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PJBS

ISSN 1028-8880

Pakistan Journal of Biological Sciences

ANSInet
Asian Network for Scientific Information
308 Lasani Town, Sargodha Road, Faisalabad - Pakistan

Pakistan Journal of Biological Sciences 12 (1): 33-39, 2009
ISSN 1028-8880

The Effects of Lamotrigine on the Acquisition and Expression of Morphine-Induced Place Preference in Mice

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Abstract: The purpose of the present study is to determine the effects of the anticonvulsant drug, lamotrigine, on the acquisition and expression of morphine-induced place preference in mice. Lamotrigine prevents the release of glutamate from presynaptic neurons and inhibits action potential in postsynaptic area by inhibiting presynaptic sodium and calcium channels. Because of such properties, lamotrigine is used for reducing craving for and use of cocaine, alcohol and abused inhalant. So, to determine the effects of lamotrigine on opiates; specifically morphine, 180 male Swiss-Webster mice (20-35 g) were used in this study. Conditioned place preference, was assessed using a biased place conditioning paradigm. In a pilot study the effects of various doses of morphine (2.5, 5 and 10 mg kg $^{-1}$), alone, or in combination with lamotrigine (1, 5 and 25 mg kg $^{-1}$) on the place conditioning paradigm were examined. Animals were injected with the aforementioned doses of lamotrigine 60 min either prior to each morphine injections (acquisition) or prior to the start of the expression on the test day (expression). Administration of different doses of morphine (2.5, 5 and 10 mg kg $^{-1}$) induced conditioned place preference whereas the administration of different doses of lamotrigine (1, 5 and 25 mg kg^{-1}) failed to induce place preference. Acquisition and expression of morphine-induced CPP were reduced by lamotrigine at doses of 1, 5 and 25 mg kg^{-1} and 5 and 25 mg kg^{-1}, respectively. Physiological mechanisms of action of lamotrigine and its potential therapeutic use in the treatment of drug-dependence are discussed.

Key words: CPP, addiction, opioid, anticonvulsant drug

INTRODUCTION

Given the grave concern for addiction to opiates and its public health consequences in many countries, it is important to determine its underlying physical and psychological mechanisms as well as its development. Such assessment enables us to develop medications that can, both, prevent the development of dependence and reverse the existing dependence. Also, a more thorough understanding of molecular mechanisms of opiate dependence can lead to the development of better treatment plans in the future. Today, the neurobiology underlying opiate dependence is well understood and has revealed that one of the most important systems involved in it is the mesolimbic dopaminergic system (Spanagel and Welss, 1999; Camí and Farré, 2003). Many studies have suggested that the mesolimbic dopaminergic neurons projecting from ventral tegmental area to nucleus accumbence, prefrontal cortex, hippocampus and amygdale are critical for the initiation of opiate reinforcement (Koob, 1992; Wise, 1998; Hyman and Malenka, 2001; Robinson and Berridge, 2003). These areas play important roles in motivating and rewarding effects of opiates (McBride *et al*., 1999) for example, the available data suggest that the opiate, morphine, exerts its effects by activating dopaminergic neurons in the Ventral Tegmental Area (VTA) thereby enhancing the release of dopamine in the mesolimbic system (Narita *et al*., 2001). Specifically, morphine increases the activation of the dopaminergic system by inhibiting Gama-Amino-Butyric Acid (GABA) neurons (Koop, 1992; Johnson and North, 1992) and augmenting the activation of glutamatergic receptors (Noda and Nebshima, 2004). Therefore, drugs that can increase GABAergic transmissions or decrease glutametergic transmissions can potentially be valuable for the treatment of morphine dependence.

The anticonvulsant drug, lamotrigine (3, 5-diamino-6 (2, 3-dichlorophenyl)-1, 2, 4-triazine), has a broad range of therapeutic activities including the treatment for partial, absence, myoclonic and tonic-clonic seizures

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(Leach and Brodie, 1995) and extrapyramidal side effects of parkinson's disease as well as reducing recurrence of depressive phases in bipolar disturbances (Bailer *et al*., 2002). In terms of the activities of lamotrigine at cellular levels, it is shown that it inhibits voltage-gated Na^+ and Ca^{2+} channel by inhibiting presynaptic Na^+ and Ca^{2+} channels thereby preventing the release of various neurotransmitters, including glutamate.

