Original Article

The Effect of Cholestasis on Rewarding and Exploratory Behaviors Induced by Opioidergic and Dopaminergic Agents in Mice

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Abstract

Background: Several investigations have indicated that cholestasis decreases opioid receptor expression in the brain following increased opioidergic neurotransmission. The opioidergic system plays an important role in regulation of reward circuits that may be produced via dopamine-dependent mechanisms. It has been suggested that the dopaminergic system of the nucleus accumbens is necessary in conditioned place preference (CPP). The aim of this study is, therefore, to test if cholestasis can alter the reward system and the involvement of opioidergic and dopaminergic systems in this phenomenon.

Methods: We used CPP and hole-board paradigms to measure the reward effect and exploratory behaviors, respectively, in mice. Cholestasis was induced by ligation of the main bile duct, using two ligatures and transecting the duct between them (BDL mice).

Results: The data showed that morphine (1 and 2 mg/kg), sulpiride (80 mg/kg) and SKF38393 (20 mg/kg) produced CPP, while naloxone (1 mg/kg) and SCH23390 (1mg/kg) produced conditioned place aversion (CPA), whereas quinpirole had no effect in sham-operated mice. However, morphine (2 mg/kg, i.p.), sulpiride (40 mg/kg) and SKF38393 (10 mg/kg) induced CPP in BDL mice compared to sham-operated mice. Naloxone- or SCH23390-induced CPA was reduced in BDL mice compared with the respective sham-operated mice. Quinpirole tended to induce aversion in BDL mice which was, however, not significant. In addition, quinpirole 1 mg/kg) and SCH23390 (1 mg/kg) increased head-dip exploratory behavior, whereas naloxone (2 mg/kg) caused a decrease in head-dip exploratory behavior in sham-operated mice. Morphine (2 mg/kg), SCH23390 (1 mg/kg) and quinpirole (0.25 and 0.5 mg/kg) induced anxiogenic-like behavior in BDL mice.

Conclusion: It can be concluded that cholestasis differentially alters the reward effects of opioidergic and dopaminergic agents.

Keywords: Cholestasis, conditioned place preference, dopaminergic agents, exploratory behaviors morphine

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Introduction

A psychological reward is fundamental to the organization of behavior, which induces pleasure and supports elementary processes such as drinking, eating, and reproduction.[1] The cortical-basal ganglia circuit is highly involved in the reward system, though cells in many other brain regions may also respond to reward. The anterior cingulate cortex, orbital prefrontal cortex, ventral striatum, ventral pallidum, and midbrain dopamine (DA) neurons are main structures in the reward network.[1] The neurotransmitter, DA, has also been shown to play an important role in reward phenomenon.[2,3] Five different DA receptors have been identified, which are G protein-coupled and are categorized as belonging to one of the two classes designated as D1-like (D1 and D5) or D2-like (D2, D3, and D4).[4,5] Autoreceptors, which are D2-like, have been identified on the presynaptic terminals of dopaminergic cells. D1-like receptors, on the other hand, can stimulate adenylyl cyclase activity and increase cyclic adenosine monophosphate (cAMP). Conversely, D2-like receptor activation either inhibits or has no effect on cAMP levels.[5]

Opiates elicit rewarding effects at the level of the mesolimbic DA system that originates from the ventral tegmental area (VTA) and projects to the nucleus accumbens (Nac).[6] A large body of evidence has demonstrated that the activation of VTA DA neurons via inhibition of GABAergic inhibitory interneurons causes an increase in DA neurotransmission to the Nac and induces a morphine reward.[7,8]

Bile duct ligation (BDL) is a well-known model of liver disease (also termed "cholestatic liver disease") in rats and, to a lesser extent, in mice and it mimics biliary liver disease in humans.[9] An increase in the endogenous opioid peptide, met-enkephalin, has been reported during cholestatic liver disease [10] and may be a predictor of reduced survival in patients with cholestasis.[10] Naloxone-induced withdrawal syndrome has also been observed to occur in cholestatic mice[11] as well as morphine-dependent mice.[12,13] Observations indicating the increase in endogenous opioids are compatible with a global down-regulation of mu-opioid receptor in the brain of BDL rats.[14] Opiates and endogenous opioids have attracted increased research interest, because opioids produce a psychologically reinforcing effect which can result in their abuse.[15]

It is believed that the conditioned place preference (CPP) paradigm reflects a preference for a context due to the contiguous as-

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sociation between the context and the drug stimulus.[16] It can be used as a model for studying the reinforcing effects of drugs with dependent liability.[17]

In view of the link between cholestasis and the opioidergic system, and the involvement of opioidergic and dopaminergic systems in regulation of reward circuits, this study aims to investigate the effect of cholestasis (BDL) on the reward system and exploratory behaviors induced by opioidergic and dopaminergic agents.

