

SHORT COMMUNICATION

Mice lacking dopamine D1 receptors express normal lithium chloride-induced conditioned taste aversion for salt but not sucrose

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Abstract

Conditioned taste aversion (CTA), is a form of Pavlovian learning wherein a novel flavour is powerfully associated with subsequent feelings of illness, and is afterwards avoided. In rats, pharmacological blockade of dopamine D1 receptors has been reported to prevent the expression of a CTA to the sweet taste of sucrose or saccharine. We used genetically modified mice to determine whether dopamine D1 receptors are necessary for the expression of a CTA. Food-deprived mice lacking the dopamine D1 receptor ($D1r^{-/-}$) did not express a LiCl-induced (125 or 254 mg/kg) CTA to the sweet taste of 0.5 M sucrose, in agreement with previous pharmacological studies. However, water-deprived $D1r^{-/-}$ mice did express normal LiCl-induced (40, 150 and 254 mg/kg) CTA to a salty taste (0.2 M NaCl). Our results suggest that activation of D1 receptors might contribute to the strength of an aversive gustatory association, but might not be required for the formation of a CTA in general.

Introduction

Conditioned taste aversion (CTA) is a form of Pavlovian conditioning first described by Garcia *et al.* (1955), in which a taste that has been associated with feelings of illness (malaise) is subsequently avoided. Dopamine might play an important role in CTA learning. Dopamine-releasing drugs such as amphetamine and cocaine can condition a powerful CTA (even at doses that animals avidly self-administer), as do selective dopamine D1 and D2 receptor agonists (SKF38393 and quinpirole, respectively; Hunt & Amit, 1987; Hoffman & Beninger, 1988; Asin & Montana, 1989; Parker, 1995; Grigson, 1997; Risinger & Boyce, 2002). Moreover, amphetamine can enhance CTA after LiCl, perhaps through increased D1 receptor activation (Fenu & Di Chiara, 2003).

Dopamine receptor antagonists, in contrast, can attenuate CTA (Grupp, 1977; Rabin & Hunt, 1989; Lin *et al.*, 1994). In rats, LiCl-induced CTA to the sweet tastes of saccharin or sucrose can be attenuated greatly by systemic administration of SCH23390, a selective D1 antagonist (Fenu *et al.*, 2001). SCH23390 itself does not condition a CTA even at 'doses well above those needed to produce catalepsy' (Asin & Montana, 1989). One explanation for these results is that blockade of D1 receptors interferes with central nervous system processes required for CTA learning. It has been proposed that D1 receptors in and near the lateral hypothalamus (LH), zona incerta (ZI), and nucleus accumbens (NAc) shell are essential for CTA learning (Cauliez *et al.*, 1996; Fenu *et al.*, 2001). In the LH/ZI region, lesion or nonselective nerve block by tetrodotoxin (TTX; which blocks voltage-gated sodium channels)

can prevent the subsequent formation of a CTA, but do not prohibit the expression of a CTA formed before the lesion (Cauliez *et al.*, 1996). Specific blockade of D1 receptors by SCH23390 in the LH/ZI also attenuated the formation of CTA subsequent to LiCl (Cauliez *et al.*, 1996). Similarly, microinjection of the D1 receptor antagonist SCH39166 into the NAc shell has been demonstrated to greatly attenuate LiCl induced CTA to saccharine in rats (Fenu *et al.*, 2001).

Here, we sought to test the hypothesis that dopamine D1 receptors play an essential role in CTA learning using a genetic model of dopamine D1 receptor deficiency (Drago *et al.*, 1994). Most studies in rats have used the sweet tastes of sucrose or saccharine as the conditioned flavour, and we replicated those studies here in $D1r^{+/+}$ and $D1r^{-/-}$ mice. In addition, because mice might learn a more robust CTA when the conditioned taste is salty (Risinger & Cunningham, 1995, 2000), we also tested the ability of mice to learn a CTA to a salty solution. Our results suggest that D1 receptors are important to, but are not required for, the expression of CTA learning.

