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Inhibition of the cyclooxygenase pathway attenuates morphine-induced conditioned place preference in mice

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Abstract

Prostanoids are shown to be important lipid mediators, not only in periphery but also in the brain, where they appear to modulate synaptic transmission. Recent studies have demonstrated that cyclooxygenase (COX) pathway might modulate the neurotransmission of γ-aminobutyric acid and dopamine in the central nervous system. In this study, we have evaluated the effects of indomethacin (a non-selective COX inhibitor) and celecoxib (a selective COX-2 inhibitor) on the acquisition of morphine-induced conditioned place preference (CPP) in male Swiss mice. Our data shows that morphine (2.5–7.5 mg/kg) induces place preference conditioning in a dose-dependent manner. Celecoxib (0.01–5 mg/kg) and indomethacin (1 mg/kg) fail to produce a significant CPP or conditioned place aversion (CPA); however, higher doses of celecoxib (10 mg/kg) and indomethacin (5 mg/kg) induce CPA. Co-administration of celecoxib (0.5–5 mg/kg) or indomethacin (1–5 mg/kg) with morphine during the conditioning phase, blocked the acquisition of morphine CPP. These results indicate that the reward properties of morphine can be modulated by inhibiting COX activity in mice.

Keywords: Cyclooxygenase pathway; Indomethacin; Celecoxib; Morphine; Conditioned place preference; Mice

1. Introduction

Synthesis of prostaglandins is accomplished in a stepwise manner by a ubiquitous complex of microsomal enzymes. The first enzyme in this synthetic pathway is fatty acid cyclooxygenase. There are two isoforms of this enzyme, cyclooxygenase-1 and -2, dubbed COX-1, COX-2. The former is constitutively expressed in most cells. In contrast, COX-2 is normally not present but may be induced by certain serum factors, cytokines, and growth factors (Morrow and Jackson Roberts, 2001). Cyclooxygenase catalyses the oxidation of unesterified polyunsaturated fatty acids within the cell membrane to form prostaglandins such as prostacyclin and prostaglandin D2 (Smith et al., 1992). Prostaglandins are transported out of the cell and, in general, act as rapidly inactivated local hormones exerting an effect very near to where they are synthesised. Operating through G-protein linked cell-surface receptors they act as regulators of second messengers such as cAMP, inositol phosphates and diacylglycerol, in turn affecting a variety of cellular processes including calcium mobilisation, protein kinase activity and protease activity (Wise, 1997).

A large number of observations have been made on the effects of prostaglandins in the central nervous system (CNS); however, their role in the brain function and animal behaviour is unclear. It has been shown that COX-2 is the predominant form in neurons, mediating prostaglandin signalling in the brain (Kaufman et al., 1996; Tocco et al., 1997; Yamagata et al., 1993). Evidence indicate that prostaglandins play a regulatory role in several forms of neural plasticity including certain forms of learning and

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memory (Teather et al., 2002). In brain, COX-2 is selectively expressed in neurons of cerebral cortex, basal ganglia (Kawasaki et al., 1993; Tocco et al., 1997), hippocampus and amygdala (Breder et al., 1995). Since COX utilises the arachidonic acid as substrate, hydrolysis of the phospholipids by either phospholipase A2, or by the combined action of phospholipase C and diacylglycerol lipase is required (Ross and Kish, 1994). Various neurotransmitters, including dopamine, glutamate and serotonin, can modulate the activity of phospholipase A2 and/or phospholipase C (Smith et al., 1992). It has been shown that dopamine D2 receptor releases arachidonic acid via coupling to phospholipase A2 (Bhattacharjee et al., 2006). Furthermore, the role of the endocannabinoid pathway and the arachidonic acid signaling in brain reward/dependence mechanisms in morphine dependence has been indicated (Gonzalez et al., 2003; Yamamoto et al., 2004).

