The paradox of drug taking: The role of the aversive effects of drugs

Anthony L. Riley*

Psychopharmacology Laboratory, Department of Psychology, American University, Washington, DC 20016, USA

ABSTRACT

In 1991, Woods described the paradoxical nature of eating, specifically, that it produced aversive and negative effects. He noted in this analysis the multiple physiological and behavior adaptations, both learned and unlearned, that were aimed at regulating food intake and reducing its aversive, disruptive effects. From this position, he argued that consumption reflected a balance of the positive and aversive effects of eating. The present review extends this analysis to drug use and abuse, i.e., that drug taking itself also is a balance of reward and aversion. Although traditionally the analysis of drug use and abuse has focused on a drug's positive and negative rewarding effects, the present review highlights the aversive effects of these same drugs, e.g., cocaine, morphine, alcohol, and describes such effects as protective in nature. This balance and the manner by which it can be impacted by subject and experiential factors are described with a focus on genetic models of drug abuse using the Lewis and Fischer inbred rat strains.

1. Food regulation

In 1991, Woods began a paper entitled “The Eating Paradox: How We Tolerate Foods” with the statement “I find myself in the hapless position of having to speak out against the virtues of eating. For a person who not only loves to eat but was trained in experimental psychology, this is nothing less than heresy” [1]. So with a title proclaiming a paradox regarding feeding and a self proclaimed heresy to come, Woods began what I think is one of his seminal papers in the field. In this case the toleration, and not general acceptance, of food. The paper fundamentally was about the disruptive nature of food to general homeostasis and the adaptations allowing food to be tolerated.

In his overview, Woods highlighted the many physiological problems associated with the chronic and excessive intake of food and the many homeostatic mechanisms that allow us to circumvent these problems as we eat. Thus, eating is like drug tolerance in that we adapt to the homeostatic disruption of food much as we adapt or become tolerant to the disruption of the exogenous administration of a drug. In his analysis, Woods raised a host of interesting questions about eating and made some predictions he viewed would be consistent with his rather unique take on food intake.

Woods noted that a host of characteristics of food intake reflect adaptations to limit the aversive or deleterious effects of eating. Beyond these characterizations, however, is the point that feeding really is a challenge to which we have to adapt and that understanding this rather unique position provides a more comprehensive account of feeding and its regulation than one which focuses only on the positive value of food.

2. The role of reward in drug taking

Although Woods’ immediate concerns were related to feeding and its regulation, this broad-based approach can and should be applied to other issues as well. The following brief analysis describes another phenomenon for which a limited and traditional analysis provides an incomplete understanding, specifically, the phenomena of drug use and abuse; the paradoxical position is that drug taking requires an understanding of drug toxicity and aversiveness.

To begin this argument, a traditional account of drug taking needs some description. Accounts of drug-taking behavior invariably begin and often end with an overview of the rewarding effects of a drug. Such rewarding effects are generally positive or negative in nature. That is, one may initiate and continue the taking of a drug because the drug produces some euphoric effect, induces creativity and/or produces a pleasant feeling, consequences the majority of us would define as positively rewarding. Initial drug taking can also be maintained by negative reward as a drug may, for example, relieve depression and internal bypass and vagotomy surgery.

Keywords: Taste aversions
Balance of reward and aversion
Drugs of abuse

* Tel.: +1 202 885 1720; fax: +1 202 885 1023.
E-mail address: alriley@american.edu.

1 Note that Hertel and Eilkelboom [101] have recently reported that animals induced to binge eat as a consequence of being exposed to alternating periods of food deprivation and ad-lib access formed aversions to a saccharin solution made concurrently available. As Woods [1] predicted, large meals can be aversive.

2 There are likely other issues that would benefit from similar analyses. Interestingly, Bernstein and Borson [102] argued that an awareness of the aversive effects of a number of manipulations would be insightful to understanding the etiology of a variety of disorders, e.g., cancer anorexia, anorexia nervosa, eating deficits associated with depression and internal bypass and vagotomy surgery.
social anxiety or relieve boredom. Independent of whether positive or negative reward, or some combination, is involved, drug taking occurs and is initially maintained by a reward process. The picture changes quite dramatically with chronic drug use as drug taking escalates and spirals out of control [2–5]. Specifically, several factors are involved with chronic drug taking that shift the control from positive to negative reward, and this shift may occur for a number of reasons. For example, the drug’s positive rewarding effects weaken with tolerance. To maintain any positive effects under these conditions requires an increase in the amount taken or the frequency with which it is taken.