Materials and methods

Animal handling and care

All procedures were in accordance with protocols approved by the IACUC at the University of Washington. Mutant mice lacking the dopamine D1 receptor gene ($D1r^{-/-}$) were generated as described (Drago *et al.*, 1994) and maintained on a congenic C57BL/6 J background in a specific pathogen-free facility. Heterozygous mice were bred to obtain mutant and wild-type littermates. After weaning, mice were housed in gender-segregated groups of 2–5 mice in

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polycarbonate mouse cages with 1/8 inch BED-O-COB bedding (Animal Specialties, Hubbard OR, USA) and nesting material ('nestlet' block; Ancare Corp., N. Belmore, NY, USA). Food (5LJ5, 'hi-energy breeder diet', 11% fat; PMI Nutritional Inc., Brentwood MO, USA) and water were available *ad libitum*, except as noted below.

Testing procedures

For CTA studies with sucrose, fasting was used to increase the motivation to consume the test solution. A total of 112 mice between 3 and 8 months of age were accustomed to intraperitoneal (i.p.) injections of phosphate-buffered saline (PBS). Before each trial, mice were moved to a fresh home cage without food. After a 24-h fast, they were transferred to individual testing cages, similar to their home cage but without food or water, and given access to sucrose (0.5 M). The sucrose solution was weighed before and after each test to determine consumption. Because the first exposure to sucrose occurred prior to aversion conditioning, this is called Trial 0. Subsequent trials (1–6) were conducted in an identical manner. The mice were not exposed to the sucrose solution before training to avoid any confound with latent inhibition (a phenomenon whereby previous exposure to a stimulus retards subsequent acquisition of a conditioned response to that stimulus), which might be affected by a congenital lack of D1 receptors. During the initial, preconditioned exposure (Trial 0), the mice were neophobic; when the tubes were removed and weighed after 1 h, few of the mice had consumed any sucrose. Because it was necessary to establish a baseline intake sufficient that changes from this baseline could be accurately determined by weighing, the tubes were immediately returned. Based on behavioural observation, the length of access to the sucrose solution was therefore set at 3 h. After the 3 h of access to sucrose, the tubes were removed and weighed and the mice were removed from the testing cage and immediately injected i.p. with LiCl (doses of either 125 or 254 mg/kg were administered by injecting 10 μ L/g body weight of a solution of either 12.5 or 25.4 mg/mL) or PBS. The $D1r^{-/-}$ mice demonstrated significantly greater neophobia than the controls when total intake was compared (Trial 0 $D1r^{-/-}$ 0.82 ± 0.14 vs. $D1r^{+/+}$ 1.31 ± 0.09 g intake; $P < 0.05$). It is not clear whether this difference was because of a slower rate or a delayed onset of intake by the $D1r^{-/-}$ mice. Immediately after injection, the mice were returned to the home cage. Food was returned at this time, and 3 days of access to food and water *ad libitum* were allowed between each test. The groups were divided such that all mice in a single home cage received the same treatment condition, either LiCl or saline, although mice receiving either dose of LiCl were cohoused. Those few fasted mice that had not consumed the test substance on the first or second testing day were not injected with LiCl, but were retested on subsequent testing days. The first trial during which the mouse drank the sucrose solution was then considered Trial 0. If a mouse had not tasted the sucrose by the third exposure, it was excluded from the study. Eight mice (one $D1r^{+/+}$ and seven $D1r^{-/-}$) were excluded for this reason.

