Assessment of the aversive effects of peripheral mu opioid receptor agonism in Fischer 344 and Lewis rats

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ARTICLE INFO

Article history:
Received 9 October 2011
Received in revised form 22 December 2011
Accepted 3 January 2012
Available online 11 January 2012

Keywords:
F344
LEW
Morphine
Loperamide
CTA
Drug abuse

ABSTRACT

The Fischer 344 (F344) and Lewis (LEW) inbred rat strains differ on a host of biochemical, neuroanatomical, immunological and behavioral endpoints. One behavioral difference of interest is their differential reactivity to the aversive effects of morphine as indexed by the conditioned taste aversion preparation (aversions acquired by F344 rats are significantly greater than those acquired by the LEW strain). This differential effect appears to be specific to opioids that work primarily on the mu opioid receptor. Given that morphine works systemically, it is unknown whether these differential effects in F344 and LEW animals are centrally or peripherally mediated. To address this issue, the present study investigated the ability of the peripherally acting mu preferring opioid agonist loperamide to induce differential taste aversions in F344 and LEW animals. Both F344 and LEW animals acquired dose-dependent taste aversions to the loperamide-associated solution with no difference between them. Additionally, control animals initially injected with vehicle during aversion training with loperamide and subsequently conditioned with morphine displayed the typical aversive profile to morphine (F344 > LEW). Although the basis for the present data is unknown, their relation to morphine-induced taste aversions and the role of the interaction of stimulus effects of drugs that produce differential abuse liability were discussed.

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1. Introduction

Previous research has demonstrated that the Fischer 344 (F344) and Lewis (LEW) inbred rat strains differ on a host of biochemical, neuroanatomical, immunological and behavioral endpoints. Initial assessments with these strains focused on their differential stress reactivity (Sternberg et al., 1992) and responsivity to immunological challenges (Sun et al., 1999). More recently, the F344 and LEW strains have been investigated relative to their differential reactivity to a variety of drugs of abuse (for a review of this issue, see Kosten and Ambrosio, 2002; Riley et al., 2009; Riley, 2011). Although the initial work with these animals assessed the rewarding effects of such drugs, subsequent investigations analyzed their differential responsivity to the drugs' aversive properties. In one of the first assessments of differences in the aversive effects of drugs in these strains, Lancellotti et al. (2001) reported that the F344 strain rapidly acquired a robust taste aversion to a morphine-associated solution. LEW rats, on the other hand, failed to acquire an aversion even at high doses and with repeated conditioning trials (for subsequent assessments, see Gomez-Serrano et al., 2009; for a review, see Riley, 2011). This strain difference in morphine-induced taste aversion learning was not likely due to a general difference in learning or in the processing of gustatory stimuli between the strains, in that LEW animals display stronger cocaine-induced taste aversions at low and intermediate doses than their F344 counterparts (Glowa et al., 1994), an effect opposite to that seen with morphine (Lancellotti et al., 2001). Instead, it is more likely that the differential acquisition of taste aversions in response to morphine administration in the F344 and LEW animals is a consequence of their differential sensitivity to its aversive effects (for similar assessments with other compounds, see Desko et al., 2011; Foynes and Riley, 2004; Glowa et al., 1994; Pescatore et al., 2005; Roma et al., 2006; Vishwanath et al., 2011).

In an attempt to isolate the specific opioid receptor on which morphine might be working to induce its behavioral effects within the aversion preparation, Davis et al. (2009) examined the ability of three opiate agonists with differential binding profiles, e.g., SNC80 (relative selectivity for the delta opioid receptor subtype), (−)-U50,488H (relative selectivity for the kappa opioid receptor subtype) and heroin (affinity for all three receptor subtypes with preference for the mu opioid receptor) to induce aversions in the F344 and LEW rat strains. Although all three drugs induced aversions, those induced by heroin were significantly stronger than those induced by...
SNC80 and (−)-U50,488H. Further, the only drug for which F344 and LEW animals differed was heroin, wherein F344 rats acquired significantly stronger aversions than the LEW strain, an effect consistent with the prior work with morphine (Lancellotti et al., 2001). Although both heroin and morphine act non-specifically on all three receptor subtypes, the differential aversions with these drugs coupled with the failure of either the delta or kappa agonists to induce strain-dependent aversions support the position that morphine’s aversive effects are likely mediated by its action at the mu opioid receptor (alone or in combination with other opioid receptor subtypes; see Davis et al., 2009) and suggest that differential action at this site mediates the observed strain differences with morphine.

