Behavioral/Systems/Cognitive

Food-Induced Behavioral Sensitization, Its Cross-Sensitization to Cocaine and Morphine, Pharmacological Blockade, and Effect on Food Intake

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Repeated administration of abused drugs sensitizes their stimulant effects and results in a drug-paired environment eliciting conditioned activity. We tested whether food induces similar effects. Food-deprived male mice were given novel food during 30 min tests in a runway (FR group) that measured locomotor activity. Whereas the activity of this group increased with repeated testing, that of a group exposed to the runways but that received the food in the home cage (FH group), or of a group satiated by prefeeding before testing (SAT group), decreased. When exposed to the runways in the absence of food, the paired group was more active than the other groups (conditioned activity); no activity differences were seen in an alternative, non-food-paired, apparatus. Conditioned activity survived a 3-week period without runway exposure. Conditioned activity was selectively reduced by the opiate antagonist naltrexone (10–20 mg/kg) and by the noncompetitive AMPA receptor antagonist GYKI 52466 [1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine hydrochloride] (5–10 mg/kg). The D_1 antagonist SCH23390 [$R(+)$-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride] (15–30 μg/kg) and D_2 antagonist sulpiride (25–125 mg/kg) reduced activity nonspecifically. A single intraperitoneal dose of cocaine (10 mg/kg) or morphine (20 mg/kg) increased activity compared with saline, the stimulant effect being larger in the FR group, suggesting "cross-sensitization" to these drugs. However, pretreatment with GYKI 52466 or naltrexone at doses that suppressed conditioned activity in FR animals suppressed cross-sensitization to cocaine. When allowed *ad libitum* access to food in the runway, FR mice consumed more pellets in a time-limited test. Thus, many of the features of behavioral sensitization to drugs can be demonstrated using food reward and may contribute to excessive eating.

Key words: conditioning; incentive learning; potentiation of feeding; glutamate; AMPA; opiate

Introduction

When given repeatedly, the stimulant effects of drugs of abuse increase (Eikelboom and Stewart, 1982; Robinson and Becker, 1986). This phenomenon is known as behavioral sensitization and may be long lasting. Addiction researchers study behavioral sensitization as an example of behavioral plasticity associated with drug abuse, in the anticipation that understanding the neural mechanisms underlying this form of plasticity may provide information on other plastic events underlying abuse. One theory of drug abuse and relapse (Robinson and Berridge, 1993, 2001) posits that behavioral sensitization occurs because repeated drug-taking sensitizes transmission in neural pathways that normally subserve conditioned incentive processes underlying drug seeking and craving.

Many aspects of behavioral sensitization appear to reflect the establishment of conditioned associations between the unconditioned stimulant properties of the drug, and the environment in

which the drug is experienced (Stewart et al., 1984; Vezina and Stewart, 1984; Stewart and Vezina, 1988; Vezina et al., 1989; Crombag et al., 1996), so that the environment in which drug has been experienced itself increases activity even when no drug is administered (conditioned activity) (Stewart, 1983). It is well established that environmental stimuli paired with primary appetitive reinforcers enhance locomotor activity (Sheffield and Campbell, 1954; Bindra, 1968). Because psychostimulant and opiate drugs are potent rewards (Volkow and Wise, 2005), environmental cues associated with them should also increase activity. Thus, a potential explanation of conditioned activity is that it reflects the reward-predictive relationship of the environment to drug, rather than the stimulant-predictive relationship. In this respect, drug reward would not be expected to differ from natural rewards.

This conditioning account would be consistent with the parallels between behavioral sensitization with other forms of learning, and synaptic plasticity. Thus, acquisition of behavioral sensitization is blocked by treatments including NMDA antagonists (Wolf and Khansa, 1991; Kalivas and Alesdatter, 1993; Stewart and Druhan, 1993) and protein synthesis inhibitors (Karler et al., 1993) that block long-term potentiation and learning. Furthermore, because dopamine by its action at D_1 receptors facilitates synaptic plasticity (Beninger and Miller, 1998; Nestler, 2001),

psychostimulant-induced increases in synaptic dopamine may facilitate the formation of particularly strong conditioned associations between the reinforcer and the environment.

The purpose of the present study was to test whether food, a natural reward, could support behavioral sensitization in mice. We monitored the locomotor activity of food-deprived mice in runways in which they were exposed daily to sweetened pellets, and compared it with that of animals placed daily into the runways but in the absence of pellets (given later in the home cage), or exposed to pellets in the runways but satiated 30 min before testing. Expression of food-induced conditioned activity was then tested for context specificity and longevity, and the involvement of dopaminergic, opioid, and AMPA glutamatergic mechanisms was assessed. Cross-sensitization to the stimulant effects of cocaine and morphine was tested, as well as the effects of naltrexone, 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine hydrochloride (GYKI 52466), and $R(+)$-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride (SCH23390) on cross-sensitization to cocaine. Finally, we evaluated the ability of a food-paired context to elicit increased food intake in previously conditioned animals.

Materials and Methods

Subjects
Subjects were male mice (C57BL/6 × SV129) bred in the Department of Psychology at the University of Sussex and weighed 25–30 g at the beginning of the experiments. They were housed in groups of two or three per cage on a 12 h light/dark cycle (lights off at 7 P.M.), at a temperature of 19–21°C and 50% humidity. One week before the acquisition of food-induced sensitization started, the mice were food restricted to reduce their body weights to ~90% of their free-feeding weight. Water was available *ad libitum*. All experiments were approved by the institutional ethics committee and were performed under United Kingdom legislation on animal experimentation [Animal (Scientific Procedures) Act, 1986].

Test apparatuses
Locomotor activity was assessed in polypropylene circular runways (internal diameter, 11 cm; external diameter, 25 cm; height, 25 cm) equipped with eight infrared photobeams spaced at regular intervals and positioned 2 cm above the floor (Mead and Stephens, 1998). The number of beam crossings after three consecutive breaks in one direction was used as a measure of forward locomotion. Context specificity was tested in rectangular metallic boxes [19 cm (width) × 45 cm (length) × 20 cm (height)] equipped with three parallel horizontal infrared beams positioned 1 cm above the floor and spaced at regular intervals along the longitudinal axis. Forward activity was scored as the number of times an animal broke two consecutive beams.

