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The effect of lithium chloride on morphine-induced tolerance and dependence in isolated guinea pig ileum

Afsaneh Alborzi [a], Shahram Ejtemaei Mehr [a], Fatemeh Rezania [a], Setareh Badakhshan [a], Tajmah Mombeini [b], Hamed Shafaroodi [c], Leila Moezi [a], Mohammadreza Nick Ravan [a], Mahdiyeh Sharifian [a], Ahmad Reza Dehpour [a,*]

[a] *Department of Pharmacology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran, P.O BOX: 13145-784*
[b] *Department of Pharmacology, School of Medicine, Shahed University, Tehran, Iran*
[c] *Department of Pharmacology, Tehran Medical Unit, Islamic, Azad University, Tehran, Iran*

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Abstract

The chronic use of opioids is often accompanied by the development of tolerance and/or dependence upon these agents due to the adaptive changes in the response of the subject to the agent. On cellular level, these phases of altered responsiveness have been shown to be the sequelae of a combination of multiple independent components acting in concert. Changes in the number, affinity, or membrane trafficking of opioids receptors, the coupling of receptors to G-proteins or in associated second messenger systems have been implicated in underlying the aforementioned phenomena. Several observations have been shown that lithium is able to contradict the expected response in animals pre-treated with morphine. These facts clearly manifest the involvement of lithium in at least one of the diverse pathways that lead to morphine dependence and/or tolerance. The aim of the present study was to investigate the effect of lithium on acute morphine-induced tolerance and dependence in an in vitro model of isolated guinea pig ileum which has been extensively used for the assessment of these effects of opioids. Morphine inhibited electrically stimulated twitch of ileum in a concentration-dependent manner ($pD_2 = 7.27 \pm 0.16$). Tolerance to this effect was induced by the incubation of ileum with $2 \times IC_{50}$ of morphine for 2 h that induced a degree of tolerance of 14.7. The co-incubation of ileum with morphine along lithium chloride (1 mM) reduced the degree of tolerance significantly ($P < 0.001$) and restored the sensitivity of ileum to the morphine inhibitory effect. Lithium chloride can also reduce the expression of tolerance to morphine significantly ($P < 0.01$). Dependence was induced by incubation with $4 \times IC_{50}$ of morphine for 2 h and was assessed based on naloxone-induced contractions (10^{-5} M). Lithium chloride (1 mM) can attenuate the development but not the expression of dependence to morphine as shown by the significant decrease in naloxone-induced contractions ($P < 0.05$). These results suggest that lithium chloride can reduce the development and expression of acute tolerance to and development of dependence on morphine in the myenteric plexus of guinea pig ileum.

Keywords: Ileum; Guinea pig; Tolerance; Dependence; Morphine; Lithium

1. Introduction

The chronic use of opioids is often accompanied by the development of tolerance and/or dependence upon these agents due to the adaptive changes in the response of the subject to the agent (Taylor and Fleming, 2001). In simple terms, tolerance can be described as the need for increasing drug dosage to achieve the same effect; whereas dependence is defined as the appearance of adverse effects on drug withdrawal.

On cellular level, these phases of altered responsiveness have been shown to be the sequelae of a combination of multiple independent components acting in concert (Taylor and Fleming, 2001). Changes in the number, affinity, or membrane trafficking of opioids receptors (Zhang et al., 1998; Whistler et al., 1999), the coupling of receptors to G-proteins (Sim-Selley et al., 2000) or in associated second messenger systems (Nestler, 1997) have been implicated in underlying the aforementioned phenomena.

In a seemingly distinct field, lithium (Li) efficacy as a mood-stabilizing agent revolutionized the treatment of patients with bipolar disorder (Brunello and Tascedda, 2003), a disease characterized by mood swings between mania and depression which

* Corresponding author. Tel.: +98 21 611 2802; fax: +98 21 640 2569.
E-mail address: dehpour@medscape.com (A.R. Dehpour).