Although these results suggest that the mu opioid receptor is involved in the behavioral differences between the F344 and LEW strains in the acquisition of morphine-induced taste aversions, it is not known whether this effect is centrally or peripherally mediated, especially given that systemically administered morphine (and heroin) act at both sites (Davis et al., 2009). Interestingly, there is relatively little work investigating central vs. peripheral mediation of taste aversion learning, and for the drugs that have been investigated, the mechanism of action appears drug specific. For example, for THC (Amit et al., 1977) and nicotine (Kumar et al., 1983; Shoabi and Stolerman, 1995), taste aversions appear to be mediated centrally; for ethanol (Crankshaw et al., 2003), lithium chloride (LiCl; Smith, 1980), acetaldehyde (Brown et al., 1978), fenfluramine (Lorden et al., 1980), and fluoxetine (Lorden and Nunn, 1982), aversions appear to be mediated via peripheral mechanisms. Interestingly, the work with morphine in outbred rats is quite consistent on the peripheral mediation of such aversions. For example, morphine administered icv (Stapleton et al., 1979) and direct infusions of morphine into either the hippocampus or caudate fail to induce taste aversions (see Amit et al., 1977). In more direct assessments of central vs. peripheral mediation, Bechara et al. (1987) reported that methylnaltrexone, an opioid antagonist that does not cross the blood brain barrier, blocked the acquisition of both morphine-induced place and taste aversions when morphine was given intraperitoneally (for a related report, see also Martin et al., 1988). Morphine-induced taste aversions are also blocked by the destruction of peripheral opioid receptors with capsaicin. In a related report (see Bechara and van der Kooy, 1985), vagotomy blocked the acquisition of both place and taste aversions induced by systemic morphine, indicating that peripherally-located opioid receptors are a necessary component of the aversive response to morphine administration.

If morphine’s effects are mediated peripherally, it would be expected that peripherally acting, mu agonists would induce aversions. Further, it would be expected that if the differential effects of morphine in the F344 and LEW strains are mediated by these receptors, such drugs would differentially induce aversions in the two strains (F344 > LEW). These predictions were tested in the following experiment in which rats from the F344 and LEW strains were given a novel saccharin solution to drink and then injected with vehicle or various doses of the peripherally acting, mu agonist loperamide (Autowers et al., 1983; DeHaven-Hudkins et al., 1999; Giagnoni et al., 1982; Nozaki-Taguchi and Yaksh, 1999; Wüster and Herz, 1978). Following this treatment, animals injected with vehicle during conditioning were subsequently given saccharin followed by morphine to confirm the typical strain difference (where F344 subjects display greater morphine-induced aversions than the LEW strain). Given that drug use and abuse are thought to be a function of the balance between the rewarding and aversive effects of a compound (Riley, 2011; Wise et al., 1976), understanding the factors that impact both these properties may lead to a better understanding of the vulnerability to drug use and abuse. Genetic mediation of these affective properties is one such factor, and the F344 and LEW animals provide a useful model to investigate genetic contributions to the relative balance between the aversive and rewarding effects of drugs.

2. Material and methods

2.1. Subjects and apparatus

Subjects were 134 experimentally naïve LEW (n = 67) and F344 (n = 67) male rats (purchased from Harlan Sprague Dawley, Indianapolis, Indiana). Subjects were run in two replicates (n = 33 per strain, Replicate 1; n = 34 per strain, Replicate 2), and all groups for each strain were represented in each replicate. Given that there were no differences between replicates in terms of the ability of loperamide [t (132) = 1.092, p = 0.277] or morphine [t (132) = 0.178, p = 0.859] to induce taste aversions, data from the two replicates were pooled for analysis and presentation. At the start of the experiment, animals were approximately 90 days of age and weighed approximately 300 g (LEW) and 250 g (F344). Animals were housed in individual wire-mesh cages and maintained on a 12:12 h light/dark cycle (lights on at 0800 h) and at an ambient temperature of 23 °C for the duration of the experiment. Rat chow (Harlan Sprague–Dawley, Indianapolis, Indiana) was provided ad libitum. All fluids were presented in 50-ml Nalgene tubes affixed to the front of the cages. Procedures recommended by the Guide for the Care and Use of Laboratory Animals (National Research Council, 1996) and the Institutional Animal Care and Use Committee at American University were followed at all times.

