and footshock stress on extracellular dopamine levels in the ventral striatum. Brain Res. 559, 29–36.
Spyraki, C., Fibiger, H.C., Phillips, A.G., 1982. Dopaminergic substrates of amphetamine-induced place preference conditioning. Brain Res. 253, 185–193.
Steckler, T., Inglis, W., Winn, P., Sahgal, A., 1994. The pedunculopontine tegmental nucleus: a role in cognitive processes? Brain Res. Rev. 19, 298–318.
Stephens, D.W., 2008. Decision ecology: foraging and the ecology of animal decision making. Cognit. Affect. Behav. Neurosci. 8, 475–484.
Steppuhn, A., Gase, K., Krock, B., Halitschke, R., Baldwin, I., 2004. Nicotine's defensive function in nature. PLoS Biol. 2 (Epub).
Sturgess, J.E., Ting, A.K.R.A., Podbielski, D., Sellings, L.H., Chen, J.F., van der Kooy, D., 2010. Adenosine A1 and A2A receptors are not upstream of caffeine's dopamine D2 receptor-dependent aversive effects and dopamine-independent rewarding effects. Eur. J. Neurosci. 32, 143–154.
Sullivan, R., Hagen, E., Hammerstein, P., 2008. Revealing the paradox of drug reward in human evolution. Proc. Biol. Sci. 275, 1231–1241.
Sullivan, R.J., Hagen, E.H., 2002. Psychotropic substance-seeking: evolutionary pathology or adaptation? Addiction 97, 389–400.
Sun, N., Laviolette, S.R., 2014. Dopamine receptor blockade modulates the rewarding and aversive properties of nicotine via dissociable neuronal activity patterns in the nucleus accumbens. Neuropsychopharmacology 39, 2799–2815.
Tan, H., Bishop, S.F., Lauzon, N.M., Sun, N., Laviolette, S.R., 2009. Chronic nicotine exposure switches the functional role of mesolimbic dopamine transmission in the processing of nicotine's rewarding and aversive effects. Neuropharmacology 56, 741–751.
Tsai, H.C., Zhang, F., Adamantidis, A., Stuber, G.D., Bonci, A., de Lecea, L., Deisseroth, K., 2009. Phasic firing in dopaminergic neurons is sufficient for behavioral conditioning. Science 324, 1080–1084.
Tzschentke, T.M., 2007. Measuring reward with the conditioned place preference (CPP) paradigm: update of the last decade. Addict. Biol. 12, 227–462.
Van Alstyne, K., Nelson, A., Vyvyan, J., Cancilla, D., 2006. Dopamine functions as an antiherbivore defense in the temperate green alga *Ulvaria obscura*. Oecologia 148, 304–311.
Van Swinderen, B., Andretic, R., 2011. Dopamine in Drosophila: setting arousal thresholds in a miniature brain. Proc. Biol. Sci. 278, 906–913.
van Zessen, R., Phillips, J.L., Budygin, E.A., Stuber, G.D., 2012. Activation of VTA GABA neurons disrupts reward consumption. Neuron 73, 1184–1194.
Verendeev, A., Riley, A.L., 2012. Conditioned taste aversion and drugs of abuse: history and interpretation. Neurosci. Biobehav. Rev. 36, 2193–2205.
Vergoz, V., Roussel, E., Sandoz, J.C., Giurfa, M., 2007. Aversive learning in honeybees revealed by the olfactory conditioning of the sting extension reflex. PLoS ONE 2, e288.
Vidal-Gadea, A.G., Pierce-Shimomura, J.T., 2012. Conserved role of dopamine in the modulation of behavior. Commun. Integr. Biol. 5, 440–447.
Waddell, S., 2013. Reinforcement signalling in Drosophila; dopamine does it all after all. Curr. Opin. Neurobiol. 23, 324–329.
Weiss, F., Imperato, A., Casu, M.A., Mascia, M.S., Gessa, G.L., 1997. Opposite effects of stress on dopamine release in the limbic system of drug-naive and chronically amphetamine-treated rats. Eur. J. Pharmacol. 337, 219–222.
Weitemier, A., Murphy, N., 2009. Accumbal dopamine and serotonin activity throughout acquisition and expression of place conditioning: correlative relationships with preference and aversion. Eur. J. Neurosci. 29, 1015–1026.
Wink, M., Roberts, M.F., 1998. Alkaloids: Biochemistry, Ecology, and Medicinal Applications. Plenum Press, New York.
Wink, M., Schmeller, T., Latz-Bruning, B., 1998. Modes of action of allelochemical alkaloids: interaction with neuroreceptors, DNA, and other molecular targets. J. Chem. Ecol. 24, 1881–1937.
Wise, R.A., 1989. Opiate reward: sites and substrates. Neurosci. Biobehav. Rev. 13, 129–133.
Wise, R.A., 1996. Neurobiology of addiction. Curr. Opin. Neurobiol. 6, 243–251.
Wise, R.A., 2004. Dopamine, learning and motivation. Nat. Rev. Neurosci. 5, 483–494.
Wise, R.A., 2009. Roles for nigrostriatal—not just mesocorticolimbic—dopamine in reward and addiction. Trends Neurosci. 32, 517–524.
Wolf, F.W., Heberlein, U., 2003. Invertebrate models of drug abuse. J. Neurobiol. 54, 161–178.
Wright, G.A., Baker, D.D., Palmer, M.J., Stabler, D., Mustard, J.A., Power, E.F., Borland, A.M., Stevenson, P.C., 2013. Caffeine in floral nectar enhances a pollinator's memory of reward. Science 339, 1202–1204.
Xiu, X., Puskar, N., Shanata, J., Lester, H., Dougherty, D., 2009. Nicotine binding to brain receptors requires a strong cation-pi interaction. Nature 458, 534–537.
Yamaguchi, T., Sheen, W., Morales, M., 2007. Glutamatergic neurons are present in the rat ventral tegmental area. Eur. J. Neurosci. 25, 106–118.
Yin, R., French, E.D., 2000. A comparison of the effects of nicotine on dopamine and non-dopamine neurons in the rat ventral tegmental area: an in vitro electrophysiological study. Brain Res. Bull. 51, 507–514.
Yokel, R.A., Wise, R.A., 1975. Increased lever pressing for amphetamine after pimozide in rats: implications for a dopamine theory of reward. Science 187, 547–549.
Zevin, S., Gourlay, S., Benowitz, N., 1998. Clinical pharmacology of nicotine. Clin. Dermatol. 16, 557–564.