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occurs in approximately 1% of the general population (Ulrich et al., 2003). Second messenger pathways have been implicated in the development and neuronal pathophysiology of bipolar disorder. Recent research on the molecular mechanism underlying the therapeutic effect of lithium has focused on how it changes the activities of cellular signal transduction system. In particular, the phosphatidyl inositol (PI) cycle has been extensively investigated since the proposal of the inositol-depletion hypothesis (Berridge et al., 1982; Berridge and Irvine, 1989). Lithium has also been shown to blunt divalent cation [calcium (Ca) and magnesium (Mg)]-induced changes in cytosolic Ca and Ca-induced hydrolysis of inositol phosphates (Haden et al., 1999).

Many of these phenomena share a common core with opioids induced changes in cells of animals treated chronically with morphine. Thus the observations where lithium has been able to counteract the expected response in subjects pre-treated with morphine can be explained.

In these observations, lithium significantly reduced self-stimulation by morphine (Liebman and Segal, 1976) where it has been reported that lithium reduced the amount of voluntary ingestion of morphine by addicted rats. These facts clearly support the involvement of lithium in at least one of the diverse pathways that lead to morphine dependence and/or tolerance.

However, since all these studies have been performed on intact animal where diverse neural and immunological mechanisms inter-collaborate and will obscure our analysis, the aim of the present study was to investigate the effect of lithium on acute morphine-induced tolerance and dependence in an in vitro model of isolated guinea pig ileum which has been extensively used for the assessment of these effects of opioids. It is shown that guinea pig isolated ileum presents an acceptable model for in-vitro studies on morphine tolerance and/or dependence (Collier et al., 1981; Dehpour et al., 2000). The opioid receptors of the myenteric plexus in guinea pig ileum show characteristics similar to those in the central nervous system (Lujan and Rodriguez, 1981), and thus will provide us with the opportunity to specifically assess the effect of lithium on morphine tolerance and dependence where the involving factors could be minimized.

2. Materials and methods

2.1. Animals

Adult male guinea pigs (300–350 g) purchased from the Institute of Razi (Tehran, Iran) were used in the experiments. Animal care and uses were in accordance with the institutional guidelines for laboratory animals. The animals were housed in colony cages (four guinea pigs each) with free access to food and water. They were maintained in a climate- and light-controlled room (12:12 h dark/light cycle) for at least 7 days before testing. Each experiment was performed with at least six to nine isolated preparations from different animals.

2.2. The preparation of the excised tissue

The method used has been described previously (Collier et al., 1981; Rezvani et al., 1983). Animals that had been fasted overnight were killed by a blow on the head. The terminal portion of the ileum, with the 10 cm nearest the caecum discarded, was kept in Tyrode solution (mM: NaCl 137, KCl 2.7, $CaCl_2$ 1.8, $MgCl_2 \cdot H_2O$ 0.5, $NaH_2PO_4 \cdot H_2O$ 0.4, $NaHCO_3$ 11.9, glucose 5) for 30 min and then washed free of faecal matter. Segments of 2–3 cm length from the same animals were placed between platinum electrodes and were fixed at a resting tension of 0.5 g in a 20 ml organ bath and, before the administration of any drug, were equilibrated for 60 min with washing out every 15 min. Electrical stimulation was applied through a parallel platinum electrode on either side of the tissue, using supramaximal rectangular pulses for all preparations (150 V of 1 ms duration at a frequency of 0.1 Hz). Twitches were recorded to a Narco Grass polygraph. The bath solution was maintained at 37 °C and bubbled continuously with O_2.

2.3. Assessment of the degree of tolerance

The method used to elicit morphine tolerance and to determine the degree of tolerance was the same as was described by Collier et al. (1981) and Rezvani et al. (1983). After 60 min equilibration, the tissues were stimulated until steady state amplitude was obtained. Morphine was added to the bath cumulatively. The half-maximal concentration of morphine that inhibited electrically induced contractions (IC_{50}) was determined.