Therefore, such reported properties of lamotrigine suggest that it can be clinically useful in the treatment of addiction to cocaine, alcohol and abused inhalants (Gass and Olive, 2008). To our knowledge, to date, no studies have been conducted to determine the efficacy of lamotrigine to reverse the addictive properties of opiates, particularly morphine. Therefore, the purpose of the present study was to investigate the effects of lamotrigine on morphine within a Conditioned Place Preference (CPP) paradigm; a design widely used to study the reinforcing properties of drugs of abuse (Carr *et al*., 1989; Bardo *et al*., 1995). Specifically, the effects of lamotrigine on the acquisition and expression of morphine-induced CPP will be assessed.

MATERIALS AND METHODS

Animals: One hundred and eighty male Swiss-Webster mice (Tehran University of Medical Sciences, Tehran, Iran) weighing 20-35 g at the beginning of the experiment were used in the present study. The animals were housed in groups of 6/cage at a constant temperature of 22±2°C on 12-12 h light/dark cycle (the lights on at 07:00 h) at the animal facilities of Tehran University of Medical Sciences department and were allowed free access to food and water inside standard polypropylene cages. The animals were allowed to adapt to laboratory conditions for at least 1 week prior to the onset of the experiment. All experiments were conducted during light phase of the light-dark cycle. All procedures were carried out in accordance with institutional guideline for animal care and use. This study was conducted from June 2007 till October 2007.

Apparatus: Place conditioning was conducted using minor modification of biased procedure (Sahraei *et al*., 2006). The apparatus consists of shuttle box (15×30×15 cm: w×l×h) that was divided into two compartments: A and B. Two compartments were identical in size but differed in shading. One compartment was white with black vertical stripes and white, texture floor. The other compartment was black with white vertical stripes and black and smooth floor. Removable wooden partition separated one compartment from the other.

Experimental procedure: The CPP paradigm took place on 5 consecutive days by using a biased procedure. The experiment consisted of the following three phases:

Pre-conditioning phase: On day 1, animals were habituated to the conditioned place preference apparatus for 10 min. The removable wall was raised, thereby, allowing each animal to freely explore the two compartments. The amount of time spent in each compartment was measured to assess unconditioned preference (the position of animals was defined by position of their front paws). In this particular experimental setup, the animals did not show an unconditioned preference for either of the compartments.

Conditioning phase: This phase consisted of a 3 day schedule of double conditioning sessions. The first day involved a morning session (9:00-12:00 h) during which animals received a single dose of morphine and were immediately placed in black compartments for 30 min. This compartment had been isolated from the other using removable panels. In evening session (16:00-18:00 h) the animals received a single injection of saline and then were placed for 30 min in the white compartment for conditioning experiments. On the second day of this phase the animals received the saline injection in the morning session followed by morphine administration in the evening session. The schedule of the third day of the conditioning phase was similar to that of the first one.

Testing phase: On the 6th day of schedule when animals had fully developed preference to morphine, they were allowed again to freely explore the two compartments for 10 min, the same amount of time as in the preconditioning phase. Then, the time spent in each compartment was computed. We defined the change in preference as the difference (in seconds) between the time spent in the drug-paired compartment on the testing day and the time spent in the saline-paired compartment on the testing day. This variable was chosen as an index of drug-induced place preference as previously described by Hand *et al*. (1989). In order to minimize the effects of time, this phase of the experiment was carried out during the day between 10:00-16:00 h.

Drugs: The drugs used in the present study were morphine sulfate (Temd. Co., Tehran, Iran) and lamotrigine (Iran Daru Co., Kermanshah, Iran). Morphine was dissolved in 0.9% saline and lamotrigine was suspended in a 1% solution of Tween 80 in saline. Morphine was injected subcutaneously (s.c.) in volume of 10 mL kg^{-1} and lamotrigine injected intraperitoneally (i.p.) in a volume of 10 mL kg^{-1}. Respective control groups received saline and 1% solution of Tween 80.