The ability to stimulate the firing rate of meso-accumbens dopaminergic neurons, to induce self-administration, as well as to produce conditioned place preference (CPP), is considered as an index of rewarding properties of drugs (Wise, 1987). It has been suggested that COX activity is involved in the development of stimulant sensitization at the level of the ventral tegmental area (VTA); and COX inhibitors are able to reduce the development of cocaine and amphetamine sensitization (Reid et al., 2002). Moreover, it has been shown that COX inhibition by diclofenac attenuates lipopolysaccharide-induced reduction in reward behaviour (anhedonia) and corticosteroid release in rats, suggesting the COX role in reward mechanism (De La Garza et al., 2004). Experimental inflammation is also shown to alter cocaine-, methamphetamine-, and morphine-induced conditioned place preference (Suzuki et al., 1996). Morphine has been shown to produce a significant and dose-dependent effect on the magnitude of place preference, providing a good model to investigate reward mechanism. Likewise, the effects of various drugs on acquisition and expression of morphine-induced place preference have also been assessed (Tzschentke, 1998). Several studies have shown a significant interaction among opioids and the cyclooxygenase pathway (Powell et al., 1999). Centrally, non-steroidal anti-inflammatory drugs (NSAIDs) may act on the terminals modulating arachidonic acid pathways involved in opioid activity (Pini et al., 1996, 1997). Additionally, arachidonic acid and its metabolites are involved in the development of opioid withdrawal (Johnson et al., 1988). Therefore, COX activation and prostaglandin production could contribute to the reward process and inhibition of COX may alter the reward process. However, the interaction of COX activity and reward mechanism has not been fully understood. In the present study, the effect of COX inhibition on the rewarding properties of morphine has been evaluated in mice, using an unbiased CPP paradigm.

2. Material and methods

2.1. Animals

Male Swiss mice (Razi Institute, Karaj, Iran), weighing 20–30 g were used. The animals were housed 6–7 per cage in a temperature-controlled (22±3 °C) colony room in a 12:12 h light:dark cycle with ad libitum food and water except during experimental procedures. Subjects were experimentally naïve and were allowed at least 3 days to acclimatize to the laboratory environment before testing began. Each mouse was used only once and each treatment groups consisted of at least 5 animals. All procedures were carried out in accordance with institutional guidelines for animal care and use. The protocol has been approved by the committee of ethics of the faculty of Sciences of Tehran University (357; 8 November 2000).

2.2. Apparatus

The place preference apparatus and its floors were made of wood and consisted of two square-based compartments (15×15×30 H cm each) separated by a guillotine door. One compartment was painted in vertical black and white shadings (with white floor) and the other compartment was painted in horizontal black and white shadings (with black floor) to create equally preferred compartments.

2.3. Drugs

The drugs used in the present study were morphine sulphate (Temad pharmaceutical, Tehran, Iran), celecoxib and indomethacin (Laboratory of Medicinal Chemistry, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran). Morphine sulphate was freshly prepared in sterile normal saline (0.9% NaCl solution), while celecoxib and indomethacin were prepared daily in Dimethyl sulfoxide 10% (DMSO; Merck, Germany) to such concentrations that requisite doses were administered in a volume of 5 ml/kg. Results of previous studies in our laboratory confirm that DMSO 10%, by itself, does not induce any significant change in preference in mice (Langroudi et al., 2005). All drugs were injected intraperitoneally (i.p.) in all experiments. Appropriate vehicle controls were performed for each experiment.

2.4. General procedure

Place conditioning was conducted using an unbiased procedure. The CPP paradigm took place on nine consecutive days. All the trials were done between 11:00 am and 13:00 pm. On the first (i.e. familiarization) and second day of the trials (i.e. pre-conditioning), each mouse was placed separately into the apparatus for 10 min, while they could freely access both compartments. The time spent in each compartment was recorded on the pre-conditioning day to determine any individual innate preference for either of the two compartments. Placement in each compartment was considered as placement of the front paws and the head (Langroudi et al., 2005). Animals showing strong unconditioned preference (>60% of the session) or aversion (<10% of the session) for any compartment were excluded from the experiments (a total number of 11 mice) (Sahraei et al., 2004). The pre-conditioning score was measured as the subtraction of the drug-paired compartment staying time from the non-drug-paired compartment staying time. After the test,

