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Fischer rats are more sensitive than Lewis rats to the suppressive effects of morphine and the aversive κ -opioid agonist spiradoline

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Abstract

Data suggest that rats avoid intake of an otherwise palatable saccharin cue when paired with a drug of abuse, at least in part, because the value of the taste cue pales in anticipation of the availability of the highly rewarding drug. Earlier support for this hypothesis was provided by the finding that relative to the less sensitive Fischer rats, Lewis rats exhibit greater avoidance of a saccharin cue when paired with a rewarding sucrose or cocaine unconditioned stimulus (US), but not when paired with the aversive agent, lithium chloride (LiCl). More recent data, however, have shown that Fischer rats actually exhibit greater, not less, avoidance of the same saccharin cue when morphine serves as the US. Therefore, Experiment 1 evaluated morphine-induced suppression of intake of the taste cue in Lewis and Fischer rats when the morphine US was administered subcutaneously, rather than ip. Experiment 2 examined the effect of strain on the suppression of intake of the saccharin cue when paired with spiradoline, a selective κ -opioid receptor agonist. The results confirm that Fischer rats are more responsive to the suppressive effects of morphine than Lewis rats and that Fischer rats also exhibit greater avoidance of the saccharin cue when paired with spiradoline, despite the fact that spiradoline is devoid of reinforcing properties. Taken together, the data suggest that the facilitated morphine-induced suppression observed in Fischer rats, compared with Lewis rats, may reflect an increased sensitivity to the aversive, κ -mediated properties of opiates.

Keywords

addiction; drug abuse; natural rewards; reward comparison; withdrawal

Introduction

A conditioned taste aversion (CTA) describes the suppression of intake of a gustatory conditioned stimulus (CS) when it is paired with an aversive unconditioned stimulus (US) such as LiCl or x-ray radiation (Garcia, Kimeldorf, & Koelling, 1955; Le Magnen, 1969; Nachman & Ashe, 1973; Nachman, Lester, & Le Magnen, 1970; Riley & Tuck, 1985). Intake of a gustatory CS also can be suppressed when a saccharin cue, for example, is paired with a highly palatable US such as sucrose. This phenomenon, termed an anticipatory contrast effect, is thought to be due to appetitive, rather than aversive conditioning. Finally, intake of the same saccharin cue can be reduced when it comes to predict a drug of abuse. This phenomenon has been interpreted widely as a CTA for over 40 years (Berger, 1972;

Cappell & LeBlanc, 1971; Cappell, LeBlanc, & Endrenyi, 1973; Le Magnen, 1969; Lester, Nachman, & Le Magnen, 1970; Nachman *et al.*, 1970; Riley & Tuck, 1985).

That said, evidence now suggests that drug-induced suppression of intake of CS intake is a far more complex phenomenon. In 1997, we suggested that rats avoid intake of a drug-paired cue because of appetitive, rather than aversive, conditioning. Specifically, we initially posited that rats reduce intake of the drug-paired cue because the taste cue (usually saccharin) pales in comparison to the value of the highly rewarding drug of abuse that is expected in the very near future (Grigson, 1997, 2008). In support, a great deal of evidence aligns avoidance of a drug-paired cue with avoidance of a cue that is paired with a highly rewarding sucrose solution and differs from that induced by a LiCl-induced CTA (Gomez & Grigson, 1999; Grigson, Lyuboslavsky, Tanase, & Wheeler, 1999; Grigson, Wheeler, Wheeler, & Ballard, 2001; Grigson, Lyuboslavsky, & Tanase, 2000; Geddes, Han, Baldwin, Norgren, & Grigson, 2008; Schroy *et al.*, 2005; see Grigson, 2008 for a review; see Verendeev & Riley, 2012 for an alternative interpretation). That said, additional investigation has revealed further complexity, linking avoidance of a drug-paired cue more with a process, than a property, and this process is dynamic and predicts vulnerability to drug. Thus, avoidance of a drug-paired taste cue is associated with a conditioned elevation in circulating corticosterone (Gomez, Leo, & Grigson, 2000), a conditioned blunting (Grigson & Hajnal, 2007) or reduction (Wheeler *et al.*, 2011) in accumbens dopamine, a conditioned increase in frank aversive taste reactivity behavior (i.e., gapes) following the intraoral delivery of the drug-paired taste cue (Wheeler *et al.*, 2008), and evidence for conditioned withdrawal (i.e., a precipitous loss of body weight) when intake of the drug-paired taste cue is followed by the administration of naloxone (Nyland & Grigson, 2013). Finally, and importantly, greater avoidance of the drug-paired cue, greater aversive taste reactivity behavior, and greater naloxone-induced withdrawal are correlated with one another and each predicts greater drug-seeking and drug-taking (Grigson & Twining, 2002; Nyland & Grigson, 2013; Wheeler *et al.*, 2008).