Experiment 1: acquisition of food-conditioned locomotor sensitization
Each daily session consisted of a preexposure run of 10 min (run A), followed by a 5 min break during which the animals were replaced in their home cages. The mice were then returned to the locomotor runways for 20 min (run B). This protocol was designed to mimic a classical protocol of behavioral sensitization to drug, in which the animals are first habituated to the activity cages/runways during a first run, and then injected with the drug or its vehicle and returned to the activity apparatus for a conditioning run.

Three separate groups of 10 animals were constituted. In the first group (food in the runways, hungry: FR), the animals received 20 sweetened pellets (20 mg each; Noyes Precision pellets, Formula P; Research Diets, New Brunswick, NJ) scattered in the runways when returned for run B. In the second group (food in the home cage, hungry: FH), the mice were exposed to the runways as described for the FR group, except that no sweetened pellets were available in the apparatus. Twenty sweetened pellets per animal were given in the home cage 45 min after the end of the

behavioral session. A third group (food in the runways, satiated: SAT) was as the FR group, including the availability of sweetened pellets, except that the animals were satiated 30 min before the behavioral session by receiving the same sweetened pellets *ad libitum* in their home cage. All animals were fed with standard laboratory chow in the afternoon (at 3–4 P.M.) at varying time intervals (60–90 min) after testing, to limit possible association between testing and chow feeding. Animals were not habituated to sweetened pellets before the beginning of the experiments to avoid interference with subsequent conditioning. FR animals ate all pellets in the runways after two to three sessions.

Experiment 2: context specificity of the food-induced conditioned locomotor response
At the end of the acquisition phase, the animals of the FR and the FH groups were either exposed to the runways or to the rectangular activity boxes. The protocol was identical as for acquisition sessions, except that forward activity was measured in the absence of sweetened pellets (conditioned activity). After full recovery of their performance level (three to four acquisition sessions), the animals were retested in a counterbalanced order.

Longevity of the food-induced conditioned locomotor response
After three to four acquisition sessions, FR and FH animals were retested for conditioned activity in the locomotor runways (day 1). No sweetened pellets were given. Next session was a normal acquisition session, sweetened pellets being available. Then daily sessions were suspended for 3 weeks, the animals remaining under food deprivation. On day 22, the mice were reexposed to the runways in the absence of sweetened pellets to evaluate conditioned activity.

Experiment 3: effects of dopaminergic antagonists on the expression of food-induced conditioned activity
Two groups of 9–10 naive animals were constituted (FR and FH groups). At the end of the acquisition phase, these animals were injected with the D_1 receptor antagonist SCH23390 (at 15 or 30 μg/kg, i.p.) or vehicle following a Latin square design; no sweetened pellets were given. The animals were injected 5 min before run A, to assess possible effects on anticipatory activity. After each drug testing session, the animals were submitted to three to four normal acquisition sessions (sweetened pellets available) to allow full recovery of their performance level. Two more FR and FH ($n = 7$–9) groups were constituted from naive animals to test the effects of the D_2/D_3 receptor antagonist sulpiride (25, 75, or 125 mg/kg) versus vehicle, using the same experimental design, except that sulpiride was injected 30 min before run A.

Experiment 4: effects of opiate and AMPA receptor antagonists on the expression of food-induced conditioned activity
The FH and FR animals from the longevity experiment were successively injected with the nonselective but long-lasting opiate antagonist naltrexone (10 and 20 mg/kg, i.p.) or vehicle, and the AMPA antagonist GYKI 52466 (5 or 10 mg/kg, i.p.) or vehicle, following a Latin square design; no sweetened pellets were available during run B. Naltrexone was administered 30 min before run A; GYKI 52466 was injected immediately before run A because of its short half-life. After each drug testing session, the animals were submitted to three to four normal acquisition sessions to allow full recovery of their performance level.

Experiment 5: effects of cocaine and morphine challenge injection
Two groups of 10 naive animals were constituted: an FR group and an FH group. At the end of the acquisition phase, the animals received either a challenge injection of cocaine (10 mg/kg, i.p.) or a vehicle (saline) injection immediately before run B; no sweetened pellets were given. Run B lasted only 10 min. After full recovery of their performance level (three to four sessions), the animals were retested in a counterbalanced order. Similarly, two more groups of eight FR and eight FH animals were constituted to test the effects of a morphine challenge injection. At the end of the acquisition phase, the animals received either morphine (20 mg/kg, i.p.) or vehicle (saline) injection 15 min before run A; no sweetened pellets were given. Run B lasted 10 min. After full recovery of their performance level, the animals were retested in a counterbalanced order.
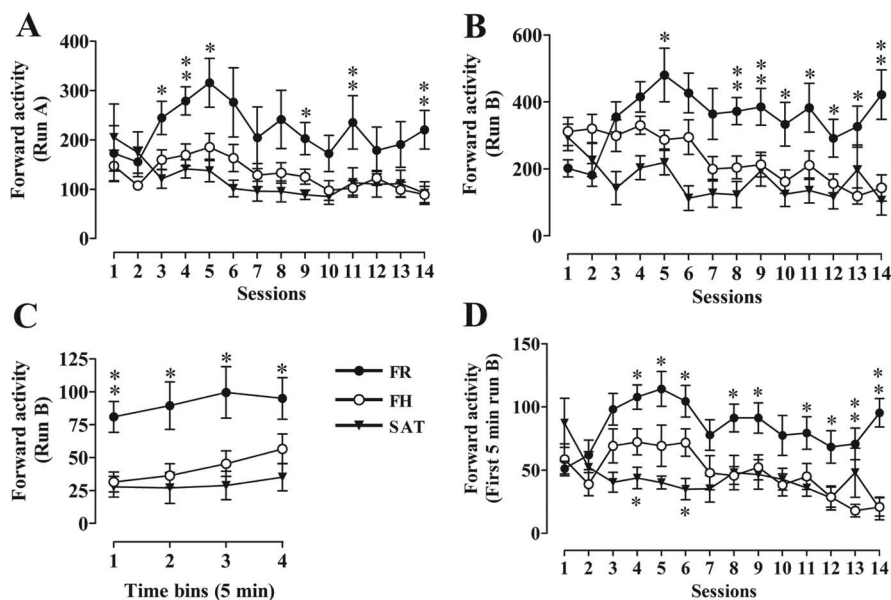
Figure 1. Acquisition of food-induced conditioned activity. Repeated daily exposure (14 sessions) to the locomotor runways resulted in increased forward activity (means ± SEM) during run A (***A***) and run B (***B***) in hungry animals receiving sweetened pellets in the apparatus (FR) (*n* = 10) compared with hungry animals receiving sweetened pellets in their home cage (FH) (*n* = 10) and animals satiated with sweetened pellets available *ad libitum* 30 min before testing (SAT) (*n* = 10). Allocating the activity counts to bins of 5 min over the last four sessions (means ± SEM) indicated that locomotor activity increased by the end of run B in FH animals repeatedly exposed to the runways (***C***), justifying for a separate analysis of the first 5 min of run B (***D***) (*$p <$ 0.05; **$p <$ 0.01, ANOVA followed by Newman–Keuls *post hoc* analysis).