Conversely, the processes underlying tolerance produce classical withdrawal symptoms in the absence of the drug [6,7]. Behaviors such as drug taking that reduce these effects are negatively rewarded. In addition, other physiological effects, e.g., stress related [2], are recruited with chronic drug use, and further drug taking is negatively rewarded by their removal. Independent of whether one is discussing initial or escalating drug use, it is clear that the major factor driving or maintaining drug self-administration is reward and understanding the multifaceted patterns of such drug taking necessitates an understanding of reward and the changes in such reward with, and consequent to, further drug taking.

3. The affective properties of drugs

Although it would be difficult to argue that such reward principles are not involved in drug taking, with such a position one might have only a partial picture of the myriad of factors that might underlie drug use and abuse. We have argued, along with others [8–12], that drugs, like food, have both rewarding and aversive effects and it is the balance of these effects which determines the likelihood that a drug will be taken. Although the rewarding effects of drugs of abuse are well established and characterized in their ability to maintain drug self-administration [13], a variety of these drugs also produce conditioned taste aversions, an index of a drug’s aversive effects [14–16]. In the initial demonstration of taste aversion learning, animals given access to a novel taste followed by radiation subsequently avoided consumption of the taste ([17]; see also [18–21]; for a history of taste aversion learning, see [22]). Although originally demonstrated with radiation as the aversive agent, such aversions were soon reported to be conditioned by a host of compounds, almost all of which were classified as aversive by other indices of toxicity. Interestingly, and often considered paradoxically [15,23–25], a wide variety of drugs of abuse have also been reported to induce aversions, suggesting that such drugs have both rewarding and aversive effects. Such effects have often been reported at the same time in the same animal, indicating that the rewarding and aversive effects of these drugs are not simply a function of the specific parameters under which they are tested [26,27] (see also [28–30]).

Although drug taking is generally described to be a function of its rewarding effects, the results from work with drug-induced taste aversions suggest that drug taking might also be impacted by its aversive effects. We are suggesting that the overall hedonic effect of a drug, and thus its likelihood of use and abuse, is a function of the balance between these rewarding and aversive effects. This balance is illustrated for a hypothetical drug in Fig. 1 which depicts the pattern of drug self-administration with increases in drug dose. Typically, the self-administration of a drug follows an inverted U-shaped function (blue line) such that its self-administration increases with increasing doses to some asymptotic level and then decreases with further increases in the dose. The ascending part of the curve presumably reflects increases in the drug’s rewarding effects; the descending function presumably reflects saturation of receptors or an attainment of some maximal rewarding effect (green line) that requires less of the drug as dose increases [31]. Although these patterns may certainly be influenced as described, other factors, in this case the drug’s aversive effects (red line), also increase with dose. As the aversive and toxic effects of the drug increase, the balance between reward and aversive shifts and reduces drug self-administration.

4. Factors affecting the aversive effects of drugs

Traditionally, the focus on drug taking has been on reward and what factors affect it, e.g., dose of the drug, route of administration, drug history, and sex. What the current position argues is that the focus needs to be wider to include the drug’s aversive effects and the myriad of factors known to impact them. As illustrated in Table 1, the range of factors that are known to affect a drug’s aversive effects is extensive and includes experiential variables such as drug history, drug interactions, stress levels and circadian cycle and subject variables such as sex, age and strain.

5. Genetic contribution to drug toxicity

Over the past 30 years, my laboratory has examined a number of these factors, specifically, drug history, sex, drug interactions and genetic influences. It is the latter which will be examined in more detail in the present review. Investigations of the possible impact of genetic

---

Table 1

Factors affecting the aversive effects of drug.