Avoidance of the drug-paired taste cue, then, is key as it can predict drug-taking. In accordance, it is anticipated that conditions or factors that promote or are associated with higher drug taking also should support greater conditioned avoidance in the taste-drug paradigm. One such factor is strain. For example, Lewis rats have been described as reward-sensitive or addiction-prone because they reportedly exhibit greater responsiveness to drugs of abuse relative to Fischer rats. Lewis rats more readily acquire cocaine, opiate, and alcohol self-administration than the less responsive Fischer rats (Ambrosio, Goldberg, & Elmer, 1995; George & Goldberg, 1989; Kosten *et al.*, 1997; Martin *et al.*, 1999; Suzuki, George, & Meisch, 1988). Lewis rats also show a greater preference for a location paired with drugs of abuse (Guitart, Beitner-Johnson, Marby, Kosten, & Nestler, 1992; Kosten, Miserendino, Chi, & Nestler, 1994). In addition to the behavioral differences between Lewis and Fischer rats, these strains also can be distinguished by differences in the mesolimbic dopamine system at the cellular and molecular level. Chronic treatment with a drug of abuse alters cellular architecture and physiology in the ventral tegmental area (VTA) and nucleus accumbens (NAc) in outbred Sprague-Dawley rats (Nestler, 1995, 1992). Strikingly, drug-naïve Lewis rats exhibit these characteristics innately. Relative to drug-naïve Fischer rats, Lewis rats naturally exhibit smaller dopaminergic cells, fewer neurofilaments, and more tyrosine hydroxylase in the VTA. In the NAc, they exhibit less tyrosine hydroxylase, reduced D₂ dopamine receptor and dopamine transporter (DAT) levels, and elevated adenylate cyclase, cyclic AMP-dependent protein kinase, and Δ FosB (Flores, Wood, Barbeau, Quirion, & Srivastava, 1998; Guitart *et al.*, 1992; Haile, Hiroi, Nestler, & Kosten, 2001; Nestler, 1995, 1992).

