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Histamine H_3 receptor modulates nociception in a rat model of cholestasis

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ABSTRACT

Cholestasis is associated with changes including analgesia. The histaminergic system regulates pain perception. The involvement of histamine H_3 receptors in modulation of nociception in a model of elevated endogenous opioid tone, cholestasis, was investigated in this study using immepip and thioperamide as selective H_3 receptor agonist and antagonist respectively. Cholestasis was induced by ligation of main bile duct using two ligatures and transsection the duct between them. Cholestatic rats had increased tail-flick latencies (TFLs) compared to non-cholestatics. Administration of immepip (5 and 30 mg/kg) and thioperamide (10 and 20 mg/kg) to the cholestatic groups significantly increased and decreased TFLs compared to the saline treated cholestatic group. Immepip antinociception in cholestatic animals was attenuated by co-administration of naloxone. Immepip and thioperamide injections into non-cholestatic animals did not alter TFLs. At the doses used here, none of the drugs impaired motor coordination, as revealed by the rotarod test. The present data show that the histamine H_3 receptor system may be involved in the regulation of nociception during cholestasis in rats.

1. Introduction

A possible role of histaminergic neurotransmission in the modulation of pain has been postulated (Mobarakeh et al., 2000; Mobarakeh et al., 2006; Onodera et al., 1994; Schwartz et al., 1991). Histamine can act at four known type of histamine receptors, including H_3 receptors (Cannon et al., 2007a, b; Mobarakeh et al., 2009). Histamine has been shown to modulate nociception through histamine H1 (Farzin et al., 2002; Malmberg-Aiello et al., 1998; Mobarakeh et al., 2000; Oluyomi and Hart, 1991), H2 (Farzin et al., 2002; Lamberti et al., 1996; Oluyomi and Hart, 1991) and H_3 receptors (Farzin et al., 2002, Lamberti et al., 1996). The new histamine H_4 receptor is mainly expressed in hematopoietic cells, indicating its function in inflammatory and immunomodulatory responses (de Esch et al., 2005; Jablonowski et al., 2004; Tiligada et al., 2009).

Histamine H_3 receptors that are located throughout the periphery and within the CNS, have been suggested to play a role in pain perception (Cannon et al., 2007a; Mobarakeh et al., 2009; Pillot et al., 2002). Both nociceptive (Farzin et al., 2002; Malmberg-Aiello et al., 1994) and antinociceptive (Cannon et al., 2003; Cannon and Hough, 2005; Rouleau et al., 1997) effects have been suggested for stimulation of histamine H_3 receptors. Histamine H_3 receptor antagonists have been also reported to potentiate or inhibit opioid antinociception (Mobarakeh et al., 2009; Owen et al., 1994; Suh et al., 1996, 1999; Suzuki et al., 1994). Therefore, it seems that there is conflicting data on the effects of histamine H_3 receptors on pain modulation and on opioid-induced antinociception. Histamine H_3 receptors are presynaptically located which mediate inhibition of histamine and other neurotransmitters release. Two distinct H_3 receptor-mediated presynaptic effects (autoreceptor for histamine release or heteroreceptor for other neurotransmitters) may be a reason for doing further studies on H_3 receptors in pain modulation (Mobarakeh et al., 2009).

Cholestatic liver disease is associated with increased endogenous opioids (Swain et al., 1992, 1994; Thornton and Losowsky, 1989). Observations compatible with the increased endogenous opioids in cholestasis include precipitation of an opioid withdrawal-like syndrome in patients with cholestasis as well as in bile duct ligated animals (Dehpour et al., 2000; Thornton and Losowsky, 1988) and also a global down-regulation of mu-opioid receptor in the brain of rats with cholestasis due to bile duct ligation (Bergasa et al., 1992). Previous published studies have shown that several neurotransmitter receptors are involved in modulation of cholestasis induced antinociception (Dehpour et al., 2000; Rastegar et al., 2002; Hasanein et al., 2007; Hasanein and Javanmardi, 2008). The effects of histamine H_3 receptors on control of pain motivated our interest to examine the possible effects histamine H_3 receptor on modulation of nociception in a rat model of elevated endogenous opioid tone, cholestasis.

