Drugs of abuse are typically discussed in terms of their rewarding effects and how these effects mediate drug taking. However, these drugs produce aversive effects that could have an important role in the overall acceptability of a drug and its likelihood of being self-administered. Rewarding and aversive effects, then, could be interpreted as separate behavioral effects, with the balance of the two determining overall drug acceptability. Interestingly, the role of aversive effects on drug acceptability in the self-administration preparation has received limited attention in this context. This chapter examines the aversive effects of drugs and discusses their role in drug taking. If these aversive effects serve a protective function, manipulations that alter or decrease these effects could have implications for drug taking. Several factors have been reported to alter conditioned taste aversion (CTA) learning, a preparation used in the assessment of the aversive effects of drugs in general. Two of these factors, drug history and strain, are reviewed here. By reviewing these, we intend to demonstrate the protective nature of aversive effects in the initiation and escalation of drug taking and to provide evidence that reductions in aversive effects could produce changes in patterns of drug self-administration that could lead to an increased vulnerability to abuse drugs by altering the reward–aversion balance. The aim of this chapter is not to question the importance of rewarding effects in self-administration but rather to provide evidence that aversive effects are an important factor that needs to be considered in discussions of drug-taking behavior.

Keywords: conditioned taste aversion; drug abuse; aversion; reward; animal models

Introduction

Drugs of abuse are typically discussed in terms of the rewarding effects they produce and how these effects mediate drug-taking behavior. However, these same drugs produce aversive effects that could have an important role in the overall acceptability of a drug and its likelihood of being self-administered. Rewarding and aversive drug effects, then, could be interpreted as two separate behavioral effects, with the balance of the two determining overall drug acceptability. Interestingly, the role of aversive drug effects on drug acceptability in the self-administration preparation has received only limited attention in this context. This chapter examines the aversive effects of drugs of abuse and discusses their role in drug taking. If these aversive drug effects serve a protective function, manipulations that alter or decrease these effects could have implications for drug taking. Several factors have been reported to alter conditioned taste aversion (CTA) learning, a preparation used in the assessment of the aversive effects of drugs in general. Two of these factors, drug history and strain, are reviewed here. By reviewing these, we intend to demonstrate the protective nature of aversive drug effects in the initiation and escalation of drug taking and to provide evidence that reductions in aversive drug effects could produce changes in patterns of drug self-administration that could lead to an increased vulnerability to abuse drugs by altering the reward–aversion balance. The aim of this chapter is not to question the importance of rewarding drug effects in self-administration but rather to provide evidence that aversive drug effects are also an important factor that needs to be considered in discussions of drug-taking behavior.
Conditioned taste aversion learning

One of the first demonstrations of CTA learning was in 1951 when John Garcia and his colleagues noticed that rats decreased consumption of water from plastic bottles that had been present during a prior exposure to radiation (John Garcia, personal communication, 2006; for a review of the history of taste aversion learning, see Freeman and Riley). Garcia argued that the decrease in consumption was a function of the acquired association of the taste of the water (from the specific plastic bottles in which the water was presented, which presumably imparted a taste to the water) with the aversive effects of radiation, a likely explanation because the same rats readily consumed water in glass bottles in their home cage. To systematically test this possibility, Garcia et al. explicitly paired a novel saccharin solution with radiation. Consistent with the initial demonstration in 1951, rats receiving the saccharin–radiation pairings decreased consumption of this solution, whereas rats receiving saccharin that had not been paired with irradiation continued to consume it (Fig. 1). The effects of radiation, therefore, were causing a decrease in consumption of the novel fluid, demonstrating that radiation had noticeable effects (presumably aversive) that could be associated with other stimuli, such as taste. This decrease in consumption was not a direct effect of radiation, however, because animals receiving radiation but not paired with saccharin continued to consume the saccharin solution at control levels. The effects of the radiation treatment, therefore, were associated with the novel tasting saccharin, and this association produced the decrease in saccharin consumption on subsequent presentations; that is, irradiation had conditioned a taste aversion.

Specialized form of learning

After these initial demonstrations and assessments, Garcia and his colleagues (and others) reported several findings that now characterize the phenomenon of taste aversion learning. For example, Garcia et al. demonstrated that radiation-induced taste aversions could be acquired with only a single pairing of the taste and radiation (Fig. 1). It was then reported that such aversions could be acquired even when long delays were imposed between presentation of the taste and radiation. Finally, Garcia and Koelling reported that aversions appeared to be selectively acquired to tastes; that is, other stimuli (such as audiovisual cues) present during radiation- or lithium chloride (LiCl)—induced sickness were not readily associated with these unconditioned stimuli (US) (Fig. 2). These specific findings, that is, one-trial learning, learning over long delays and selective associations, took the phenomenon of aversion learning beyond an interesting example of conditioning with radiation to an example of conditioning that appeared somewhat at odds with traditional associative models. Traditional models of learning generally assumed that control was established only after many conditioning trials, typically with short delays between the conditioned stimuli (CS) and US and equally well with most CS–US combinations. CTAs appeared to be a specialized form of learning that facilitated the specific associations (e.g., between taste and illness) that are important for the animal’s survival. Because natural toxins in the environment are probably found in food sources, the ability to acquire such taste–illness associations rapidly, over the long delays that naturally occur with digestion and selectively with foods, prevents the subsequent ingestion of the same toxin. Therefore, these associations are highly

Figure 1. Median saccharin preference scores after aversion conditioning where saccharin was paired with a low (30 rads) and high (57 rads) dose of radiation. Profound decreases in saccharin consumption occurred, and these decreases were still apparent after 30 days of extinction. Reproduced with permission from “Conditioned aversion to saccharin resulting from exposure to gamma radiation,” by Garcia et al.
Davis & Riley

Figure 2. (A) Effects of conditioning cue (audio visual or gustatory) on avoidance learning in rats. Only gustatory cues are associated with internal nausea, whereas audio visual cues are associated with external pain sensations.3 (B) Description of conditionability of cues to specific consequences. Reproduced with permission from Perspectives in Ethology (p. 24), by J. Garcia et al. (1972), New York: Plenum.228

After these initial studies investigating aversion learning induced by radiation and LiCl, research began to focus on determining what other compounds could induce a CTA. Naturally, many of the first compounds investigated were those substances with known aversive effects, such as common emetics, poisons, and classical toxins, because aversion learning was viewed as an adaptation that enabled an animal to avoid poisons or toxins in available food sources. Apomorphine, a nonselective dopamine agonist with potent emetic effects,12,13 was one of the first compounds to be extensively investigated in the taste aversion preparation14–18 (for aversions in humans, see Cannon et al.19). Interestingly, aversions with this emetic were robust and acquired after only one CS–US pairing15,16,18 and could withstand the same long CS–US delays that were reported previously with radiation.4,16 Concurrent with these investigations, the emetic LiCl continued to be a popular compound used in aversion learning, primarily for investigating how manipulations to the standard aversion procedure would affect acquisition of a CTA.20–25 Research investigating other aversive compounds in this procedure steadily increased throughout the 1970s and into the 1980s, with many well-known toxins reportedly inducing CTAs, such as red squill,26 strychnine sulfate,26 sodium fluoride,27 acetaldehyde,28 physostigmine sulfate,29 and paraquat30 (for a review, see Riley and Tuck31). From these results, it was evident that taste aversions could be induced by more than just radiation (and LiCl) and that the conditions under which these aversions were acquired (e.g., one-trial learning and long delays) were not radiation specific. Interestingly, CTAs induced by toxins and emetics were conditioned at doses lower than those necessary to adversely affect many other behaviors, including food and water consumption (for a review, see Riley and Tuck31). These assessments suggested that CTA learning was a sensitive measure of drug toxicity in addition to being an adaptive type of learning.

