The role of the aversive effects of drugs in self-administration: assessing the balance of reward and aversion in drug-taking behavior

Andrey Verendeev and Anthony L. Riley

Since the first experimental demonstration that a drug of abuse supports instrumental behavior, drugs have been discussed in the context of their rewarding effects, which are assumed to drive and maintain drug-taking behavior. Indeed, drug reward has been fundamental in the formulation of most models of drug use, abuse, and addiction. Over the last several decades, however, drugs of abuse have been increasingly recognized as complex pharmacological compounds producing multiple stimulus effects, not all of which are rewarding. The aversive effects of such drugs, for example, have been described by a number of researchers working in the field, although few attempts have been made to investigate the role of these aversive effects in drug taking. The present paper offers a historical perspective on the view that drugs of abuse are complex pharmacological compounds with multiple stimulus effects. In doing so, we argue that the discussion of drug reward only may be insufficient in accounting for drug taking and we present evidence for the theoretical position that both the rewarding and the aversive effects of drugs should be taken into consideration in ongoing attempts to model drug-taking behavior. The present review summarizes several decades of research characterizing the aversive effects of major drugs of abuse, as well as more recent studies seeking to assess directly the role of drug aversion in drug taking. 

Keywords: addiction, conditioned place preference, conditioned taste aversion, drug aversion, drug reward, self-administration

Drugs as rewarding stimuli

Drug addiction is a developing disorder that is characterized by a progression from initial experimentation and nonproblem use to loss of control over the amount, frequency, and/or duration of drug intake. This escalation from controlled to compulsive use is believed to be mediated by specific drug-induced neurobiological changes that mark the shift to pathophysiology that underlies compulsive drug seeking (reviewed in Koob and Le Moal, 2006). Moreover, this transition to chronic use is likely to be modulated by a host of genetic and environmental factors that contribute toward the vulnerability to drug dependence.

In a recent discussion of human drug taking, Meyer and Quenzer (2005) describe four basic models (positive reinforcement, physical dependence, incentive sensitization, and opponent process) that address the transition from drug use to drug abuse. For all four models, drug taking is initiated and temporarily maintained by the drug’s positively rewarding effects, although other sources of reward (e.g., anxiety reduction) may also be involved. With long-term maintenance and escalation, however, the models assume different processes. For the positive reinforcement model, drug use is a function of the previous history of reinforcement of drug-taking behavior, which presumably is driven by the development of a desire to re-experience the drug-induced euphoria associated with initial drug taking, a desire that results from neuroplastic changes that accompany chronic drug taking. The physical dependence model stresses the role of withdrawal relief associated with drug taking in dependent individuals. The incentive-sensitization model argues that chronic drug taking is a function of the psychological process of incentive salience wherein certain internal and external stimuli associated with the drug use become extremely salient, resulting in an increased desire for the drug. Finally, the opponent-process model assumes that chronic drug taking is associated with the lowering of a hedonic set point and is maintained by removal of the consequent dysphoria produced by the absence of the drug. For all models, it is clear that reward plays important roles in the initiation and maintenance of drug taking and is instrumental in the transition from use to abuse.

Given the importance of the rewarding effects of drugs, it is not surprising that these effects have been well characterized in terms of their behavioral, neuroanatomical, and neurochemical effects (Koob and Le Moal, 2006). Great advances have been made in our understanding of such effects and their relationship with drug vulnerability, abuse, and addiction. Although this relationship is more complicated than initially assumed (Wise and Bozarth,
characterization of the mechanisms that mediate reward has been fundamental in our understanding of drug use and abuse.

It should be noted, however, that drugs of abuse are complex pharmacological compounds with multiple stimulus effects, not all of which are rewarding (Wise et al., 1976; Stolerman, 1992; Koob and Le Moal, 2006; Verendeev and Riley, 2012). For example, the aversive effects of drugs of abuse have also been increasingly recognized (Goudie, 1979; Gaiardi et al., 1991; Riley, 2011; Verendeev and Riley, 2012). These aversive effects have been well described for all major classes of drugs of abuse (Verendeev and Riley, 2012) and have been found to occur independent of the drugs' rewarding effects (Cunningham et al., 2009; Verendeev and Riley, 2011, 2012). Despite being well described, however, the nature of these aversive effects remains to be determined (see below; Verendeev and Riley, 2012).

It has been suggested by several authors that drug taking may be a function of the relative balance between drug reward and aversion (Stolerman and D’Mello, 1981; Gaiardi et al., 1991; Riley and Simpson, 2001; Riley, 2011; for a discussion of the interaction of drug reward and aversion in the repeated use of plant-derived drugs, see Hagen et al., 2009). If so, the discussion of drug use and abuse necessitates the examination of both of these drug effects, their interaction, and the different factors impacting them. In the present paper, we present evidence in support of the inclusion of the aversive effects of drugs in discussions of drug use and abuse. In so doing, we summarize several decades of research characterizing the aversive effects of drugs of abuse, as well as more recent studies seeking to assess directly the role of drug aversion in drug taking.