Considering the elevated endogenous opioid tone in cholestasis and the role of histamine H_3 receptors in pain perception, the present study was designed to evaluate the effects of different doses of systemically administered selective histamine H_3 receptor agonist immepip and the histamine H_3 receptor antagonist thioperamide on the modulation of antinociception induced by experimental

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cholestasis using the tail-flick paradigm, a widely used model for discovering the role of histaminegic system on pain modulation (Gogas et al., 1989; Mobarakeh et al., 2005, 2006; Nalwalk and Hough, 1995; Yanai et al., 2003). Interactions between opioid and histamine systems in this model were also examined by co-administration of naloxone and immepip.

2. Materials and methods

2.1. Drugs

These drugs were used in this study: immepip dihydrobromide, thiopermide maleate and naloxone hydrochloride (Tocris Cookson Inc., Bristol, UK). All drugs were dissolved in saline and injected subcutaneously (s.c.). The drugs were injected in a volume of 1 ml/kg.

2.2. Animals

Experiments were conducted in locally produced male Wistar rats (200–250 g). The animals were housed three per cage (50×35×30 cm) at constant room temperature (22–24 °C), and exposed to a 12 h light/dark cycle starting at 6:00 a.m. They had free access to laboratory chow and tap water. Each experimental group consisted of seven animals which were chosen randomly from different cages and each was used only once.

2.3. Surgical procedure

Laparotomy was performed under general anesthesia induced by an i.p. injection of sodium pentobarbital (50 mg/kg). Sham operation consisted of laparotomy and bile duct identification and manipulation without ligation or resection. In the bile duct ligated group the main bile duct was first ligated using two ligatures approximately 0.5 cm apart and then transsected at the midpoint between the two ligatures (Bergasa et al., 1994). In the immediate postoperative period each animal was placed in a cage by itself to prevent wound dehiscence and was moved to its original cage 4 h after surgery (Rastegar et al., 2002). Operative mortality was less than 5%. Animals were handled in accordance with the criteria outlined in the Guide for the Care and Use of Laboratory Animals (National Institutes of Health (NIH) publication 86–23; revised 1985; http://www.oacu.od.nih.gov/regs/guide/guidex.htm). All the protocols were also approved by the institutional ethics committee of Bu-Ali Sina University.

2.4. Experimental design

There were three experimental groups: unoperated controls, sham-operated controls and bile duct ligated rats. After obtaining baseline tail-flick latencies, the rats were randomized to three experimental groups (unoperated, sham and bile duct ligated). Seven days after surgery, when cholestasis is florid and the stress related to surgery has passed, tail-flick measurements were performed. Rats from all groups were studied in parallel. The animals in unoperated, sham and bile duct ligated groups received immepip (1, 5, 30 mg/kg, s.c.), thioperamde (5, 10, and 20 mg/kg, s.c.) or an equivalent volume of saline subcutaneously. The μ-opioid receptor antagonist naloxone (10 mg/kg, s.c.) was co-administered with immepip (5 mg/kg, s.c.) in the experiments in which we examined the pharmacological interactions between opioid and histamine systems in cholestasis. The different groups used in these experiments were shown in Table 1. The protocol of drugs administration was based on the previous published studies that assessed the effect of histamine H_3 receptor system on the pain control (Cannon et al., 2003, 2007b; Cannon and Hough, 2005; Girard et al., 2004; Suzuki et al., 1994).

Table 1
The different groups and the number of animals used in the present experiments.