From toxins to drugs of abuse

Although investigations of CTA learning were based in examinations of the aversive effects of toxins and poisons, a wider range of compounds were being used in the CTA preparation. One group of compounds that received (and continues to receive) considerable attention in CTA investigations is drugs of abuse. These compounds were being viewed as stimuli with multiple behavioral effects because drugs of abuse could support self-administration, serve as discriminative stimuli, and affect learning and memory in various behavioral preparations.32–34 CTA learning, then, was viewed as a
viable assay uniquely suited to investigate any potential aversive effects of drugs of abuse. The first reports investigating the CTA-inducing effects of drugs of abuse, such as alcohol, morphine, amphetamine, cocaine, and Δ9-tetrahydrocannabinol (THC), demonstrated that these compounds were capable of supporting aversion learning in a manner similar to that reported with radiation, emetics, and other toxins, such as one-trial learning (for a report of long-delay learning with cocaine). These reports with drugs of abuse provided evidence that these clearly rewarding drugs also had negative or aversive effects that could be examined in the CTA preparation.

That drugs of abuse may have both rewarding and aversive effects is not unexpected because drug effects are generally dose dependent (with toxicity usually occurring at higher doses). That each of these effects is evident at the same dose is less intuitive. Such an outcome was reported by Reicher and Holman, who took advantage of a combined CTA–CPP (conditioned place preference; for reviews on CPP) design to examine concurrently the rewarding and aversive effects of a single injection of amphetamine in individual animals. Specifically, in their report individual subjects were exposed to distinct environmental and gustatory cues that were paired with amphetamine administration and to different distinct environmental and gustatory cues that were paired with saline administration. On subsequent tests, animals preferred the environment in which they had received amphetamine but avoided the distinctly flavored solution encountered in that environment (Fig. 3). This report demonstrated that the same injection of amphetamine could produce both a rewarding and aversive effect in the same animal and that each of these effects could condition a behavioral effect (approach and avoidance, respectively) (for a report demonstrating similar effects with morphine, see Simpson and Riley).

A study by White, Sklar, and Amit also provided an interesting take on the aversive and rewarding effects of drugs of abuse. These investigators trained rats to run down an alley to obtain a food reward. Immediately after consumption of the food, the rats were injected with morphine, LiCl, or vehicle. For the morphine-treated rats, running speed increased (400% compared to baseline levels), whereas the amount of food consumed in the goal box actually decreased by 30%, effects consistent

Figure 3. Taste aversions (top) and place preferences (bottom) in animals tested in a combined procedure where saccharin access was paired with morphine injections that preceded placement into one compartment of a CPP apparatus (drug-paired side). On vehicle days, animals received water followed by saline injections that preceded placement into the opposite compartment of the place preference apparatus (non–drug-paired side; water consumption not shown). From left to right: animals receiving vehicle during conditioning; animals receiving 1 mg/kg during conditioning; animals receiving 5 mg/kg morphine during conditioning. Top: Taste aversions were acquired at both doses of morphine. Bottom: Acquisition of morphine-induced CPPs was evident in all animals receiving morphine during conditioning. Error bars represent the standard error of the mean. Redrawn from Simpson and Riley.
with morphine’s rewarding and aversive effects, respectively. Interestingly, rats injected with LiCl also decreased the amount of food consumed in the goal box; however, their running speed to reach the goal box decreased dramatically as well, indicating that the changes seen with morphine were not a function of changes in food intake alone. From this report, it was evident that morphine, at the same dose and route of administration (and in the same animal), had both rewarding (increased running speed to gain access to morphine administration) and aversive (decreased food consumption in the box where morphine was administered) effects that were occurring concurrently after administration (for other demonstrations of these concurrent affective properties of drugs of abuse, see Simpson and Riley48 and Wise et al.50). Examination of these compounds in both the CTA and CPP designs is necessary to more fully understand each drug’s complete range of behavioral effects.

From toxicology to drug abuse

Such an understanding is also important in the context of the use and abuse of drugs, that is, their self-administration. Specifically, the likelihood and rate at which an animal self-administers a drug of abuse is dependent on the overall balance between its rewarding and aversive effects.31–34 That is, an animal’s overall drug intake is determined by the interaction (or balance) of these affective consequences. In this context, a highly rewarding drug with minimal aversive effects would be more likely to be self-administered than a similarly rewarding drug with pronounced aversive effects. The rewarding and aversive effects of a drug, however, need not be inversely related; for example, a drug that is weakly aversive is not necessarily highly rewarding and vice versa. It is more likely that these affective consequences are two separate effects that occur independently and interact only to determine drug acceptability and to influence overall drug intake during self-administration (see forthcoming text). This balance is depicted in Figure 4, which illustrates the intersection of these processes during self-administration and how these effects might affect overall drug taking. The rewarding effects (topmost dotted line) and aversive effects (bottom dotted line) of a drug occur independently. The interaction of these effects is depicted by the self-administration curve (solid line). When rewarding drug effects are increasing and aversive drug effects are minimal, self-administration is high. However, when aversive drug effects increase, noticeable changes occur to the pattern of self-administration exhibited; that is, self-administration is reduced (vertical dashed lines). The rewarding effects of the drug do not necessarily weaken with increases in dose; overall drug intake is determined (self-administration line) by the balance of the rewarding and aversive effects. Viewing overall self-administration of a drug in the context of both its rewarding and aversive effects refocuses the way in which one might examine drug-taking behavior (and the risks of drug use and abuse). For example, increases or decreases in drug taking are generally assumed to reflect changes in the rewarding effects of the drug. If, however, drug intake is a function of several affective properties (both reward and aversion) then variations in either of these properties may affect the drug’s overall acceptability.1

1In the rest of the chapter, a focus is placed on assaying the aversive effects of drugs of abuse and evaluating (and implicating) their involvement in drug self-administration (as a limiting or protectant factor). Such an analysis does not suggest that this is the only
Factors affecting drug self-administration: assessment of drug history

One way to assess the possible effect of the aversive effects of drugs on drug self-administration is to evaluate how drug self-administration is parametrically modulated and how aversions are affected by these same procedural variations. The range of parametric factors known to affect (or to be related to) drug self-administration is quite large and generally falls into two classes, that is, experimental manipulations and subject characteristics (for a review, see Campbell and Carroll55). Experimental manipulations include such procedural variations as dose and route of drug administration, duration of exposure or drug access, concurrent drug administration (agonists and antagonists), drug history, and lesions of various nuclei thought to mediate the rewarding effects of the drug. Subject characteristics include variables, such as sex, age, species, and strain. For our analysis, only one factor from each class is discussed in relation to how it affects self-administration and taste aversion learning. Thus, some indication of how changes in the aversive effects of the drug may mediate in part some of the changes seen in self-administration is described and discussed.

In relation to the classical experimental parameters known to affect drug self-administration, one factor receiving considerable attention is that of drug history. Drug history can be considered to vary along a continuum (reflective of an individual’s lifespan), for example, from the prenatal period to adolescence to adulthood (where exposure could be distal, i.e., days before self-administration, or proximal, i.e., immediately preceding self-administration) (see Riley and Simpson56). Although each of these periods of drug exposure is important (and affects self-administration), the period receiving the most analysis is that of adult exposure. In this context, changes in self-administration are consistently reported in adult animals with a recent history of drug access (either from experimenter-administered injections or prior self-administration of a different drug). Animals with such a history typically acquire self-administration quicker and at lower doses or obtain more drug infusions than animals lacking this history57–63 (for a review, see Schenk and Partridge,64 but see Morley et al.65). For example, Horger et al.66 reported that animals receiving once-daily cocaine injections for 12 consecutive days prior to access to self-administration of cocaine responded for a dose of cocaine that did not maintain cocaine-lever responding in saline-preexposed rats; that is, the effective dose shifted to the left. Further, a history of amphetamine injections increases breakpoints for amphetamine self-administration in rats on a progressive-ratio schedule of reinforcement.67 These changes are apparent not only when the preexposed and self-administered drugs are the same but also when different drugs are administered during preexposure. For instance, a history of amphetamine or nicotine administration also results in a more rapid acquisition of cocaine self-administration, with drug-experienced animals exhibiting a more reliable pattern of self-administration during the first several cocaine self-administration sessions.68 Psychostimulants are not the only compounds for which changes in drug self-administration occur after drug preexposure to either the same drug or a different drug. Similar changes have been reported for morphine, ethanol, methamphetamine, mescaline, and others69–81 (but see Panlilio et al.82).