**Aversive effects of drugs of abuse**

Garcia et al. (1955), in a paper published in *Science*, reported that rats avoid consumption of a preferred saccharin solution if its initial consumption was followed by exposure to ionizing radiation. This required only one pairing of the taste and radiation exposure, was dose dependent (i.e. higher levels of gamma radiation resulted in greater suppression of intake), and appeared to be quite robust (i.e. rats persisted in taste avoidance for at least 30 days despite continuous exposure to both water and the saccharin solution). Termed a conditioned taste aversion (CTA), this phenomenon was interpreted in classical conditioning terms; specifically, the taste (CS) was paired with the radiation-induced nausea (US), resulting in a conditioned avoidance (CR) of the taste on a subsequent exposure. According to early interpretations, CTA was a specialized form of learning that allowed organisms to quickly recognize and reliably avoid potentially poisonous substances (see Freeman and Riley, 2009 and Verendeev and Riley, 2012 for a review of the history of CTA as well as discussion of the unique nature of this phenomenon).

Shortly after CTA was described in irradiated animals, a number of reports showed similar effects using other treatments, both pharmacological (e.g. well-known poisons and toxins; Garcia and Ervin, 1968; Freeman and Riley, 2009) and nonpharmacological (e.g. full body rotation; Braun and McIntosh, 1973). Quite surprisingly, a number of drugs of abuse, known for their rewarding effects, were also found to support CTA learning. For example, Goudie et al. (1978) administered rats a novel saccharin solution to drink, followed by an injection of a drug vehicle or one of four doses of cocaine (5, 10, 20, or 36 mg/kg intraperitoneally). This taste–drug pairing was repeated for several trials, after which the subjects were presented with the saccharin on a taste-avoidance test. Cocaine induced avoidance of saccharin in a dose-dependent manner (cf. Garcia et al., 1955), with the lowest dose (5 mg/kg) being ineffective in producing an avoidance and the largest dose producing the greatest suppression of saccharin consumption. Moreover, suppression was greater after several conditioning trials than after a single pairing (at least for the two largest doses tested; see Fig. 1).

Although cocaine was one of the first drugs for which CTAs were characterized (see also Ferrari et al., 1991; Glowa et al., 1994), the list of drugs that can support taste-avoidance learning includes all major drugs of abuse: amphetamine (Cappell and LeBlanc, 1971; Carey and Goodall, 1974; Booth et al., 1977; Verendeev and Riley, 2011), morphine (White et al., 1977; Riley et al., 1978; Bechera and van der Kooi, 1985; Verendeev and Riley, 2011), heroin (Grigson et al., 2000; Davis et al., 2009), nicotine (Etscorn, 1980; Kumar et al., 1983; Iwamoto and Williamson, 1984; Etscorn et al., 1986; Pescatore et al., 2005; Rinkero et al., 2008), ethanol (Cappell et al., 1973; Cunningham, 1979; Roma et al., 2006), caffeine (White and Mason, 1985; Steigerwald et al., 1988; Brockwell et al., 1991; Vishwanath et al., 2011), tetrahydrocannabinol (Corcoran et al., 1974; Kay, 1975; Fischer and Vail, 1980; Parker and Gillies, 1995), MDMA (Lin et al., 1994; Albaugh et al., 2011), and various hallucinogens (Cappell and LeBlanc, 1971; De Beun et al., 1993; Parker, 1993, 1996) (for a bibliography of psychoactive substances that can support taste avoidance learning, see http://www.ctalrarning.com).

**Factors affecting the aversive effects of drugs**

The ability of drugs of abuse to support CTA learning suggested that drugs had some intrinsic aversive properties. It is important to note, however, that these properties were not fixed, but were a function of a number of experimental and subject variables. For example, as discussed above, Goudie et al. (1978) reported that the magnitude of suppression of intake of
Drug history weakens the ability of drugs of abuse to produce CTA faster (Chambers et al., 2011; see also Ferrari et al., 2001). Route of administration was also important. For example, Riley et al. (1978) found moderate, albeit significant, suppression following intraperitoneal morphine. Later studies found that morphine administered subcutaneously resulted in a much more robust suppression (see, for example, Lancellotti et al., 2001; Verendeev and Riley, 2011; see also Ferrari et al., 1991 for a direct comparison between intraperitoneal and subcutaneous cocaine to produce CTA).

Other factors reported to influence the ability of drugs to produce aversive effects were age, sex, drug history, and strain. For example, adolescent rats appear less sensitive to the aversive effects of drugs compared with adult rats (reviewed in Schramm-Sapyta et al., 2009). Male rats appear more responsive to the aversive effects of drugs than female rats, as evidenced by their ability to acquire CTAs faster (Chambers et al., 1981; Sherrill et al., 2011a).