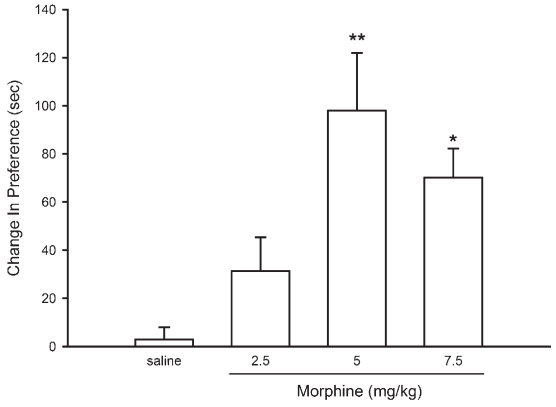

Fig. 1. Effect of morphine sulphate on the induction of conditioned place preference in opioid-naive mice. In a 6-day schedule, animals received saline (5 ml/kg) or morphine (2.5, 5 and 7.5 mg/kg, i.p.) in the 1st, 3rd and 5th days of conditioning. The data are shown as means of change in preference ±S.E.M. *$P<0.05$ and **$P<0.005$ different from the group treated with saline (Tukey–Kramer's multiple comparison tests).

the animals were grouped randomly. Each group consisted of 5–6 mice. The conditioning phase consisted of six 40-min conditioning sessions held on six consecutive days (Tahsili-Fahadan et al., 2006). Animals were placed in the concerned compartment by isolating the compartment using a removable partition. The mice received the considered drugs on days 1, 3, and 5, and vehicle injections on days 2, 4, and 6 of the conditioning phase according to the experimental design. The procedure was counterbalanced within each group for injection order (vehicle or drug) and the floor color (white or black) of the compartment that was paired with the drug. On the ninth day of the trials (i.e. post-conditioning; 24 h after the last conditioning session, with no preceding injections), the partition was raised and the animals were placed in the apparatus for 10 min, with free access to both compartments. An observer who was unaware of the treatment group for each animal recorded the time spent in each compartment. The post-conditioning score was measured in the same way as the pre-conditioning score. The data obtained from pre-conditioning (2nd day of trial, 10 min observation) and post-conditioning (9th day of trial, 10 min observation) stages were used to calculate "change in preference" (described in Data analysis). To measure the locomotor activity, the ground areas of the two compartments were divided in two equal segments by a transverse line which could not be seen by animal (Tzschentke and Schemidt, 1997) and locomotion for each animal was measured as the number of crossings from one half to the other over 10 min testing in the post-conditioning day (Belzung and Barreau, 2000) by a separate experimenter blind to groups and treatments. None of the drugs and treatments that were used in the study altered locomotor activity.

2.5. Morphine dose–response curve

In this experiment, the ability of different doses of morphine sulphate (2.5, 5 and 7.5 mg/kg) to produce place preference was investigated. Animals received morphine immediately before placement in the conditioning apparatus. A control group that received saline (10 ml/kg) in all sessions was included in order to confirm that the injection and conditioning schedule did not affect the time spent in the compartments.

2.6. Effect of indomethacin and celecoxib on the acquisition of place preference conditioning in the absence and presence of morphine

To investigate the ability of indomethacin (a non-selective COX inhibitor) or celecoxib (a selective inhibitor of COX-2) alone to induce place preference, in the first experiment, two doses of indomethacin (1 and 5 mg/kg) and five different doses of celecoxib (1, 2, 5, 10 and 20 mg/kg) were used based on the inhibitory doses of celecoxib on inflammation (Francischi et al., 2002; Navidpour et al., 2006; Pinheiro and Calixto, 2002). The drugs were injected 25–30 min prior to placement in apparatus under the schedule and the ability of these drugs to induce a significant change in preference on the post-conditioning day was evaluated. One additional group received DMSO (5 ml/kg) 25–30 min prior to placement in apparatus and served as a control. In the second experiment, the effects of indomethacin or celecoxib on place preference induced by morphine were investigated. Therefore, based on the results of experiment 2, animals received per se non-effective doses of celecoxib (1, 2 and 5 mg/ kg), indomethacin (1 mg/kg), or DMSO (5 ml/kg) 30 min before the administration of the most potent dose of morphine (5 mg/kg), obtained from morphine dose–response experiment, under the schedule.