<table>
<thead>
<tr>
<th>Deprivation level</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Sex</td>
</tr>
<tr>
<td>Social context</td>
<td>Housing condition</td>
</tr>
<tr>
<td>Physical dependence</td>
<td>Ambient temperature</td>
</tr>
<tr>
<td>Body weight</td>
<td>Drug route</td>
</tr>
<tr>
<td>Drug dose</td>
<td>Drug duration</td>
</tr>
<tr>
<td>Drug history</td>
<td>Spacing of drug</td>
</tr>
<tr>
<td>Strain of animal</td>
<td>Hormonal levels</td>
</tr>
</tbody>
</table>
influences on the aversive effects of drugs include drug-induced taste aversion learning in transgenic mice and quantitative trait loci mapping relative to aversions and drug intake (for reviews, see [10,32]).

On area that has received considerable attention in aversion learning is the analysis of inbred rat strains. Such strains are derived from full-sibling matings for at least 20 consecutive generations, as opposed to selectively bred strains in which the constituent members are unrelated [33]. Two of the most popular strains in such investigations are the C57BL/6J (C57) and DBA/2J (DBA) mice in which these strains have been examined primarily for their ability to acquire alcohol-induced taste aversions [34–36]. In these assessments, the DBA mice acquire alcohol-induced aversions at lower doses and display more robust alcohol-induced aversions than the C57 strain. Cunningham and his colleagues [32] have argued that these differences in aversive reactions to alcohol are likely responsible for their differences in oral alcohol self-administration where C57 mice consume more alcohol than DBA mice [37]. In support of this position, Broadbent et al. [38] examined alcohol-induced taste aversions and oral self-administration of alcohol in 15 inbred mouse strains and reported a significant inverse correlation between these two behaviors (see also [36,39] for related comparisons). This analysis suggests that the overall self-administration of alcohol in these inbred strains is highly impacted by the perceived aversiveness of alcohol where alcohol consumption is limited by such aversive reactions.

My laboratory has done parallel work with the inbred Fischer (F344) and Lewis (LEW) rat strains that are genetically divergent and whose behavioral differences have been well documented (for reviews, see [10,40–42]). One area in which these animals differ dramatically is in their intake of drugs. With few exceptions, the LEW animals are reported to self-administer more cocaine, morphine and alcohol than the F344 strains [43–46]. Further, the LEW rats display greater preferences for environments associated with morphine, i.e., a conditioned place preference, than the F344 strain and do so at lower doses [47–49]. Because of these differences, these strains have been used as animal models to examine the role of specific genotypes in drug-taking behavior, a use supported by the fact that they also differ in the biochemical and neurophysiological substrates thought to mediate drug reward. For example, Nestler and his colleagues have examined brain stem systems involved in morphine withdrawal and the role of mesolimbic activity in the rewarding properties of drugs of abuse [48,50,51] and reported clear and distinct strain differences in the biochemical and neurophysiological activity in these brain areas. Such differences argued that these strains have different responses to the rewarding effects of drugs, and thereby different likelihoods of taking these drugs, at the outset (Fig. 2).

6. Comparisons of the F344 and Lew inbred rat strains

Given the position that drug use is a function of the balance between the drug’s rewarding and aversive effects, we have extended these analyses to assess the aversive effects of drugs in the F344 and LEW strains, specifically if, and to what degree, the two strains might differ in the acquisition of taste aversions induced by drugs known to be rewarding and for which the two strains differ in their rewarding effects (for reviews, see [10,52,53]). The present review focuses on the opiates.

In one of the first assessments, we used morphine sulfate as the aversive agent. Morphine sulfate was chosen for several reasons. First, it is a compound that supports self-administration and conditions place preferences in both outbred rats and in the LEW and F344 strains. Interestingly, both the rate and amount of morphine self-administration is greater in the LEW rat as compared to the F344 strain [47,48]. Secondly, morphine readily conditions taste aversions in outbred animals, so the procedures for inducing such aversions have been well characterized [29,54].