Drug history weakens the ability of drugs of abuse to produce CTA, which implies that previous drug exposure attenuates the aversive effects of drugs (reviewed in Riley and Simpson, 2001). Finally, the ability of drugs to produce CTA differs across different strains of rats and mice (Cunningham et al., 2009; Riley et al., 2009). All these reports suggested that the aversive effects of drugs of abuse are not static, but can be influenced by a number of different factors. Although aversions can be impacted by a wide variety of factors, it is important to note that the vast majority of drugs induce aversions across a wide variety of parametric conditions in almost all organisms tested (including humans; see Garb and Stunkard, 1974; Klosterhalfen and Klosterhalfen, 1985; Logue, 1985; Garcia and Riley, 1998; Freeman and Riley, 2009; see also Reilly and Schachtman, 2009).

**Reward and aversion: independent effects**

The finding that drugs that were reliably self-administered by animals and able to produce place preferences (see Tzschentke 2007), also supported CTA learning presented a conundrum (Gamzu, 1977; White et al., 1977; Goudie, 1979; Hunt and Amit, 1987). How could drugs that are rewarding in both rats and humans also produce avoidance of taste stimuli with which they were paired? One simple solution for this dilemma was to argue that any specific drug may have both rewarding and aversive effects, but that these effects are dependent on the specific parameters under which they are examined. Indeed, Cappell and LeBlanc (1971), in a study assessing the ability of amphetamine to induce CTA, did just this and pointed to the ‘gross and obvious’ (p. 355) differences between the experimental procedures measuring drug reward and aversion that could potentially explain the apparent paradox.

However, this argument met with some criticism when it was reported that a drug could produce both rewarding and aversive effects under the same experimental conditions. For example, Wise et al. (1976) presented rats with a novel saccharin solution to drink and allowed them to self-administer 0.5 mg/kg apomorphine for a single session. They found that individual rats both self-administered intravenous apomorphine and subsequently avoided the saccharin solution. Moreover, there was a strong relationship between the two: individual rats that self-administered the most apomorphine showed the greatest avoidance of saccharin intake. The authors were led to conclude that drugs of abuse exert multiple stimulus effects, both positive and negative. They noted: ‘These data, then, demonstrate for the first time that the same drug injection can be both positive reinforcing and aversive. The demonstration of both properties in the same animals, in the same test session, rules out arguments that differences in paradigms can account for the fact that in one paradigm a drug seems aversive while in the other paradigm the same drug seems reinforcing. Thus it must be concluded that injections of abused drugs do not represent simple positive pharmacological stimuli; rather, drug injections must be viewed as compound stimuli with both positive and negative elements’ (Wise et al., 1976, p. 1274).

In a related study, White et al. (1977) trained rats to run down a straight alley for food available in a goal box.

---

**Fig. 1**

Mean (±SEM) saccharin consumption over three saccharin–cocaine pairings and the final taste avoidance test (trial 4) of rats injected with one of the four doses of cocaine (5, 10, 20, or 36 mg/kg) or a drug vehicle (saline control). Adapted with permission from Fig. 1 of Goudie et al. (1978).
Immediately after consumption, rats were injected with one of the two doses of morphine sulfate (9 or 15 mg/kg) and returned to the empty goal box for 50 min. Over trials, rats increased their running speed to reach the goal box, but decreased the amount of food consumed. Similar to Wise et al. (1976), this study showed that a drug of abuse produced both rewarding and aversive effects in the same animal and by the same drug injection, as indicated by the increase in running speed and decrease in food consumption, respectively (see also Reicher and Holman, 1977; Sherman et al., 1980; for more recent reports, see Ettenberg and Geist, 1991, 1993; Simpson and Riley, 2005; Verendeev and Riley, 2011). Although both effects are produced, their temporal nature is unknown. Indeed, from work with ethanol and cocaine, the specific timing of these two responses differs, suggesting that they are drug specific (see, for example, Cunningham et al., 1997; Ettenberg et al., 1999).

Nature of drug aversion

The ability of drugs of abuse to produce drug reward and drug aversion under the same conditions suggested to some investigators a functional relationship between the two. According to these authors (Hunt and Amit, 1987; Grigson, 1997), the ability of drugs of abuse to produce drug aversion depended on their ability to produce drug reward. That is, rather than being dichotomous, which might suggest some differences in the underlying mechanisms, the aversive effects of drugs of abuse were interpreted in the context of their reinforcing effects. In this context, two possible mechanisms for drug aversion have been suggested: drug novelty (Hunt and Amit, 1987) and reward comparison (Grigson, 1997; see Verendeev and Riley, 2012, for a full discussion of these and other interpretations).

According to the drug novelty hypothesis of Hunt and Amit (1987), the rewarding effects of drug administration provide a novel discriminative state for the animal, which, although positively reinforcing under most conditions (i.e., self-administration and place preference conditioning), may have aversive effects when paired with a novel taste solution. These authors acknowledge the regulated homeostatic state of the animal and argue that disruption of homeostasis (by a drug’s rewarding effects) serves as a negative punishing effect within the CTA procedure. The rewarding and suppressing effects of drugs, therefore, are not dichotomous but share a common discriminative profile, and their ability to serve as either positively reinforcing or negatively punishing depends on the conditions of the experimental manipulation.