2.7. Data analysis

Conditioned place preferences could be operationally defined as a reliable shift from baseline to test in the time spent in a drug-paired environment following drug-place conditioning; although, other ways of defining place preference are available. To facilitate this analysis, Change in Preference

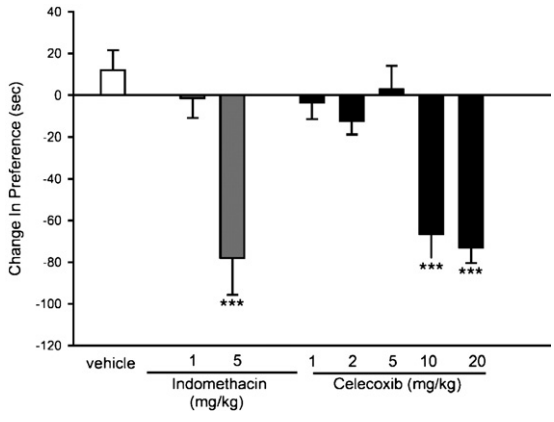

Fig. 2. Effects of indomethacin (a non-selective COX inhibitor) and celecoxib (a selective COX-2 inhibitor) on conditioned place preference (CPP) in mice. In a 6-day schedule, animals received indomethacin (1 and 5 mg/kg, i.p), celecoxib (1, 2, 5, 10 and 20 mg/kg, i.p.) or their vehicle (DMSO 10%; 5 ml/kg, i.p.) in the 1st, 3rd and 5th days of conditioning. The data are shown as means of change in preference ±S.E.M. ***$P<0.001$ different from the group treated with DMSO 10% (Tukey–Kramer's multiple comparison tests).

scores (CIP) were computed for each animal by calculating the difference between post- and pre-conditioning scores (pre-conditioning = 2nd day of trial, 10 min observation and post-conditioning = 9th day of trial, 10 min observation; Langroudi et al., 2005; Tahsili-Fahadan et al., 2006). All results are presented as mean±S.E.M. Data for CIP and locomotion were assessed by Two-way analysis of variance (ANOVA) or one-way ANOVA. If a significant F value was obtained, post hoc analyses (Tukey–Kramer's multiple comparison tests) were performed to determine the effects of various treatments on induction of place preference and changes in locomotion. P-values less than 0.05 were considered as significant. Calculations were performed using the SPSS statistical package (version 11.5).

3. Results

Fig. 1 shows the dose–response curve for place conditioning induced by morphine in mice. Statistical analysis, indicated that morphine induced place preference (one-way ANOVA; $F(3,20)=7.453$, $P=0.002$). Tukey–Kramer's multiple comparison tests revealed that the doses of 5 and 7.5 mg/kg of morphine induced place preference in comparison to control groups; however, saline (5 ml/kg) or morphine 2.5 mg/kg failed to produce significant conditioning in animals and no preference for either compartment was seen. The maximum response was observed with 5 mg/kg of morphine; therefore, this dose was employed in all subsequent experiments.

Fig. 2 shows the effect of different doses of indomethacin, celecoxib, or their vehicle, on place preference. Analysis showed a significant effect for indomethacin (one-way ANOVA; $F(2,15)=14.334$, $P<0.001$) and celecoxib on place aversion (one-way ANOVA; $F(5,30)=15.835$, $P<0.001$). Further analysis revealed that celecoxib (1, 2 and 5 mg/kg) and indomethacin (1 mg/kg) failed to produce a significant effect ($P>0.05$); however, celecoxib at 10 and 20 mg/kg and indomethacin at 5 mg/kg produced a significant conditioned place aversion (CPA; $P<0.001$).