In this study [55], male F344 and LEW rats were allowed 20-min access to a novel saccharin solution to drink followed immediately by an intraperitoneal (ip) injection of vehicle, 18, 32 or 50 mg/kg morphine. All subjects were then given 3 water-recovery days in which they were allowed 20-min access to water with no injections. This cycle was repeated three times at which point subjects were given saccharin in a final aversion test. Control subjects from each strain readily consumed the saccharin solution, increasing its consumption over repeated exposures with the dissipation of neophobia to the novel saccharin [56]. Morphine-injected F344 rats displayed robust aversions to the morphine-associated saccharin, decreasing consumption over the repeated conditioning trials. Interestingly, these aversions were not dose-dependent in that all doses of morphine induced aversions of comparable levels in F344 rats.

Conversely, no dose of morphine induced aversions in the LEW strain. Paralleling the conclusions of Cunningham et al. [32] relative to C57 and DBA mouse strains, we argued that the differences between the F344 and LEW strains in morphine self-administration (LEW>F344) may be due to the fact that morphine is aversive in the F344 strain instead of, or in addition to, any differences in morphine’s rewarding effects.

![Fig. 2. Saccharin consumption over repeated conditioning trials in which rats from the F344 and LEW strains were given pairings of saccharin and vehicle or varying doses of morphine (10.0, 32.0 or 56.0 mg/kg). *Indicates that F344 rats drank significantly less saccharin than LEW rats (p<0.05). Reprinted from Lancellotti et al. [57] with permission from Elsevier.](image-url)
7. The aversive effects of drugs: caveats

Instead of focusing solely on explanations regarding reward when discussing different patterns of drug intake, this interpretation argues that other factors may be involved in modulating this behavior, i.e., the possible aversiveness of the drug itself. Although consistent with our earlier stated position of self-administration being a function of the balance between the drug’s aversive and rewarding effects, this conclusion is based on one specific interpretation of the results from the Lancellotti et al. [55] study and that is that the differences in the acquisition of the aversion are a function of differences in morphine’s aversive effects. This is an assumption and one that has been nicely addressed by others who have examined taste aversion learning and the interpretations of the changes that one might see with various manipulations, e.g., transgenic mutations, lesions [10,32]. As described, in this preparation animals are given a novel solution to drink and then injected with one of a number of compounds. The aversiveness of the compound is indexed by the subsequent decrease in consumption of the solution due to its association with the drug’s aversive effects. A re-presentation of Table 1 with inclusion of additional factors and a change of title illustrates that taste aversion learning can be affected by many variables that may or may not impact the aversiveness of the drug, e.g., CS intensity, CS-US delay, number of conditioning trials.

Simply interpreting any differences in aversion learning between strains as due to differences or changes in aversiveness may be incorrect. As noted, such concerns were raised by Cunningham et al. [32] in an analysis of genetic differences in aversion learning that focused primarily on inbred and selectively bred mouse strains. As he and his colleagues noted, differences in aversion learning may reflect a variety of factors, many of which directly impact learning and memory and not necessarily the aversive effects of a drug (see Figure 19.2, page 413). In fact, sensitivity to the aversive effects of the specific drug being assayed is only one entry in their table, and only a few entries in ours, see Table 2. To make conclusions about drug aversiveness, these other factors must be experimentally removed as possible bases for any differences reported (see also [57]).

Evidence that the strain differences we report with morphine are not due to some of these factors known to affect taste aversion learning but instead to drug aversiveness comes from other work that we have done with the F344 and LEW strain [58]. Specifically, we have examined the ability of cocaine to induce taste aversions in the F344 and LEW rat strains under conditions similar to that described for morphine. As with our work with morphine, both groups of subjects injected with vehicle consumed saccharin on the initial exposure and maintained this high level throughout conditioning. Interestingly, and unlike with morphine, LEW subjects displayed significantly stronger cocaine-induced aversions than the F344 rats at the two highest doses of cocaine (see Fig. 3), suggesting that cocaine is more aversive for this strain, a conclusion opposite to that we made with morphine (see also [59,60]; though see [49]).

Together, the data from the work with morphine [55] and cocaine [58] argue that differences between the F344 and LEW strains are not a function of strain differences in a variety of factors that could be affecting aversion learning (see [32]). In each assessment, the same conditioning and testing procedures were used. If the differences with morphine were a function of these general issues that affect learning and memory, the differences with cocaine (LEW→F344) should be in the same direction as those with morphine (F344→LEW) and not opposite. Some factors’ other than those affecting basic learning and memory must be at play. We have argued it is differential sensitivity of the two strains to the aversive effects of morphine and cocaine.