Drug history and taste aversion learning

Although the effects of drug history on drug self-administration are generally discussed in the context of changes in the drug’s rewarding effects,58,64,66,68 such a history also consistently and significantly affects taste aversion conditioning.56,83–86 In general, providing animals with a drug history (often termed US preexposure) in the CTA design consists of administering noncontingent drug injections (of the aversion-inducing agent or another drug) prior to aversion conditioning. Such exposure reliably attenuates aversion learning; that is, taste aversions are weakened in these animals relative to control subjects receiving noncontingent vehicle injections during preexposure. In the initial report of the US preexposure effect, Brookshire and Brackbill87 demonstrated that repeated
injections of apomorphine prior to aversion conditioning with apomorphine significantly attenuated the subsequent apomorphine-induced aversion. After this initial study, a host of compounds including emetics, such as LiCl and cyclophosphamide, were reported to produce similar attenuation of aversion learning.88–92 An attenuation of learning after preexposure is not necessarily unique to the CTA preparation. For example, in other classical conditioning preparations, exposure to the US or to the CS (latent inhibition) before conditioning retards subsequent learning.9,93,94

More relevant to the issue of drug self-administration is the fact that a variety of drugs of abuse, such as morphine, cocaine, ethanol, nicotine, and amphetamine,48,95–102 also produce the preexposure effect when they are administered before aversion conditioning with these same compounds. In one of the initial assessments of drug preexposure in taste aversion learning, ethanol preexposure was shown to attenuate ethanol-induced aversions.93 Specifically, animals were given access to a 3–5% decarbonated ethanol beer solution or water for 35 days preceding aversion conditioning during which animals received five saccharin–ethanol (2 or 5 g/kg of body weight) pairings. Subjects receiving only water during the preexposure phase developed robust, dose-dependent ethanol-induced aversions. In contrast, ethanol-experienced animals displayed attenuated aversions relative to subjects receiving saline preexposure. Specifically, ethanol-preexposed animals injected with 2 g/kg ethanol during conditioning drank saccharin comparable to that of control animals conditioned with vehicle; ethanol-preexposed animals injected with 5 g/kg ethanol during conditioning also displayed attenuated aversions, although they did display aversions relative to the saline-conditioned subjects (Fig. 5).95 Subsequent work with drug preexposure in the CTA design has shown comparable effects of drug history on aversion learning, although the effects of such history are a function of a wide variety of parameters, such as number of preexposures, pattern of preexposure, dose of preexposure and conditioning drug, and delay between preexposure and conditioning.56

The specific mechanism responsible for the attenuating effects of drug preexposure on taste aversion conditioning remains unknown and a subject of considerable debate.56,84,90 Berman and Cannon,95 as well as many later investigations,98,103,104 argued that such attenuation in conditioning is a function of adaptation or tolerance to the aversive effects of the drug during preexposure (for other interpretations, see de Brugada et al.,105 Gamzu,85 and Parker et al.106). If tolerance to the conditioning drug is indeed occurring during preexposure, the preexposure effect itself should be influenced by parameters known to produce tolerance in other preparations. In this context, one might expect the effects of preexposure to be weakened if the conditioning dose were increased (relative to the preexposure dose). As noted in the preceding text, such an effect was evident in the initial report on preexposure with

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**Figure 5.** Prior exposure to ethanol weakens the aversive effects of this drug during subsequent taste aversion learning. Animals were preexposed to a 3–5% decarbonated ethanol beer solution as their only fluid for 35 days. On the first day, all animals were given saccharin alone; on the following trials, saccharin was paired with injections of vehicle (left), 2 g/kg ethanol (center), or 5 g/kg ethanol (right). Animals receiving vehicle during conditioning did not show any reductions in consumption, regardless of their preexposure condition (left). Naïve (open symbols) animals receiving saccharin paired with ethanol decreased consumption across trials (center and right). Experienced animals receiving saccharin paired with ethanol displayed attenuated ethanol-induced taste aversions. Redrawn from Berman and Cannon.95
drugs of abuse, for example, ethanol. In that study, the degree of the preexposure effect was indirectly related to the conditioning dose, suggesting that tolerance could be surmounted with increases in dose. Further, the preexposure effect might also be expected to weaken as the interval between preexposure and conditioning increases (because of waning of the tolerance-inducing drug treatment). Such an effect has been reported with morphine. For example, animals injected with morphine 7 days prior to morphine aversion conditioning displayed a robust attenuation of the aversion. As the number of days between preexposure and conditioning increased, the attenuating effects of morphine preexposure decreased accordingly. However, morphine-induced taste aversions remained attenuated relative to drug-naive controls even after 28 days between preexposure and conditioning, suggesting some residual tolerance even with this extended period. A similar pattern of results has been reported with amphetamine, although the attenuating effects of this preexposure are not as long lasting as those of morphine. Interestingly, rats also display the preexposure effect with morphine regardless of the environment in which morphine preexposure and aversion conditioning occur, supporting the position that the preexposure effect with morphine is most likely a nonassociative process (e.g., tolerance) and not a consequence of an association between the drug’s effects and specific environmental cues (for other investigations of tolerance, see Barker and Johns, Cannon et al., and Stewart and Eikelboom). The fact that the drug’s aversive effects weaken with such exposure may have implications for the basis of the effects of drug history on drug self-administration. That is, increases in self-administration after drug preexposure could be a function of a decrease in the drug’s aversive effects, a decrease that shifts the overall acceptability of the drug (with the aforementioned balance of reward and aversion; see Fig. 4). This increased drug intake could occur in the absence of any direct change in the rewarding effects of the drug. That is, with such exposure may have implications for the basis of the effects of drug history on drug self-administration.

Such an assessment has been reported by Risinger and Cunningham in their analysis of the factors affecting ethanol intake in the DBA/2J (D2) mouse strain. The D2 strain typically acquires robust ethanol-induced taste aversions and does not readily self-administer ethanol in oral self-administration preparations. According to Risinger and Cunningham, the aversive effects of ethanol in this strain (as indexed by its rapid acquisition of ethanol-induced taste aversions) limit its self-administration. Consistent with other work on ethanol (see foregoing text), exposure to ethanol in this strain prior to aversion conditioning significantly weakens the acquisition of these aversions (Fig. 6). Interestingly, a similar pattern and number of ethanol preexposures increases oral ethanol consumption in the D2 strain, a finding that supports the position that the relative balance of aversion and reward affects overall drug intake and that intake is affected by changes in either of these effects (here, the drug’s aversive effects).