For CTA studies with salt as the conditioned flavour, water deprivation was used to increase the motivation to consume the mildly salty test solution. A total of 45 $D1r^{+/+}$ and $D1r^{-/-}$ mice were housed individually and acclimated to i.p. injections and 22-h daily water deprivation over 8 days. Mice were then tested every other day. On a test day, mice were given access to a solution of 0.2 M NaCl for 1 h at 10.30 h, at the same time and in the same type of bottle that they were usually presented with water. This was followed by injection of LiCl (doses of 40, 150 or 254 mg/kg were administered by injecting 10 μ L/g body weight of a solution of 4, 15 or 25.4 mg/mL) at

11.00 h. Mice that did not drink any of the test solution on subsequent trials were not injected with LiCl. To avoid dehydration on LiCl-pairing days, water was given for 1 h at 16.30 h.

Data analysis

Intake data collected as grams were converted to a percentage of baseline (Trial 0) for each mouse as follows: $[100/\text{intake of mouse A during Trial 0 (mL)}] \times \text{intake of mouse A during Trial B (mL)} = \text{percentage of baseline intake for mouse A during Trial B}$. The data were analysed by repeated measures analysis of variance (ANOVA) using the program STATISTICA 6.0 (StatSoft, Tulsa OK, USA). For CTA studies with sucrose Tukey's *post hoc* analysis revealed no significant effect of LiCl dose in either genotype and the doses were pooled for further analysis. Comparisons of volume intake were made by Student's *t*-tests.

Results

Both $D1r^{+/+}$ and $D1r^{-/-}$ mice demonstrated neophobia towards the sucrose solution on the first exposure (Trial 0), which diminished with repeated unpunished (i.e. PBS-paired) exposures in the control groups (Fig. 1A and B). The neophobia of the smaller $D1r^{-/-}$ mice ($D1r^{-/-}$, 20.8 ± 1.1 g; $D1r^{+/+}$, 26.6 ± 0.9 g) might have been greater than that of the $D1r^{+/+}$ mice, because their intake on the first exposure was lower (0.82 ± 0.14 vs. 1.31 ± 0.09 mL; $P < 0.05$ by unpaired Student's *t*-test). After repeated unpunished exposures in the control groups, the intake by the $D1r^{-/-}$ and $D1r^{+/+}$ mice

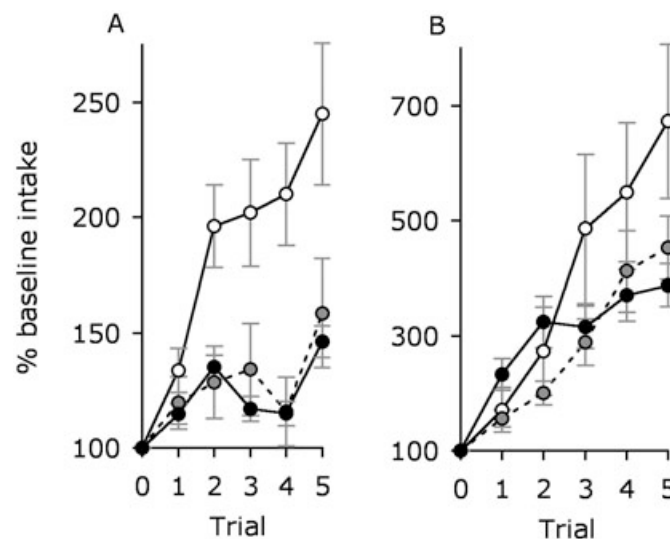


FIG. 1. $D1r^{+/+}$ (A), but not $D1r^{-/-}$ (B), mice expressed a conditioned aversion to 0.5 M sucrose after LiCl. (A) Unpunished (PBS) $D1r^{+/+}$ mice ($n = 16$, open circles) gradually increased their intake of 0.5 M sucrose after a 24 h fast across trials. By comparison, hungry $D1r^{+/+}$ mice that received 125 mg/kg ($n = 20$, grey circles) or 254 mg/kg LiCl ($n = 22$, black circles) after each trial manifested a significant aversion to the sucrose ($F_{1,56} = 5.34$, $P < 0.05$). (B) The smaller $D1r^{-/-}$ mice initially demonstrated lower absolute intake of 0.5 M sucrose after a 24-h fast as compared with the $D1r^{+/+}$ mice, but across trials they reached the same level of intake as the unpunished $D1r^{+/+}$ mice. $D1r^{-/-}$ mice that received PBS ($n = 10$, open circles), 125 mg/kg ($n = 14$, grey circles), and 254 mg/kg LiCl ($n = 22$, black circles) manifested an equivalent reduction of neophobia across repeated exposures, and no aversion associated with prior LiCl, even at the higher dose of 254 mg/kg ($F_{1,44} = 0.03$, $P = 0.87$). Values plotted are the average percentage baseline intake \pm SEM.