8. The nature of aversive?

Stating this is one thing. Documenting its basis is yet another issue. Part of the problem in such documenting is the lack of consensus as to what it is about a drug that makes it successful in inducing an aversion. The debate about the nature of the aversive effects of drugs is longstanding and has generated many hypotheses. Beginning with the work of Garcia and his colleagues [17], it was speculated that aversions were mediated by malaise produced by the aversion-inducing agent. Problems arose, however, when compounds with known toxicity failed to induce aversions (for a review, see [16]) and drugs that were generally thought to be rewarding were shown to be quite effective as aversion-inducing agents [14,61]. These extensions forced new hypotheses such as drug novelty, stress and disruptions in homeostasis as possible bases for aversion learning (for excellent reviews, see [15,23,25,62–64]; see also [65,66]). Each hypothesis has strengths and weaknesses, but after more than 50 years there is still no agreement.

Despite this lack of consensus, we have begun this process by examining some specifics with morphine and other opiates. In this work, we have argued that morphine likely induces taste aversions by its activity at the mu receptor because LEW and F344 rats do not differ in aversions induced by the kappa agonist U50,488H and the delta agonist SNC80 [67]. Further, its actions at the mu receptor are likely central because LEW and F344 rats do not differ in aversions induced by the peripherally acting mu opiate agonist loperamide [52]. Stating that morphine is acting centrally at mu receptors to induce its aversive effects, however, does not indicate what brain areas might be involved.

We have begun examining this by measuring the effects of morphine and cocaine on c-Fos activity [68] (for reviews on c-Fos and its activity in taste processing and aversion learning, see [69–74]) in brain areas implicated in aversion learning [57,75,76]. Interestingly, we found that both morphine and cocaine at doses and by routes of administration that are effective in inducing a taste aversion resulted in c-Fos activity in these brain areas. More importantly, these brain areas were differentially activated in the LEW and F344 strains. That is, when morphine was administered to LEW and F344 rats, it produced more c-Fos activity in aversion-related areas in the F344 rat than the LEW strain, an effect consistent with the fact that F344 rats

---

4 Since our initial reports with morphine and cocaine, we have extended our analysis of aversion learning with the LEW and F344 strain to a host of other drugs including alcohol [103], nicotine [104] and heroin [67]. In each case, the F344 strain displays greater taste aversions than the LEW rats. Interestingly, there are no strain differences for aversions induced by LiCl [105], the opiate agonists US04888H and SNC-80 [106] and naloxone-precipitated withdrawal [107].

5 This is not to suggest that these are the only areas implicated in aversion learning. In fact, a number of specific brain nuclei, including the basolateral and central amygdala and the insular cortex, appear to play important roles in taste processing as well as associative function (for reviews, see [57,89,108]).
display greater morphine-induced taste aversions than the LEW strain (see Fig. 4 (left panel)). Conversely, when cocaine was administered, it produced greater c-Fos activity in aversion-related areas in the LEW rat than the F344 strain, again an effect consistent with the fact that LEW rats display greater cocaine-induced taste aversions than the F344 strain (see Fig. 4 (right panel)). When c-Fos activity was examined in brain areas associated with motor activation, e.g., caudate nucleus, c-Fos activity was activated by cocaine only and comparably in LEW and F344 rats. Interestingly, cocaine and morphine induced comparable levels of c-Fos activation in brain reward areas, e.g., nucleus accumbens shell [68].

9. Environmental modulation of F344/LEW phenotypes

The basic position that drug use and abuse might be a function of the balance of the aversive and rewarding effects of a drug is one that we have argued should be considered when discussing general drug use. 

---

**Fig. 3.** Saccharin consumption over repeated conditioning trials in which rats from the F344 and LEW strains were given pairings of saccharin and vehicle or varying doses of cocaine (18.0, 32.0 or 50.0 mg/kg). *Indicates that LEW rats drank significantly less saccharin than F344 rats (p < 0.05). Reprinted from Glowa et al. [60] with permission from Springer-Verlag.