The position that tolerance is the mechanism underlying the preexposure effect with drugs of abuse has received considerable empirical support (see preceding text). Such mechanisms may not account for all effects of drug preexposure. For example, have demonstrated that for the emetic LiCl, the effects of drug preexposure in aversion learning are associative. Specifically, cues associated with LiCl preexposure (e.g., the preexposure injection ritual) block subsequent LiCl-induced aversion learning, and when these associations are degraded, the preexposure effect is diminished (i.e., preexposed animals acquire aversions similar to controls) (for a review, see Riley and Simpson).
Because drug preexposure can attenuate CTAs and affect patterns of drug self-administration, an examination of how this manipulation affects CPP may be important to this discussion. If CPP is affected by such preexposure, it would suggest that changes in the rewarding effects of ethanol, too, could affect the subsequent self-administration of ethanol. Similar to drug preexposure and CTA learning, exposure to a drug before conditioning in the CPP design is reported to affect place preference conditioning. 115–120 On the other hand, several studies investigating the effects of drug preexposure on CPP report no change in preference scores in animals receiving drug preexposure.121–125 For example, Cunningham et al.123 reported that DBA/2J mice receiving injections of ethanol prior to place preference conditioning with ethanol displayed no change in preference scores relative to animals receiving preexposure to saline injections. Further, mice receiving this same preexposure regimen displayed an attenuation of ethanol's aversive effects.123 These data are important because a similar preexposure regimen increases oral ethanol consumption (self-administration) in these mice, a strain that typically avoids oral consumption of ethanol.69 In addition, ethanol preexposure has no parallels in the aversion literature that might address such changes. The fact that aversions are weakened by drug preexposure does address this question indirectly in that it does illustrate that the aversive effects of a drug can be influenced by repeated exposures. The assumption underlying this conclusion is that the aversive effects of a drug are not static but that they can be changed (as tolerance to these effects occurs with exposure). Although limited, there are also some data outside the drug preexposure design that are suggestive that with chronic drug use, the aversive effects of a drug do diminish. This was reported by Siegel, Parker, and Moroz,214 who examined the changes in morphine-induced taste aversion learning with repeated conditioning trials. From most of the work with such repeated conditioning with classical emetics, aversions simply get stronger; that is, animals decrease consumption over trials, often totally avoiding the consumption of the emetic-associated solution after three to five pairings.24,91 In the Siegel et al.214 report, when morphine was initially paired with saccharin consumption, animals also decreased consumption (comparable to effects seen with other drugs). With repeated conditioning trials, however, saccharin consumption stabilized and then began increasing. After more than 40 trials, consumption had recovered to the preconditioning baselines (although never to or above control levels). These patterns are consistent with changes in the aversive effects of morphine with repeated exposures; that is, the animal became tolerant to morphine's aversive effects. Little work exists that directly addresses the role of changes in a drug's aversive effects to the changes in drug taking over time (i.e., maintenance and escalation). Such assessments are important to determining the role of such changes (if any) in the patterns of drug intake associated with chronic use.
subject characteristics affecting drug self-administration: strain

Subject characteristics are also important in drug self-administration. One subject characteristic receiving considerable attention is that of animal strain, primarily because of its implication for genetic influences on drug intake. Specifically, the study of strain differences in drug intake is used to assess the possible genetic contributions to an inherent susceptibility to drug use and abuse. One popular method to study the influence of genotype on drug intake is to examine this behavior in different inbred and selectively bred strains of rats and mice. Two strains extensively used in this way are the inbred Fischer 344 (F344) and Lewis (LEW) rats (for reviews, see Kosten and Ambrosio and Riley). In brief, LEW animals (compared to the F344 rats) typically display greater acquisition of self-administration of several drugs of abuse, such as morphine and other opiates, nicotine, alcohol, and cocaine. On the basis of such findings, the LEW strain is suggested to be more sensitive to the rewarding effects of these drugs than the F344 strain. Other widely studied strains include several inbred mice that display differential oral self-administration patterns of ethanol. In a report by Yoneyama et al., 22 different inbred strains of mice were tested for their preference and intake of different concentrations of sweetened and unsweetened ethanol solutions. Similar to that reported in previous research, the C57BL/6J (B6) mice voluntarily consumed ethanol at a dose greater than 10 mg/kg/day. On the other hand, the D2 mouse strain consumed less than 2 mg/kg/day, demonstrating the large range in ethanol consumption among inbred mouse strains. In addition to inbred mice, several strains of rats (e.g., the alcohol preferring [P] and alcohol nonpreferring [NP] rats and the high–alcohol drinking and the low–alcohol drinking rats) have been selectively bred for specific ethanol preferences (on the basis of ethanol choice in two-bottle tests).

Strain differences in aversion learning

The underlying basis of these strain differences is typically assumed to be due to variations in drug reward, such that one strain is more sensitive to the drug's rewarding effects than the other strain. This heightened sensitivity results in greater drug intake. As has been described throughout this chapter, however, aversive drug effects are also important to overall drug acceptability, and an investigation of how these various strains acquire drug-induced CTAs could provide insights into differences in their drug taking. Such investigations are extensive and have often revealed dramatic strain differences in the sensitivity to the aversive effects of drugs. Because differences between strains in aversion learning are thought to be a consequence of inherent differences in the sensitivity to the aversive effects of the drug, inbred and selected strains are viewed as a useful tool for examining the underlying genetic mediation of rat model processes involved in chronic and persistent use (and abuse). Similar dual modeling has recently been proposed by Belin et al. in their analysis of drug-taking behavior in the high responder and high impulsivity rat. This analysis focuses only on the role of a drug's aversive effects in the initial acquisition of drug taking (for an analysis of the role of such effects in long-term drug intake in the F344 and LEW rat strains, see Stephens and Riley).
aversive drug effects. In so doing, differences in taste aversion learning may reveal certain genetic backgrounds that are more or less prone to substance use and abuse, a differential vulnerability related to differences in the sensitivity to the drug’s aversive effects (for a discussion of other interpretations, see Cunningham et al.\textsuperscript{123}).

Interestingly, two strains that have received considerable attention in this context are the F344 and LEW rat strains. Specifically, these strains have been compared in their ability to acquire taste aversions induced by many compounds, including morphine, nicotine, and alcohol. In one of the initial assessments investigating drug-induced taste aversions in these strains, Lancellotti et al.\textsuperscript{142} reported that morphine induced more robust aversions in the F344 strain than in the LEW strain. More specifically, F344 and LEW rats received five pairings of saccharin followed by a subcutaneous (s.c.) injection of morphine (18, 32, or 50 mg/kg) or vehicle. The F344 rats displayed a significant decrease in consumption of the morphine-associated saccharin solution (relative to F344 rats receiving vehicle) after only a single conditioning trial; this decrease was maintained throughout the rest of conditioning.\textsuperscript{142}

In contrast, the LEW rats did not display a significant decrease in consumption at any of the doses tested and even after repeated conditioning trials. In fact, morphine-conditioned LEW rats drank saccharin in amounts comparable to that displayed by LEW rats injected with vehicle (Fig. 7). Importantly, F344 and LEW control animals (those receiving vehicle injections following saccharin consumption) drank similar amounts of saccharin at each trial, demonstrating no inherent difference in their preference for saccharin or their overall level of fluid consumption. Similar differences emerge when heroin is the aversion-inducing agent. When saccharin is paired with one of three doses of heroin (3.2, 5.6, and 10 mg/kg), F344 rats develop robust heroin-induced CTAs.\textsuperscript{146} Similarly treated LEW rats display no significant decreases in consumption (Fig. 8A). Under similar conditions, the F344 and LEW strains do not differ in aversion learning induced by opioids with relative selectivity at the delta and kappa opioid receptor subtypes. For example, although both the delta receptor agonist, SNC80, and the kappa receptor agonist, U50,488H, induce taste aversions in F344 and LEW rats, the two strains do not differ in the degree of aversions induced by these compounds (Fig. 8B and C; Davis et al.\textsuperscript{146}). Because these compounds are considered to have low abuse potential,\textsuperscript{147,148} these data suggest that the opioid-induced strain differences in aversion learning between the F344 and LEW animals are associated with opioids that have a high potential for abuse (i.e., morphine and heroin) and are not simply a function of opioid insensitivity in the LEW animals.