Treatments	Groups		
	Unoperated	Sham	Bile duct ligated
Saline	$N=7$	$N=7$	$N=7$
Immepip (1 mg/kg)	$N=7$	$N=7$	$N=7$
Immepip (5 mg/kg)	$N=7$	$N=7$	$N=7$
Immepip (30 mg/kg)	$N=7$	$N=7$	$N=7$
Saline	$N=7$	$N=7$	$N=7$
Thioperamide (5 mg/kg)	$N=7$	$N=7$	$N=7$
Thioperamide (10 mg/kg)	$N=7$	$N=7$	$N=7$
Thioperamide (20 mg/kg)	$N=7$	$N=7$	$N=7$
Saline + immepip (5 mg/kg)	$N=7$	$N=7$	$N=7$
Naloxone(10 mg/kg) + immepip (5 mg/kg)	$N=7$	$N=7$	$N=7$
		N Total = 210	

2.5. Measurement of antinociception responses

The effect of administration of different doses of immepip, thiopermide and combination of immepip and naloxone on tail-flick latency was investigated in the experimental groups. Ambient temperature of the room was maintained at 24 ± 0.5 °C. Following a 45 min acclimation period, the tail-flick latency was measured by exposing the dorsal surface of the tail to radiant heat and recording the time required to remove the tail from the noxious thermal stimulus. Radiant heat was applied 3–9 cm proximal to the tip of the rat's tail; removal of the tail activated the photocell and determined the latency (0.1 s accuracy). To avoid tissue damage, the trial was automatically terminated if a response did not occur within 10 s (cut-off time) (Javanmardi et al., 2005). Tail-flick latencies were measured at 30 min after injection of the drugs in experimental groups. The operator was unaware of the specific surgical or treatment groups to which an animal belonged.

2.6. Rota rod test

Changes in performance were assessed using a rotarod apparatus (Ugo Basile, Italy) in which rats were required to walk against the motion of a rotating drum, with the speed increasing from 4 to 40 r/min over 5 min. The time taken to fall of the rotarod was recorded as the rotarod latency (s). On day before the test, the animals were trained twice. On the test day, rotarod latencies were measured following drugs or saline administration. In all experiments a 300 s cut-off was employed.

2.7. Statistical analysis

Data are expressed as mean ± S.E.M. ($n=7$). Analysis of data was performed using one-way ANOVA or two-way ANOVA. Following a significant F value, post hoc analysis (Tukey's test) was performed for multiple comparisons of unoperated, sham and bile duct ligated groups in each experiment. $P<0.05$ was considered statistically significant in all tests.

3. Results

Two days after bile duct ligation the animals exhibited obvious signs of cholestasis (jaundice, dark urine and steatorrhea) and signs persisted thereafter (Rastegar et al., 2002).

3.1. Effect of cholestasis on tail-flick latency in bile duct ligated animals

There were no significant differences in tail-flick latency between animals before the operation. The tail-flick latency of saline treated bile duct ligated animals significantly ($P<0.01$) increased (3.92 ± 0.26

vs. 2.5 ± 0.1, 4 ± 0.29 vs. 2.9 ± 0.1) compared to the unoperated group (Figs. 1, 2). Sham operation caused a minor and not significant increase in tail-flick latency compared to saline treated unoperated animals; however it was still significantly ($P<0.05$, $P<0.01$) lower than animals in bile duct ligated group (Figs. 1, 2).

3.2. Effects of immepip on cholestasis induced antinociception

The effect of immepip administration on antinociception induced by cholestasis is shown in Fig. 1. Two-way ANOVA indicated a significant difference between the responses induced in the presence or absence of immepip on tail-flick test in different animal groups ($F(6, 77) = 5.76$, $P<0.001$). Post hoc analysis showed that there was no difference in tail-flick latency between the lowest dose of immepip used in this study (1 mg/kg) and saline treated cholestatics (4.9 ± 0.27 vs. 3.92 ± 0.26). Administration of 5 and 30 mg/kg immepip caused a greater increase in tail-flick latency in cholestatics ($P<0.01$, $P<0.001$, respectively) compared to the saline treated animals (5.32 ± 0.35 vs. 3.92 ± 0.26, 6.67 ± 0.44 vs. 3.92 ± 0.26, respectively). The 30 mg/kg dose of immepip produced the greatest increase in tail-flick latency compared to the saline treated cholestatic group (6.67 ± 0.44 vs. 3.92 ± 0.26) which was also greater than the latency in immepip (5 mg/kg) treated cholestatics ($P<0.01$). Immepip injection, at any of the doses used here, in unoperated and sham groups did not change tail-flick latency compared to the respective saline treated animals (Fig. 1).