Materials and Methods

1. Animals

Male NMRI mice that weighed 25–30 g were used. The animals were housed in standard polypropylene cage colonies maintained at 22 ± 2°C under a 12:12 hr light-dark cycle (lights on at 07:00) and had free access to food and water. Animals were allowed to adapt to laboratory conditions for at least one week before surgery. Each animal was used only once. Eight animals were used in each experimental group. The experiments were carried out during the light phase of the cycle. Animal treatment and maintenance were conducted in accordance with the Principles of Laboratory Animal Care (NIH 98 publication No. 85–23, revised 1985) and in line with the Animal Care and Use Guidelines of Tehran University of Medical Sciences, Tehran, Iran.

2. Surgical procedure

There were two experimental groups: sham-operated and BDL mice. Laparotomy was performed under general anesthesia induced by an intraperitoneal (i.p.) injection of ketamine hydrochloride (50 mg/kg) plus xylazine (5 mg/kg). The sham-operation consisted of a laparotomy and bile duct identification and manipulation without ligation or resection. In the BDL group, the main bile duct was first ligated using two ligatures approximately 0.5 cm apart and then transected at the midpoint between the two ligatures.[18] Immediately after the operation each animal was placed alone in a cage to prevent wound dehiscence and then moved to its original cage 4 hr after surgery.[19] The animals were allowed to recover from the surgery for one week. Operative mortality was less than 5%.

3. Conditioned place preference (CPP) protocol

The CPP apparatus was based on one that was used previously.[20] Compartments A and B were identical in size (40 × 30 × 30 cm) but differed in shading. Compartment A was white with black horizontal stripes 2-cm wide on the walls and had a textured floor. Compartment B was black with vertical white stripes 2-cm wide and had a smooth floor. Compartment C (40 × 15 × 30 cm) was painted red and was attached to the rear of compartments A and B; it had removable wooden partitions that separated it from the other compartments. When the partitions were removed, the animal could freely move between the two compartments (A and B) via compartment C. Preference times and locomotor activity were recorded by a video camera with the monitor and a computer-recording system installed in an adjacent room. Raw data of the behaviors were manually analyzed.

3.1.1. Place conditioning

One week after BDL or the sham-operation, CPP was conducted using an unbiased procedure according to previous studies.[21,22] CPP consisted of a five-day schedule with three distinct phases: preconditioning, conditioning, and testing.

3.1.2. Preconditioning

The animals were placed in the middle of the apparatus and allowed to freely explore the three compartments for 15 min (900 s). The time spent by the animals in each compartment was recorded for 900 s. The position of the mice was defined by the position of their front paws. Animals that showed strong unconditioned aversion (less than 33% of the session time, i.e., 300 s) or preference (more than 67%, i.e., 600 s) for any compartment were discarded. Animals were then randomly assigned to one of two groups for place conditioning. After assigning the compartments, there were no significant differences between time spent in the drug-paired and the vehicle-paired compartments during the preconditioning phase. A total of eight animals were used for each subsequent experiment.[8]

3.1.3. Conditioning

The place conditioning phase began one day after the preconditioning phase. This phase consisted of six, 45-min sessions (three saline and three drug pairing) conducted twice daily (from days 2 to 4) with a 6-hr interval between tests. On each of these days, animals received one conditioning session with drug and another with saline. During these sessions, the animals were confined to one compartment by closing the removable wall. Animals of each group were injected with drug and immediately confined to one compartment of the apparatus for 45 min. Six hours later, the animals received saline and were confined to the other compartment for 45 min. The treatment compartment and order of administration of the drug and saline were counterbalanced for each group during conditioning.

3.1.4. Testing

The testing phase was carried out on day 5, one day after the last conditioning session. Each animal was tested only once. For testing, the removable wall was raised and the animals were free in the apparatus for 15 min. The time spent in the drug-paired compartment was recorded for each animal and the change in preference was calculated as the difference (in seconds) between the time spent in the drug-paired compartment on the testing day and the time spent in this compartment on the preconditioning day.

3.2. Locomotor activity

Locomotor testing was carried out on the fifth day of the schedule for the mice that had undergone place conditioning using the CPP apparatus, and was in a morphine-free state. To measure locomotor activity, the floor of the CPP compartment was divided into four equal-sized squares. Locomotion was measured as the number of crossings from one square to another during 15 min.

4. Hole-board apparatus and exploratory behavior testing

The hole-board test is a simple method for examining the response of an animal to an unfamiliar environment that was first introduced by Boissier and Simon.[23] This test has been used to evaluate emotional behavior, anxiety and/or response to stress in animals.[24] The observation and measurement of different behaviors in this test results in a comprehensive understanding of an animal's behavior. The hole-board apparatus (Borj Sanat Co., Tehran, Iran) consisted of gray Perspex panels (40 cm × 40 cm × 2.2 cm) with 16 equidistant holes that were 3 cm in diameter in the floor, which were constructed based upon a previous method.[24] The board was positioned 15 cm above a table. For anxiety testing, at 5 min after CPP testing, the animals were individually placed in the center of the board facing away from the observer and head-dip numbers were recorded by photocells arranged below the holes for a period of 5 min. Increases or decreases in

head-dip indicated anxiolytic-like or anxiogenic-like behavior, respectively. Other behavioral performances such as latency to the first head-dip and the numbers of rearing, grooming and defecation were manually recorded by the observer during the test. Since latency to head-dip, grooming and rearing parameters did not change throughout all the experiments, two-way analysis of variance (ANOVA) results for these behaviors are not shown.