was similar (2.15 ± 0.14 vs. 1.97 ± 0.09 , respectively), suggesting that the $D1r^{-/-}$ mice are equally capable of finding and ingesting the sucrose. Injection of LiCl after exposure to the sucrose caused the $D1r^{+/+}$ mice to significantly reduce intake of the sucrose solution as compared with the intake of PBS-treated $D1r^{+/+}$ controls ($F_{1,56} = 5.34$, $P < 0.05$). There was no significant effect of LiCl dose on subsequent aversion. By contrast, $D1r^{-/-}$ mice treated with LiCl demonstrated no aversion (Fig. 1B), even at the higher dose of LiCl ($F_{1,44} = 0.03$, $P = 0.87$). During the testing interval, mice of both genotypes actively explored the chambers, and the $D1r^{-/-}$ mice did not manifest any marked locomotor deficit. In fact, mice of both genotypes seemed significantly more active in the testing chambers than in the home cage. On observation, both genotypes demonstrated behavioural signs of malaise after injection of LiCl, including body elongation with contraction of the abdominal walls, hindlimb extension, elevation of the tail, hunched posture and several hours of inactivity. This response was less pronounced following the lower dose of LiCl.

In contrast to the neophobia demonstrated by hungry mice towards the sucrose solution, thirsty $D1r^{+/+}$ and $D1r^{-/-}$ mice avidly consumed the 0.2 M NaCl solution during the first 1-h exposure (1.10 ± 0.10 vs. 1.12 ± 0.20 mL, respectively). At the highest dose of LiCl (254 mg/kg) $D1r^{+/+}$ mice demonstrated a strong avoidance of the salty solution after a single pairing (Fig. 2A). The CTA expressed by mice to a salty taste seemed more robust than the CTA that was conditioned by the same dose of LiCl to a sweet taste, in agreement with earlier reports (Risinger & Cunningham, 1995, 2000). Whereas mice given a high dose of LiCl after the salty taste avoided that taste (their intake was reduced to less than a quarter of what it had been before conditioning), the

same dose after sucrose caused an aversion only as compared with the subsequent intake of unpunished controls (Fig. 1A). The $D1r^{-/-}$ mice expressed a CTA to the salty taste that was not different from that of the $D1r^{+/+}$ controls (Fig. 2B). Mice lacking dopamine D2 receptors (Kelly *et al.*, 1997) also demonstrated no deficit with the salty taste (data not presented).

Discussion

At a minimum, the expression of successful CTA learning requires that the conditioned flavour be detected, that the malaise be detected, that the flavour be associated with the malaise, that the flavour–malaise association be retrieved, and the animal express that learning and memory in performance. Our results are consistent with several pharmacological studies in rats (Asin & Montana, 1989; Caulliez *et al.*, 1996; Fenu *et al.*, 2001; Fenu & Di Chiara, 2003) wherein D1 receptor blockade prevented the subsequent expression of a conditioned aversion to a sweet flavour, even after repeated pairing with LiCl. Thus D1 receptor activation may be required for at least one of the brain processes involved by the acquisition and expression of taste aversion learning. Sucrose preference has been reported to be normal in $D1r^{-/-}$ mice (El-Ghundi *et al.*, 2003), and in genetically modified mice lacking dopamine (Cannon & Palmiter, 2003). In addition, D1 antagonists blocked the subsequent expression of CTA to sweet tastes when they were administered after consumption of the test solution (Caulliez *et al.*, 1996; Fenu *et al.*, 2001), but not when the antagonist was given prior to consumption (Fenu *et al.*, 2001). Thus, it is unlikely that D1 receptor activation is required for the perception of sweet taste, or that D1 receptor inactivation interferes with the ability to taste sweets. Our own behavioural observations suggest that $D1r^{-/-}$ mice experience equivalent interoceptive malaise after LiCl. In addition, D1 receptor antagonists did not attenuate the reduction of water intake caused by malaise after LiCl (Caulliez *et al.*, 1996). It seems unlikely then that the deficit demonstrated by $D1r^{-/-}$ mice with a sweet taste was caused by an inability to perceive malaise.