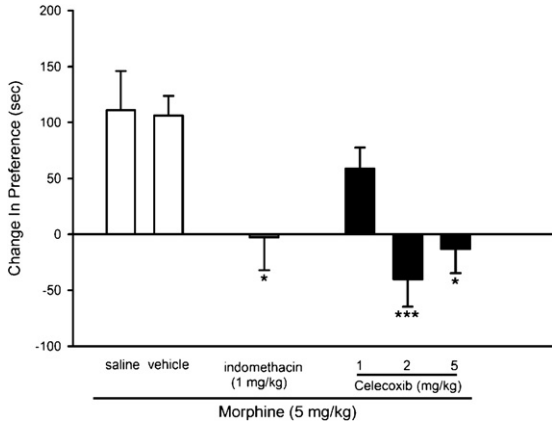

Fig. 3. Effects of indomethacin and celecoxib on acquisition of morphine-induced conditioned place preference (CPP) in mice. In a 6-day schedule, animals received saline (5 ml/kg, i.p.), vehicle for indomethacin and celecoxib (DMSO 10%; 5 ml/kg, i.p.), indomethacin (1 mg/kg, i.p.) or celecoxib (1, 2 and 5 mg/kg, i.p.) 30 min before injection of morphine (5 mg/kg, i.p.) in the 1st, 3rd and 5th days of conditioning. The data are shown as means of change in preference ±S.E.M. *$P<0.05$ and **$P<0.005$ different from the groups pre-treated with saline and vehicle (Tukey–Kramer's multiple comparison tests).

As Fig. 3 shows, a significant interaction among lower and non-effective doses of indomethacin (one-way ANOVA; $F(2,13)=5.428$, $P=0.019$) or celecoxib (one-way ANOVA; $F(4,22)=8.558$, $P<0.001$) and morphine on the induction of place conditioning was seen.

4. Discussion

The present study concerned the effects of administration of indomethacin, a non-selective COX inhibitor, and celecoxib, a selective COX-2 inhibitor, on the acquisition of morphine-induced place preference conditioning.

COX is the rate-limiting enzyme involved in the synthesis of prostanoids from arachidonic acid. Prostanoids have been demonstrated to be important lipid mediators, not only in periphery but also in the brain (Breder et al., 1995), where they appear modulate synaptic transmission (Williams, 1997). Recent studies demonstrated that COX pathway might modulate the neurotransmission of GABA and dopamine in the CNS (Ono et al., 1992; Vaughan et al., 1997; Ross et al., 1999; Melis et al., 2000). COX inhibitors such as indomethacin inhibited catalepsy induced by the dopamine receptor inhibitors, haloperidol and raclopride (Ono et al., 1992; Ross et al., 1999). Also, COX blockade has been shown to potentiate opioid inhibition of GABA-ergic synaptic transmission (Vaughan et al., 1997), and it has been recently reported that COX inhibitors, indomethacin and nimesulide, potentiate the stimulant effect of morphine on dopaminergic neurons projecting to the nucleus accumbens (Melis et al., 2000). Since the dopaminergic and GABA-ergic transmission is part of the reward pathway, these reports suggest the involvement of COX pathway in the modulation of reward mechanism in CNS.

Analgesic agents make up well over half of the over-the-counter drug market (Abbott and Hellemans, 2000). Morphine and related opioid drugs are widely used as analgesics in the management of severe pain. However, repeated administration of these agents leads to the development of opioid tolerance and physical dependence, factors that limit their therapeutic usefulness. It has been suggested that activation of neuropeptide transmitters calcitonin gene-related peptide (CGRP) and substance P receptors contributes to the induction and expression of opioid physical dependence and that this activity may be partially expressed through the intermediary actions of prostaglandins (Trang et al., 2002). Accordingly, it has been shown that both indomethacin and mefenamic acid prevent expression of the withdrawal contracture on naloxone challenge in guinea-pig isolated ileum (Johnson et al., 1988).