The second hypothesis, according to which drugs of abuse suppress taste consumption because of their rewarding effects, has been proposed more recently by Grigson (1997) and is known as reward comparison (see Flaherty, 1996). According to the reward comparison hypothesis, when presented with two rewarding stimuli (e.g., a taste and a drug), “[r]ats decrease intake of a gustatory CS … because the rewarding properties of the gustatory stimulus pale in comparison to those of the impending drug of abuse” (Grigson, 1997, p.134). In other words, CTA is not a measure of drug aversion, but instead a measure of drug reward.

Although interesting, these two hypotheses are not well supported by evidence. If, according to these positions, drug reward and drug aversion are not separate but dependent on each other (as drug aversion is a function of drug reward for both of the above-mentioned positions), the ability of a drug to produce reward and the ability of the drug to produce aversion should covary. Moreover, manipulations should affect the two in a similar and a consistent manner. For example, Hunt and Amit (1987) argued that pharmacological manipulations that block the rewarding effects of drugs also attenuate their suppressing effects (see also Sklar and Amit, 1977). Although there is some evidence to support this position (e.g., pimozide, a dopamine receptor antagonist, has been shown to attenuate amphetamine and cocaine self-administration as well as amphetamine-induced and cocaine-induced CTAs), several other studies show that some pharmacological manipulations affect a drug’s rewarding and aversive effects differentially. Further, Simpson and Riley (2005) examined the effects of morphine pre-exposure on morphine-induced place preference and taste avoidance in the same subjects. They found that pre-exposure to morphine enhanced place preference but attenuated taste avoidance, a result incompatible with the position that drug reward and aversion are mediated by the same mechanism. Similar dissociations of drug reward and drug aversion have been found in other studies that examined this phenomenon in the same subjects (Martin et al., 1988; Gatardi et al., 1991) or in separate groups of subjects (LeBlanc and Cappell, 1974; Cappell et al., 1975; Dacanay and Riley, 1982; Domjan and Siegel, 1983; Riley et al., 1984; Harris and Aston-Jones, 2003; He et al., 2004; Manzanedo et al., 2005).

In addition to pre-exposure and pharmacological treatments, the rewarding and aversive effects of drugs can be dissociated using a number of other manipulations. For example, adolescent rats are more sensitive to the rewarding effects, but less sensitive to the aversive effects of drugs than adult rats (see above; see also Schramm-Sapyta et al., 2009 for a review). Lesion data also show that drug reward and aversion are anatomically dissociable. Sellings et al. (2008), for instance, found that 6-OHDA lesions of the nucleus accumbens medial shell, but not core, attenuated nicotine-induced place preference, whereas lesions of the nucleus accumbens core, but not the medial shell, blocked nicotine-induced taste avoidance (see Verendeev and Riley, 2012 for a review of the role of reward in the mediation of taste avoidance).
In a recent test of the relationship between drug reward and drug aversion, we (Verendeev and Riley, 2011) examined the relationship between the ability of two different classes of drugs (an opiate and a psychostimulant) to produce drug reward and drug aversion in the same animal. Using the combined CTA/conditioned place preference (CPP) procedure (cf. Simpson and Riley, 2005), we assessed the relationship between morphine-induced and amphetamine-induced place preference and taste avoidance in individual subjects at two different doses (5 and 10 mg/kg morphine and 3 and 5 mg/kg amphetamine). Specifically, rats were given a novel saccharin solution to drink, injected with a drug, and placed in the CPP apparatus. We then examined the change from baseline in saccharin consumption (decrease from baseline in saccharin consumption indicated avoidance) and change from baseline in the time spent on the drug-paired side (DPS) of the CPP apparatus (increase in the time spent of the DPS indicated preference).

First, we found that individual subjects differed considerably in their sensitivity to the rewarding and aversive effects of both morphine and amphetamine. Individual subjects were sensitive to the rewarding effects of drugs but not to their aversive effects and vice versa, or, individual subjects were sensitive to both or neither of these effects. Second, we found no relationship between the ability of either drug to produce a place preference and its ability to produce a taste avoidance (see Fig. 2). Specifically, animals were divided into high and low responders for all conditions and the relationships between the change in saccharin consumption and change in time spent on the DPS were analyzed. We found only one significant relationship between the two in any of the conditions: animals administered 5 mg/kg amphetamine that showed the strongest aversions were less likely to show an increase (or showed an actual decrease) in the time spent on the DPS (a relationship opposite to what would be expected if a drug’s aversive effects depended on its rewarding effects). Apart from this single significant relationship out of 16 possible, it seems to be the case that the ability of a drug to produce drug aversion is not dependent on the drug’s ability to produce drug reward.