**Fig. 4.** c-Fos activation in the PBN and LPN (left panel) and iNTS, cTS and AP (right panel) in the F344 and LEW rat strains following injections of saline, morphine or cocaine. Left panel: *significant difference from saline (p < 0.05); **significant difference from saline (p < 0.01); ##significant strain difference (p < 0.01). Right panel: *significant difference from saline (p < 0.05); **significant difference from saline (p < 0.01); *significant strain difference (p < 0.05); **significant strain difference (p < 0.01). Reprinted from Grabus et al. [70] with permission from Elsevier.
vulnerability [10,52,53]. The current focus on the F344 and LEW strains was chosen just to illustrate one of many factors that might impact a drug’s aversive effects and thereby its abuse vulnerability. As noted, the specific focus on these two strains was on the possible role of genotype in this analysis.

The fact that the F344 and LEW strains display differential sensitivity to the aversive and rewarding effects of a drug is clear. That this response is mediated or constrained by specific genotypes is less clear. Generations of brother/sister matings have certainly yielded homogenous (within) and distinct (between) genotypes. However, the specific phenotypic expression of aversion and reward can be clearly impacted by a host of environmental challenges. In one of our first assessments of this, we examined the effects of stress on the acquisition of morphine-induced place preferences in the F344 and LEW strains [47]. In this procedure, we paired the non-preferred side of a conditioned place preference chamber with various doses of morphine in rats of both strains (for reviews of place preference conditioning, see [77,78]). Some groups of each strain were injected with the benzodiazepine inverse agonist DCDM and placed in restraint tubes prior to morphine place preference conditioning; other groups of each strain were injected chronically with the nonpeptide CRH Type 1 antagonist antalarmin prior to conditioning. Thus, animals were either stressed or had stress reduced, respectively, and the effects of these stress manipulations on conditioning were assessed. Such manipulations in outbred rats have been reported to affect both place preference conditioning and HPA activity [79–82]. In non-treated subjects, clear dose–response place preferences were conditioned with morphine which were strain dependent (LEW>F344). The effects of stress induction and reduction were interesting in that stress induction reduced morphine-induced CPP in the LEW rats with no effect in the F344, and stress reduction increased morphine-induced place preferences in the F344 strain and decreased CPP in the LEW strain (see Fig. 5).

The issue here is less the specific direction of the effects of these stress manipulations than the fact that the aforementioned differences between the rewarding effects of morphine in these two genetically divergent strains can clearly be modulated by environmental challenges, in this case, stress. We have recently run related assessments in which we examined stress and morphine-induced taste aversions in F344 and LEW rats. In this assessment [83], we examined the effects of diurnal cyclicity on the acquisition and expression of morphine-induced taste aversions. The two strains have been reported to differ significantly in their circadian cycles of corticosterone [84,85], and our position was that if morphine-induced

![Graph](image-url)

**Fig. 5.** Mean difference in time (s) spent on the drug-paired side between the preconditioning and postconditioning tests for Sprague–Dawley (D), LEW (L) and F344 (F) animals exposed to either vehicle/home cage (V) or DCCM/restraint stress (D) (left panel) or vehicle (V) or antalarmin (A) (right panel) and conditioned with 1, 4 or 10 mg/kg morphine. Left panel: *indicates that groups pretreated with antalarmin (A) differed from groups pretreated with vehicle (V) (all p’s<0.05). Right panel: *indicates that animals pretreated with DCCM (D) and restraint stress differed from animals pretreated with vehicle (V) (all p’s<0.05). Reprinted from Grakalic et al. [49] with permission from Springer-Verlag.
taste aversions were mediated or impacted by stress in these animals then their different corticosterone cycles would likely affect the acquisition of such aversions.

Specifically, different groups of F344 and LEW rats were given a novel saccharin solution to drink and injected ip with varying doses of morphine. The procedural difference from our prior work was that we did this conditioning at different times of the animals’ day–night cycle. When we injected 3.2 mg/kg morphine during the day, we replicated the F344/LEW differences in morphine-induced taste aversion learning, i.e., F344 rats displayed significantly stronger aversions than LEW rats (see Fig. 6). However, when we conditioned with this same dose at night, all groups showed an aversion with no differences among groups (F344 = LEW = SD). Thus, the clear strain differences we reported with morphine, differences we use to talk of genetic differences between the two strains, can be impacted and in this case eliminated by changes in the training and testing procedures. That the effect of circadian cyclicity was dependent upon the dose of morphine further illustrates the complex nature of the effects of genotype on behavior and their modulation by environmental factors.