Conditioned place preference (CPP) has been widely used to assess the rewarding effect of various drug and non-drug treatments. The test is based upon the principle that, when a primary reinforcer is paired with a contextual stimulus, the contextual stimulus can acquire secondary reinforcing properties. These secondary reinforcing properties, which are presumably

established due to a Pavlovian contingency, are thought to be capable of eliciting an operant approach response or place preference which results in a significant increase in the time spent in the drug-paired place (Tzschentke, 1998). Several studies have examined the effect of various drug and non-drug treatments on CPP for morphine and other drugs of abuse. Our data indicates that morphine induces a significant CPP in mice; indeed intraperitoneal administration of 5 and 7.5 mg/kg of morphine induced a significant shift in preference for the environment previously paired with the drug. This is in accordance with our previous findings and the results of others in this respect (Mackey and Van der Kooy, 1985; Tahsili-Fahadan et al., 2006). Also, it has been shown celecoxib (10 and 20 mg/kg) and indomethacin (5 mg/kg) significantly decrease the time spent in the environment paired with the drugs during the conditioning phase (CPA). In addition, lower and non-effective doses of indomethacin or celecoxib can alter the rewarding properties of morphine and decrease morphine-induced CPP.

The ability of various NSAIDs and other widely used analgesics to induce place preference has been previously studied. Results of this study indicate that indomethacin and celecoxib attenuate the place preference produced by morphine. However, it has been previously shown that phenacetin produces an unambiguous CPP at doses that produced anti-nociceptive effects, not surprising considering the historical evidence for abuse (Abbott and Hellemans, 2000). Evidence indicate that acetaminophen – the first metabolite of phenacetin and probably responsible for some of its effects after systemic treatments – produces a very significant CPP; while dipyrone, an agent that has peripheral antinociceptive effects that are not mediated by COX inhibition, produced a strong place aversion when administered by the systemic route, ICV administration led to a CPP only at doses that produced anti-nociception. Additionally, it has been suggested that the prototypical non-specific COX inhibitor indomethacin is not able to produce a significant change in place preference (Abbott and Hellemans, 2000). Moreover, nimesulide is shown to be able to induce CPP in rats (Fattore et al., 2000). These differences could be attributed to different drugs and doses used in this study, animals (mice versus rat), routes of administration (IP versus ICV), and conditioning methods (6 versus 10 days of conditioning; unbiased versus biased design). Opposite effects on the induction of place preference, from central and peripheral injections, have been reported for morphine (Bechara and van der Kooy, 1985). Moreover, it has been reported in some studies that cocaine produces CPP only when administered intraperitoneally, but not subcutaneously (Mayer and Parker, 1993). However, to fully explain the findings obtained in the present work, a possible pharmacokinetic interaction between indomethacin or celecoxib and opioid can not be excluded, even if only limited knowledge about the pharmacokinetic interactions between these drugs is available. Also, the critical role of COX activity for the development of stimulant sensitization has been previously shown. Indomethacin has been found to completely block the development of cocaine sensitization and partially reduce the development of amphetamine sensitization. 6-MNA, which affects both COX-1 and COX-2 though with higher affinity at COX-2, blocks the development of both cocaine and amphetamine (Reid et al., 2002).

In conclusion, results of the present study indicate that both selective and non-selective inhibitors of COX-2, celecoxib and indomethacin, in doses that cannot induce any significant change in preference by themselves, are able to attenuate the conditioned place preference induced by morphine in mice. Since conditioned place preference is considered both a reliable and highly predictive animal model of drug-induced reward and abuse potential of drugs (Tzschentke, 1998), the present results raise the possibility that these drugs might also exert an aversive, and potentially therapeutic, effect in opioid abuse in man. More generally, our study supports the hypothesis that the inhibition of COX cascade might participate in the modulation of the reward pathways, probably through an involvement of dopaminergic or GABA-ergic systems. It has been shown that indomethacin inhibits catalepsy induced by the dopamine receptor inhibitors, haloperidol and raclopride (Ono et al., 1992; Ross et al., 1999) and COX inhibition potentiates opioid inhibition of GABA-ergic synaptic transmission (Vaughan et al., 1997). Nevertheless, additional investigations are necessary to determine the exact mechanism of such interaction.

Acknowledgments

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