If taste avoidance produced by drugs of abuse is not mediated by their rewarding effects, what then is the nature of the drugs’ aversive effects? Several hypotheses have been put forward, but none has proved conclusive (see Verendeev and Riley, 2012 for a full discussion of these positions as well as their criticisms). One recent account of a drug’s aversive effects was summarized recently by Parker et al. (2009). Termed the ‘conditioned fear’ hypothesis, this position argues that drugs upset the tight homeostatic state of the animal, resulting in conditioned fear of the drug-associated internal state (for a summary, see Verendeev and Riley, 2012). Although supported by a number of observations, it is yet to be determined what exactly is disrupted by the drug injection, which may be drug specific (e.g. psychostimulant anxiogenesis vs. alcohol toxicity).

It is important to note, in this context of the nature of the aversive effects of drugs, that the suppression of intake induced by such effects does not necessarily support the position that an aversion is produced to the drug-associated taste. In fact, it has been suggested that the term ‘taste aversion’ may inaccurately describe the ability of drugs of abuse to produce suppression of consumption of taste stimuli. Comparing the ability of emetic agents and rewarding drugs to produce conditioned aversive responses to a taste CS, Parker and colleagues found that drugs of abuse, unlike classical toxins, do not produce conditioned aversive reactions, although both produce conditioned suppression of a taste CS at comparable magnitude (Parker, 1995). This led her to conclude that the term ‘conditioned taste aversion’ was inappropriately applied to describe drug-induced suppression and that the term ‘conditioned taste avoidance’ should be used instead (see Verendeev and Riley, 2012, for a more detailed discussion of this).

Impact of drug aversion on drug taking
Irrespective of the exact nature of the aversive effects of drugs, on which there is no current consensus, it is clear...
that the positive rewarding and negative aversive effects of drugs are independent processes. If drugs of abuse produce both rewarding and aversive effects, it follows that to better understand drug vulnerability in both rats and humans, it is necessary to understand both effects and the interplay between them. Indeed, it has been suggested by several authors that drug taking may be a function of the relative balance between drug reward and aversion (Stolerman and D’Mello, 1981; Gaiardi et al., 1991; Riley and Simpson, 2001; see also Riley et al., 2009), with the drug’s aversive effects serving as a limiting factor in drug taking. If so, successful modeling of drug-taking behavior (both problem and nonproblem use) should take into account the relative input of both rewarding and aversive effects of drugs as well as different factors that affect these two properties.

If drug use is a function of the balance between drug reward and drug aversion, one would expect that knowing the relative strength of these two effects would enable direct predictions of drug intake. Although it is often not feasible to know the relative contributions of a drug’s rewarding and aversive effects to the overall drug experience, which may vary from one individual to another (see Verendeev and Riley, 2011), it is nonetheless possible to examine the role of drug reward and drug aversion in drug taking. One way to do this is by studying the effects of different manipulations that differentially impact a drug’s rewarding and aversive effects and subsequently examine these manipulations in relation to drug self-administration. Here, we will focus on two examples of such an approach: drug history and genetic models.

**Drug history**

Drug history has been examined in animal models in the context of US pre-exposure. In a standard procedure, animals are administered a drug (US) before conditioning: in other words, the animal is no longer drug-naive when its rewarding and aversive effects are subsequently examined. The effects of drug history within US pre-exposure are a function of the number of pre-exposure sessions, the dose of the drug used during drug pre-exposure, and the interval between drug pre-exposure and subsequent conditioning (Riley and Simpson, 2001). The effects of previous drug experience are then examined in comparison with animals that receive no such experience with the drug (i.e. drug-naive). Using the CPP design as a measure of drug reward and the CTA design as a measure of drug aversion, such drug experience (i.e. US pre-exposure) impacts the rewarding and aversive effects of drugs differentially. We will consider the effects of drug history on drug reward first.

In an attempt to examine whether previous drug exposure produces tolerance or sensitization to the rewarding effects of drugs, Lett (1989) administered repeated injections of amphetamine, morphine, or cocaine to rats before place preference conditioning with these drugs. The following parameters were varied for pre-exposure (dose and the number of pre-exposure sessions) and CPP conditioning (dose and the number of conditioning trials), respectively: amphetamine – 1.5 mg/kg (six injections) and 1.5 mg/kg (three trials); morphine – 5 mg/kg (five injections) and 5 mg/kg (one trial); and cocaine – 20 mg/kg (10 injections) and 2.5 mg/kg (three trials). Lett (1989) reported that whereas animals treated with either amphetamine or cocaine during conditioning showed place preferences for the DPS of the CPP apparatus, animals with previous amphetamine or cocaine experience, respectively, showed significantly enhanced place preferences compared with animals with no drug pre-exposure (see Fig. 3). Rats with no morphine pre-exposure showed no significant place preference, a finding that was attributed to the use of a single drug-place pairing. Interestingly, animals that received previous morphine exposure did show a significant place preference, which suggested that the rewarding effects of morphine were also enhanced by drug pre-exposure under this condition as well (see Fig. 3). Subsequent research with these compounds confirmed that drug history enhances the rewarding effects of amphetamine (Nocjar and Panksepp, 2002), morphine (Gaiardi et al., 1991; Shippenberg et al., 1996; Simpson and Riley, 2005), and cocaine (Shippenberg and Heidbreder, 1995), as well as other drugs of abuse (Shoaib et al., 1994).