2.2. Drugs and solutions

Loperamide hydrochloride (Sigma) was dissolved in 10% dimethylsulfoxide (DMSO) and saline (5 mg/ml), and morphine sulfate (generously supplied by the National Institute on Drug Abuse) was dissolved in saline (5 mg/ml). All drug doses were expressed as the salt form and were administered subcutaneously (sc); doses used for loperamide were selected from dose ranges previously reported (see Medvedev et al., 1998; Shinoda et al., 2007). Sodium saccharin (Sigma) was prepared as a 1 g/l solution in tap water.

2.3. Procedure

2.3.1. Phase I: Habituation

After 23 2/3-h water deprivation, rats were given 20-min access to water, beginning at 1000 h. This procedure was repeated daily until all rats were approaching and drinking from the tube within 2 s of its presentation. Once this criterion was reached, aversion conditioning began.

2.3.2. Phase II: Loperamide conditioning

On Day 1 of this phase, animals received 20-min access to a novel saccharin solution during their daily fluid-access period. Immediately following saccharin access, rats within each strain were assigned to one of four groups such that consumption was comparable across groups and injected with one of four doses of loperamide. Specifically, subjects were injected with 0 mg/kg (vehicle; n = 16 per strain), 10 mg/kg (n = 17 per strain), 18 mg/kg (n = 17 per strain) or 32 mg/kg (n = 17 per strain) of loperamide, yielding Groups F0, F10, F18, F32, L0, L10, L18 and L32. For each group, the letter denotes the strain of the animal and the number denotes the dose of loperamide administered. On Days 2–4 of this phase, all animals received 20-min access to water during the fluid-access period. No injections were given following this access. This cycle of one conditioning day followed by 3 water-recovery days was repeated for three full cycles. The fourth conditioning trial was treated as a one-bottle test of the aversion to saccharin.

2.3.3. Phase III: Morphine conditioning

Following 3 water-recovery days, animals injected with vehicle during Phase II, i.e., Groups F0 and L0, were given 20-min access to...
saccharin. Immediately following saccharin access, rats within each strain were assigned to one of two groups such that consumption was comparable between groups and injected with either vehicle or morphine (5 mg/kg), yielding Groups FV-V, FV-M, LV-V and LV-M (n’s = 8 per group). For each group, the first two letters denote the strain of the animal and the treatment during Phase II; the third letter denotes the injection given following saccharin in Phase III. On the 3 days following morphine conditioning, all subjects were given 20-min access to water. No injections followed these water-recovery sessions. This procedure of conditioning followed by 3 water-recovery days was repeated for four additional cycles. On the day following the last cycle of Phase III, all subjects were given 20-min access to saccharin in a one-bottle test.

2.4. Statistical analysis

An Independent Sample’s t-test revealed that LEW and F344 rats differed in consumption on the initial saccharin exposure at the outset of Phase II (t(132) = 6.692, p < 0.001). Consequently, each strain was evaluated independently. For each strain, differences in mean saccharin consumption during loperamide conditioning (Phase II) was analyzed using a 4 × 4 mixed analysis of variance (ANOVA) with a between-subjects factor of Dose (0, 10, 18, 32 mg/kg) and a within-subjects factor of Trials (1–4). Given that saccharin consumption at the outset of Phase III did not differ between F344 and LEW animals (t(132) = 0.636, p = 0.528), saccharin consumption during morphine treatment (Phase III) was analyzed using a 2 × 2 × 5 mixed ANOVA with between-subjects factors of Strain (F344; LEW) and Drug (VEH; MOR) and a within-subjects factor of Trials (1–5). Where appropriate, one-way ANOVAs followed by Tukey’s post-hoc tests were performed on each trial to analyze differences in saccharin consumption between groups; significance was assessed at α ≤ 0.05.