The tissues were made tolerant by adding morphine to the Tyrode solution in different concentrations ($2 \times IC_{50}$ of morphine) or time course (2 h) in each concentration. The tissues were washed every 15 min over a period of 2 h with Tyrode solution containing the same concentration of morphine. At the end of the incubation, the tissues were stimulated as previously until a steady amplitude comparable to that observed before preincubation with drug was obtained. The IC_{50} of morphine was then redetermined, while the concentration of morphine in the media was maintained. The degree of tolerance induced was expressed as a ratio, IC_{50} tolerant/IC_{50} non-tolerant. The effect of lithium on morphine tolerance was determined by incubating the tissue with modified Ringer solution; 1 mM of NaCl replaced by LiCl. Again the degree of tolerance in this preparation was measured.

2.4. Assessment of morphine dependence

The methods used to elicit morphine dependence and typical contracture response of ileum to repeated challenge with morphine and naloxone were the same, as reported previously (Collier et al., 1981; Capasso et al., 1998). The ilea were allowed to equilibrate for 40–60 min without washing and the response to acetylcholine (10^{-6} M) was determined three times so that the response could be expressed as a percentage of the acetylcholine maximum response. The preparation was electrically stimulated for 10–20 min (0.5 ms duration at a frequency of 0.1 Hz at supramaximal voltage). Before the addition of morphine to the bath, the electrical stimulation was switched off and the medium was renewed. Morphine ($4 \times IC_{50}$) was added to the bath and after 2 h, the exposure to naloxone (10^{-5} M) induced a strong contracture. After washout, another acetylcholine response was elicited (to verify whether ileum responsiveness was modified

after the withdrawal contracture). The amplitude of contracture produced by naloxone challenge is expressed as a percentage of the maximum contraction obtained with the subsequent addition of acetylcholine to the same piece of tissue, according to a modification of the method of Collier et al. (1981):

$$\frac{\text{Response to naloxone}}{\text{Maximum response to acetylcholine}} \times 100 = \text{Tension ratio}$$

In order to assess the effectiveness of lithium on morphine dependency, Tyrode solution containing Li^+ and morphine (in the same concentration as the organ bath) was prepared by replacing 1 mM of the original NaCl with LiCl; warmed to the same degree as the organ bath, and when necessary was gradually replaced with the medium in immediate contact with the tissue, so that the preparation was never devoid of nutrient and the morphine. In another set of experiments, LiCl (terminal concentration in the organ bath: 1 mM) was added to the medium immediately before the addition of naloxone. In each case the relative tension ratio was measured and compared.

2.5. Drugs

Drugs used were morphine sulphate (Temad Pharmaceutical, Tehran, Iran), LiCl (Merck Pharmaceuticals), naloxone (Tolid Daru, Tehran, Iran) and acetylcholine (Sigma, St. Luis, MO, USA). All drugs were dissolved in deionized water.