We have also examined the impact of maternal behavior on the genotypic differences reported in morphine-induced taste aversion learning between the F344 and LEW strains [86]. Specifically, at birth F344 pups were cross-fostered to LEW dams and LEW pups were cross-fostered to F344 dams. Control LEW and F344 pups were in-fostered to dams of their own strain. When all pups were 90 days of age, they were run through our typical morphine-induced taste aversion procedure. As expected from our earlier work [55], in-fostered F344 rats displayed robust aversions to the morphine-paired saccharin solution while in-fostered LEW pups did not avoid the morphine-associated saccharin (see Fig. 7). An interesting finding was produced in the cross-fostered pups. Specifically, cross-fostered F344 subjects, i.e., those raised by a LEW dam, displayed weaker taste aversions relative to the in-fostered F344 rats. Further, cross-fostered LEW pups reared by F344 dams now displayed taste aversions. The two cross-fostered groups displayed aversions intermediate to their in-fostered pairs.

Fig. 6. Mean (±SEM) saccharin consumption on the taste aversion test expressed as a percentage of Trial 1 consumption ([saccharin consumption during test/saccharin consumption during trial 1] *100) for Sprague–Dawley (SD), Lewis (LEW) and Fischer (F344) rats trained during the light phase (left side of each panel) or dark phase (right side of each panel) with 3.2 mg/kg morphine (Panel A), 10.0 mg/kg morphine (Panel B), or saline (Panel C). *indicates that SD rats drank significantly more than LEW and F344 rats (p<0.05). #indicates that F344 rats drank less than SD and LEW rats (p<0.05). Reprinted from Gomez-Serrano et al. [85] with permission from Elsevier.
These results parallel other work from our lab examining the effects of cross-fostering in that with few exceptions, e.g., carrageenan-induced inflammation [87], the phenotypic displays that are characteristic of the LEW and F344 strains can be modulated by which strain raises the LEW and F344 pups [87, 88]. Further, this effect of modulation by cross-fostering is not limited to morphine-induced taste aversions in that cross-fostering effects have also been produced when cocaine is the aversion-inducing agent [60, 89]. Interestingly, the effects of cross-fostering are only evident in the F344 strain for cocaine, i.e., the effects are asymmetrical, an effect we have also seen with several other behavioral indices, e.g., open-field activity [88]. The basis for the effects of cross-fostering on the display of aversion learning is not known, but the fact that these two strains display dramatically different maternal behavior with LEW more elaborate than F344 [87] suggests that epigenetic factors along the lines reported by Meaney and his colleagues in their analysis of the relationship between maternal behavior and stress [90–92] may modulate and/or mediate the behavioral effects reported with aversion learning.

10. Balance of reward and aversion: caveats

The purpose of the present overview is to discuss the possible role of the aversive effects of drugs to their use and abuse. This overview is not meant in any way to challenge the role of a drug's rewarding effects in such vulnerability, but only to argue that an analysis of the multifaceted effects of a drug may give a more complete understanding of the various factors important in drug-taking behavior and thus greater insights into its etiology and treatment [12]. In this context, the current overview is similar to that of Woods [1] who argued that an awareness of both the aversive and rewarding effects of food intake gives a better and more complete understanding of eating and its regulation.

While we and others have argued the importance of the examination of both factors, there are some important caveats to consider. First, and as noted above, both factors must be concurrently examined, not only to document the role each may play in drug intake but also to see their relative contributions and their possible interaction. Second, although we have used the genetics of drug taking to illustrate this point, it is important to note that this is only one factor from a list of many (see Table 1) known to impact the aversive effects of a drug and thereby the vulnerability to drug taking. It is only recently that such factors have been examined in relation to aversion learning and their contribution to drug use been discussed, e.g., see [93–98] for discussions of adolescent aversion learning.