It has been suggested that signalling via D1 receptors strengthens the consolidation of gustatory short-term memory during CTA learning (Caulliez *et al.*, 1996; Fenu & Di Chiara, 2003). A pharmacological and genetic literature supports the idea that dopamine receptors are important for adequate performance in associative learning tasks involving both rewarding and aversive consequences (Acquas *et al.*, 1989; Fremeau *et al.*, 1991; Miner *et al.*, 1995; Caulliez *et al.*, 1996; Baker *et al.*, 1998; El-Ghundi *et al.*, 1999; Karasinska *et al.*, 2000; Azzara *et al.*, 2001; Fenu *et al.*, 2001; Ranaldi & Wise, 2001; El-Ghundi *et al.*, 2003). However, we demonstrated here that $D1r^{-/-}$ mice manifest a strong aversion to a salty taste after association with LiCl.

The difference we have observed between the sweet and salty taste studies in $D1r^{-/-}$ mice could be explained in at least two ways. One the one hand, it is possible that the central neural processes that mediated the learning of gustatory associations were fundamentally different between the two studies. We demonstrated that, in normal mice, the same dose of LiCl paired with the salty taste elicited a much stronger aversion than when paired with sucrose. Factors that might have contributed to the greater expression of CTA in the salt studies include taste, deprivation state and differences in the housing and testing conditions, e.g. (Grigson *et al.*, 2000; Risinger & Boyce, 2002). Whereas deprivation was used to enhance motivation to consume the test substance in both experiments, food and water deprivation are distinct states. If the mechanism of CTA learning was different in the two studies, it is possible that D1 receptor activation is