Drug treatments

Morphine dose-response analysis: In a pilot study, the effects of subcutaneous administration of different doses of morphine (2.5, 5 and 10 mg kg^{-1}) on the induction of CPP (Fig. 1) were determined. Either morphine or saline was injected in a 3 day schedule of conditioning as described in details in experimental procedure. CPP development was assessed by subtracting the time spent in the saline-paired compartment from the time spent in the drug-paired compartment on the testing day. To eliminate the possibility of morphine-induced motor effects influencing the response, animals were tested in a morphine-free state.

Effects of lamotrigine alone and in combination with morphine on the acquisition of CPP: Effects of intraperitoneal injection of different doses of lamotrigine on the acquisition of morphine-induced conditioned place preference and saline (s.c.) was assessed in a 3 day schedule of conditioning. Lamotrigine (1, 5 and 25 mg kg^{-1}) (Fig. 2) was injected daily for 3 consecutive days. Sixty minute before the administration of morphine; the conditioning scores were calculated in a drug-free state (testing day). Intraperitoneal injections of the same doses of lamotrigine alone, during conditioning, were also used to assess their effects on CPP. Then, the conditioning scores were recorded in a drug-free state on the test day.

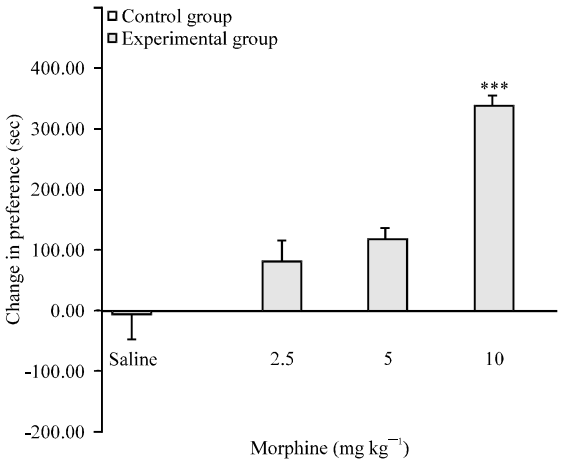

Fig. 1: Illustrates place preference conditioning by morphine. Different doses of morphine (2.5, 5 and 10 mg kg^{-1}) and saline were administered subcutaneously (s.c.) in a 3 day schedule of conditioning. On the test day, the animals were observed for 10 min period. The change of preference was assessed as the differences between the time spent in the drug-paired compartment and time spent in the saline-paired compartment on the testing day. Data are expressed as Mean±SEM of 6 animals per group. ***$p<0.001$ compare with saline control group