Interestingly, similar enhancing effects of drug pre-exposure on the rewarding effects of drugs were found when different drugs were used for pre-exposure and conditioning. For example, in addition to examining within-drug effects, Lett (1989) examined the effects of morphine pre-exposure on amphetamine and cocaine place preferences as well as the effects of amphetamine on morphine-induced CPP. Morphine (5 mg/kg) was found to enhance the rewarding effects of both amphetamine (1.5 mg/kg) and cocaine (2.5 mg/kg), and amphetamine (1.5 mg/kg) was found to enhance the rewarding effects of morphine (1 mg/kg), as evidenced by significant increases in the percent time spent on the DPS in drug-experienced versus drug-naive animals (Lett, 1989). Although some subsequent research has extended these findings to other drug interactions (Hutchison and Riley, 2012), other studies have failed to do so (Le Pen et al., 1998; Busse et al., 2005).

Although US pre-exposure has been found to enhance the rewarding effects of drugs (at least when examined within the same drug), its effects on the aversive effects of drugs are opposite, that is, such pre-exposure attenuates the ability of drugs to produce taste avoidance. The attenuating effects of US pre-exposure on the ability of drugs of abuse to condition CTAs have been well documented (see Riley and Simpson, 2001 for a review; see also Hall, 2009). For example, Riley and Diamond (1998) examined the effects of previous cocaine exposure...
on cocaine-induced CTAs. Animals were administered cocaine (32 mg/kg) injections every fourth day for a total of five injections before conditioning with cocaine (at the same dose). The authors reported that in drug-naive animals, cocaine produced a robust suppression of intake of the drug-paired solution; however, cocaine did not exert an effect in the cocaine pre-exposed animals (see Fig. 4).

Similar effects of US pre-exposure on the aversive effects of drugs (i.e. attenuation) have been reported for other drugs examined under similar conditions (see Riley and Simpson, 2001 for a comprehensive review). The ability of exposure to one drug in attenuating CTAs induced by another has also been examined extensively within the US pre-exposure literature (Cappell et al., 1975; Goudie and Thornton, 1975; Vogel and Nathan, 1976; Gamzu, 1977; Brown et al., 1979; Switzman et al., 1981; Ton and Amit, 1983; Bienkowski et al., 1998; Hutchison et al., 2010; Rinker et al., 2011). Unlike CPP, where the results are mixed, the attenuating effects of cross-drug pre-exposure seem to be more robust within the CTA preparation.

It is important to note here that the effects of drug history on the rewarding and aversive effects of drugs can be subject to a number of different manipulations and are likely dependent on a number of different factors. Earlier, we mentioned that the aversive effects of drugs are not fixed and can be influenced by different experimental and subject variables. It is likely that these same variables can also influence the effects of drug history on drug reward and drug aversion; some effects of this kind have been reported (see Riley and Simpson, 2001; Tzschenkentke, 2007 for a more detailed discussion).

Another important caveat to mention is that most studies that examined the effects of drug pre-exposure on subsequent place preference or taste avoidance conditioning did so in separate animals and across different studies. To evaluate the effects of drug history on drug reward and drug aversion more directly, these assessments should be performed in the same animals and under the same parametric conditions. Recently, Simpson and Riley (2005) examined the effects of morphine pre-exposure on morphine-induced place preference and taste avoidance in the same subjects. Rats were first administered subcutaneous injections of 5 mg/kg morphine every other day for a total of five injections. They were then trained in a combined CTA/CPP procedure (see above), wherein a single injection of morphine (1 or 5 mg/kg) was administered to condition both a place preference and a taste avoidance. Both preferences and aversions were conditioned and, similar to what has been reported in between-subject analyses, pre-exposure to morphine enhanced place preference and attenuated taste avoidance within the same subjects.

If drug history enhances the rewarding effects of a drug and attenuates its aversive effects, the resulting overall drug experience should be shifted toward a relative increase in its perceived rewarding effects. On the basis of the view that drug taking is a function of the balance between drug reward and drug aversion, we might expect that previous drug history will result in increased drug taking. Several lines of evidence support this position. For example, Rodd-Henricks et al. (2002) examined the effect...
of ethanol exposure early in life on ethanol self-administration in adulthood and found that drug history increased drug taking later in life. Specifically, adolescent rats were either allowed free access to a 15% ethanol solution for 30 days or received no such exposure. In adulthood, drug-experienced and drug-naive rats were allowed to self-administer 15% ethanol in a choice (ethanol vs. water) procedure. Following acquisition, rats were also compared in extinction as well as reacquisition of responding for ethanol. Compared with drug-naive animals, rats with a previous history of ethanol exposure acquired self-administration faster. Moreover, drug-experienced rats showed a greater resistance to extinction (i.e. higher rates of responding when ethanol was no longer available) as well as greater responding for ethanol during reacquisition. These findings are consistent with the above-mentioned view that drug history alters the balance between drug reward and drug aversion in such a way as to make drug taking more probable (i.e. enhanced rewarding effects, attenuated aversive effects). Similar results have been reported with ethanol (Siciliano and Smith, 2001; Pascual et al., 2009; Sherrill et al., 2011b).