3.3. Effects of thioperamide on cholestasis induced antinociception

Fig. 2 shows the effect of thioperamide administration on antinociception induced by cholestasis. Two-way ANOVA indicated a significant difference between the responses induced in the presence or absence of thioperamide on the tail-flick test in different animal groups ($F(6, 77) = 12.8$, $P<0.001$). Thioperamide injection at the dose of 5 mg in the cholestatic group decreased the tail-flick latency compared to the saline treated cholestatics (3.6 ± 0.1 vs. 4 ± 0.29) but the difference was not statistically significant ($P>0.05$). Administration of thioperamide (10 and 20 mg/kg) in cholestatic groups caused significant reductions in tail-flick latency (2.25 ± 0.23, 1.97 ± 0.16, respectively) than saline administration in the bile duct ligated group (4 ± 0.29) ($P<0.001$, $P<0.001$). However, among the former two groups the differences were not significant (Fig. 2). Thioperamide administration to unoperated and sham groups, at any of the doses used here, did not alter tail-flick latency compared to the respective saline treated groups (Fig. 2).

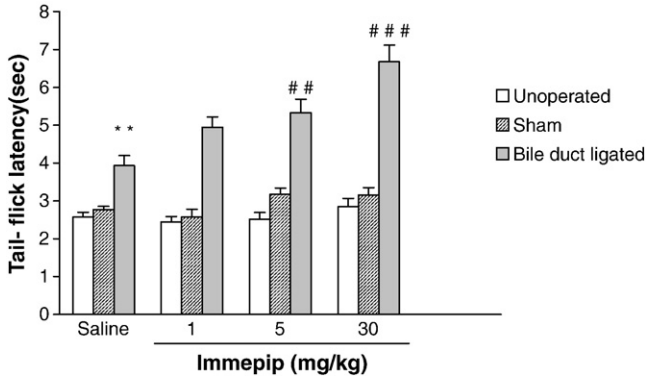

Fig. 1. Effects of saline and immepip (1, 5 and 30 mg/kg, s.c.) administration on tail-flick latency(s) in bile duct ligated, sham-operated (sham) and unoperated rats. Data expressed as mean ± S.E.M. ($n = 7$). ** Difference from saline treated unoperated rats ($P<0.01$) # # Difference from saline treated bile duct ligated rats ($P<0.01$) # # # Difference from saline treated bile duct ligated rats ($P<0.001$).

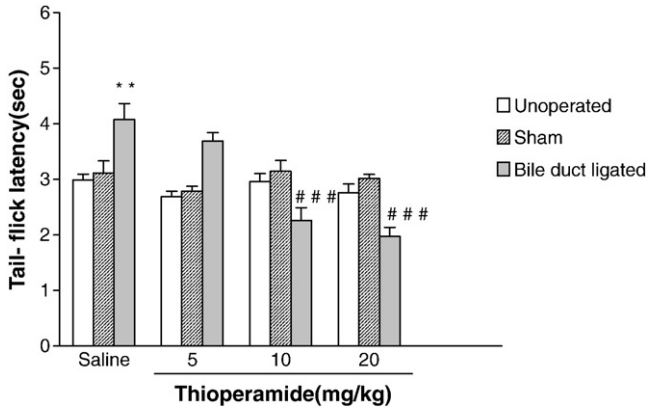

Fig. 2. Effects of saline and thioperamide (5, 10 and 20 mg/kg, s.c.) administration on tail-flick latency(s) in bile duct ligated, sham-operated (sham) and unoperated rats. Data expressed as mean ± S.E.M. ($n = 7$). ** Difference from saline treated unoperated rats ($P<0.01$) # # # Difference from saline treated bile duct ligated rats ($P<0.001$).