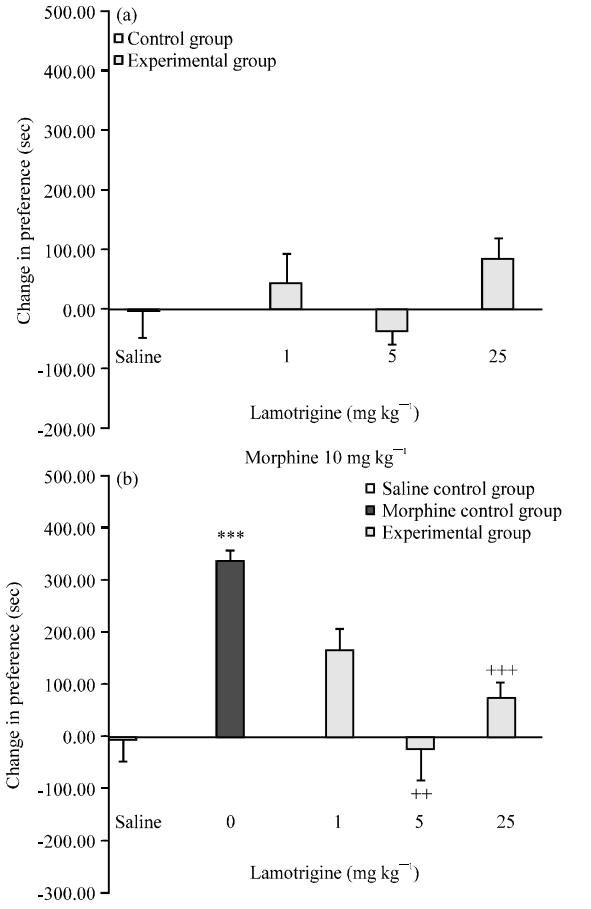

Fig. 2: The effects of intraperitoneal injection of lamotrigine, alone (a) or in combination with morphine (b), on the acquisition of conditioning place preference. The animals received lamotrigine (1, 5 and 25 mg kg^{-1} i.p.) or vehicle/saline (10 mL kg^{-1}) with or without morphine (10 mg kg^{-1}), in a 3 day schedule of conditioning. On the test day, the animals were observed for a 10 min period. The change of preference was assessed as the differences between the time spent in the drug-paired compartment and time spent in the saline-paired compartment on the testing day. Data are expressed as Mean±SEM of 6 animals per group. ***$p<0.001$ compared with saline control group. $^{+++}p<0.001$, $^{++}p = 0.001$ and $^{+}p<0.05$ compared with morphine/vehicle control group

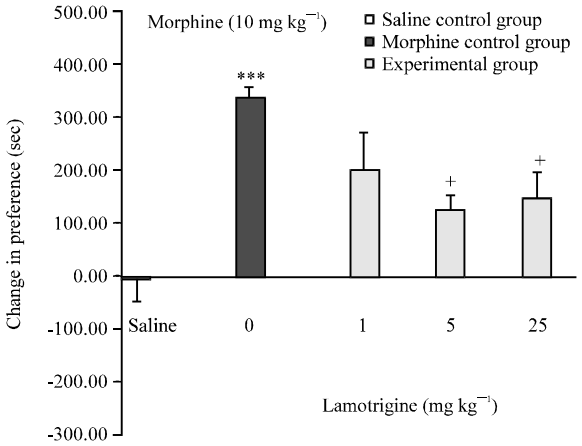

Fig. 3: The effects of intraperitoneal injection of lamotrigine on the expression of morphine induced place preference. All animals received morphine (5 mg kg^{-1}, s.c.) or saline in a 3 day schedule of conditioning. On the test day, the different doses of lamotrigine (1, 5 and 25 mg kg^{-1}) or vehicle (10 mL kg^{-1}) were administered before testing and each animal was observed for a 10 min period. The change of preference was assessed as the differences between the time spent in the drug-paired compartment and time spent in the saline-paired compartment on the testing day. Data are expressed as Mean±SEM of 6 animals per group. ***$p<0.001$ compared with saline control group. $^{+}p<0.05$, *$p<0.05$ compared with morphine/vehicle control group

Effects of lamotrigine on the expression of morphine-induced conditioned place preference: In order to test the effects of lamotrigine on the expression of morphine-induced conditioned place preference, different doses of lamotrigine (1, 5 and 25 mg kg^{-1}) were injected once on testing day (day 5), 60 min prior to conditioning place preference testing. The respective control groups received 1% solution of Tween 80 in volume of 10 mL kg^{-1} per side, intraperitoneally (Fig. 3).

Statistical analysis: The experimental data were expressed as Mean±SEM. Group differences were tested by one- or two-way Analysis of Variance (ANOVA) followed by Tukey post-hoc test. Significance level of difference were based on $p<0.05$. Calculations were performed using the SPSS statistical package.

RESULT

Effects of morphine on CPP paradigm: As shown in Fig. 1, subcutaneous injection of different doses of morphine sulfate (2.5, 5 and 10 mg kg^{-1}) caused a significant increase in time spent in drug-paired compartment compared to that spent in the saline-paired compartment ($F(3, 20) = 14.57$, $p<0.001$). Subcutaneous injection of saline in control groups in the conditioning compartment did not produce any preference or aversion for either place. As such, the dose of 10.0 mg kg^{-1} of morphine was shown to be effective in producing CPP and therefore was selected for the experiments. Present data analysis revealed that the time of the experiment (morning or afternoon) did not influence the development of CPP given that testing was performed at different times on the testing days.