3. Results

3.1. Phase II: Loperamide conditioning

F344: The Trial × Dose mixed ANOVA on mean saccharin consumption over conditioning (Phase II) revealed significant effects of Trial [F(3,189) = 163.219, p < 0.001] and Dose [F(3,63) = 97.907, p < 0.001] as well as a significant Trial × Dose interaction [F(9,189) = 32.968, p < 0.001]. In relation to this interaction, a subsequent one-way ANOVA revealed significant differences between doses of loperamide on Trials 2, 3 and 4 (all p’s < 0.001). Tukey’s post-hoc analysis indicated that on Trials 2, 3 and 4 LEW animals injected with 10, 18 and 32 mg/kg loperamide consumed significantly less saccharin than LEW animals injected with vehicle (p’s < 0.001). Further, on Trial 3 LEW animals injected with 32 mg/kg loperamide consumed significantly less saccharin than LEW animals injected with 10 mg/kg loperamide (p < 0.05; see Fig. 1, Panel B). A Strain × Dose univariate ANOVA on saccharin consumption during the one-bottle test (Trial 4) of Phase II revealed a significant main effect of Dose [F(3,126) = 269.794, p < 0.001] and no other significant effects or interactions. Tukey’s post-hoc analysis revealed that animals injected with 10, 18 and 32 mg/kg loperamide consumed significantly less saccharin than vehicle-injected animals (p’s < 0.001) and animals injected with 32 mg/kg loperamide consumed significantly less saccharin than animals injected with 10 mg/kg loperamide (p < 0.05). There was no significant effect of Strain (alone or in combination with Dose).

3.2. Phase III: Morphine conditioning

The Strain × Drug × Trial mixed ANOVA on mean saccharin consumption over morphine conditioning (Phase III) revealed significant main effects of Trial [F(4,112) = 8.618, p < 0.001], Strain [F(1,28) = 27.816, p < 0.001] and Drug [F(1,28) = 94.208, p < 0.001], as well as significant Trial × Strain [F(4,112) = 10.311, p < 0.001], Trial × Drug [F(4,112) = 51.493, p < 0.001], Strain × Drug [F(1,28) = 32.35, p < 0.001] and Trial × Strain × Drug [F(4,112) = 18.689, p < 0.001] interactions. In relation to this final interaction, a subsequent one-way ANOVA indicated significant group differences on Trials 2–5 (all p’s < 0.001). Tukey’s post hoc analysis revealed that on Trials 2–5 F344 animals injected with morphine consumed significantly less saccharin than F344 animals injected with vehicle (all p’s < 0.001; see Fig. 2, Panel A), indicative of the formation of a robust taste aversion to morphine in F344 animals. LEW animals injected with morphine consumed significantly less saccharin than LEW animals injected with vehicle only on Trials 4 and 5 (both p’s < 0.05; see Fig. 2, Panel B). On Trials 2–5, F344 animals injected with morphine consumed significantly less saccharin than comparably treated LEW animals (all p’s < 0.005),
indicative of strain differences in the acquisition of the morphine-induced aversion. Vehicle-injected animals did not differ in saccharin consumption during this phase (all p's > 0.05).

4. Discussion

The F344 and LEW inbred rat strains display differential acquisition and expression of taste aversions in response to morphine (and heroin) administration (Davis et al., 2009; Lancellotti et al., 2001). It is unknown whether this differential response is mediated centrally or peripherally given that systemic morphine (and heroin) works at both sites (Davis et al., 2009). To test a possible peripheral mediation of aversions in the two strains, the present experiment examined the ability of the peripherally acting, mu preferring agonist loperamide to produce aversions in F344 and LEW rats. In this assessment, F344 and LEW animals developed comparable dose-dependent aversions to the loperamide-associated solution, i.e., loperamide induced aversions that were not strain dependent. These results are in marked contrast to those with systemically-acting opioid agonists, e.g., morphine, where the F344 strain displays greater aversions than the LEW strain. Interestingly, animals initially injected with vehicle during loperamide conditioning and subsequently conditioned with morphine displayed a profile similar to that typically reported with morphine. As described, F344 animals displayed a robust taste aversion relative to LEW animals and their own vehicle-controls, where LEW animals displayed a weak and late-onset taste aversion to the morphine-associated solution. The differences reported here with morphine are unlikely a function of differential latent inhibition in the two strains, given that they parallel those seen in animals without such a history (Lancellotti et al., 2001). It is important to note, however, that latent inhibition has not been examined in these two strains and any role that it might have in animals with familiarization to the taste CS is not known (although the highly correlated prepulse inhibition response does not differ between the two strains under baseline conditions; see Varty and Geyer, 1998).