3.4. Effects of naloxone injection on the antinociception induced immepip

In order to examine the pharmacological interactions between opioid and histamine systems in cholestasis, naloxone (10 mg/kg), an opioid receptor antagonist, was co-administered with a histamine H_3 receptor agonist to different experimental groups (Fig. 3). As shown in Fig. 3, antinociception produced by injection of 5 mg/kg immepip in cholestatics (5.27 ± 0.29) was attenuated by co-administration of naloxone (3.8 ± 0.24) ($P<0.001$).

3.5. Effects of immepip and thioperamide injection on motor function

The drugs, at the doses used in the present experiments, did not modify gross behavior of the rats. Moreover, motor function of rats treated with different doses of the drugs was evaluated using the rotarod test. Immepip and thioperamide injection in the experimental groups did not affect rotarod latencies compared to saline treated group (data not shown). Motor coordination in the treated animals was therefore not affected in these experiments.

4. Discussion

In the present study, effects of selective histamine H_3 receptor agonist and antagonist were investigated on pain perception in an experimental model of elevated endogenous opioid tone, cholestasis, using the tail-flick test. Several neurotransmitter systems are involved in modulation of nociception in cholestasis (Dehpour et al., 2000;

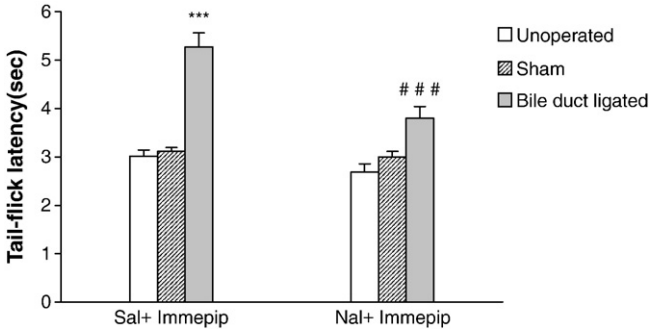

Fig. 3. Effects of naloxone (Nal) (10 mg/kg, s.c.) and immepip (5 mg/kg, s.c.) co-administration on tail-flick latency (s) in bile duct ligated, sham-operated (sham) and unoperated rats. Data expressed as mean ± S.E.M. ($n = 7$). *** Difference from saline + immepip treated unoperated rats ($P<0.001$) # # # Difference from saline + immepip treated bile duct ligated rats ($P<0.001$).

Rastegar et al., 2002; Hasanein et al., 2007; Hasanein and Javanmardi, 2008). This study shows that the histamine H_3 receptor system may also be involved in the regulation of antinociception induced by elevated endogenous opioid tone during cholestasis and lends credence to several reports of pain modulation by the histamine and opioid receptors (Owen et al, 1994; Suh et al., 1999; Suzuki et al., 1994; Mobarakeh et al., 2006, 2009).

Opioid tone is increased in acute liver disease, which could be mediated by increased levels of opioid peptides (Swain et al., 1992, 1994). Accordingly, an increased nociception threshold has been reported in cholestatic animals (Bergasa et al., 1994; Dehpour et al., 2000; Rastegar et al., 2002). In the present experiments, cholestatic animals exhibited an increased in tail-flick latency on day 7 after the operation that is consistent with two previous studies showing that the strongest antinociceptive effect could be observed on day 7 after operation in cholestatic rats (Rastegar et al., 2002; Nelson et al., 2006). We have also recently shown that the antinociception induced by cholestasis in saline treated bile duct ligated animals was blocked by naloxone injection which provides further support for the involvement of endogenous opioids play in the cholestasis induced antinociception (Hasanein, 2009). Our current findings expand on previous observations and demonstrate that antinociception in bile duct ligated animals was significantly potentiated by systemic injection of the selective H_3 receptor agonist, immepip at doses of 5 and 30 mg/kg but not 1 mg/kg. We further examined the involvement of histamine H_3 receptors by using different doses of a selective histamine H_3 receptor antagonist thioperamide. As thioperamide (10 and 20 mg/kg, s.c.) decreased pain in cholestatic animals, the involvement of these receptors in the present model of pain would be more confirmed. Different doses in these experiments were selected bases on pilot study and previous published studies (Cannon and Hough, 2005; Cannon et al., 2007b; Suzuki et al., 1994; Owen et al., 1994) to show the effects of the agonist and the antagonist in a dose response manner. The pharmacological interactions between opioid and histamine systems in cholestasis were further assessed by co-administration of naloxone and immepip. Naloxone decreased the antinociception induced by sub maximal dose of the histamine H_3 receptor agonist. The dose of naloxone as a saturating dose has been also used in previous published studies (Oluyomi and Hart, 1991, Malmberg-Aiello et al., 1998, Hasanein, 2009) to show the pharmacological interaction between histamine and opioid systems in pain modulation.