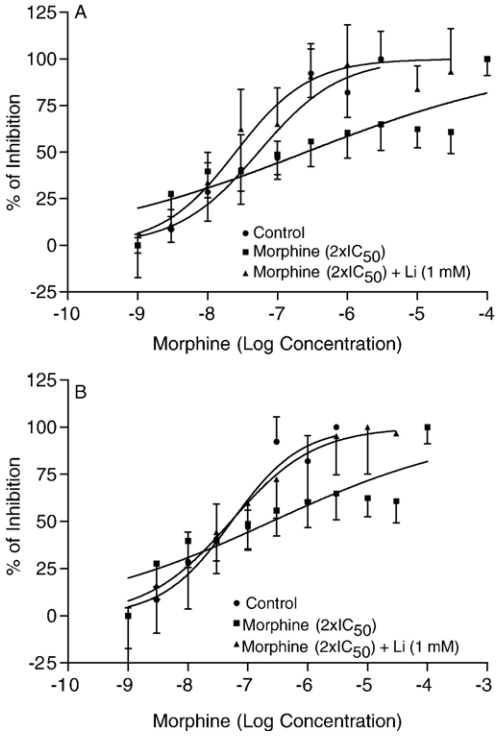

Fig. 1. Concentration–response curve for morphine inhibition of electrically induced contractions in isolated guinea pigs ileum. (A) The effect of lithium on the development of tolerance to morphine after incubation with morphine ($2\times IC_{50}$) (■), morphine ($2\times IC_{50}$)+LiCl (1 mM)(▲) for 2 h[a]. (B) The effect of lithium on the expression of tolerance to morphine. 2 h incubation with: morphine ($2\times IC_{50}$)[a] (■) and adding lithium (1 mM)[b] (▲) immediately before assessment of the morphine inhibitory effect on electrically induced contraction. a $P<0.001$ compared to the control (non-tolerant) (●) group. b $P<0.001$ compared to the corresponding tolerant (■) group.

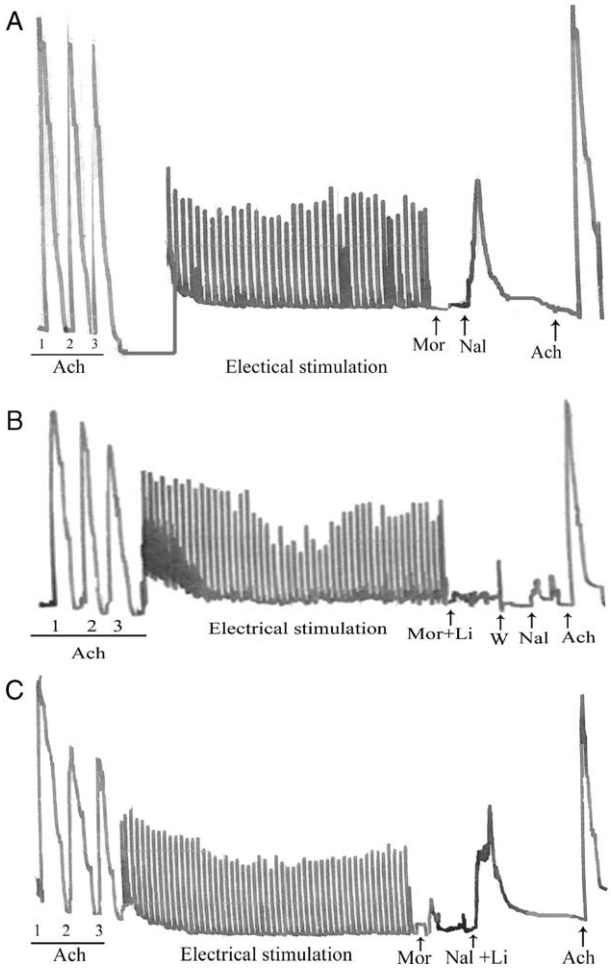

Fig. 2. Typical tracing of opioid dependence on isolated guinea pig ileum. (A) 3 similar acetylcholine response (Ach), electrical stimulation, injection of morphine (Mor) followed after 2 h of incubation period by naloxone (Nal) which induces contraction. After washout, another Ach response was performed. (B) The effect of LiCl (1 mM) (Li) on the development of morphine dependence in isolated guinea pig ileum. (C) The effect of LiCl (1 mM) (Li) on the expression of morphine dependence in isolated guinea pig ileum.

2.6. Statistical analysis

Data are expressed as the mean±S.E.M. One-way analysis of variance (ANOVA) was used to compare the mean pD_2 value, negative logarithm of IC_{50} and tension ratios in various experiments. $P<0.05$ was considered as the significant level for differences between groups.