Modulation of cocaine effects by AMPA, opiate, or dopamine D_1 receptor antagonists
FR and FH animals previously treated with naltrexone and GYKI 52466 were used in this experiment. After three to four acquisition sessions, they received either GYKI 52466 (10 mg/kg, i.p.) before run A followed by cocaine (10 mg/kg, i.p.) before run B, or vehicle (saline) before run A followed by cocaine before run B; no sweetened pellets were given. After full recovery of their performance level, the animals were retested in a counterbalanced order. Then, they were retested in the same conditions, but receiving either naltrexone (20 mg/kg) or SCH23390 (30 μg/kg) instead of GYKI 52466. GYKI 52466 and SCH23390 were injected immediately before run A, and naltrexone was administered 30 min before run A.

Experiment 6: ability of food-paired environment to facilitate eating
FR and FH animals previously treated with sulpiride were tested in the same experimental conditions as during acquisition sessions, except that run B lasted 5 min only and that 80 sweetened pellets were then available. Forward activity was monitored during run A and run B. The amount of pellets available for each mouse was weighed before and after run B (taking into account any spillage). Food intake per mouse was expressed either in grams or as a percentage of the animal's body weight.

Drugs
Cocaine hydrochloride, SCH23390, naltrexone (Sigma, Poole, UK), and morphine hydrochloride (McFarland Smith, Edinburgh, UK) were dissolved in sterile 0.9% saline and injected intraperitoneally in a volume of 10 ml/kg. (±)Sulpiride (Tocris, Avonmouth, UK) as well as the AMPA antagonist GYKI 52466 (IDR, Budapest, Hungary) were dissolved in a small volume of hydrochloric acid (0.1 M), diluted with sterile 0.9% saline to final concentration and brought to pH 6.5–7 with NaOH (1 M).

Statistical analyses
Experiment 1. Data were analyzed using two-way ANOVAs with group (FR, FH, SAT) as the between-subject factor, and session as the within-subject factor. When a statistically significant effect was found, *post hoc* analysis was performed by using the Student–Newman–Keuls test. Sub-

sequent one-way ANOVAs with session as the within-subject factor were calculated for each group to examine changes in activity over sessions.

Experiment 2. Differences in locomotor activity between FR and FH groups in different contexts were analyzed using Student's *t* test for independent samples. Concerning longevity experiment, data were analyzed using two-way ANOVAs with group as the between-subject factor and day (1 or 22) as the repeated measure.

Experiments 3 and 4. Data over different treatment conditions were analyzed using two-way ANOVAs with group (FR, FH) as the between-subject factor, and dose as the repeated measure. Subsequent one-way ANOVAs with session as the within-subject factor were used to examine dose-dependent changes in activity over sessions.

Experiment 5. Data over different treatments were analyzed using two-way ANOVAs with group (FR, FH) as the between-subject factor, and treatment or pretreatment as the repeated measure.

Experiment 6. Differences in food intake between FR and FH groups in different contexts were analyzed using a Student's *t* test for independent samples.

Results
Experiment 1
Mice were allowed to explore circular runways for 10 min (run A) before being removed briefly to allow sweetened pellets to be placed in the runway, and were then returned (run B). As shown in Figure 1*A*, repeated daily exposure to food in the runways during run B over 14 sessions led to a persistent high level of locomotor activity during run A (anticipatory activity) in the group that received food in the runway while hungry (FR group), but not in mice that received food in the home cage (FH) or mice that were satiated by feeding before placing in the runway (SAT) (group effect: $F_{(2,26)}$ = 6.53, $p <$ 0.01; sessions effect: $F_{(13,338)}$ = 3.39, $p <$ 0.0001). Over the 14 sessions, activity was higher in the FR group than in both FH and SAT groups (*post hoc*, $p <$ 0.01), attributable to significant decrease of activity across sessions in FH ($F_{(13,117)}$ = 2.93; $p <$ 0.01) and SAT ($F_{(13,104)}$ = 2.15; $p <$ 0.05) groups, but not in the FR group ($F_{(13,117)}$ = 1.37; NS).

Similarly, giving sweetened pellets in the runways also resulted in increasing locomotor activity during run B in the FR group, whereas activity decreased in FH and SAT groups (group effect: $F_{(2,26)}$ = 8.00, $p <$ 0.01; sessions effect: $F_{(13,338)}$ = 3.53, $p <$ 0.0001; G × S interaction: $F_{(26,338)}$ = 3.99, $p <$ 0.0001) (Fig. 1*B*). Over the course of training, activity was higher in the FR group than in both FH and SAT groups (*post hoc* significance vs FH group: $p <$ 0.05; vs SAT group: $p <$ 0.01), reflecting a significant increase across sessions in the FR group ($F_{(13,117)}$ = 3.12; $p <$ 0.001), most of which occurring after three to five sessions, but a decrease in FH ($F_{(13,117)}$ = 6.21; $p <$ 0.0001) and SAT ($F_{(13,104)}$ = 3.70; $p <$ 0.0001) groups.