In addition to focusing on only one factor in the present review, only a single drug was discussed, i.e., morphine. Morphine was chosen due to the fact that much is known about its rewarding effects in general and in the F344 and LEW animal model. Other drugs, e.g., alcohol, nicotine, cocaine and caffeine, have also been analyzed in relation to their ability to induce aversions in the F344 and LEW rat strains, and with few exceptions, it is the F344 strain which shows the greatest drug-induced taste aversions, indicative of a greater sensitivity to the aversive effects of these drugs. There is an exception, however, and this exception may be meaningful in the discussion of the balance of reward and aversion in drug intake. As noted earlier, this exception is cocaine. First, LEW rats self-administer cocaine at a higher rate than do F344 rats, suggesting a greater sensitivity to cocaine's rewarding effects in the LEW strain. At the same time, the LEW strain displays stronger cocaine-induced taste aversions (see above), suggesting that the LEW strain is also more sensitive to cocaine's aversive effects. The issue becomes how the LEW strain displays greater self-administration of cocaine than the F344 strain despite the drug being more aversive.

When one talks about the balance between aversion and reward, one might expect that there is relationship between the two, i.e., if the rewarding effect is high, the aversive effect might be expected to be low (and vice versa). This is not necessarily the case. It may be, yet it is not necessary. In fact, when the specific relationship between reward and aversion has been examined in individual subjects [99], the effects are unrelated, i.e., a strong aversion does not predict a weak place preference (and vice versa). Similar relationships, or the lack thereof, have been reported in serial assessments [100] and cross procedure comparisons [38]. What is important is the relative balance of the two. A drug can be both rewarding and aversive. It is their balance that determines the likelihood of its self-administration. As described, cocaine is both rewarding and aversive in the LEW strain, and given that the drug is readily self-administered suggests that this balance leans more to drug reward, i.e., its rewarding effects are stronger than its aversive effects. When a drug is rewarding with no aversive effects, the story seems simple; it become complicated when the two affective properties are not inversely related. However, even under these conditions one can predict abuse liability if the relative contribution of the factors is known.

11. Conclusions

The purpose of this short review is not to be exhaustive in the analysis of factors that may impact the aversive effects of drugs. Instead, it is to illustrate that this affective component of drugs may be important to understanding drug-taking behavior. It is similar to what Woods attempted to highlight in his original paper in 1991. Like the regulation of food intake, the regulation of drug taking is multifaceted. Recognition of the multiple factors involved in this regulation is essential to developing models aimed at understanding its etiology and treatment.

Acknowledgements

The research from this lab on which this review was based was supported by grants from the MacArthur and Mellon Foundations. The author would like to thank Jennifer L. Cobuzzi, Jennifer A. Rinker and Katherine M. Serafine for technical support. Requests for reprints should be sent to Anthony L. Riley, Psychopharmacology Laboratory, Department of Psychology, American University, Washington, DC 20016, USA.

References


Fig. 7. Saccharin consumption over repeated conditioning trials in which female rats from the F344 and LEW strains were given pairings of saccharin and vehicle or morphine (32 mg/kg) (from Gomez-Serrano & Riley [88]). Group F/L refers to F344 pups reared by LEW dams and L/F refers to LEW pups reared by F344 dams. Groups F/F and L/L refer to F344 and LEW pups reared by unrelated dams of their own strain. Trials 2 and 3: * indicates that Group FF drank significantly less than Groups LL, LF and FL (all p’s < 0.05). Trials 4 and Final Test: * indicates that Group FF drank significantly more than Groups LF, FL and FF (all p’s < 0.05).


[28] Beiter-Johnson D, Guitart X, Nestler EJ. Dopaminergic brain reward regions of the Fischer and Lewis rat strains: effects on ethanol consumption, ethanol and cocaine self-administration, and sensitization of ethano.


[38] Parker LA. Taste avoidance and taste aversion: evidence for two different processes. Learn Behav 2003;31:165–72.

[39] Parker LA, Limebeer CL, Rana SA. Conditioned disgust, but not conditioned taste avoidance, may reflect conditioned nausea in rats. In: Reilly S, Schachtman TR,