3. Results

Morphine inhibited the electrically stimulated contraction of guinea pig ileum in a concentration-dependent manner (pD_2=7.27±0.16). After the incubation of tissues with $2\times IC_{50}$ of morphine for 2 h, the concentration–response curve for the inhibitory effect of morphine was shifted significantly to the right

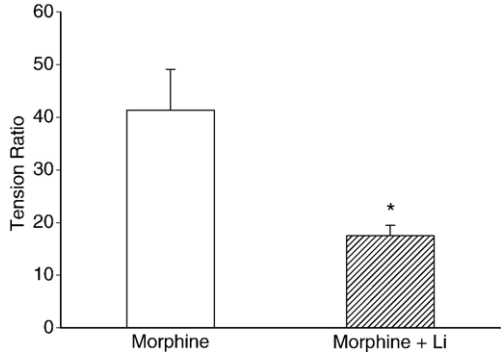

Fig. 3. The effect of lithium (1 mM) on the development of dependence on morphine in isolated guinea pig ileum. * $P<0.05$ compared to the corresponding group incubated with morphine ($4\times IC_{50}$).

($pD_2=6.60\pm0.33$) ($P<0.001$) and the degree of tolerance was 14.7.

Lithium chloride (1 mM) co-incubated with $2\times IC_{50}$ of morphine decreased the degree of tolerance significantly to 0.47 ($P<0.001$), and restored the sensitivity of GPI to morphine inhibitory effect ($pD_2=7.59\pm0.19$) (Fig. 1A). The incubation of tissues with lithium chloride (1 mM) alone without morphine for 2 h did not have any significant affect on the IC_{50} inhibitory effect of morphine ($pD_2=7.68\pm0.14$) ($P>0.05$).

In order to assess the lithium effect on the expression of tolerance to morphine, after incubation of tissues with $2\times IC_{50}$ of morphine for 2 h, lithium chloride was added immediately before adding the cumulative concentration of morphine. Lithium reduced the expression of tolerance to morphine significantly ($pD_2=7.28\pm0.29$) ($P<0.01$) (Fig. 1B) and restored the sensitivity of tissues to the inhibitory effect of morphine (degree of tolerance=0.97). Lithium did not have any significant effect on the inhibitory effect of morphine in non-tolerant GPI when it was added immediately before morphine ($pD_2=7.39\pm0.14$) ($P>0.05$).

Regarding the induction of morphine dependence in GPI, tissues were incubated with $4\times IC_{50}$ of morphine for 2 h and thereafter added naloxone (10^{-5} M), which induced a large contraction (tension ratio=41.33 ± 17.45) (Fig. 2A). Incubation of tissues with lithium chloride (1 mM) along with morphine ($4\times IC_{50}$) significantly inhibited the development of dependence and reduced tension ratio to 17.57 ± 4.88 ($P<0.05$) (Figs. 2B and 3).

For assessment of the effect of lithium on the expression of dependence to morphine in GPI, lithium chloride (1 mM) was added immediately before adding of naloxone (10^{-5}). Lithium chloride (1 mM) cannot reduce the expression of dependence to morphine in GPI and there was not any significant change in the tension ratio (tension ratio=56.73 ± 13.16, $P<0.33$) (Fig. 2C).

4. Discussion

There has been no previous demonstration of the inhibitory effect of lithium on the induction to and tolerance on morphine in isolated tissues in vitro. The purpose of this study was to find out whether this cation has inhibitory effects on the acute induction and development of these phenomena in the guinea pig ileum model.

In early studies, the administration of Li to morphine-dependent rats caused a reduction in the self-administration of morphine (Tomkiewicz and Steinberg, 1974). A decrease in self-stimulation facilitated by morphine after administration of lithium has also been noted by Liebman and Segal (1976). Lithium has also been shown to interact with morphine-induced analgesia in mice (Saarnivaara and Mannisto, 1976). The interaction happens at doses well below the lower end of the Li^+ therapeutic range (Dehpour et al., 1994, 1995). In our study we were faced with comparable results. Lithium can inhibit morphine-induced tolerance and dependence in isolated guinea pig ileum shown by diminished naloxone-precipitated withdrawal and an increase in morphine IC_{50} in isolated guinea pig ileum incubated with morphine. Since the neural elements of the myenteric plexus anatomically and neurochemically closely resemble those of the central nervous system (Lujan and Rodriguez, 1981), these results allow us to propose that lithium may suppress both physical dependency and tolerance upon morphine. The results are consistent with various findings which could in part explain the mechanism responsible for the observed phenomena.