Given that loperamide is a peripherally-acting opioid with limited access to the CNS (Awouters et al., 1983; DeHaven-Hudkins et al., 1999; Giagioni et al., 1982; Nozaki-Taguchi and Yaksh, 1999; Wüster and Herz, 1978), aversions induced by loperamide are likely mediated by peripherally-located opioid receptors. The fact that loperamide can induce such aversions by its action at these peripheral sites is consistent with other assessments of opiate-induced aversions in outbred animals in which peripheral sites of action have been implicated. For example, differential manipulations that result in the destruction of peripherally located opiate receptors (Bechara and van der Kooy, 1985; Bechara et al., 1987) result in the loss of morphine-induced place and taste aversions. Additionally, the administration of opiate antagonists, such as methylnaltrexone that do not readily cross the blood brain barrier, block morphine-induced place and taste aversions (Bechara et al., 1987). Further, administration of morphine into the hippocampus and caudate putamen (Amir et al., 1977) or via an intracerebroventricular (ICV) route (Hunt et al., 1983) fails to induce taste aversions (though see Liu and Grigson, 2005 for evidence of aversions induced by icv DAMGO).

What remains to be explained is what the present results mean in relation to the reported differences between the F344 and LEW strains in morphine-induced taste aversions (Lancellotti et al., 2001; see also Davis et al., 2009). As noted, morphine-induced aversions are significantly greater in the F344 strain relative to LEW rats (see also present results with morphine). Given that peripherally-acting loperamide induces aversions that are not strain-dependent suggests one of two possibilities in relation to the effects with morphine. First, morphine may act on different subtypes (and/or varieties) of peripheral opiate receptors (Pasternak, 2004; Wolozin and Pasternak, 1981) than does loperamide and these different sites of peripheral action may mediate the differential effects produced by the two drugs (i.e., strain differences with morphine; no strain differences with loperamide). A second possibility is that morphine may be acting centrally to produce its strain-dependent effects.

In relation to the possible differences between morphine and loperamide in their peripheral activity, Shannon and Lutz (2002) reported that 10 times more naloxone (a mu-prefering opioid antagonist) was required to antagonize the analgesic effects of loperamide than morphine when both compounds were administered subcutaneously. This suggests that loperamide and morphine work on separate subsets of opiate receptors in the peripheral nervous system or that they possess differential binding affinity to their preferred receptor type that might lead to different aversive profiles. Others argue, however, that loperamide and morphine work on the same receptor subtype (Awouters et al., 1983; Mackery et al., 1976; Manara and Bianchetti, 1985), so it is unknown to what degree, if any, differential binding in the periphery mediates the reported differences in aversion learning in response to morphine and loperamide. Further, if it were the case that these compounds work on different opiate receptors to produce their effects, it would also have to be demonstrated that LEW and F344 rats differ in binding to morphine at such peripheral sites to account for the differential behavioral effects with morphine. In the absence of direct assessments matching the parameters under which the behavioral differences have been reported, the possibility of such differential peripheral action between the F344 and LEW rats remains speculative.

An alternative explanation for the differential mediation of aversions in the F344 and LEW strains with morphine is associated with its central activity following systemic administration. In this context, morphine may be acting centrally on some subset of receptors, e.g., kappa opioid receptors, to induce taste aversions and the strains differ in kappa opioid receptor activation. Although possible, Davis et al. (2009) have recently reported that when the kappa agonist...
U50,488H was used to induce taste aversions, aversions were acquired in both the F344 and LEW strains, but there was no strain difference. Another possibility involving central mediation concerns morphine’s rewarding effects which are generally associated with its central action (Bechara and van der Kooy, 1985; Koob and Nestler, 1997). It is possible that morphine’s central activity modulates any aversive effects produced by its peripheral action. Accordingly, this position argues that the peripheral aversive effects produced by morphine are similar in the LEW and F344 strain but the central, rewarding effects differ. Given that the LEW strain has been reported to display greater opiate-induced conditioned place preferences and more robust opiate self-administration (Ambrosio et al., 1995; Martin et al., 1999; Sánchez-Cardoso et al., 2007), these animals are generally assumed to display greater sensitivity to the opiate’s rewarding effects. This greater rewarding effect may be impacting morphine’s perceived aversiveness, reducing its ability to induce taste aversions. Given that loperamide acts peripherally due to either its restriction by the blood–brain barrier (DeHaven-Hudkins et al., 1999; Giagnoni et al., 1982; Nozaki-Taguchi and Yaksh, 1999; Stahl et al., 1977) or its accumulation in peripheral tissues and subsequent rapid metabolism (Awouters et al., 1983; Wüster and Herz, 1978), its ability to activate central receptors is minimal, if at all, and aversions are comparable for the two strains. Although this interaction of central and peripheral activity is possible, in the absence of any direct test of central opiate modulation of peripheral aversions, this, too, must remain speculative (see also Liu and Grigson, 2005). The position suggests that drugs have multiple stimulus effects that may interact in such a way to impact their perceived effect which in turn may impact use and abuse vulnerability (Riley, 2011; Stolerman and D’Mello, 1981; Verendeve and Riley, 2011; Wise et al., 1976).