Genetic models

Another way to study the role of drug reward and drug aversion in drug taking is to examine these effects in selectively bred mouse and rat lines (Crabbe, 2002) as well as inbred strains of these species (see Riley et al., 2009). Selectively bred lines share the common phenotype of interest (such as sensitivity to either rewarding or aversive effects of a drug or high or low propensity for drug self-administration) by virtue of selective breeding over a number of generations. Inbred strains, however, are more genetically homogeneous as a result of successive uninterrupted full-sibling matings (Beck et al., 2000). Multiple selectively bred lines and inbred strains of mice and rats are available, and these have been indispensable in studies of drug use and abuse.

The use of these genetic models in relation to the relative roles of drug reward and aversion in drug intake has usually focused on examination of the relative sensitivity of the selected line or inbred strain to either the rewarding or aversive effects in relation to drug taking. In other words, if two particular lines or strains have been described in terms of their sensitivity to the rewarding effects of a drug (usually measured by CPP) or to the aversive effects of a drug (measured by CTA), they would be compared for their propensity for drug taking. Conversely, if two particular lines or strains were described in terms of their drug consumption (either high or low), their relative sensitivities to both the rewarding and the aversive effects would subsequently be compared.

In mice, several selectively bred lines have been used to examine the relationship between ethanol consumption and the sensitivity to either the rewarding or the aversive effects of ethanol. For example, Phillips et al. (2005) used short-term selective breeding to create mouse lines different in their free choice ethanol consumption or ethanol-induced conditioned taste avoidance. After four generations of selective breeding, high-drinking mice (i.e. greater ethanol self-administration) showed greater ethanol-induced CPP compared with low-drinking mice. In contrast, mice selectively bred for greater sensitivity to the aversive effects of ethanol (as evidenced by their greater suppression of a drug-paired saccharin solution) showed reduced ethanol consumption when given the opportunity to consume 10% ethanol and had a lower overall ethanol preference ratio than did mice selectively bred for weaker sensitivity to the aversive effects of the drug. Similar results have been reported in another study that selectively bred mice for high and low ethanol preference (Chester et al., 2003): mice that showed higher ethanol preference showed attenuated taste avoidance to 2 and 4 g/kg ethanol compared with those of mice with low ethanol preference.

One of the most widely used inbred mouse strains is the C57BL/6J (C57) mouse, which has been noted for its high level of ethanol consumption (see Cunningham et al., 2009). When compared with other strains, such as the DBA/2J (DBA) mouse, which shows low levels of ethanol consumption, the C57 strain consistently consumes more ethanol (Horowitz and Whitney, 1975; Risinger and Cunningham, 1992, 1995, 1998). When these two strains are compared for their sensitivity to ethanol, DBA mice show consistently greater CTAs than C57 mice at various doses of ethanol (Horowitz and Whitney, 1975; Risinger and Cunningham, 1992, 1995, 1998; see also Balknap et al., 1978).

Selected lines of rats also support the above-mentioned work with ethanol. For example, Froehlich et al. (1988) reported that ethanol-prefering rats that consumed more ethanol than ethanol-nonpreferring rats showed reduced taste avoidance when conditioned with 1 g/kg ethanol than their nonpreferring counterparts. In a related study, University of Chile, low-ethanol-drinking rats consumed less ethanol than high-ethanol-drinking rats, and showed greater sensitivity to the aversive effects of ethanol, evidenced by significant ethanol-induced CTA at 1.5 g/kg (which was not evident in high-drinking rats) and stronger ethanol-induced CTA at 2 g/kg than their high-drinking controls (Quintanilla et al., 2001). The selectively bred Wistar Kyoto (WKY) strain, which consumes less ethanol than Marshall (M520) rats, acquired taste avoidance at a lower dose than M520 rats (i.e. they showed higher sensitivity to the aversive effects of ethanol; Cannon and Carrell, 1987).