The histamine H_3 receptor has been shown to modulate opioid analgesia (Mobarakeh et al., 2009; Owen et al, 1994; Suh et al., 1996, 1999; Suzuki et al., 1994). In fact, the interaction between opioids and histamine H_3 receptor system is a very interesting subject for study. However, there are conflicting data on the effects of histamine H_3 receptors on pain modulation and on opioid-induced antinociception. The discrepancy may be due to differences in the species used, the analgesic tests used, types of histamine H_3 receptor agonists and antagonists and the routes of administration (Farzin et al., 2002; Malmberg-Aiello et al., 1994; Mobarakeh et al., 2009; Owen et al., 1994; Suh et al., 1996, 1999; Suzuki et al., 1994). In our experiments, immepip potentiated antinociception in an experimental model of elevated endogenous opioid tone. According to previous studies systemic injection of histamine H_3 receptor agonists potentiates morphine antinociception while histamine H_3 receptor antagonists attenuate opioid-induced antinociception (Owen et al, 1994; Suh et al., 1996, 1999; Suzuki et al., 1994). So, the effects of systemically administered histamine H_3 receptor agonist and antagonist on nociceptive threshold in our experiment are consistent with these previous studies. It is well known that histamine H_3 receptors have a mainly presynaptic localization and as inhibitory autoreceptors mediate inhibition of histamine release and biosynthesis in histaminergic nerve terminals (Arrang et al., 1983, 1987; Schwartz et al., 1986). Therefore, a decrease in the release of histamine by histamine H_3 receptor agonist and an increase in the release of histamine by histamine H_3 receptor antagonist may be involved in the effects of immepip and thioperamide on modulation of antinociception in this model of elevated endogenous opioid tone. The above mechanism has been suggested to contribute to the effects of histamine H_3 receptor agonists and antagonists on morphine induced antinociception (Owen et al., 1994; Girard et al., 2004; Suzuki et al., 1994).

Both agonist and antagonist at any doses used in these experiments did not alter tail-flick latency in the unoperated and sham groups. It has been previously reported that systemic injection of immepip at 1–30 mg/kg did not affect the hot plate and tail-flick tests but induced analgesic effects in paw pressure and formalin tests (Cannon et al., 2003, 2007b, Cannon and Hough, 2005). Subcutaneous administration of thioperamide at 5–25 mg/kg was also devoid of effects in some animal models of pain (Cannon and Hough, 2005, Cannon et al., 2007a, b; Girard et al., 2004; Owen et al., 1994; Suzuki et al., 1994). Therefore, the effect of systemically administered immepip and thioperamide on thermal nociceptive threshold in our experiments is consistent with these previous published studies.

The drugs, at the doses used in the present experiments, did not modify gross behavior. Moreover, they did not impair motor coordination, as revealed by the results of the rotarod test. It has also been reported that immepip did not affect motor coordination at doses 5 and 30 mg/kg (Cannon and Hough, 2005). These observations suggest that systemic administration of the agonist and antagonist, in this range of doses, had no significant effect on motor function in rats and thus the observed effects are likely to be related to the antinociceptive and nociceptive actions of the drugs.

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