5. Drugs

The drugs used in the present study were morphine sulfate (Temad Co., Tehran, Iran); naloxone, quinpirole, and sulpiride (Sigma Chemical Co., St. Louis, CA, USA); 1-phenyl-7,8-dihydroxy-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride (SKF38393); and R(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride (SCH23390). All drugs were dissolved in sterile 0.9% saline just prior to the experiment, with the exception of sulpiride, which was dissolved in vehicle. The vehicle was one drop of glacial acetic acid (Hamilton micro syringe) that was made up to a volume of 5 mL with sterile 0.9% saline and then diluted to the required volume. Control animals received either saline or vehicle. All drugs were administered i.p. in a volume of 10 mL/kg. The doses of drugs used in this study and the interval between drug injections were based on our previous studies.[17,24]

Table 1. Two-way ANOVA and post hoc analyses results for the effect of BDL upon behaviors induced by morphine (experiment 1), naloxone (experiment 2), quinpirole (experiment 3), sulpiride (experiment 4), SKF38393 (experiment 5), and SCH23390 (experiment 6).

Experiment	Behaviors	Treatment effect		BDL effect		Treatment-BDL interaction		Effect of BDL on behaviors induced by drugs
		$F_{(3,56)}$	*P*	$F_{(1,56)}$	*P*	$F_{(3,56)}$	*P*	**Effect of BDL on behaviors induced by morphine**
Experiment 1	CPP	19.73	0.000	28.77	0.000	3.09	0.034	Decreased
	Head-dip counts	2.74	0.052	2.30	0.135	2.97	0.040	Decrease head-dips
	Locomotion	1.31	0.279	2.20	0.144	0.99	0.406	No effect
	Defecations	6.29	0.001	1.11	0.297	1.77	0.164	No effect
Experiment 2		$F_{(4,70)}$	*P*	$F_{(1,70)}$	*P*	$F_{(4,70)}$	*P*	**Effect of BDL on behaviors induced by naloxone**
	CPP	8.90	0.000	20.11	0.000	3.07	0.022	decreased CPA
	Head-dip counts	4.92	0.001	1.74	0.192	2.11	0.089	No effect
	Locomotion	4.04	0.005	0.34	0.563	1.87	0.126	No effect
	Defecations	0.32	0.865	0.94	0.335	1.55	0.197	No effect
Experiment 3		$F_{(3,56)}$	*P*	$F_{(1,56)}$	*P*	$F_{(3,56)}$	*P*	**Effect of BDL on behaviors induced by Quinpirole**
	CPP	1.58	0.203	0.00	0.984	1.26	0.298	No effect
	Head-dip counts	8.05	0.000	26.65	0.000	3.20	0.317	Decreased
	Locomotion	2.95	0.041	2.68	0.107	3.17	0.031	Decreased
	Defecations	1.08	0.364	0.96	0.332	1.53	0.218	No effect
Experiment 4		$F_{(3,56)}$	*P*	$F_{(1,56)}$	*P*	$F_{(3,56)}$	*P*	**Effect of BDL on behaviors induced by sulpiride**
	CPP	9.90	0.000	56.42	0.000	7.23	0.000	Increased
	Head-dip counts	2.81	0.047	12.03	0.001	2.12	0.01	No effect
	Locomotion	4.50	0.007	0.49	0.488	0.11	0.955	No effect
	Defecations	0.75	0.529	2.85	0.097	2.04	0.119	No effect
Experiment 5		$F_{(3,56)}$	*P*	$F_{(1,56)}$	*P*	$F_{(3,56)}$	*P*	**Effect of BDL on behaviors induced by SKF38393**
	CPP	13.04	0.000	5.64	0.021	3.88	0.014	Increased
	Head-dip counts	2.1	0.001	1.29	0.261	0.25	0.863	No effect
	Locomotion	6.61	0.001	0.54	0.467	2.26	0.091	No effect
	Defecations	0.69	0.561	0.41	0.841	2.97	0.039	Increased
Experiment 6		$F_{(3,56)}$	*P*	$F_{(1,56)}$	*P*	$F_{(3,56)}$	*P*	**Effect of BDL on behaviors induced by SCH23390**
	CPP	11.84	0.000	0.24	0.624	1.53	0.217	Decreased CPA
	Head-dip counts	5.60	0.002	15.45	0.000	4.20	0.03	Decreased
	Locomotion	2.18	0.101	2.69	0.107	1.56	0.208	No effect
	Defecations	0.96	0.416	2.94	0.092	1.99	0.127	No effect

6. Drug treatments

Effects of morphine, naloxone, quinpirole, sulpiride, SKF38393 or SCH23390 with or without BDL upon the behaviors