Lewis rats, then, should exhibit greater drug-induced suppression of CS intake than Fischer rats. This is the case for caffeine (Vishwanath, Desko, & Riley, 2011) and it clearly is the case for cocaine (Glowa, Shaw, & Riley, 1994; Grigson & Freet, 2000). It is not, however, the case for nicotine (Pescatore, Glowa, & Riley, 2005), alcohol (Liu, Showalter, & Grigson, 2009; Roma, Flint, Higley, & Riley, 2006), heroin (Davis, Rice, & Riley, 2009), or morphine (Lancellotti, Bayer, Glowa, Houghtling, & Riley, 2001). Given that avoidance of the drug-paired taste cue reliably predicts drug-taking, at least as tested with cocaine, it is important that we understand what mediates this opposite pattern of behavior in Lewis and Fischer rats when the taste cue is paired with these other drugs of abuse – particularly opiates. Like other drugs, opiates are highly complex. Morphine is known to have actions at μ -, δ -, and κ -opioid receptors and evidence suggests that, while the reinforcing properties of drugs are mediated by μ - and δ -receptors (Self & Stein, 1992; Mignat, Wille, & Ziegler, 1995; Raynor *et al.*, 1994; Shippenberg, Bals-Kubik, & Herz, 1987), the aversive properties of morphine are mediated by κ -receptors (Anderson, Morales, Spear, & Varlinskaya, 2013; Spanagel, Almeida, Bartl, & Shippenberg, 1994; Tejeda *et al.*, 2013). Liu and Grigson (2005) have shown that Lewis and Fischer rats are equally sensitive to the suppressive effects of a 0.5 $\mu\text{g}/\mu\text{l}$ dose of the μ -receptor agonist, DAMGO, when administered ICV. However, Fischer rats have been shown to be more sensitive to κ -opioid receptor agonists than Lewis rats in antinociception tests (Barrett *et al.*, 2002). Therefore, greater suppression of CS intake in Fischer rats may be the result of innate differences in the opioid system, specifically in the sensitivity to the aversive properties of opiates as mediated by activity at κ -receptors. Arguing against this hypothesis are data from Davis *et al.* (2009) showing a similar level of avoidance of a saccharin cue for Lewis and Fischer rats when paired with the kappa-agonist, U50, 488H. In their studies, however, rats are restricted to 20 min access to fluid daily and this regimen has been associated with less drug-induced suppression of CS intake (Glowa *et al.*, 1994; Grigson & Freet, 2000). In our hands, rats are given 5 min access to the taste cue in the morning and 1 h to rehydrate each afternoon. Under these circumstances, avoidance of the taste cue is more robust (e.g., Grigson & Freet, 2000).

The present set of studies, then, was designed to revisit the hypothesis that greater sensitivity to κ -opioid receptor agonist action mediates greater avoidance of a morphine-paired taste cue by Fischer rats. Thus, Experiment 1 revisited morphine-induced suppression of saccharin intake in Fischer vs. Lewis rats using a 15 mg/kg dose of morphine administered subcutaneously (sc) in rats maintained on a less restrictive water deprivation regimen. Experiment 2 tested whether the strain differences obtained with morphine were mimicked when intake of a saccharin CS was paired with a range of doses of spiradoline, a selective κ -opioid agonist that does not have reinforcing properties (Dykstra, Preston, & Bigelow, 1997; Barrett *et al.*, 2002; Cook, Barrett, Roach, Bowman, & Picker, 2000; Glick, Maisonneuve, Raucci, & Archer, 1995; Morgan, Cook, & Picker, 1999; Picker, Mathewson, & Allen, 1996; France, Medzihradsky, & Woods, 1994). As alluded to, in both cases, testing occurred during a 5 min access period in the morning and all rats received a full h access to water each afternoon to rehydrate.

Experiment 1: Conditioned taste avoidance with subcutaneous morphine

Methods

Subjects—The subjects were 12 naïve, male Fischer rats weighing between 252 and 306 g and 12 naïve, male Lewis rats weighing between 274 and 312 g. They were housed individually in stainless steel hanging cages, maintained in a temperature and humidity controlled animal care facility, and kept on a 12/12 light dark cycle (lights on at 7:00 a.m.). All tests were performed in the light phase of the cycle.

Apparatus—The rats were tested in their home cages using inverted Nalgene graduated cylinders with stainless steel spouts. Intake was measured to the nearest 0.5 ml.

Procedure

Deprivation: The rats were given access to dH₂O for 5 min each morning and for 1 hr each afternoon for 14 days.

Testing: During testing, all subjects were given 5 min access to the 0.15% saccharin solution and 5 min later were injected sc with either saline (n=6 Lewis, n=6 Fischer) or a standard 15 mg/kg dose of morphine (n=6 Lewis, n=6 Fischer). There was one taste-drug pairing every other day for 8 trials. All rats received access to water for 5 min each morning and for 1 hr each afternoon on the days between injections.