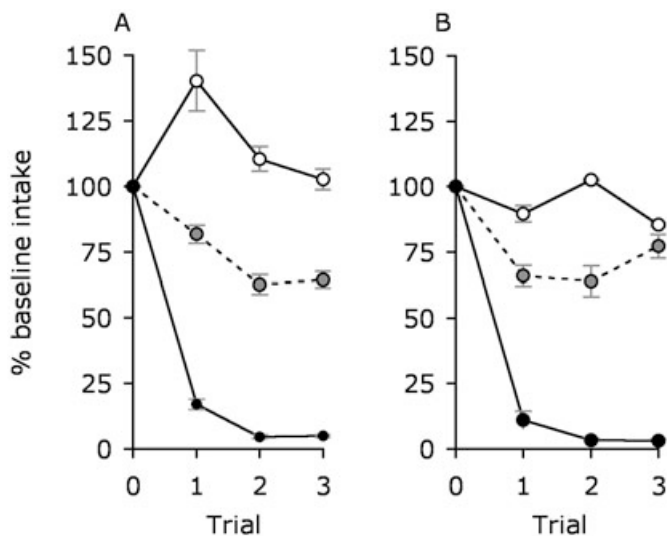


FIG. 2. Both $D1r^{+/+}$ (A) and $D1r^{-/-}$ (B) mice demonstrated dose-dependent CTA to 0.2 M NaCl after LiCl. (A) Intake of NaCl as a percentage of baseline in $D1r^{+/+}$ mice after 40 ($n = 8$, open circles), 150 ($n = 8$, grey circles) or 254 mg/kg LiCl ($n = 7$, black circles). Mice reduced intake as compared with baseline after both 150 and 254 mg/kg LiCl. (B) Intake of NaCl as a percentage of baseline in $D1r^{-/-}$ mice after 40 ($n = 8$), 150 ($n = 8$) or 256 mg/kg LiCl ($n = 6$). Mice reduced intake as compared with baseline after both 150 and 254 mg/kg LiCl. No difference was observed between the response of the $D1r^{+/+}$ and $D1r^{-/-}$ mice at the two higher doses. At the lowest dose of LiCl (40 mg/kg) there was a significant effect of genotype ($P < 0.05$), because the $D1r^{+/+}$ ($n = 8$) drank slightly more than the $D1r^{-/-}$ ($n = 8$) mice. This difference might have been caused by greater learning or neophobia by the $D1r^{-/-}$, but is most likely a sampling error, as it is not supported by similar trends at higher doses of LiCl. Values plotted are the average percentage baseline intake \pm SEM.

necessary for CTA learning only under certain conditions, such as those used for the sucrose study. On the other hand, it is also possible that the difference simply reflects the relative strength of the underlying aversions. If D1 receptor activation is not essential to CTA learning, but is able to strengthen the expression of a CTA, it is possible that we would observe diminished expression of the weak CTA for sucrose, but not the strong CTA for salt, in the *D1r*^{-/-} mice.

The latter explanation is supported by several observations. D1 receptor blockade also failed to abolish CTA to a sweet taste when a two-bottle choice paradigm was used (Asin & Montana, 1989; Lin *et al.*, 1994). We used a one-bottle (no choice) test because this protocol is better suited to assess subtle changes in the relative strength of a CTA, however, the two-bottle test is more sensitive to the presence of a weak aversion. The inability of the D1 receptor antagonist to diminish the expression of a CTA in the two-bottle tests suggests that D1 activation is not required for the formation of aversive gustatory associations. In agreement with this idea, when Fenu *et al.* (2001) assessed CTA by taste reactivity, D1 receptor blockade with SCH23390 did not attenuate the loss of hedonic responses, and only partially reduced aversive responding, although the same dose of SCH23390 completely abolished expression of LiCl-induced CTA when rats were given saccharin *ad libitum*. The failure of D1 receptor blockade to abolish changes in taste reactivity after CTA conditioning again suggested that some learning of the negative gustatory association occurred in the absence of D1 receptor activation. Finally, dopamine-depleting 6-hydroxydopamine (6-OHDA) lesions (> 98% depletion of dopamine in the NAc), did not prevent rats from learning a flavour aversion to a sweet taste paired with LiCl as assessed by changes in taste reactivity (Berridge & Robinson, 1998). Thus NAc dopamine receptor activation is not required for aversive flavour conditioning, even in response to sweet tastes. However, activation of D1 receptors during aversive conditioning might be necessary for subsequent robust expression of the CTA in a one-bottle test.

In conclusion, we demonstrate that mice lacking D1 receptors were able to acquire and express a CTA to a salty solution paired with LiCl. In contrast, *D1r*^{-/-} mice did not express an appropriate CTA to a sweet taste paired with LiCl, in agreement with previous pharmacological reports. We cannot exclude the possibility that hungry *D1r*^{-/-} mice might have learned that the sweet taste of 0.5 M sucrose predicted aversive consequences after repeated pairing with LiCl, but did not adjust their intake accordingly. However, the ability of the *D1r*^{-/-} mice to learn the association with a salty flavour suggests that it is possible to learn and express a conditioned flavour aversion in the absence of functional D1 receptors.

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Abbreviations

6-OHDA, 6-hydroxydopamine; CTA, conditioned taste aversion; LH, lateral hypothalamus; i.p., intraperitoneal; NAc, nucleus accumbens; PBS, phosphate-buffered saline; TTX, tetrodotoxin; ZI, zona incerta.

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