Interaction between morphine and lithium may happen in different levels and through various pathways. Altered phosphorylation has long been considered to underlie, at least in part, many of the physiological sequelae of persistent activation of opioid receptors (Chakrabarti et al., 1998). Studies in rat locus ceruleus have demonstrated that after chronic systemic morphine administration, the phosphorylation state of multiple proteins [substrate for PKA (protein kinase A)] is augmented (Guitart and Nestler, 1989). In the guinea pig ileum preparations, the consequence of chronic morphine is accompanied by up-regulation of PKC (protein kinase C). Studies have also shown that chronic morphine up-regulates specific adenylyl cyclase isoforms (Rivera and Gintzler, 1998), all of which in concordance with adenylyl cyclase 'superactivation' and cAMP 'overshoot' characteristic of opioid withdrawal (Zhang et al., 1998; Chakrabarti et al., 1998). On the other hand, Li^+ exerts an inhibitory effect directly on the catalytic subunit of adenylyl cyclase (Mork and Geisler, 1987; Newman and Belmaker, 1987), keeping with the hypothesis that lithium inhibits agonist-induced cAMP accumulation (Kofman and Patishi, 1999); thus providing a common ground for interaction with morphine (Sharma et al., 1975, 1977; Duman et al., 1988).

Another point of interaction between Li^+ and morphine-induced changes in the cellule is the nitric oxide(NO)-cGMP pathway (Kanba et al., 1985, 1986). The involvement of NO in these phenomena has been suggested by reports showing that the nitric oxide synthase inhibitors abolish some aspects of the naloxone-precipitated withdrawal and attenuate the expression of both tolerance and physical dependence in in-vivo rodent models (Adams et al., 1993; Cappendijk et al., 1993; Dambisya and Lee, 1995). It is also shown that N^G-nitro-L-arginine methyl ester (L-NAME) could prevent morphine-induced dependence in the guinea pig ileum model (Capasso et al., 1998). Simultaneous administration of L-Arg, a precursor of NOS (nitric oxide

synthase), with lithium has to some extent decreased the effect of lithium on withdrawal signs (Dehpour et al., 2000). Other studies have documented that Li^+ inhibits the synthesis of cyclic GMP mediated by neurotransmitter (Kanba et al., 1985, 1986). It can be deduced that lithium modifications on morphine dependence and tolerance could be at least to some extent due to the NOS involvement (Dehpour et al., 2000).

Furthermore, it has been shown that acute opioid exposure decreases calcium fluxes in neurons (Bradford and Crowder, 1986; Crowder et al., 1986). Tolerance to this effect develops during chronic morphine exposure and there are important changes in the permeability to Ca including the appearance of an increased number of voltage-operated Ca channels in brain tissue (Ramkumar and El-Fakahany, 1984). Therefore, when opioids are withdrawn or naloxone is applied, the neuronal influx of calcium probably becomes too elevated (Bongianni et al., 1986; Baeyens et al., 1987). On the other hand, lithium leads to an increase in intracellular calcium content (Abajo et al., 1987) which consequently may attenuate the appearance of increased number of voltage-operated Ca channels in the brain.

In conclusion, our study on guinea pig ileum confirmed the previous surveys performed on intact animal, meaning that lithium can inhibit the induction of morphine-induced tolerance and dependence in the guinea pig ileum model. The interaction may be due to the decreased activity of nNOS (neuronal nitric oxide synthase), to alterations in neurotransmitter release or may involve changes in nNOS gene expression. The underlying mechanism(s) warrant further investigation.

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