The time course of locomotor activity during run B in animals repeatedly exposed to the runways was assessed by expressing activity counts in bins of 5 min over the last four sessions (11–14) (Fig. 1*C*). Activity was higher in FR animals than in FH and SAT animals (group effect: $F_{(2,26)}$ = 7.29; $p <$ 0.01), with a general
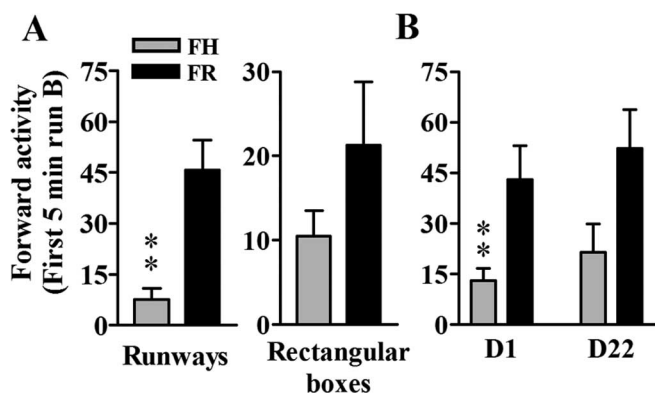
Figure 2. Context specificity and longevity of food-induced conditioned activity (means + SEM). When tested in the runways in the absence of sweetened pellets, animals given repeated sweetened pellets presentations in this context (FR) ($n = 10$) displayed higher locomotor activity than animals given pellets in their home cage (FH) ($n = 10$), during the first 5 min of run B (**A**, left) (*$p < 0.05$, **$p < 0.01$, Student's t test). When tested in a different context (**A**, right), FR animals were not significantly more active than FH animals. Note that the scales are different. The difference of activity observed between FR ($n = 9$) and FH ($n = 10$) animals in the runways at day 1 (D1) persisted over 3 weeks [until day 22 (D22)] of interruption in daily exposure to the apparatus (**B**) (*$p < 0.05$; **$p < 0.01$, Student's t test).

tendency to increase by the end of the run (time effect: $F_{(2,26)} = 7.01$; $p < 0.001$). However, such a tendency reached significance only in FH animals ($F_{(3,27)} = 5.25$; $p < 0.01$), and not in FR ($F_{(3,27)} = 2.61$; NS) nor SAT animals ($F_{(3,27)} = 1.23$; NS). The most significant differences between FR and FH/SAT groups were seen during the first 5 min of run B ($F_{(2,26)} = 10.28$; $p < 0.0001$), despite the time needed by FR animals to eat the sugar pellets (all pellets were eaten in ~3–4 min). Taking this result into consideration, we narrowed statistical analysis to data from the first 5 min of run B (Fig. 1D). FR animals, but not FH or SAT animals, displayed a significant increase in their locomotor activity over 14 sessions (most of the increase occurring in three to four sessions) when sweetened pellets were available during run B (group effect: $F_{(2,26)} = 8.52$, $p < 0.01$; sessions effect: $F_{(13,338)} = 5.95$, $p < 0.0001$; G × S interaction: $F_{(26,338)} = 3.80$, $p < 0.0001$). Again, activity was higher over the 14 sessions in the FR group than in FH and SAT groups (*post hoc* significance, $p < 0.01$). Subsequent one-way ANOVA indicated a significant increase in activity in the FR group over sessions ($F_{(13,117)} = 4.80$; $p < 0.0001$) but a significant decrease in FH ($F_{(13,117)} = 4.86$; $p < 0.0001$) and SAT ($F_{(13,104)} = 4.07$; $p < 0.0001$) groups.

Experiment 2
When tested in the circular runways in the absence of sweetened pellets, animals from group FR were more active than FH animals during run A ($t_{(18)} = 2.72$, $p < 0.05$; activity ± SEM: FH, 33.90 ± 5.84; FR, 80.60 ± 16.25), during run B ($t_{(18)} = 3.39$, $p < 0.01$; activity ± SEM: FH, 28.10 ± 13.86; FR, 152.60 ± 34.02), and, more specifically, during the first 5 min of run B ($t_{(18)} = 4.02$; $p < 0.01$) (Fig. 2A). When tested in a different context (rectangular activity boxes) not previously paired with food, and in the absence of sweetened pellets, FR animals did not differ from FH animals in forward activity during run A ($t_{(18)} < 1.63$, NS; activity ± SEM: FH, 24.10 ± 4.25; FR, 44.80 ± 11.77), run B ($t_{(18)} = 1.48$, NS; activity ± SEM: FH, 39.30 ± 8.74; FR, 72.70 ± 20.87) or during the first 5 min of run B ($t_{(18)} = 1.34$, NS) (Fig. 2A).

When runway training was paused for 3 weeks, an increase in locomotor activity during run A and run B was observed in both groups of animals, but FR animals continued to be more active than FH animals (activity ± SEM: run A, day 1, FH, 43.10 ± 7.98; FR, 80.11 ± 13.08; day 22 FH, 64.10 ± 12.93; FR, 156.00 ± 39.74; run B, day 1, FH, 39.10 ± 13.34; FR, 170.67 ± 43.26; day 22, FH, 110.40 ± 19.91; FR, 228.89 ± 68.90). Two-way ANOVAs with group and testing day as factors revealed significant main effect of group ($F_{(1,17)} = 6.61$, $p < 0.05$; $F_{(1,17)} = 5.67$, $p < 0.05$, respectively) and testing day ($F_{(1,17)} = 8.28$, $p < 0.05$; $F_{(1,17)} = 8.02$, $p < 0.05$, respectively) with no significant interaction. In contrast, interruption had no significant effect on activity during the first 5 min of run B, FR animals remaining more active than FH animals (group effect: $F_{(1,17)} = 8.19$, $p < 0.05$; testing day effect: $F_{(1,17)} = 2.17$, NS) (Fig. 2B).

Experiment 3
Pretreatment with SCH23390 had no effect on locomotor activity during run A (group effect: $F_{(1,17)} = 0.90$, NS; dose effect: $F_{(2,34)} = 0.86$, NS). FR animals were more active than FH animals during run B (group effect: $F_{(1,17)} = 5.17$, $p < 0.05$), a pattern that was not modified by SCH23390 injections (dose effect: $F_{(2,34)} = 2.06$, NS) (Table 1). This was attributable to the absence of SCH23390 effect in the FR group ($F_{(2,16)} = 0.32$; NS), whereas a decrease of activity was observed in the FH group ($F_{(2,18)} = 6.20$; $p < 0.01$). Focusing on the first 5 min of run B (Fig. 3A), FR animals were again more active than FH animals and SCH23390 injections failed to suppress this difference (group effect: $F_{(1,17)} = 16.51$, $p < 0.001$), although at the highest dose it tended to reduce locomotor activity (dose effect: $F_{(2,34)} = 3.60$, $p < 0.05$). This effect, however, did not reach significance in either the FR ($F_{(2,16)} = 2.11$; NS) or the FH ($F_{(2,16)} = 2.65$; NS) group.