Independent of the mechanism underlying the differential expression of morphine-induced taste aversions in F344 and LEW animals (F344 > LEW), it is important to note that there are other compounds for which the strains display differential aversions. Specifically, F344 animals display greater nicotine- and ethanol-induced aversions than LEW rats (Pescatore et al., 2005; Roma et al., 2006), while LEW animals display stronger cocaine- and caffeine-induced aversions than F344 rats (Glowa et al., 1994; Vishwanath et al., 2011). Given that these compounds come from very different drug classes and that the direction of the differences in the acquisition of taste aversions in the two strains is drug dependent, it is unlikely that any common neurochemical or neuroanatomical pathway mediates the aversions or the differences between the two strains. Although the basis for the differences remains unknown, further examination of other compounds in their ability to induce aversions in the two strains may provide a more thorough characterization of the basis for the reported strain differences.

The focus of the present work was to identify the central or peripheral mediation of the aversive effects of morphine in the F344 and LEW strains. This emphasis makes the assumption that the avoidance of tastes previously paired with morphine (or any drug) is a function of the drug’s aversive effects. It should be noted, however, that there are other interpretations of this behavioral avoidance (for a history of aversion learning, see Freeman and Riley, 2009). One particular position argues that the avoidance of drug-associated tastes does not reflect anything about the aversive effects of the drug at all, but instead reflects the drug’s rewarding properties. This position, the reward comparison hypothesis, argues that the reduction in the intake of the drug-paired taste is a function of the acquired association between the taste and the rewarding effects of the drug such that when presented with the taste on subsequent exposures the rat anticipates the drug. Given that the taste palates in comparison to the drug, it is avoided (Grigson, 1997; Grigson et al., 2009). This hypothesis predicts that there should be a direct relationship between the ability of a drug to suppress consumption and produce their rewarding effects, given that avoidance is a function of the drug’s rewarding effects. Interestingly, data in support of this position is limited and a number of investigations have demonstrated that the rewarding and suppressive effects of drugs are dissociable (see Gaiardi et al., 1991; Martin et al., 1988; Simpson and Riley, 2005). Most recently, Verendeve and Riley (2011) performed a direct test of the reward comparison hypothesis by investigating individual subject differences in sensitivity to the rewarding and aversive effects of both morphine and amphetamine. Specifically, they ran a concurrent CTA/CPP preparation in which animals were given access to a novel saccharin solution, injected with morphine (or amphetamine) and then placed in one compartment of a place preference chamber. Under these conditions, taste aversions and place preferences were acquired, but there was no relationship between the two, i.e., individual animals that displayed strong taste aversions were just as likely to show weak or strong place preferences, and vice versa (see also Turene et al., 1996). Taken together, these data provide evidence that the subjective effects produced by drugs of abuse can in fact be dissociated and the rewarding effects of drugs are not likely mediating the reduced consumption of the taste in the conditioned taste aversion preparation.

The present assessment is the first of its kind to address the issue of whether the strain difference observed in morphine-induced taste aversions might be mediated via central or peripheral mechanisms. This assessment was made by examining if the peripherally acting mu agonist loperamide differentially induced aversions in the two strains. As reported, the F344 and LEW rat strains do not differ in their acquisition of aversions induced by the peripherally acting, mu agonist loperamide, despite the fact that they display the typical aversive profile (F344 > LEW) in response to the systemic opioid morphine. Although the basis for the differential reactivity of these strains to morphine is not known, these results suggest a central mediation of the strain difference in morphine-induced aversions, possibly involving the drug’s rewarding effects.

Acknowledgments

This research was supported by a grant from the Mellon Foundation to A.L.R. The Mellon Foundation had no further role in the study design, data collection, analysis and interpretation, the writing of the report, or the decision to submit the manuscript for publication.

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