Six experiments (EXP) were designed for this study. For all EXP, the drugs were injected i.p. The sham-operated and BDL animals received different doses of morphine (0.5, 1 and 2 mg/kg in EXP.1), naloxone (0.5, 1, 1.5 and 2 mg/kg in EXP.2), quinpirole (0.25, 0.5 and 1 mg/kg in EXP.3), sulpiride (20, 40 and 80 mg/kg in EXP.4), SKF38393 (5, 10 and 20 mg/kg in EXP.5) or SCH23390 (0.25, 0.5 and 1 mg/kg in EXP.6) during the conditioning phase of the CPP. In EXP.4 the control group received vehicle (10 mL/kg), however, in the other EXPs the control groups received saline (10 mL/kg). The conditioning scores were then measured in a drug-free state on the test day. The exploratory behaviors of animals were recorded by the hole-board task after place conditioning testing.

7. Statistical analysis

Comparisons between groups were made with two-way ANOVA using SPSS 17.0 software. Following a significant F value, post hoc analysis (Tukey's test) was performed for assessing specific inter-group comparisons. $P < 0.05$ between the experimental groups was considered statistically significant. We used Sigmaplot software to draw the figures. In all experiments, Table 1 shows two-way ANOVA results for latency to first head-dip, grooming, rearing and defecation.

Results

1. Induction of cholestasis

Two days after BDL, the animals showed signs of cholestasis (jaundice, dark urine, and steatorrhea), which has been tested qualitatively and quantitatively by other investigators.[25,26] Table 1

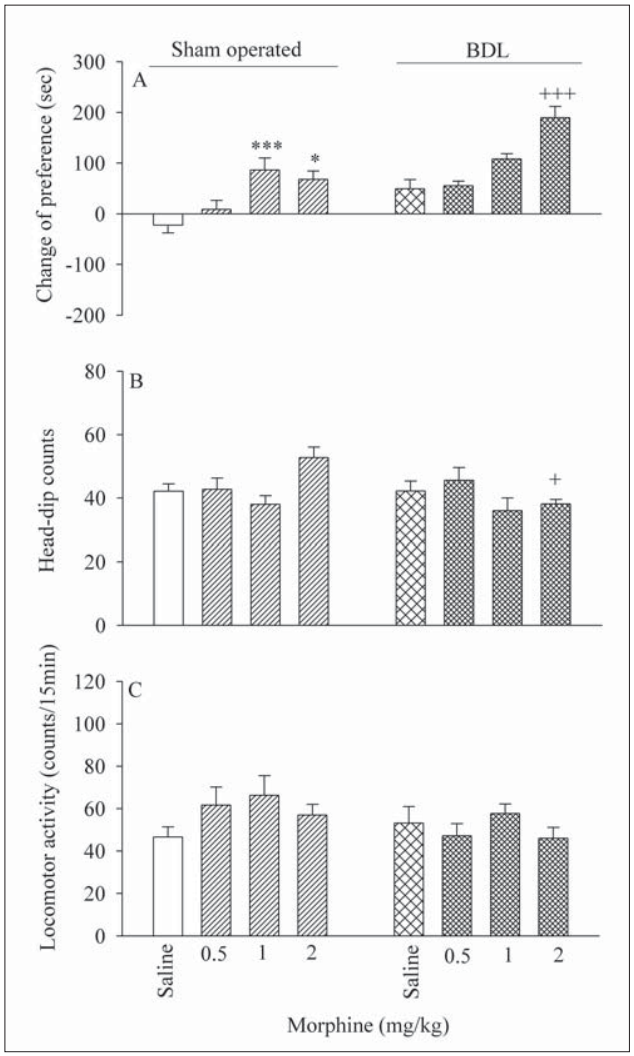

Figure 1. Effect of morphine with or without BDL on the acquisition of CPP and exploratory behaviors. Panel A shows the effect of morphine in a 3-day schedule of conditioning in sham-operated and BDL mice on CPP. In panel B, the numbers of head-dip counts were examined after CPP testing. In addition, locomotor activity was assessed during the post-conditioning day (panel C). Data are expressed as mean ± SEM. $^{*}P < 0.05$ and $^{***}P < 0.001$ different from the saline control group. $^{+}P < 0.05$ $^{+++}P < 0.001$ different from the respective groups.