The differences in aversion learning between the F344 and LEW rats are not restricted to morphine and heroin. For example, the F344 rats also display stronger ethanol- and nicotine-induced aversions. More specifically, F344 rats receiving pairings of saccharin and 1.25 or 1.5 g/kg of ethanol acquire significantly stronger aversions to saccharin than do LEW rats,\textsuperscript{144} although unlike the pattern seen
Figure 8. Mean saccharin consumption in F344 and LEW rats conditioned with different opioid agonists. (A) Heroin (3.2, 5.6, or 10 mg/kg) induced significant decreases in consumption across trials in the F344 rats only. (B) No strain differences emerged in when aversions were conditioned with various doses of the kappa opioid receptor agonist, U50,488H (0.28, 0.90, or 1.6 mg/kg). (C) Comparable changes in saccharin consumption across trials emerged when F344 and LEW animals were conditioned with various doses of SNC80 (5.6, 10, or 18 mg/kg), a delta opioid receptor agonist. Error bars represent the standard error of the mean.

In contrast to morphine and heroin, ethanol does induce aversions in both strains relative to control animals. Similarly, Pescatore et al. reported strain differences in nicotine-induced aversions. F344 animals given pairings of saccharin and 0.8 mg/kg of nicotine consume significantly less saccharin than LEW animals receiving the same dose (although aversions are evident in both strains). In contrast to these results with drugs of abuse, minimal differences are evident when aversions are conditioned with the emetic LiCl. Both strains display comparable dose-dependent LiCl-induced aversions.
Overall, these data suggest an increased sensitivity to the aversive effects of a variety of drugs of abuse in the F344 strain.\(^5\)

**Relationship between self-administration and CTA**

Although the F344 and LEW strains vary greatly in their ability to acquire taste aversions induced by a variety of drugs of abuse (presumably reflecting differences in their sensitivity to the aversive effects of the drugs), the issue is the relevance of such differences to the reported differences seen in drug self-administration. The differences in the aversive effects associated with these compounds could have implications for the patterns of self-administration evident in these two strains. If aversive drug effects can limit drug intake, it might be expected that the vulnerability of drug taking would be related (indirectly) to these aversive effects. Therefore, comparing these differences in aversion learning to patterns of self-administration might reveal a genotype that is more or less likely to use or abuse certain drugs. For instance, morphine induces aversions in the F344 strain, whereas the same doses of morphine have no effect in the LEW strain (see preceding text). Such results might predict a decrease in the likelihood of self-administration of morphine in the F344 animals relative to the LEW strain. Again, such an assumption would be based on the fact that although both drugs may be rewarding in these strains, the aversive effects associated with administration of morphine might serve to limit drug intake in the F344 rats. It is the F344 strain that is more resistant in their acquisition of morphine self-administration. For example, Ambrosio et al.,\(^{131}\) reported that the LEW strain more quickly acquired self-administration of morphine (1 mg/kg/infusion) than the F344 rats.\(^{134,136,150,151}\) After several self-administration sessions, these strains display similar levels of morphine intake, suggesting possible adaptation to morphine’s aversive effects in the F344 strain. Such a suggestion is supported by the fact that drug preexposure in this strain dramatically weakens aversion learning, suggestive of tolerance to morphine’s aversive effects with repeated exposure.\(^{152}\)

In addition to morphine, ethanol and nicotine are also compounds for which these strains display differences in CTA learning and self-administration. As noted, the F344 strain develops stronger aversions induced by both ethanol and nicotine than do the LEW animals.\(^{143,144}\) Interestingly, when allowed to self-administer ethanol orally, members of the LEW rats display increased response rates, earn more ethanol deliveries, and display higher blood ethanol levels than the F344 rats.\(^{136,144,153}\) Further, although F344 rats will acquire oral self-administration of ethanol, this drug serves only as a weak reinforcer in this strain.\(^{135}\) The greater aversive effects associated with ethanol in the F344 strain could serve to limit intake of this drug compared to the LEW animals. In addition to these differences, only the LEW strain acquires self-administration of nicotine during a 23-h unlimited access preparation.\(^{132}\) This strain also displays increased responding as the dose of nicotine is reduced and maintains responding for nicotine at doses as low as 0.0009 mg/kg. In a limited-access preparation, both LEW and F344 rats fail to acquire nicotine self-administration,\(^{134}\) which could be a consequence of the aversive effects of nicotine that are evident in both strains (although weaker in the LEW rats). With continued nicotine access, however, these aversive effects might no longer limit drug intake in the LEW strain.
leading to increased overall nicotine acceptability and self-administration.6

The relationships between taste aversions and self-administration for these strains are consistent for morphine, ethanol, and nicotine; that is, the strain that shows the strongest drug-induced taste aversions is the one that displays the slowest acquisition of drug self-administration. Although consistent with these compounds, the results with cocaine do not show a similar relationship. For example, in the first assessment of differences in aversion learning in the LEW and F344 strains, Glowa et al.141 reported that cocaine-induced taste aversions were stronger in the LEW strain than in the F344 rats.145,155,7 Specifically, Glowa et al.141 allowed both strains limited access to a novel saccharin solution and followed saccharin access with injections of various doses of cocaine (18, 32, and 50 mg/kg; Fig. 9). Again, if aversive drug effects are a limiting factor in drug taking, these results would predict that the LEW strain would display less cocaine self-administration than the F344 strain, opposite effects of those described for morphine, ethanol, and nicotine (in which LEW rats display greater self-administration then do the F344 rats). As noted, however, it is the LEW strain that displays a faster acquisition of cocaine self-administration.133

In the context of the data described thus far, the effects of cocaine in the LEW strain seem counterintuitive; if aversive drug effects limit drug intake, stronger taste aversions would predict a retarded acquisition of cocaine self-administration in this strain (LEW). Because these results do not demonstrate an inverse relationship like those of the other compounds, it suggests that the relationship between CTAs and self-administration is not a simple one. Although one might expect an inverse relationship between self-administration and aversions, it is the relative balance between reward and aversion that affects the overall acceptability (i.e., self-administration) of a compound. Therefore, a drug could be both more rewarding and aversive in any specific strain. It would be the relative balance of these two that would be important in determining whether that strain would display greater self-administration. For cocaine, this drug could be more rewarding (as indexed by greater CPPs; see Kosten et al.156) and more aversive (as indexed by greater CTAs) for LEW subjects. The fact that this strain displays greater self-administration of cocaine would simply reflect the fact that its rewarding effects are greater than its aversive effects, allowing the overall balance to drive drug taking (and to a greater degree than that seen in the F344 strain).8

In addition to the inbred F344 and LEW strains, the C57BL/6J and DBA/2J inbred mice have received a great deal of attention in the CTA literature, primarily because of their reported differences

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6 Although strain differences are clearly evident, the basis for these differences is not known. Because these strains differ on several neurochemical and neuroanatomical substrates that mediate a range of effects produced by drugs of abuse, strain differences in these substrates probably mediate these behavioral differences (for a discussion of these substrates, see Fernandez et al.,221 Flores et al.,222 Freeman et al.,223 and Sánchez-Cardoso et al.134). Although which sites are involved in the affective differences between the LEW and F344 strains remains an empirical issue, the F344 and LEW strains do provide a useful model to investigate inherent differences in the affective consequences associated with drug administration.7 Cocaine CTAs in these strains vary depending on the sex of the subject. Greater cocaine-induced aversions have been reported in LEW females.141,145 but consistent differences have not been found between the males of these strains145,152,156 (but see Grignon and Freet155), suggesting that the relationship between strain and cocaine’s aversive effects can be influenced by sex. Interestingly, the differences with morphine between the two strains are evident in both males and females; that is, F344 rats of both strains display greater morphine-induced taste aversions than those of the LEW strain. Thus, in such analyses both the strain and sex need to be identified because these appear to interact in the examination of drug-induced taste aversion conditioning, an interaction previously reported in other strain comparisons224 and in outbred strains.178