Effects of lamotrigine alone and combined with morphine on the acquisition of CPP: Figure 2 show the effects of lamotrigine alone and in combination with morphine (10.0 mg kg^{-1}) on the acquisition of CPP. Two-way ANOVA indicates a significant differences between the response to lamotrigine (1, 5 and 25 mg kg^{-1}) and that to lamotrigine plus morphine (10.0 mg kg^{-1}) (Factor morphine, $F(1, 40) = 17.20$, $p<0.001$; factor lamotrigine, $F(3, 40 = 8.301$, $p<0.001$; factor morphine plus lamotrigine, $F(3, 40) = 7.984$, $p<0.001$).

In addition, one-way ANOVA revealed that lamotrigine alone induced neither a significant place preference nor place aversion ($F(3, 20) = 1.98$, $p>0.05$). Furthermore, lamotrigine dose-dependently inhibited the morphine-induced place preference (one-way ANOVA: $F(3, 20) = 13.454$, $p<0.0001$).

Effects of lamotrigine on the expression of morphine-induced place preference: As shown, administration of various doses of lamotrigine (5 and 25 mg kg^{-1}) attenuated the expression of morphine-induced CPP ($F(3, 20) = 4.173$, $p<0.05$) whereas at 1 mg kg^{-1} it had no effects on the expression of morphine-induced place preference (Fig. 3).

DISCUSSION

In the first phase of the present study, we showed that subcutaneous injection of morphine produced a dose-related Conditioned Place Preference (CPP) in mice. These findings are consistent with those of earlier studies by Olmstead and Franklin (1997), Tzschentke (1998, 2007) and Camí and Farré (2003) which suggested that, the conditioning procedure used in the present study can be used to investigate the rewarding effects of morphine. Studies related to the ability of opioids to produce CPP (Mattes *et al*., 1996; Narita *et al*., 2001; Liang *et al*., 2006) have shown that opioids, namely, morphine, exert their effects via binding to

endogenous opioid receptors such as μ in the Ventral Tegmental Area (VTA) and Nucleus Accumbens (NA) as well as augmenting dopaminergic transmission in the mesocorticolimbic area both of which result in the development of motivational and rewarding effects of morphine. This, in turn, leads to the production of CPP. Specifically, morphine affects μ receptors on GABAergic (Koob, 1992; Wise, 1998; Johnson and North, 1992) and glutametergic neurons (Gass and Olive, 2008) in the VTA and NA by reducing GABAergic neurons' activities and conversely, increasing glutaminergic neuron's activities. The consequence of this change in the activities of GABAergic and glutametergic neurons causes the release of dopamine in the nucleus accumbens (Salamone *et al*., 2005; Pontieri *et al*., 1995) thereby producing morphine-induced positive reinforcement (Wise, 1998; Robinsonl and Berridge, 2003).

In the second phase of the present study, the effects of the anticonvulsant drug, lamotrigine, on the development of CPP or CPA was determined. A review of the CPP literature reveals that very few, if any; studies have examined the effects of anticonvulsant drugs on CPP (Tzschentke, 2007). It has been shown that different types of anticonvulsants including topiramate (10 and 50 mg kg^{-1} i.p.) (Gremel *et al*., 2006), the ERK (ras-dependent protein kinase) inhibitor SL327 (50 and 100 mg kg^{-1} i.p.) (Valjent and Maldonado, 2000; Valjent *et al*., 2001; Salzmann *et al*., 2003), the type IV phosphodiesterase inhibitor rolipram (1 mg kg^{-1} i.p.) (Font *et al*., 2006), D-penicillamine (50 and 75 mg kg^{-1} i.p.), a thiol amino acid (Font *et al*., 2006), the potassium channel blockers quinine (50 mg kg^{-1} i.p.) and 4-aminopyridine (2 mg kg^{-1} i.p.) (Meririnne *et al*., 1999), do not produce CPP. Consistent with these findings, present results showed that lamotrigine, at various doses, failed to produce such effect. This finding is a further testimony to the idea that anticonvulsants may produce their effects by interfering with the activity of dopaminergic neurons and reducing their ability to produce CPP.