Although increasing doses of sulpiride reduced activity in all mice during run A, FR animals remained more active than FH animals (group effect: $F_{(1,14)} = 6.02$, $p < 0.05$; dose effect: $F_{(3,42)} = 8.32$, $p < 0.01$). Likewise, FR animals displayed higher locomotor activity during run B (group effect: $F_{(1,14)} = 11.72$, $p < 0.01$), and sulpiride pretreatment, although reducing activity with increasing doses, had no significant effect on this difference (dose effect: $F_{(3,42)} = 4.67$, $p < 0.01$) (Table 1). Finally, during the first 5 min of run B only, FR mice were more active than FH mice (group effect: $F_{(1,14)} = 7.65$, $p < 0.05$), and sulpiride reduced locomotor activity in a similar way in both groups (dose effect: $F_{(3,42)} = 4.86$, $p < 0.01$) (Fig. 3B).

Experiment 4
Naltrexone pretreatment reduced locomotor activity during run A, FR animals failing to be significantly more active than FH animals (group effect: $F_{(1,16)} = 2.02$, NS; dose effect: $F_{(2,32)} = 6.82$, $p < 0.01$). In contrast, FR animals displayed higher activity than FH animals during run B (group effect: $F_{(1,16)} = 7.58$, $p < 0.05$), a difference that naltrexone tended to suppress (dose effect: $F_{(2,32)} = 1.72$, NS) (Table 1). As shown in Figure 3C, FR animals were more active than FH animals during the first 5 min of run B (group effect: $F_{(1,16)} = 11.36$, $p < 0.01$). Naltrexone specifically reduced conditioned activity in FR animals, without affecting locomotor activity in FH animals (dose effect: $F_{(2,32)} = 5.74$, $p < 0.05$; G × D interaction: $F_{(2,32)} = 6.09$, $p = 0.01$). Subsequent one-way ANOVA indicated a dose-dependent decrease in activity in FR animals ($F_{(2,14)} = 6.11$; $p < 0.05$) but no effect in FH animals ($F_{(2,18)} = 0.90$; NS).

Treatment with the AMPA antagonist, GYKI 52466, tended to decrease locomotor activity in both groups during run A (dose effect: $F_{(2,34)} = 3.02$, NS), FR and FH animals displaying similar levels of activity (group effect: $F_{(1,17)} = 1.37$, NS). GYKI 52466

Table 1. Effects of SCH23390, sulpiride, naltrexone, and GYKI 52466 on food-induced conditioned activity (means ± SEM) measured during run A and run B (20 min)

| Pharmacological treatment	Dose (mg/kg)	Forward activity during run A		Forward activity during run B	
		Group		Group	
		FH	FR	FH	FR
SCH23390	0	37.8 ± 12.13	51.67 ± 13.45	76.50 ± 18.85	124.11 ± 35.83
	0.015	42.50 ± 7.85	58.89 ± 17.28	58.10 ± 20.26	125.89 ± 45.35
	0.03	65.33 ± 19.84	51.10 ± 12.20	10.00 ± 3.85	88.44 ± 40.69
Sulpiride	0	93.43 ± 20.35	168.22 ± 30.63	62.00 ± 12.83	199.44 ± 37.22
	25	92.14 ± 28.65	148.22 ± 25.55	60.14 ± 15.59	210.67 ± 47.23
	75	40.86 ± 12.94	110.22 ± 25.70	40.29 ± 15.27	138.22 ± 24.98
	125	36.29 ± 7.33	68.89 ± 11.42	32.43 ± 12.42	125.33 ± 24.95
Naltrexone	0	67.50 ± 22.97	102.12 ± 23.40	30.30 ± 12.44	145.00 ± 52.11
	10	44.80 ± 9.13	59.25 ± 13.74	36.20 ± 9.01	107.12 ± 39.41
	20	21.80 ± 9.19	40.50 ± 14.04	32.30 ± 12.58	59.25 ± 15.94
GYKI 52466	0	33.60 ± 6.80	86.78 ± 31.94	45.70 ± 18.33	167.55 ± 68.06
	5	53.90 ± 6.34	79.56 ± 29.61	28.10 ± 10.89	134.89 ± 47.13
	10	41.30 ± 6.34	37.44 ± 8.88	7.00 ± 3.26	7.22 ± 2.36
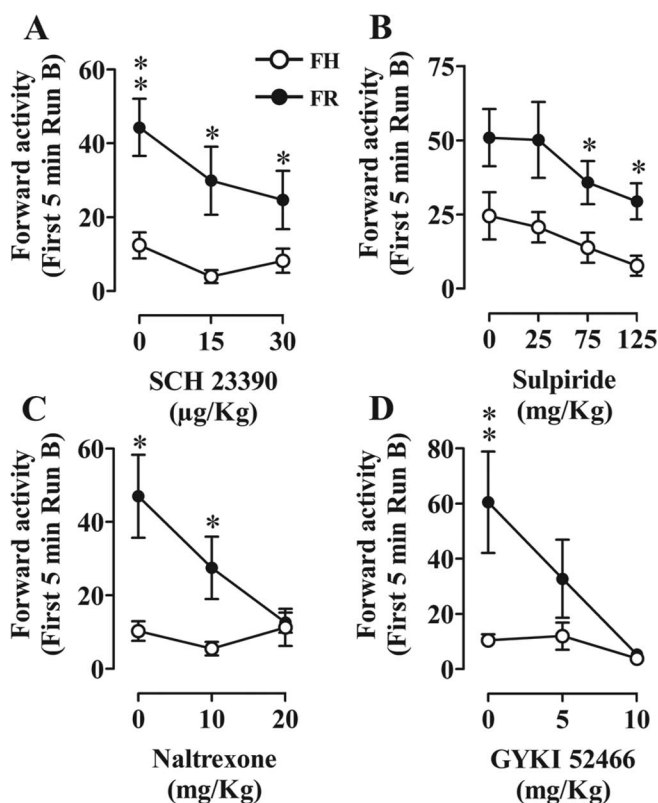
Figure 3. Effects of SCH23390 (**A**), sulpiride (**B**), naltrexone (**C**), and GYKI 52466 (**D**) on food-induced conditioned activity (means ± SEM). SCH23390 and sulpiride failed to suppress food-conditioned response during the first 5 min of run B in animals previously exposed to sweetened pellets in the runways (FR) (n = 9 per drug) compared with animals receiving sugar pellets in their home cage (FH) (n = 7–10 per drug). In contrast, food-induced hyperactivity was completely inhibited after naltrexone or GYKI 52466 pretreatment in FR animals (n = 8–9 per drug), at doses (20 and 10 mg/kg, respectively) that had no effect on basal activity in FH animals (n = 10 per drug) (*p < 0.05, **p < 0.01, Student's t test to compare FH and FR groups for each dose).