8 Such a suggestion is supported by recent neurochemical work by Grabus et al.225 showing that cocaine-induced c-Fos activity in brain areas associated with reward (e.g., nucleus accumbens) and aversions (e.g., parabrachial nucleus) were both greater in LEW rats than in the F344 strain. On the basis of this activity, LEW rats appear to be more sensitive (or responsive) to both the rewarding and aversive effects of cocaine. Interestingly, after injection of morphine, both strains showed comparable c-Fos activation in the accumbens, yet the F344 strain displayed greater c-Fos activity than LEW rats in the parabrachial nucleus, an effect consistent with their reported differences in aversion learning.
in free-choice ethanol preference. Ethanol preferences in these two strains are well established, with the C57BL/6J mice displaying greater consumption of and preference for ethanol-containing solutions than the DBA/2J strain. Horowitz and Whitney examined whether the two strains also displayed differences in ethanol’s aversive effects, differences that could be mediating their differential preferences for oral ethanol. Interestingly, the C57BL/6J mice develop weaker ethanol-induced taste aversions than the DBA/2J mice, providing evidence that the degree of CTA is inversely related to ethanol consumption. Many studies after this initial investigation have also confirmed these differences between the C57BL/6J and DBA/2J mice and have broadened the number of inbred strains displaying differences in ethanol-induced CTA.109,110 For example, Broadbent et al.110 examined ethanol-induced CTAs in 15 inbred strains of mice (including the C57BL/6J and DBA/2J strains) that were reported to display different degrees of severity of ethanol’s effects. The rate of acquisition of ethanol-induced taste aversion was significantly correlated with severity of ethanol withdrawal (directly correlated) and ethanol preference (indirectly correlated) in home-cage drinking tests, such that strains displaying greater aversions also displayed more severe withdrawal responses and decreased home-cage ethanol preference. These data suggest that ethanol’s aversive effects can limit ethanol intake and cause an animal to display a decreased preference for solutions containing various concentrations of ethanol. More important, this sensitivity to ethanol’s aversive effects appears to be genetically mediated, with the variations in CTA between the C57BL/6J and DBA/2J mice strains. These differences in CTA learning in these strains are not due to general sensitivity to aversive agents, such as LiCl or the ability to acquire CTA in general (but see Risinger and Cunningham), but appear instead to reflect inherent differential sensitivities to ethanol’s aversive effects.

Inbred strains of rats and mice previously described are not the only strains that display different drug-induced CTAs. Several selectively bred strains of rats and mice have been developed and are an important tool to investigate the genetic mediation of aversive effects of drugs. Selective breeding studies typically select animals on the basis of the demonstration of a specific phenotype, such that animals that exhibit low levels of the phenotype are bred with one another and animals displaying high levels of the phenotype are bred in a similar manner. Success at selectively choosing and breeding for a certain phenotype demonstrates genetic control of that specific characteristic (for a review, see Cunningham et al.52). For example, Elkins, Walters, and Orr (see also Elkins161) selectively bred animals from a population of Sprague–Dawley rats that developed either strong (taste aversion prone [TAP]) or weak (taste aversion resistant [TAR]) cyclophosphamide-induced aversions. In later investigations, TAP and TAR rats were examined for differences in behaviors, such as rotation-induced CTAs, ethanol-induced loss of righting reflex and CTA, and radial arm maze learning,160,162,163 to determine what other behaviors possibly correlated with an increased or

Figure 9. Mean saccharin consumption in F344 and LEW rats conditioned with different doses of cocaine (0, 18, 32, or 50 mg/kg). The LEW strain acquired dose-dependent, robust cocaine-induced aversions. For the F344 strain, however, only the 50-mg/kg dose of cocaine induced significant decreases in saccharin consumption across trials comparable to the LEW strain. Error bars represent the standard error of the mean. Redrawn from Glowa et al.141
decreased sensitivity to develop cyclophosphamide-induced CTAs. Interestingly, these strains did not show reliable differences in standard learning preparations, such as the radial arm maze and bar pressing for food pellets, but they did show differences in cocaine- and ethanol-induced CTAs, with TAP rats displaying more robust aversions with both of these drugs.$^{160,164}$ Interestingly, TAP rats displayed a decrease in ethanol consumption and preference relative to the TAR rats.$^{165,166}$ Although the TAP and TAR lines were not selectively bred to display any different reactivity to ethanol, these strains do display differences in the acquisition of ethanol-induced taste aversions. These data suggest that a general sensitivity (or insensitivity) to general aversion learning could have implications for ethanol acceptability and intake.

The inherent differences in the behavioral responses to drugs of abuse are not limited to inbred and selectively bred rodent lines. Interestingly, outbred rat strains also show differences in drug self-administration studies even though these strains have not been specifically bred to display any drug- or non–drug-induced behaviors. Sprague–Dawley rats, a common outbred animal used in many different behavioral studies, do not acquire intravenous (i.v.) self-administration of the CB1 receptor agonist, WIN55,212-2, whereas Long–Evans and Lister Hooded rats display robust acquisition of this behavior.$^{167,168}$ However, Sprague–Dawley rats will self-administer THC directly into reward-associated brain areas, including the posterior ventral tegmental area and the shell of the nucleus accumbens.$^{169}$ These data suggest that intracranial self-administration of cannabinoid compounds in Sprague–Dawley rats might be necessary to avoid the aversive effects associated with i.v. administration, which prevent cannabinoids from serving as reinforcers in systemic self-administration procedures.$^{170}$ Although aversion learning with these specific compounds is lacking (i.e., WIN55,212-2; for aversion learning with THC, see Elsmore and Fletcher$^{41}$ and Parker and Gillies$^{171}$), these data provide an interesting possibility that the outbred Sprague–Dawley rats might display decreased systemic self-administration of cannabinoid compounds because of increased aversive effects compared to other outbred strains. More important, these data demonstrate how different rodent lines, regardless of any breeding manipulations, can be inherently sensitive to the affective consequences of drugs of abuse.

**Caveats**

**Beyond history and strain**

The logic for this analysis is that the aversive effects of drugs (as indexed in the CTA procedure) may play a role in the vulnerability to drug use and abuse. The role that it would play would be as a protectant factor, limiting drug intake. Therefore, the aversive effects of a drug would work together with a drug’s rewarding effects to affect overall acceptability. The preceding discussion has focused on how drug history and strain (as a representative experimental manipulation and subject characteristic, respectively) can affect the aversive effects associated with drug administration and how these effects might influence drug self-administration. As noted, these are not the only factors that can affect drug self-administration. For example, sex has been examined extensively in the self-administration preparation, with female animals typically self-administering lower drug doses relative to males and females typically escalating to addiction much more quickly than males. In one of the initial reports in this area, Lynch and Carroll$^{172}$ demonstrated that female rats more quickly acquired cocaine and heroin self-administration and self-administered more cocaine than did their male counterparts$^{173,174}$ (for similar results with methamphetamine, see Roth and Carroll$^{175}$; for PCP [phencyclidine] see Carroll et al.$^{176}$). These data suggest that females are more sensitive to the rewarding effects of drugs. If the aversive effects of drugs affect self-administration, it might be predicted that females would display greater taste aversions induced by drugs of abuse. Although such results have been reported for a variety of drugs, for example, cocaine and ethanol,$^{177–179}$ such differences are not always apparent.$^{180,181}$ It is possible that females are more sensitive to both the rewarding and the aversive effects of some drugs, and with this increased sensitivity, lower drug doses can maintain behavior in females compared to males. With the lack of data assessing sex differences in aversion learning with drugs of abuse, a thorough analysis of how sex affects both CTAs and self-administration is difficult.