Results and Discussion

Saccharin Intake—Saccharin intake was analyzed using a 2 x 2 x 8 mixed factorial analysis of variance (ANOVA) varying strain (Lewis or Fischer), drug (saline or 15 mg/kg morphine), and trials (1–8). The results showed that Fischer rats exhibited greater morphine-induced avoidance of the saccharin cue compared with Lewis rats as demonstrated by a significant Strain x Drug x Trials interaction, $F(7, 140) = 3.71$, $p < .01$, (Figure 1). Newman-Keuls post hoc tests revealed that, while both Fischer and Lewis rats avoided the saccharin cue after one pairing, Fischer rats in the saccharin-morphine group consumed significantly less saccharin than Lewis rats on trials 2–8, $ps < .05$. These data are consistent with Lancellotti *et al.* (2001), but still surprising, as Lewis rats more readily acquire morphine self-administration (Martin *et al.*, 1999) and exhibit greater morphine-induced conditioned place preferences (Guitart *et al.*, 1992). What, then, is mediating avoidance of the drug-paired taste cue in these Fischer rats? Experiment 2 will use our testing parameters and a range of doses of spiradoline to test our hypothesis that differential sensitivity to kappa agonist activity may mediate this strain effect.

Experiment 2: Conditioned Taste Avoidance with Spiradoline

Experiment 1 confirmed that Fischer rats are more responsive to the suppressive effects of morphine compared with Lewis rats. Since Lewis rats are more responsive than Fischer rats in other measures of reward (Martin *et al.*, 1999; Guitart *et al.*, 1992) and the two strains appear to be equally sensitive to the suppressive effects of the μ agonist DAMGO (Liu & Grigson, 2005), we hypothesize that the Fischer rats may be more sensitive to the aversive κ -mediated properties of morphine. To test this hypothesis, we compared the suppressive effects of spiradoline, a selective κ -receptor agonist (France *et al.*, 1994), on intake of a saccharin CS in Lewis and Fischer rats using the same parameters as those employed with morphine. Spiradoline is a potent analgesic, but has little reward value itself, and is known to reduce the reinforcing properties of other drugs of abuse (Barrett *et al.*, 2002; Cook *et al.*, 2000; Glick *et al.*, 1995; Morgan *et al.*, 1999; Picker *et al.*, 1996). Therefore, if Fischer rats are more responsive to κ -receptor activity, they also should exhibit greater spiradoline-induced suppression of CS intake.

Methods

Subjects—Subjects were 49 naïve, male Fischer rats weighing between 208 and 245 g and 49 naïve, male Lewis rats weighing between 217 and 270 g at the start of the experiment. Rats were housed and maintained as described in Experiment 1.

Apparatus—Subjects were tested in their home cages using inverted Nalgene graduated cylinders with stainless steel spouts as described.

Procedure

Deprivation: The rats were given access to dH₂O for 5 min each morning and for 1 hr each afternoon for 5 days until intake stabilized.

Testing: During testing, all rats were given 5 min access to the 0.15% saccharin solution and 5 min later were injected sc with saline or 0.25, 0.5, 1.0, 5.0, or 10.0 mg/kg spiradoline (n=6–13/cell). There was one taste-drug pairing every other day for 7 trials followed by a CS only test trial. All rats received supplemental dH₂O for 1 hr each afternoon to maintain hydration.

Results and Discussion

Saccharin Intake—Saccharin intake was analyzed using a 2 x 6 x 8 mixed factorial analysis of variances (ANOVA) varying strain (Lewis or Fischer), drug (saline, 0.25 mg/kg, 0.5 mg/kg, 1.0 mg/kg, 5.0 mg/kg, or 10.0 mg/kg spiradoline), and trials (1–8). The results showed that Fischer rats were more responsive than Lewis rats to the aversive κ -opioid receptor agonist, spiradoline (Figures 2 and 3), as indicated by a significant Strain x Drug x Trials interaction, $F(35, 602) = 2.31, p < .001$. Newman-Keuls post hoc analysis indicated that while Fischer rats significantly reduced saccharin intake on trials 2 and 5 when it predicted even the lowest dose of spiradoline (0.25 mg/kg), Lewis rats only began to suppress intake with the 0.5 mg/kg dose. In addition, Fischer rats consumed less saccharin than Lewis rats on trials 2–8, when tested with both the 0.5 and 1.0 mg/kg dose of spiradoline, $p < .05$. These data show that Fischer rats are more responsive to the suppressive effects of κ -receptor activation as mediated by spiradoline.