reduced locomotor activity in both groups during run B, but this decrease was more pronounced in FR than in FH animals (group effect: $F_{(1,17)} = 4.06$, NS; dose effect: $F_{(2,34)} = 9.10$, $p < 0.001$; G × D interaction: $F_{(2,34)} = 3.73$, $p < 0.05$) (Table 1). GYKI 52466 injections specifically reduced conditioned activity in FR animals during the first 5 min of run B (Fig. 3D), without modifying locomotor activity in FH animals (group effect: $F_{(1,17)} = 5.23$, $p < 0.05$; dose effect: $F_{(2,34)} = 10.30$, $p < 0.001$; G × D interaction: $F_{(2,34)} = 6.43$, $p < 0.01$). Subsequent one-way ANOVA indicated a significant dose effect of GYKI 52466 in FR animals ($F_{(2,16)} = 8.73$; $p < 0.01$) but no effect in FH animals ($F_{(2,16)} = 1.38$; NS).

Experiment 5
To test whether the behavioral sensitization to food showed cross-sensitization to cocaine, we injected cocaine immediately before run B (Fig. 4A). After saline injection and in the absence of sweetened pellets, animals from the FR group showed increased activity during run B (10 min) relative to FH mice (conditioned activity; $t_{(18)} = 2.15$, $p < 0.05$); injection of cocaine enhanced forward activity, when compared with saline injection, in both groups, but the increase in activity after cocaine was higher in the FR than the FH group. A two-way ANOVA with group (G) and drug (D) as factors revealed significant effect of group ($F_{(1,18)} = 9.46$; $p < 0.01$) and drug treatment ($F_{(1,18)} = 23.90$; $p < 0.001$), with a significant G × D interaction ($F_{(1,18)} = 6.18$; $p < 0.05$).

Cross-sensitization to morphine was assessed by injecting morphine 15 min before run A (Fig. 4B). Forward activity was increased by morphine pretreatment in FR and FH animals during run A (drug effect: $F_{(1,14)} = 10.93$, $p < 0.01$), with no difference between groups (group effect: $F_{(1,14)} = 0.11$, NS; saline FH, 62.62 ± 16.49; FR, 87.50 ± 25.98; morphine FH, 210.62 ± 40.10; FR, 219.50 ± 80.34). During run B, morphine challenge enhanced activity in both groups when compared with saline (drug effect: $F_{(1,14)} = 5.10$, $p < 0.05$), and activity remained higher in FR animals than in FH animals (group effect: $F_{(1,14)} = 21.55$, $p < 0.001$).

The participation of food-conditioned activity in cross-sensitization to cocaine effects was tested by pretreating the animals with GYKI 52466 and naltrexone, at doses that were shown to block conditioned activity in previous experiments, or SCH23390, which, even at a dose that decreased globally locomotor activity, was not able to suppress conditioned activity. Preinjection of vehicle or GYKI 52466 had no effect on activity during run A, FR animals failing to be more active then FH animals (pretreatment effect: $F_{(1,16)} = 0.23$, NS; group effect: $F_{(1,16)} = 0.23$, NS; activity ± SEM: saline FH, 38.20 ± 11.01; FR, 63.87 ± 24.44; GYKI 52466 FH, 51.10 ± 5.15; FR, 37.25 ± 7.54). During run B, pretreatment with GYKI 52466 before the cocaine challenge completely suppressed the difference in activity observed after vehicle pretreatment between FR and FH animals (pretreatment effect: $F_{(1,16)} = 8.52$, $p = 0.01$; group effect: $F_{(1,16)} = 8.02$, $p < 0.05$; P × G interaction: $F_{(1,16)} = 11.07$, $p < 0.001$) (Fig. 4). No effects of vehicle versus naltrexone pretreatment or FR versus FH group were observed in the animals during run A (pretreatment effect: $F_{(1,16)} = 1.03$, NS; group effect: $F_{(1,16)} = 1.18$, NS; activity ± SEM: saline FH, 28.20 ± 7.24; FR, 58.50 ± 28.31; naltrexone FH, 27.90 ± 8.91; FR, 33.38 ± 8.31). During run B, FR animals pretreated with naltrexone before cocaine challenge failed to display higher activity than FH animals as observed after vehicle pretreatment (pretreatment effect: $F_{(1,16)} = 4.48$, $p = 0.05$; group effect: $F_{(1,16)} = 7.30$, $p < 0.05$; P × G interac-

tion: $F_{(1,16)} = 7.56$, $p < 0.05$) (Fig. 4). Finally, SCH23390 pretreatment reduced the hyperactivity observed in FR animals compared with FH animals during run A (pretreatment effect: $F_{(1,16)} = 13.38$, $p = 0.05$; group effect: $F_{(1,16)} = 4.00$, NS; P × G interaction: $F_{(1,16)} = 5.77$, $p < 0.05$; activity ± SEM: saline, FH, 38.20 ± 9.05; FR, 111.87 ± 30.67; GYKI 52466 FH, 25.00 ± 4.13; FR, 48.12 ± 25.86). However, during B, although SCH23390 reduced the locomotor response to cocaine in both groups, it failed to suppress the difference of activity observed between FR and FH animals (pretreatment effect: $F_{(1,16)} = 18.46$, $p < 0.001$; group effect: $F_{(1,16)} = 7.77$, $p < 0.05$; P × G interaction: $F_{(1,16)} = 4.05$, NS) (Fig. 4).