Another factor reported to affect drug self-administration is the age during which this behavior
is acquired. For example, Levin et al.\textsuperscript{182} demonstrated that adolescent animals self-administered threefold more nicotine over a 2-week period than did adult animals\textsuperscript{183,184} (for a review, see McBride et al.,\textsuperscript{185} but see Shram et al.\textsuperscript{186,187}). In addition to nicotine, similar age differences are reported for self-administration of cocaine\textsuperscript{174} (but see Kantak et al.\textsuperscript{188}), amphetamine,\textsuperscript{189} and ethanol,\textsuperscript{190–192} suggesting that adolescent animals might be more likely to use and abuse drugs during this developmental period. As might be expected, age is also a factor in aversion learning with drugs of abuse.\textsuperscript{193} For example, several investigations have reported weaker acquisition of taste aversion learning in adolescent animals than adults. Schramm-Sapyta et al.\textsuperscript{194,195} reported that adolescent rats are less sensitive to the aversive effects of cocaine and THC (as indexed in aversion learning), suggesting that decreases in these effects might be related to increased drug taking during this developmental period (for similar results with nicotine, see Shram et al.\textsuperscript{196}). Moreover, adolescent rats also develop weaker LiCl-induced taste aversions than adult animals.\textsuperscript{194} With these results, it is possible that adolescent rats are not necessarily less sensitive to the aversive effects of drugs of abuse only but that they are less likely to form aversions in general. Although such sensitivity may not be specific to drugs of abuse, the reduced sensitivity would nonetheless affect drug use and abuse. That is, adolescent animals may be more vulnerable to use and abuse drugs because the limiting factor of aversive drug effects would not be able to help regulate drug intake. If so, the protective role that aversive drug effects are thought to have would be diminished, possibly leading to increased self-administration in animals during the adolescent period. Together, these data suggest that the age of onset of drug use could have implications for the vulnerability to continue or even abuse drugs throughout adolescence and into adulthood.

Parametric generalizations

If the aversive effects of a drug play a protectant factor in limiting drug intake, it might be expected that the factors known to affect taste aversion learning would also affect drug self-administration. To assess this relationship, we compared data from the two designs. In several instances, most specifically drug history and strain, it was noted that when aversions were weakened (or strengthened), self-administration was affected in the opposite way; that is, weaker taste aversions were associated with greater drug self-administration. Although supportive of the position that the aversive effects of drugs influence drug self-administration, the parametric conditions under which the two behavioral effects (i.e., self-administration and taste aversion conditioning) were examined differ in a myriad of ways and in ways that limit the conclusions that can be drawn from the comparisons. Such parametric differences include the route of administration, frequency of drug injection, dose of the drug, and control. For example, self-administration studies typically employ the i.v. route. In contrast, CTA manipulations normally use experimenter-administered injections most commonly occurring via the s.c. or intraperitoneal (i.p.) routes. Animals in self-administration assessments typically have daily access to the drug for specific periods each day that may vary from 1 to 23 h. Animals in a taste aversion study are injected with a drug infrequently, typically once a day every third or fourth day. The dose of the drug used in self-administration studies are typically small (e.g., 1.0 mg/kg/infusion), whereas they are generally larger by several factors in work assessing taste aversion learning. Although the daily cumulative doses in the two designs may actually not always be that different, the fact that one represents multiple periodic changes in blood level (self-administration) versus the single large bolus (CTA) illustrates yet another difference between the two designs.

Any one of these differences might be used to argue that any conclusions based on the comparisons between taste aversion learning and self-administration must be made cautiously. Although these differences do exist, as noted earlier there are studies that provide support for the assumptions we have made concerning the relationship between aversions and drug self-administration. Specifically, taste aversions have been induced under parametric conditions that support self-administration. For example, animals receiving saccharin paired with self-administered apomorphine display an aversion to the saccharin solution\textsuperscript{50} and maintain self-administration. Further, the number of self-injections of apomorphine predicted the strength of the CTA such that the more injections self-administered, the stronger the CTA. Similarly,
Gomez\textsuperscript{197} reported that rats given saccharin access immediately prior to a cocaine self-administration session developed an aversion to the saccharin solution. Further, animals that self-administered the most cocaine also displayed the greatest decrease in saccharin consumption (see also Gomez\textsuperscript{198}). These data strongly suggest that the aversive effects of a drug are evident when the drug is taken. Because most CTA studies do not use this method of drug administration, however, a direct comparison between the effects displayed in aversion studies with different patterns of drug self-administration is still limited by these parametric differences. It is important that work assessing the role of aversions in drug self-administration demonstrate taste aversion conditioning under conditions that more closely parallel demonstrations of self-administration, e.g., smaller doses, given i.v., spaced in delivery.

**Interpretations**

Throughout this chapter, CTAs are assumed to be due to the aversive effects of a drug. In fact, the demonstration of a taste aversion has been taken as evidence of a drug’s having aversive effects. Such effects as indexed by the aversion design are then thought to affect the vulnerability to drug self-administration (by interacting with the drug’s rewarding effects). These aversive effects are viewed as a protective factor in drug use and abuse and might decrease the overall acceptability of a drug. However, this is not the only explanation of the phenomenon of drug-induced taste aversion learning. The explanations for aversion learning are many and have been a subject of debate for the past 50 years. As noted, aversion learning had its foundation in basic toxicology, and it is no surprise that the initial view on its mediation (and one still prominent) is that drugs are aversive or toxic and it is this property of the drug that is responsible for the resulting aversion. An animal will come to avoid the taste of a solution that is predictive of a drug’s toxic or aversive effects. This is the view that underlies the logic of our report.

Drug toxicity is by no means the only proposed mediator of aversion learning. Some investigators have suggested that aversions induced by drugs of abuse do not reflect toxicity but instead the novel state induced by the drug. This novelty (possibly resulting in a stress response) is sufficient to induce an aversion (for a review, see Hunt and Amit\textsuperscript{199}). This position arose from the apparent paradoxical effects seen with drugs of abuse; that is, rewarding drugs also produced significant taste aversions. The fact that such drugs were rewarding seemed counterintuitive to an interpretation based on toxicity. This position also held that although both emetics (and classical toxins) and drugs of abuse all conditioned aversions, they did so via different mechanisms. Specifically, emetics could very well be aversive and toxic, and these effects could become associated with various tastes and mediate aversion learning with those compounds. Effects produced by drugs of abuse, however, may be qualitatively different from those of toxins. The state produced by a rewarding drug would be considered novel to the animal, possibly producing a type of “drug shyness” that is then associated with other novel things in the environment (e.g., tastes, such as saccharin). On later presentations, the saccharin solution is avoided because of its association with this state produced by the drug. This effect is considered clearly distinct from the nausea or sickness that is thought to mediate aversions induced by emetics. In light of the idea that aversions to emetics and drugs of abuse are qualitatively distinct effects, taste reactivity studies have shown that conditioned disgust reactions (chin rubs, gapes, paw treading) are apparent only when CTAs are conditioned with emetics, such as LiCl (for a review, see Parker\textsuperscript{200}). However, these same disgust reactions are not apparent when drugs of abuse are the aversion-inducing agent (but see Parker and Gillies\textsuperscript{171}). For example, Parker\textsuperscript{201} reported that sucrose paired with cocaine, methamphetamine, or PCP produced avoidance of the drug-associated solution, but conditioned disgust reactions were not evident after these sucrose–drug pairings. Interestingly, LiCl, administered at doses producing aversions equal in strength to those of the drugs of abuse employed, did elicit conditioned disgust reactions.\textsuperscript{201} These data suggest that CTAs induced by drugs of abuse do not produce sickness or a dislike of the associated solution but do produce an avoidance of the solution possibly due to a novelty-induced fear response.\textsuperscript{200} Because sickness is not necessary to cause avoidance of a novel solution by drugs of abuse, several other lines of evidence have been used to support the drug novelty hypothesis. Low drug doses (with no obvious signs of illness) and antiemetic drugs, such as scopolamine,
both produce CTAs, further suggesting that drug-induced sickness is not necessary for CTA learning with drugs of abuse.\textsuperscript{199}

Although drug novelty could be a factor in aversion learning, it cannot explain the phenomenon entirely. For example, animals typically display greater aversions as the number of conditioning trials increases. These effects would argue that drug novelty increases over conditioning trials (if novelty itself was the US mediating the conditioning). Given the fact that habituation to drug novelty is thought to occur with continued drug exposure,\textsuperscript{85,202} one would predict decreases in aversion learning with continued drug administration. Further, although exposure to a drug prior to CTA conditioning typically attenuates subsequent aversion learning, an effect consistent with a novelty hypothesis, several reports have demonstrated clear and significant decreases in consumption (after previous drug exposure) with further conditioning. For example, Riley and Simpson\textsuperscript{102} reported that cocaine preexposure significantly attenuated a cocaine-induced aversion (at the same dose as that used in preexposure) on the first few saccharin–cocaine pairings. As the number of these pairings increased, cocaine-preexposed subjects conditioned with cocaine actually displayed significant decreases in consumption, indicating that these animals had indeed developed an aversion.\textsuperscript{102,203} Again, if drug novelty was the primary factor mediating aversion learning, increasing the number of conditioning trials should not have had any effect on acquisition of the cocaine-induced aversion in preexposed animals habituated to the drug.