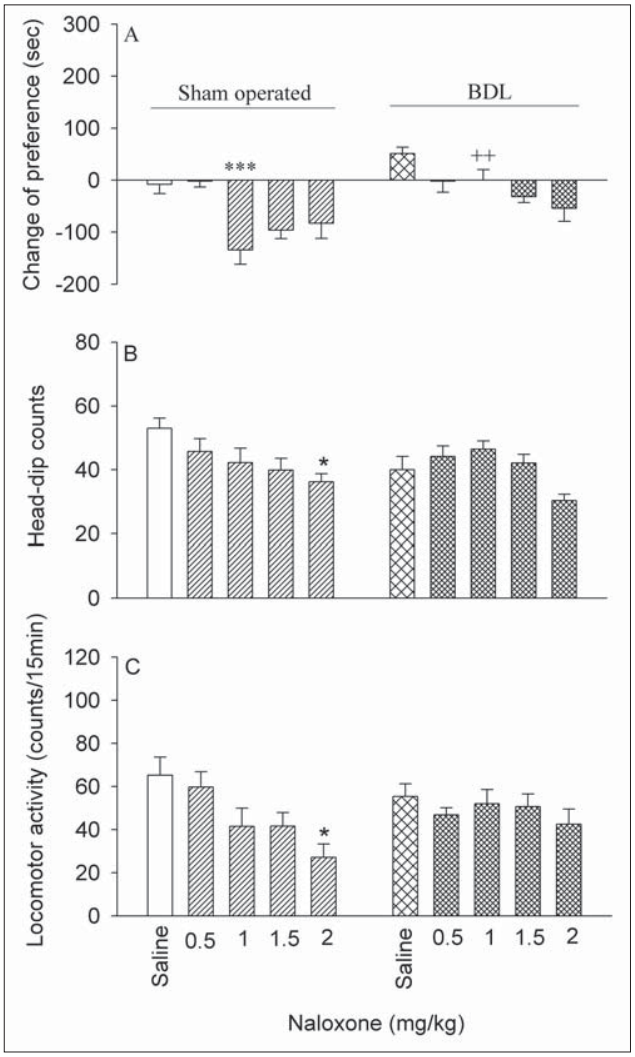

Figure 2. Effect of naloxone with or without BDL on the acquisition of CPP and exploratory behaviors. Panel A shows the effect of naloxone in a 3-day schedule of conditioning in sham-operated and BDL mice on CPP. In panel B, the numbers of head-dip counts were examined after CPP testing. In addition, locomotor activity was assessed during post-conditioning day (panel C). Data are expressed as mean ± SEM. $^{*}P < 0.05$ and $^{***}P < 0.001$ different from the saline control group. $^{+++}P < 0.001$ different from the respective group.

summarizes the results of two-way ANOVA, *P* values, and behavior effects for all EXP.1-.6.

2. Effect of BDL on behaviors induced by morphine

Two-way ANOVA and post hoc comparison of the means indicated that the dose response curve of morphine shifted to the right in BDL animals (Figure 1A) while the drug decreased head-dip counts (Figure1B) but did not alter locomotor activity (Figure 1C), latency to head-dip, grooming, rearing, and defecation responses induced by morphine.

3. Effect of BDL on behaviors induced by naloxone

Two-way ANOVA and post hoc comparison of the means indicated that BDL significantly decreased conditioned place aversion (CPA; Figure 2A) but did not alter head-dip counts (Figure 2B), locomotor activity (Figure 2C), latency to head-dip, grooming, rearing, and defecation responses induced by naloxone. The highest dose of naloxone, alone, decreased head-dip counts, and locomotor activity.

4. Effect of BDL on behaviors induced by quinpirole

Two-way ANOVA revealed that BDL decreased head-dip counts (Figure 3B) and locomotor activity (Figure 3C) while it did not alter CPP (Figure 3A), latency to head-dip, grooming, rearing, and defecation. Furthermore, post hoc analysis showed that sole administration of quinpirole increased head-dip counts as compared to the sham-operated control group, while BDL decreased locomotor activity compared to the BDL control group.

5. Effect of BDL on behaviors induced by sulpiride

Two-way ANOVA and post hoc analysis revealed that the dose response curve of sulpiride for CPP shifted to the left in BDL animals (Figure 4A). BDL did not alter head-dip counts (Figure 4B), locomotor activity (Figure 4C), latency to head-dip, grooming, rearing, and defecation induced by sulpiride.