General Discussion

Both the reward comparison hypothesis and the conditioned aversive state (e.g., withdrawal) hypothesis predict that Lewis rats would demonstrate greater avoidance of a drug-paired taste cue than Fischer rats. As mentioned, Lewis rats typically are more responsive than Fischer rats to the cataleptic (Cadoni & Di Chiara, 2007), locomotor stimulating (Cadoni & Di Chiara, 2007), and rewarding properties of cocaine and morphine as measured by conditioned place preference (Guitart *et al.*, 1992; Kosten *et al.*, 1994; but see Roma, Davis, & Riley, 2007), acquisition of drug self-administration (Ambrosio *et al.*, 1995; Haile & Kosten, 2001; Kosten *et al.*, 1997; Martin *et al.*, 1999; Ranaldi, Bauco, McCormick, Cools, & Wise, 2001), and progressive ratio responding (Martin *et al.*, 2003; Martin *et al.*, 1999; but see Kosten, Zhang, & Haile, 2007). In accordance, Lewis rats also exhibit greater avoidance of a saccharin cue when paired with cocaine than Fischer rats (Glowa *et al.*, 1994; Grigson & Freet, 2000; but see Kosten *et al.*, 1994).

This prediction, however, was not confirmed for morphine. Thus, the results of Experiment 1, as well as previously published data (Lancellotti *et al.*, 2001), demonstrate that morphine-induced suppression of CS intake is markedly greater in Fischer than Lewis rats. The same is true for heroin (Davis *et al.*, 2009), which is rapidly deacetylated to morphine (Nakamura, Thornton, & Noguchi, 1975) in the brain. This seeming conundrum may be explained if differential sensitivity to the aversive properties of opiates is taken into account. Thus, while it has been shown that Lewis and Fischer rats share similar sensitivity to the suppressive effects of μ -opioid receptor activation, at least at the dose tested (Liu & Grigson, 2005), the results of Experiment 2 clearly demonstrate an increased sensitivity to the suppressive effects of the κ -opioid receptor agonist, spiradoline, in Fischer rats compared with Lewis rats. This raises the possibility that, in the case of morphine, suppression of CS intake is mediated by activation of primarily μ receptors (i.e., reward) in the Lewis rats, but is

augmented by an additional mechanism (i.e., aversion) via κ receptor activation in the Fischer rats.

By a strict reward comparison vs. CTA analysis, one might conclude that morphine-induced suppression of CS intake is primarily due to a reward comparison effect in the Lewis rats (i.e., drug-induced devaluation of the saccharin cue), and something akin to a classic CTA in the Fischer rats. In support, Grabus, *et al.*, (2004) reported that Fischer rats showed greater morphine-induced c-Fos activity than Lewis rats in the nucleus of the solitary tract and in the pontine parabrachial nucleus, two nuclei involved in CTA learning (Grigson, Shimura, & Norgren, 1997; Grigson, Reilly, Shimura, & Norgren, 1998; McCaughey, Giza, Nolan, & Scott, 1997; Spencer, Eckel, Nardos, & Houpt, 2012). Likewise, Fischer rats showed smaller percent increases in c-Fos in reward related nuclei than Lewis rats in response to morphine administration. Finally, morphine also elicited less dopamine release in the nucleus accumbens core and shell regions in Fischer than the Lewis rats (Cadoni & Di Chiara, 2007; Di Chiara *et al.*, 2004).