Experiment 6

The ability of the runways to elicit food intake was assessed in FR and FH animals by giving them access to 80 sweetened pellets during a 5 min run B. Activity during both runs A and B was monitored, and the total amount of sweetened pellets eaten was measured. Activity during run A was higher in FR animals than in FH animals ($t_{(14)} = 2.34$, $p < 0.05$; activity ± SEM: FH, 88.14 ± 12.94; FR, 207.44 ± 49.33). In contrast, activity during run B (5 min), when sweetened pellets were available *ad libitum*, was significantly higher in FH mice than in FR mice ($t_{(14)} = -4.85$, $p < 0.0001$; activity ± SEM: FH, 24.00 ± 3.30; FR, 7.78 ± 1.49). Lower activity in FR animals was attributable to their significantly higher intake of sweetened pellets than FH animals, as expressed in grams ($t_{(14)} = 2.70$, $p < 0.05$; amount consumed ± SEM: FH, 0.78 ± 0.1; FR, 1.08 ± 0.03) or as a percentage of their body weight ($t_{(14)} = 3.58$, $p < 0.01$; intake ratio ± SEM: FH, 3.05 ± 0.45; FR, 4.77 ± 0.17).

Discussion

In the present study, food-deprived mice, repeatedly exposed to palatable food in a specific context, displayed progressive and persistent increases in locomotor activity in that context. In contrast, animals receiving the food in their home cage, or animals in which the rewarding properties of the food were previously devalued by satiation, showed a decrease in locomotor activity after repeated exposure to the same context. These data resemble the development of behavioral sensitization to repeated intermittent exposure to drugs of abuse such as cocaine. After sensitization, placing mice in the food-paired environment, even in the absence of food, resulted in heightened activity. Notably, the amplitude of both the anticipatory response (during run A), and conditioned hyperactivity were greatest when the FR animals were placed in the same context as that in which they received the repeated food pairings. No significant difference in activity between groups was observed in a different, unconditioned environment.

To our knowledge, our results are the first report of locomotor sensitization to palatable food in rodents. A previous study (Schroeder et al., 2001) failed to observe sensitization in rats repeatedly exposed to chocolate chips in activity cages. However, unlike the present study, the animals were not food deprived. Negative energy balance may thus be critical in establishing food-induced
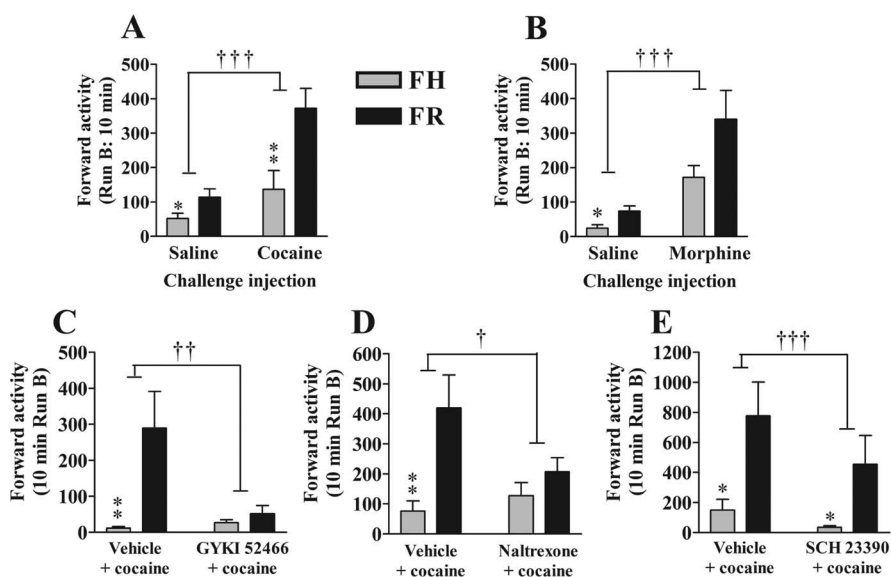

Figure 4. Effects of a challenge cocaine (*A*) or morphine (*B*) injection on food-induced conditioned response (means + SEM). Cocaine was injected immediately before run B; morphine administered 15 min before run A. Cocaine and morphine increased locomotor activity in all animals; however, their stimulant effect was markedly potentiated in food-conditioned animals (FR) (*n* = 8 –10), compared with controls (FH) (*n* = 8 –10). Effects of pretreatment with GYKI 52466 (*C*), naltrexone (*D*), or SCH23390 (*E*) on cross-sensitization to cocaine. GYKI 52466 injected immediately before run A or naltrexone injected 30 min before run A suppressed cross-sensitization to cocaine in FR animals (*n* = 9), and activity was not different from FH animals (*n* = 7). SCH23390 reduced the stimulant effects of cocaine but failed to suppress the difference of activity between FR and FH animals (*$p < 0.05$, **$p < 0.01$, Student's *t* test to compare FR and FH groups in each condition; †$p < 0.05$, ††$p < 0.01$, †††$p < 0.001$, ANOVA).

locomotor sensitization. Food restriction both facilitates dopaminergic transmission, especially in the nucleus accumbens (Cadoni et al., 2003; Carr et al., 2003; Haberny et al., 2004; Lindblom et al., 2006), and increases the rewarding and stimulant properties of dopamine receptor agonists (Carr et al., 2001) and stimulant drugs (Deroche et al., 1993; Bell et al., 1997; Cabeza de Vaca et al., 2004). Facilitation of dopaminergic transmission in nucleus accumbens, and plasticity in associated pathways (Haberny et al., 2004; Haberny and Carr, 2005) may be a prerequisite for establishing behavioral sensitization to food.

Comparison of food sensitization with behavioral sensitization to drugs of abuse reveals several common features. Behavioral sensitization to addictive drugs persists for months after the treatment ceases (Paulson et al., 1991; Castner and Goldman-Rakic, 1999). In the present study, both the anticipatory response and conditioned hyperactivity to food reward persisted over a period of 3 weeks without exposure to the food-paired environment, showing that both of these responses were long-lasting. We have not yet tested longer periods.

Our finding that the food-paired context acquired the ability to evoke a conditioned locomotor response is consistent with observations (Bindra, 1968) that environmental stimuli paired with primary reinforcers stimulate locomotor activity, an effect that has been repeatedly confirmed (Jones and Robbins, 1992; Hayward and Low, 2005; Barbano and Cador, 2006). Furthermore, the locomotor activity observed in food-sensitized animals exposed to the food-paired context when food was omitted, was similar in amplitude to their activity measured when food was available. This result suggests that the sensitized locomotor activity observed in response to food presentation was a response conditioned to the environment, rather than one elicited by the food.