6. Effect of BDL on behaviors induced by SKF38393

Two-way ANOVA and post hoc analysis showed that the dose

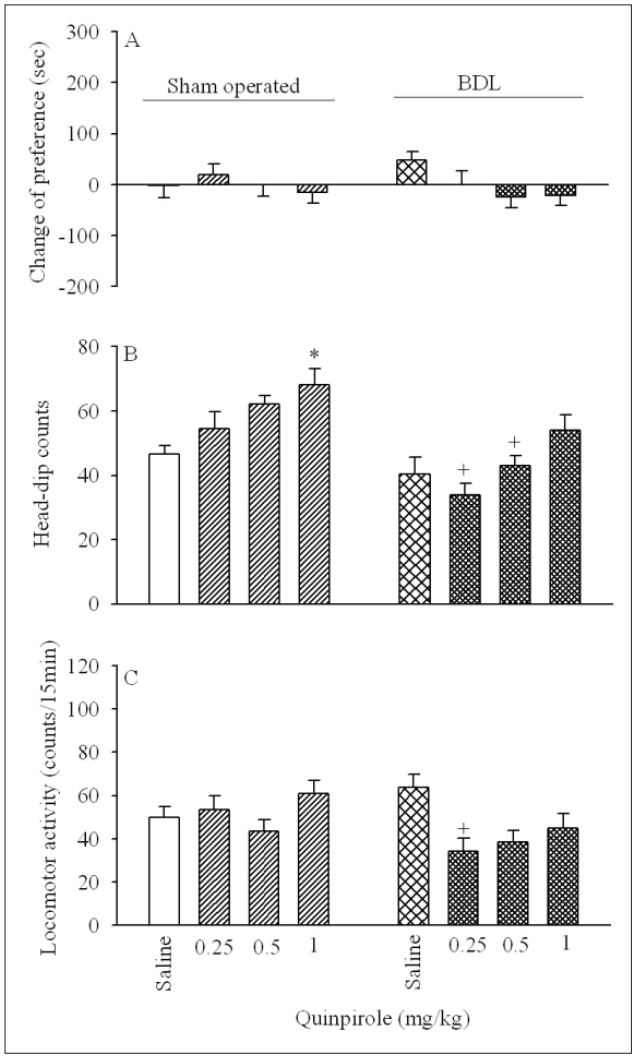

Figure 3. Effect of quinpirole with or without BDL on the acquisition of CPP and exploratory behaviors. Panel A shows effect of quinpirole in a 3-day schedule of conditioning in sham-operated and BDL mice on CPP. In panel B, the numbers of head-dip counts were examined after CPP testing. In addition, locomotor activity was assessed during post-conditioning day (panel C). Data are expressed as mean ± SEM. $^{*}P < 0.05$ different from the saline control group. $^{+}P < 0.05$ different from the respective group.

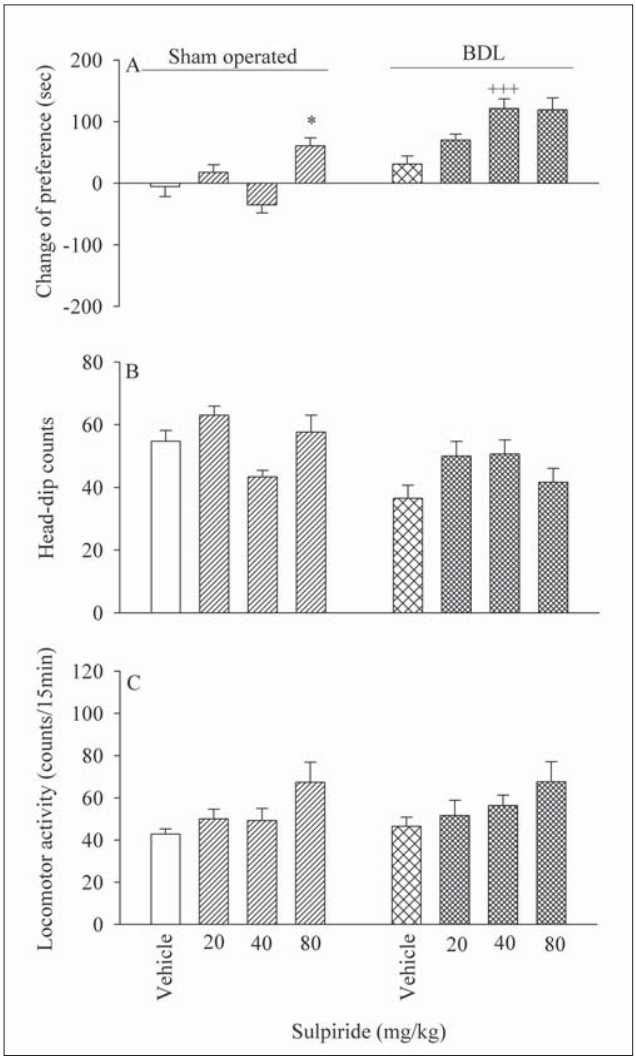

Figure 4. Effect of sulpiride with or without BDL on the acquisition of CPP and exploratory behaviors. Panel A shows the effect of sulpiride in a 3-day schedule of conditioning in sham-operated and BDL mice on CPP. In panel B, the numbers of head-dip counts were examined after CPP testing. In addition, locomotor activity was assessed during post-conditioning day (panel C). Data are expressed as mean ± SEM. $^{*}P < 0.05$ different from the saline control group. $^{+++}P < 0.001$ different from the respective group.

response curve of SKF38393 shifted to the left in BDL animals (Figure 5A). BDL increased defecation but did not alter head-dip counts (Figure 5B), locomotor activity (Figure 5C), latency to head-dip, grooming, and rearing. Post hoc analysis showed that sole administration of SKF38393 increased CPP and locomotor activity compared to the sham-operated control group.

7. Effect of BDL on behaviors induced by SCH23390

Two-way ANOVA revealed that BDL decreased CPA (Figure 6A) and head-dip counts (Figure 6B) but did not alter locomotor activity (Figure 6C), latency to head-dip, grooming, rearing, and defecation induced by SCH23390.