As mentioned, however, conditioned avoidance of a drug-paired taste cue appears, ultimately, to be due more to a process than to a property, per se. Thus, in Sprague-Dawley rats, greater avoidance of an opiate- or cocaine-paired cue is associated with the onset of a conditioned state involving aversion (Wheeler *et al.*, 2008) and withdrawal (Nyland & Grigson, 2013) and greater indices of aversion and withdrawal are associated with greater cocaine self-administration (Grigson, 2008; Nyland & Grigson, 2013; Wheeler *et al.*, 2008). That said, at issue here is how these processes develop in Lewis and Fischer rats and how or if differential sensitivity to κ -agonist action affects this development. The spiradoline data suggest that the Fischer rats are more sensitive to κ -agonist activity. If the conditioned aversion that develops in the Fischer rats is akin to a classic conditioned taste aversion (i.e., linked to aversive properties of the opiate), then Fischer rats would not be expected to exhibit a great deal of instrumental responding for drug (e.g., heroin) following exposure to the drug-paired taste cue. If, on the other hand, avoidance of the taste cue in Fischer rats reflects the development of a robust conditioned aversive state, involving the onset of intense conditioned withdrawal, then the Fischer rats would be expected to take even more drug, and with a shorter latency, than the Lewis rats. The former interpretation (i.e., the CTA hypothesis) is more likely, given that Fischer rats exhibit less, not more, preference for a location paired with drug and more recent data show fairly equal spontaneous and precipitated withdrawal in Fischer and Lewis rats (Cobuzzi & Riley, 2011; Stephens & Riley, 2009). Regardless of the outcome, such a follow up drug self-administration study would help to dissociate avoidance of the taste cue when induced by a more classic CTA from that which is mediated by the development of a conditioned aversive state involving craving, withdrawal, and seeking. Moreover, it may illuminate the possibly interdependent and competitive role of μ and κ agonist activation in the development of this phenomenon (Barrett *et al.*, 2002; Cook *et al.*, 2000; Glick *et al.*, 1995; Morgan *et al.*, 1999; Picker *et al.*, 1996).

In sum, rats avoid intake of a taste cue that predicts the availability of a drug of abuse. The degree of avoidance of the taste cue depends upon all manner of factors, including strain and drug. Lewis rats more greatly avoid intake of a cocaine-paired saccharin cue than do Fischer rats; while Fischer rats more greatly avoid intake of a morphine paired taste cue than do Lewis rats. The reason for this stark dissociation is not clear, but the present data suggest that it may have to do with the complexity of morphine action (i.e., involving activation of μ -, κ -, and δ -receptors) and with the relative sensitivity of Lewis and Fischer rats to these actions. Thus, as occurred with morphine, Fischer rats also exhibited far greater avoidance of a saccharin cue that had been paired with the selective kappa agonist, spiradoline, than did the Lewis rats. As mentioned, this pattern of behavior differs from that obtained with

another kappa agonist, U50-488H (Davis *et al.*, 2009). Despite some procedural differences, the reason for this discrepancy is unknown. Future studies will need to address the kappa agonist hypothesis more directly by attempting to block the suppressive effects of morphine in Fischer rats with a kappa antagonist, for example. Finally, and perhaps of more importance, future studies should seek to determine the relationship between conditioned avoidance of a drug-paired cue (via whatever mechanism) and the development of drug-seeking, drug-taking, and addiction.

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Experiment 1: Morphine (sc)-induced suppression of saccharin intake

Figure 1.

Mean ($\pm$ SEM) intake (ml/5min) of saccharin as it predicted a sc injection of saline (open circles or squares) or morphine (closed circles or squares) in Fischer and Lewis rats.

Asterisks indicate significance compared with controls, $p < .05$.

Experiment 2: Spiradoline-induced suppression of saccharin intake in Fischer rats

Figure 2.

Mean (± SEM) intake (ml/5min) of saccharin as it predicted a sc injection of saline (open circles) or spiradoline (closed circles) in Fischer rats. Asterisks indicate significance compared with controls, $p < .05$.

Experiment 2: Spiradoline-induced suppression of saccharin intake in Lewis rats

Figure 3.

Mean (± SEM) intake (ml/5min) of saccharin as it predicted a sc injection of saline (open squares) or spiradoline (closed squares) in Lewis rats. Asterisks indicate significance compared with controls, $p < .05$.