The establishment of behavioral sensitization and condi-

tioned activity to drugs depends on mechanisms related to those underlying some forms of long term potentiation, in that these phenomena are blocked by NMDA antagonists, protein synthesis inhibitors, and dopamine D_1 antagonists. The same mechanisms are not specifically required for the expression of sensitization or conditioned activity, which seem not to depend critically on D_1 receptor-mediated mechanisms (Beninger and Hahn, 1983; Cervo and Samanin, 1996; McFarland and Ettenberg, 1999). Nevertheless, presentation of cues predictive for sucrose availability evokes dopamine release in the nucleus accumbens (Roitman et al., 2004), suggesting a potential role for dopamine receptors in the food-induced conditioned response. In the present study, neither the D_1 antagonist SCH23390 nor the D_2/D_3 antagonist sulpiride reliably suppressed the expression of conditioned locomotion, at doses that already tended to decrease basal activity. Thus, activation of D_1 and D_2/D_3 receptors may play only a nonspecific role in the expression of food-conditioned activity, as with drug-conditioned activity.

Pretreatment with the opiate antagonist naltrexone abolished food-conditioned activity in FR animals, whereas it had little effect on the activity of controls, suggesting that opioid receptors are involved in the expression of food-induced sensitization. We are unaware of data on the effects of opioid blockade on the expression of cocaine sensitization, although naltrexone blocks the expression of behavioral sensitization to methamphetamine (Chiu et al., 2005). The ability of another opioid antagonist, naloxone, to decrease operant responding for food reinforcers (Glass et al., 1999) and food-conditioned locomotor activity in the presence of food (Hayward and Low, 2005), as well as the ability of the μ-agonist morphine to induce context-dependent conditioned feeding (Kelley et al., 2000) suggests a role for opiate receptors in food-conditioned responses.

The development and expression of cocaine-induced behavioral sensitization is associated with alterations in glutamatergic neurotransmission (Wolf, 1998; Vanderschuren and Kalivas, 2000). Among glutamate receptors, AMPA receptors appear to be specifically involved in controlling the expression of drug-induced conditioned activity (Pierce et al., 1996; Cornish and Kalivas, 2001; Carlezon and Nestler, 2002; Boudreau and Wolf, 2005), and AMPA receptor competitive antagonists NBQX [2,3-dihydroxy-6-nitro-7-sulfamoylbenzo(*F*)-quinoxaline] and DNQX (6,7-dinitroquinoxaline-2,3-dione) suppress conditioned activity to amphetamine and cocaine in mice (Cervo and Samanin, 1996; Mead and Stephens, 1998; Mead et al., 1999). In rats, the noncompetitive AMPA receptor antagonist GYKI 52466 blocks the expression of conditioned responses to cocaine (Hotsenpiller et al., 2001). In the present study, GYKI 52466 abolished food-conditioned activity, without influencing spontaneous activity (during the first 5 min of run B), suggesting that the expression of food-conditioned activity, like drug-conditioned activity, depends on the activation of AMPA receptors.

Once animals are sensitized to one drug, they often show cross-sensitization to other drugs (Vezina et al., 1989). In the present study, the ability of cocaine and morphine to increase locomotor activity was markedly enhanced in animals sensitized to food, compared with the control group. Although this increased response could be described as cross-sensitization, an alternative account is that cocaine or morphine's ability to stimulate activity was more easily seen if animals were already showing enhanced locomotion in the food-paired environment (Stephens and Mead, 2004). However, because in the converse experiment, previous exposure to amphetamine causes sensitization of the locomotor response to food stimuli (Jones et al., 1990;

Avena and Hoebel, 2003), it may be that pairing a context with either drugs or food results in facilitation of signaling in common underlying pathways.

Behavioral sensitization can be viewed as the result of associative learning processes involving drug-environment conditioning. According to this view, repeated administration of drugs in the same environment allows contextual cues to acquire the properties of a conditioned stimulus (CS), whereas the drug acts as an unconditioned stimulus. Presentation of the CS alone (the context) then becomes sufficient to trigger a drug-like conditioned response. Because the association of environmental stimuli with reward must be learned, the learning process, rather than the drug effect, provides the incremental nature of behavioral sensitization (Tilson and Rech, 1973; Pert et al., 1990). Applied to the phenomenon of cross-sensitization, this account predicts that drugs preventing the expression of conditioned activity should also suppress cross-sensitization to other rewards. We tested this prediction in food-conditioned animals, by administering GYKI 52466 and naltrexone before exposing them to cocaine. Both pretreatments suppressed cross-sensitization to the stimulant effects of cocaine. In contrast, pretreatment with SCH23390, which failed to suppress conditioned activity in FR animals, decreased locomotor activity in both groups, but failed to suppress cross-sensitization to cocaine. Thus, the cross-sensitization to cocaine observed in food-conditioned animals reflects the acute effects of the drug on the expression of conditioned response to the food-paired environment.

Together, the present results suggest that behavioral sensitization occurs not only to drugs of abuse, but also to a natural reward, food, and that these forms of sensitization have many features in common. On the one hand, the present data suggest that the ability of natural rewards to support behavioral sensitization and conditioned activity may imply a role for sensitization in incentive motivation for food. On the other hand, they may also suggest that an answer to the question of why drug seeking comes to dominate behavior, in a way that conventional reward seeking does not (Robinson and Berridge, 1993, 2001), does not lie in the ability of drugs to support behavioral sensitization.

Finally, we asked whether the conditioning of an environment to food that resulted in environment-associated increases in activity, might also affect feeding behavior. Discrete tone or light cues, paired with food while rats are food deprived, subsequently elicit feeding (Petrovich et al., 2002; Holland and Petrovich, 2005); similarly, food-sensitized mice consumed more food in the conditioning apparatus than a control group with identical exposure to the runways, but which had experienced the novel food in the home cage. Thus, the conditioned environment increased food consumption, possibly through the ability of such CSs to activate amygdala outputs to the lateral hypothalamus via accumbens and prefrontal cortex (Petrovich et al., 2005). Whether both the ability to increase locomotor activity and to stimulate feeding depend on related circuitries, and whether these are the same as circuitries activated during behavioral sensitization to drugs is an intriguing question.

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