Discussion

The molecular mechanisms of acute and chronic liver injury have been tested in rats and mice whose liver injuries were inflicted by BDL.[27,28] Due to easier genetic manipulations and pharmacological interventions, the BDL mice model has been widely used to study cholestatic liver injury. Researchers have stated that the expression and secretion of serotonin, endogenous opioid peptides and neurotrophins as well as their corresponding receptors increase during cholestatic diseases.[29,30] In cholestasis, the liver is not the only source of met-enkephalin although it alters expression of the delta opioid receptor to which met-enkephalin preferentially binds.[31] Thus, one can propose that met-enkephalin has a local function in the cholestatic liver. Although the reason for alteration in the number of opioid receptors in cholestasis is not yet fully understood, it has been shown that increase in the availability of opioid peptides in the periphery may facilitate their alteration into the central nervous system.[32]

The present data showed that the conditioning treatments with different doses of morphine produced a dose-related place preference in sham-operated mice, while no change in locomotor activity was found. The data were consistent with those of previous reports, which have suggested that the conditioning procedure could

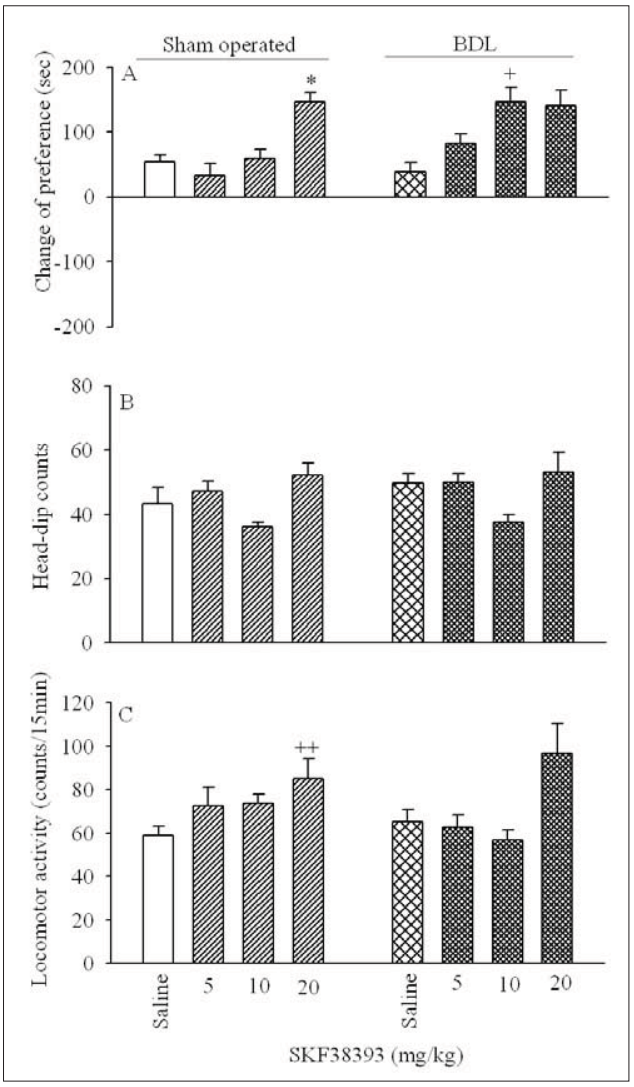

Figure 5. Effect of SKF38393 with or without BDL on the acquisition of CPP and exploratory behaviors. Panel A shows the effect of SKF38393 in a 3-day schedule of conditioning in sham-operated and BDL mice on CPP. In panel B, the numbers of head-dip counts were examined after CPP testing. In addition, locomotor activity was assessed during post-conditioning day (panel C). Data are expressed as mean ± SEM. $^{*}P < 0.05$ different from the saline control group. $^{+}P < 0.05$ different from the respective group.