Although the above-mentioned rat strains have been used to document the relative sensitivities to drugs of abuse, primarily ethanol, the major work in rats in relation to drug use is with the Fischer (F344) and Lewis (LEW) inbred rat
strains. F344 and LEW rats, which differ in a number of behavioral and physiological characteristics (most notably in the regulation of the hypothalamic–pituitary–adrenal axis, wherein F344 rats are significantly more reactive to various physical and psychological stressors than LEW rats), have also been reported to differ in their sensitivity to the rewarding and aversive effects of drugs of abuse as well as in their self-administration (see Kosten and Ambrosio, 2002). Assessment of differences between these strains in their responsivity to the rewarding and aversive effects of drugs in relation to self-administration provides further support for the position that both drug reward and drug aversion should be considered in the analysis of drug-taking behavior.

Specifically, F344 rats have been described to be less sensitive to the rewarding effects of morphine (as measured by CPP; Guitart et al., 1992; although see Davis et al., 2007) and more sensitive to its aversive effects (as measured by CTA; Lancellotti et al., 2001) than LEW rats. When these two strains are compared in morphine self-administration, F344 rats consistently take less morphine than LEW rats (Ambrosio et al., 1995). When examined with cocaine, however, the results are less straightforward. Specifically, LEW rats show a greater CTA response than F344 rats (Glova et al., 1994; Grigson and Freet, 2000), but self-administer cocaine to a greater degree than F344 rats (Kosten et al., 1997; although see Haile and Kosten, 2001; Haile et al., 2005; Freeman and Riley, 2009 for a discussion of how the aversive effects of cocaine may limit the escalation of cocaine self-administration). Although these results appear inconsistent with the position that a drug’s aversive effects limit drug taking, it is important to emphasize that drug taking is a function of the balance between drug reward and drug aversion. Therefore, even though LEW rats are more sensitive to the aversive effects of cocaine than F344 rats (see above), LEW rats also appear to be much more sensitive to the rewarding effects of cocaine, as evidenced by the fact that LEW rats show more robust cocaine-induced place preference compared with the F344 strain (Guitart et al., 1992). This pattern of differential sensitivity to both the rewarding and the aversive effects of cocaine in LEW and F344 rats further underlies the importance of considering the relative sensitivity to both the rewarding and the aversive effects of drugs rather than sensitivity to either of these effects alone.

**Balance of reward and aversion**

So far, we have described studies in separate groups of animals and comparisons across separate studies. Although mostly consistent with the position that drug use is a function of both the rewarding and the aversive effects of drugs, for more conclusive support, the role of drug reward and aversion in drug self-administration should be assessed in the same animals. If drug taking is a function of both its rewarding and aversive effects, drug intake should reflect the relative contribution of these effects. To date, no published work exists on such assessments of reward, aversion, and self-administration in the same animal. Preliminary data from our laboratory using the combined CTA/CPP procedure, followed by drug self-administration suggest that rats most sensitive to the aversive effects of morphine (as measured by CTA) self-administer less morphine than rats least sensitive to its aversive effects (Verendeev et al., 2012). Although supportive of the position that the balance of reward and aversion is important in (and predictive of) drug self-administration, such analysis awaits critical evaluation and replication.

**Conclusion**

This and other studies show that drugs of abuse are not simple stimuli that produce only rewarding effects. Rather, drugs of abuse are complex pharmacological compounds that produce both positive rewarding and negative aversive effects. In this paper, we have attempted to show that both of these effects should be taken into account in our attempts to model drug-taking behavior, and we have provided evidence from drug history and selectively bred mouse and rat strains, as well as from recent work directly assessing the role of drug reward and aversion in drug taking, that support this position. If this view is correct, drug self-administration should no longer be simply viewed only as a function of drug reward. The aversive effects of drugs should be taken into consideration in our attempts to understand drug use, abuse, and addiction.

**Acknowledgements**

There are no conflicts of interest.

**References**


Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.


Iwamoto ET, Williamson EC (1984). Nicotine-induced taste aversion: character-


Klosterhalfen S, Klosterhalfen W (1985). Conditioned taste aversion and

Koob GF, Le Moal M (2006). Neurobiology of addiction. Amsterdam/Boston:
Elsevier/Academic Press.

Acquisition and maintenance of intravenous cocaine self-administration in

Kosten TA, Ambrosio E (2002). HPA axis function and drug addictive behaviors:
insights from studies with Lewis and Fischer 344 inbred rats. Psychoneur-
ondocrinology 27:35–69.


Lancellotti D, Bayer BM, Glowa JR, Houghting RA, Riley AL (2001). Morphine-
induced conditioned taste aversions in the LEWN and F344/N rat strains.
Pharmacol Biochem Behav 68:603–610.

and amphetamine by chronic prior treatment. J Comp Physiol Psychol 87:
691–698.

alcohol does not sensitize to the rewarding effects of cocaine. Neuroreport
9:2867–2891.

Le DT (1988). Repeated exposures intensify rather than diminish the rewarding
effects of amphetamine, morphine, and cocaine. Psychopharmacology (Berlin)

effects of dopaminergic blockade on MDMA and d-amphetamine conditioned


the rewarding effects of morphine depends on dopamine. Neuroreport
16:201–205.


Klosterhalfen S, Klosterhalfen W (1985). Conditioned taste aversion and


Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.