Although such effects of anticonvulsants have been well established, there has been one study that showed the administration of riluzole, a glutamate release inhibitor, leads to the development of CPP (Tzschentke and Schmidt, 1998b), a finding inconsistent with ours. The reason(s) for such an inconsistency could lie in the fact that other properties of lamotrigine including its inhibitory effects on the flow of sodium and calcium ions or other unexplained laboratory conditions might have significantly contributed to obtaining such results.

In the present study, the effects of lamotrigine on the acquisition and expression of morphine-induced place preference were studied to assess the extent of the involvement of the glutamatergic system in morphine-induced CPP. Present findings showed that the administration of lamotrigine can prevent the development of morphine-induced CPP in mice (acquisition); a finding consistent with other reports that showed glutamate receptor antagonists prevent morphine-induced CPP (Tzschentke and Schmidt, 1998), whereas, when administered alone, it did not have any effects on CPP. Specifically, on conditioning days, when administered an hour before the morphine administration, lamotrigine exhibited a does-dependent decrease on the acquisition of morphine-induced CPP. One way to explain this finding is that lamotrigine not only decreases the activity of glutamatergic system (Bardo *et al*., 1995) but also it decreases extracellular levels of dopamine in the VTA and nucleus accumbens (Bonci and Malenka, 1999). As such, given that the production of CPP is dependent upon the activation of the dopaminergic system (a system through which morphine exerts its effects), the inhibitory effects of lamotrigine on the dopaminergic system seems to be a viable explanation for the lack of CPP development in the present study. Specifically, the reduction of dopamine transmission leads to the suppression of morphine-induced euphoria and as a result morphine loses its ability to act as a euphoric unconditioned stimulus.

Lamotrigine also affects the glutaminergic system and reduces the release of glutamate. So, the fact that lamotrigine prevented the formation of morphine-induced CPP also implies that the formation CPP is, to some extent, dependent on the glutaminergic system. Thus, it seems that the glutaminergic system might also be involved in morphine's ability to produce euphoric effects and that lamotrigine by interfering with this system causes morphine to lose its ability to act as an euphoric cue.

In the last phase of present experiments, administration of lamotrigine before testing showed a dose-dependent decrease in the expression of morphine-induced CPP. Such findings suggest that lamotrigine might be interacting with the mechanism(s) involved in the expression of morphine-induced CPP in a dose dependent manner. Specifically, it can be suggested that lamotrigine might be exerting its effects by decreasing glutamate release and the number of action potentials in the presynaptic and post synaptic areas, respectively; as well as decreasing dopamine release in the nucleus accumbens and ventral tegmental area.

One way to explain the ability of lamotrigine to defuse morphine's rewarding properties could be due to glutameterigc system's interference with the activity of the dopaminergic system and reducing morphine's influence on this system thereby preventing the formation of

morphine's rewarding and motivating effects in the VTA and NA. Specifically, administration of lamotrigine might have reduced the activities of the glutametergic neurons projecting from prefrontal cortex, the hippocampus and amygdala to the VTA and NA. Therefore, exposure to the environmental cues that activate these regions might not have stimulated the dopaminergic neurons in the VTA and NA and thus might have prevented them from exerting their rewarding effects.

As such, it seems that lamotrigine's activity on different systems in the CNS, on the one hand and its route of administration (s.c.) in the present study; on the other, could have contributed to the activation of different regions of the nervous system and have resulted in the inhibition of the development of morphine-induced acquisition and expression.

Overall, the results of the present study showed that the administration of lamotrigine can prevent the development of psychological dependence to morphine in mice. Given the existing literature on the clinical application of lamotrigine in the reduction of craving and use of cocaine, alcohol and other inhalants, the implication of the present findings might be that lamotrigine could be potentially useful for treating opiate dependence and alleviating the withdrawal symptoms manifested by the discontinuation of the opiate use.

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