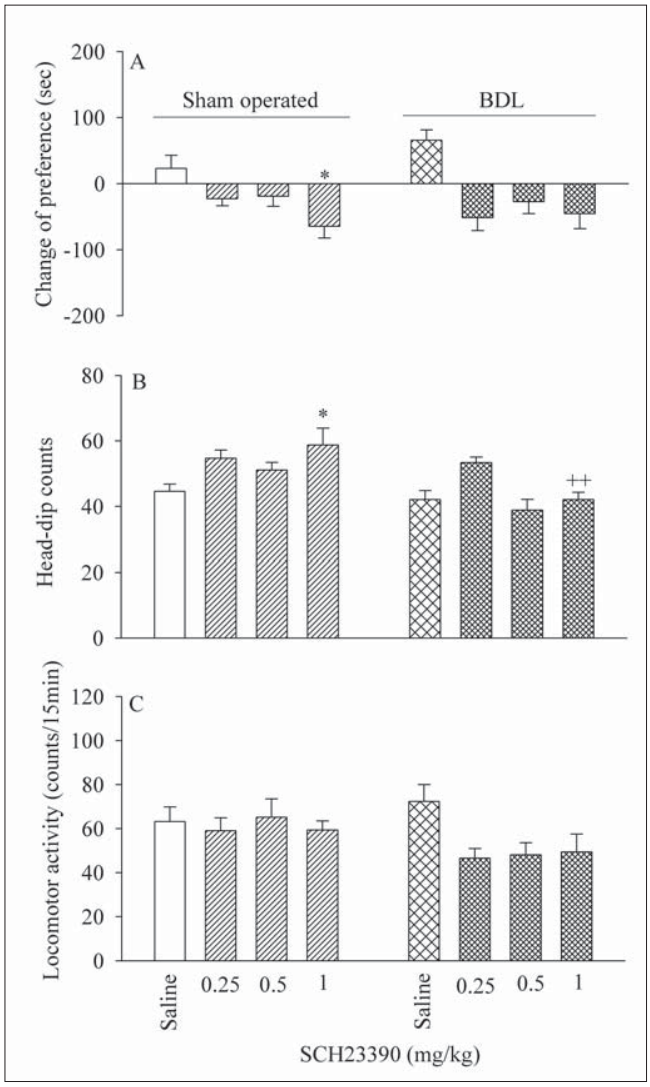

Figure 6. Effect of SCH23390 with or without BDL on the acquisition of CPP and exploratory behaviors. Panel A shows the effect of SCH23390 in a 3-day schedule of conditioning in sham-operated and BDL mice on CPP. In panel B, the numbers of head-dip counts were examined after CPP testing. In addition, locomotor activity was assessed during post-conditioning (panel C). Data are expressed as mean ± SEM. $^{*}P < 0.05$ different from the saline control group. $^{++}P < 0.01$ different from the respective group.

be used to investigate the reward effect of morphine.[2,22] While the intermediate (medium) dose of morphine produced CPP in sham-operated mice, a higher dose of the opioid was required in BDL animals to elicit CPP. One could thus conclude that the morphine dose response curve has shifted to the right in BDL animals, which could be in line with the finding that mu-receptor levels are down regulated in BDL animals. Thus, the middle dose of morphine, which was an effective dose in sham-operated animals could be ineffective in the BDL group. In addition, previous studies have suggested that elevation of endogenous opioids may induce nitric oxide (NO) overproduction in cholestatic rats.[33] The endogenous NO could play a role in the modulation of dopaminergic effects elicited by morphine.[34] The Nac is one of the regions in which NO is implicated in the control of DA release.[35,36]

In agreement with our previous studies,[37] the administration of naloxone by itself induced CPA in mice, an effect mediated by the central nervous system.[38] BDL also reduced the CPA response that was induced in sham-operated animals. A small right-shift was observed in the aversive effects of naloxone (intermediate dose in sham versus higher dose in BDL animals), which could be related to down-regulated opioid receptors in the brain. Naloxone would compete with local met-enkephalin for binding to the delta opioid receptor expressed by proliferating bile ducts.[31]

The main DA receptor subtypes (D1 and D2) have been proposed to play a critical role in the incentive aspect of opiate reward. Activation of these receptors could be essential for the development of addiction to opiates.[8] In addition, DA D1-like receptors may play a critical role in reward-related learning. Possibly, rewarding stimuli such as morphine may produce this type of learning.[39] DA also has an essential role in associative stimulus-reward learning. Our present experiments have shown that BDL mice, compared with sham-operated mice exhibited a significant place preference at the intermediate dose of the D1 receptor agonist, SKF38393. A leftward shift can be demonstrated in the dose response curve as a result of BDL. However, the drug caused a significant CPP at the highest dose in sham-operated mice. Other investigators have found rewarding effects with intra-accumbens injections of SKF38393, but place aversions when this compound was injected systemically in rats.[40,41] In line with the findings of a previous study,[8] we also found that D1 receptor antagonist, SCH23390, induced CPA while the drug-induced CPA was lower in BDL mice.

Our results indicated that sham-operated mice failed to exhibit a place preference with the D2 receptor agonist, quinpirole, across multiple test doses, whereas BDL animals showed a small CPA when compared with their respective sham-operated mice. In contrast, the lack of place conditioning with the D2 receptor agonists, quinpirole, and 7-OH-DPAT in drug-naive animals was in line with several studies that used doses, which were thought to activate postsynaptic D2/D3 receptors.[41–43] Other investigations have shown that either place preferences[44–46] or place aversions can be induced by D2 receptor activation.[47,48] The discrepancies have been proposed to be due to different rat strains, conditioning protocols, or other methodological differences. Conversely, the D2 receptor antagonist, sulpiride, produced a significant CPP in sham-operated mice. However, the sulpiride dose response curve was shifted leftwards in BDL animals. We have suggested that sulpiride blocks presynaptic DA autoreceptors and releases DA that may act on D1 receptors and induce CPP. However, quinpirole may act on the DA D2 receptor in the post-synaptic membrane. In previous studies, no effect on place conditioning has been observed for DA antagonists, which preferentially act at DA D2 receptors.[49,50] In conclusion, induction of cholestasis can influence CPP and CPA that have been caused by both opioidergic and dopaminergic drugs, which probably occurred through down regulation phenomena.

Conflicts of interest

There are no conflicts of interest.

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