A more recent interpretation of aversion learning that does not assume that CTAs are mediated by toxicity or any aversive effects of the drug has been presented by Grigson\textsuperscript{204} and her colleagues.\textsuperscript{155,205} Similar to the drug novelty hypothesis, this position also assumes that aversions induced by drugs of abuse are qualitatively distinct from those induced by emetics; however, these effects are thought to be different from novelty-induced avoidance. This hypothesis states that drugs of abuse induce CTAs because they are rewarding. More specifically, the palatable drug-associated saccharin solution is avoided because the drug of abuse that follows is seen as having a greater rewarding value than saccharin (thus, the model is termed reward comparison). The saccharin, therefore, pales in comparison to the greater drug reward that follows and is avoided on later presentations. This hypothesis was born out of work on anticipatory contrast where an animal will decrease consumption of a less palatable solution (saccharin) when followed by a more palatable one (sucrose; Flaherty \textit{et al.}\textsuperscript{206}). Similar to anticipatory contrast, the greater the palatability (or reward) associated with the second stimulus, the greater the degree of suppression of intake of the first. That is, augmented suppression of consumption would be evident as the rewarding value of the second stimulus increased. When investigating drugs of abuse, more rewarding drugs of abuse are thought to induce more robust CTAs.

Although this hypothesis is favored by several recent investigations,\textsuperscript{155,207} it does not adequately account for drug-induced aversion learning. If reward comparison is indeed the primary factor mediating drug-induced taste aversion learning, several well-known aspects of this learning would be dramatically affected. First, according to this hypothesis one might predict that there would be a direct relationship between a drug’s aversive and rewarding effects; that is, if a taste avoidance is a function of the drug’s rewarding effects, the greater these latter effects the stronger the taste avoidance. In an analysis of the effects of route of administration on cocaine-induced taste aversions, Ferrari \textit{et al.}\textsuperscript{208} reported that animals receiving various doses of cocaine administered s.c. acquired robust, dose-dependent aversions, whereas those receiving these same doses of cocaine i.p. displayed only small reductions in consumption. Specifically, animals receiving the highest dose of cocaine (50 mg/kg) i.p. were still consuming saccharin (about 70% of that consumed by control subjects); animals receiving this dose s.c. displayed almost complete suppression of consumption (see also van Haaren and Hughes\textsuperscript{179}). Interestingly, opposite effects are noted for cocaine in the CPP design, a measure of the drug’s rewarding effects. Specifically, cocaine (20 mg/kg) conditioned a place preference only when administered i.p.\textsuperscript{209} and i.p. cocaine did not cause a significant decrease in consumption of the cocaine-paired solution (see Mucha \textit{et al.}\textsuperscript{210} for CPP induced by i.v. administration of cocaine and morphine). When this drug was administered s.c., however, no CPPs were evident, but robust CTAs were seen.\textsuperscript{209} Such results argue convincingly that there need not be a direct relationship between strength of aversions and reward.
It is interesting in this context that when individual animals are examined in a combined CTA-CPP design and the relationship between their ability to acquire a taste aversion and CPP induced by the same drug is assessed, there is no relationship between the two behavioral effects. That is, animals that display strong morphine-induced place preferences are just as likely to display weak aversions as they are strong ones. Conversely, animals with strong aversions are just as likely to display weak CPPs as they are strong ones (Verendeev and Riley, abstract submitted for presentation). This lack of a relationship between CTA and CPP matches that reported earlier by Parker and her colleagues, who assessed the relationship between CTA and CPP in animals examined serially for their ability to acquire taste aversions and place preferences induced by morphine (though see results with amphetamine). Second, the reward comparison hypothesis would predict that drug preexposure should not attenuate CTA learning. On the basis of prior work that repeated drug administration produces changes in the mesolimbic dopamine pathway, leading to an increased sensitivity to the rewarding effects of drugs of abuse, one might predict that drug preexposure would sensitize animals to the rewarding effects of a drug. If such exposure sensitizes animals to the rewarding effects of drugs, drug-induced CTA learning would be augmented as well, as a function of the drug’s increased rewarding effects. Work examining drug preexposure, however, consistently reports that drug-induced CTAs are attenuated after prior exposure, suggesting that CTAs are not a function of a drug’s rewarding effects and are not influenced by changes in the rewarding effects of drugs (see preceding text, but also see Grigson et al.). A final issue that cannot be accounted for by the reward comparison hypothesis is the fact that animals displaying weak aversions to drugs of abuse typically display increased drug intake during self-administration. For example, the LEW rats described do not develop morphine-induced aversions but display faster acquisition of morphine self-administration. In addition, the willingness of different strains of mice to acquire ethanol self-administration is inversely correlated with the degree of ethanol-induced CTA, such that animals displaying greater aversion also display lower levels of ethanol self-administration. This pattern of results is exactly opposite of what the reward comparison hypothesis would predict. That is, animals displaying the most robust aversions should be the same animals that self-administer the greatest amounts of drug. Explaining drug-induced aversion learning then as a function of a drug’s rewarding effects seems problematic with the wealth of data in opposition to what this hypothesis would predict (for further discussions of the reward comparison hypothesis in taste aversion learning, see Broadbent et al. and Huang and Hsiao). Clearly, drugs have aversive and rewarding effects, and both of these effects are important mediators of CTA and CPP learning, in addition to overall drug intake.

Conclusions

This chapter has attempted to make a case that drugs of abuse have multiple affective properties, that is, rewarding and aversive, and that these two properties interact to affect the likelihood of a drug being used and abused. Traditionally, the focus on affect has been on the drug’s rewarding properties. Obviously, to be used and abused the drug must be rewarding to maintain drug-taking behavior. Instead, the chapter has tried to document the drug’s aversive effects (as indexed by taste aversion conditioning) and to demonstrate its role in influencing drug use, specifically as a limiting or protectant factor. The recognition that such aversive effects may play a role argues that one should understand the manner by which such effects can be modulated by a variety of experimental manipulations (e.g., drug history) and how they may also be a function of a variety of characteristics of the user (e.g., genetics). Such an understanding of these aversive effects and how they vary may allow one to better predict vulnerability to use and abuse and to develop effective treatments for addiction. Further, understanding the neurochemical and neuroanatomical substrates for these aversive effects may allow one to determine any differences in susceptibility to these effects (e.g., with sex and strain) and how these substrates might change with history and chronic use, changes that may be crucial to escalated drug use. Again, this focus on a drug’s aversive effects and their role in drug use and abuse does not suggest that reward does not vary similarly and that such variations are not important to drug taking. The chapter simply argues that an analysis of reward alone (without an evaluation and discussion
of a drug’s other affective properties) provides an incomplete picture.

**Conflicts of interest**
The authors declare no conflicts of interest.

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