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Original Article

Interactive Effects of Acute and Chronic Lithium with Dopamine Receptor Antagonists on Naloxone-Induced Jumping in Morphine-Dependent Mice

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Abstract

In the present study, interactive effects of D1 and D2 dopamine receptors antagonists and different periods of lithium pretreatment on morphine dependence in mice have been investigated. This study was designed to investigate whether the hypothesis that lithium and dopaminergic mechanisms via their effects on phosphoinositide pathways and calcium flux could influence morphine withdrawal response as manifested in the jumping effect. Animals were treated subcutaneously with morphine (50, 50 and 75 mg/kg) three times daily (10 a.m., 1 p.m. and 4 p.m.) for 3 days, and a last dose of morphine (50 mg/kg) was administered on the 4th day. Withdrawal syndrome (jumping) was precipitated by naloxone (5 mg/kg) which was administered intraperitoneally 2h after the last dose of morphine. To study interactive effects of dopamine receptor antagonists and different duration of lithium pretreatment, 10 injection of morphine (3 administrations each day) for dependence and a dose of 5 mg/kg of naloxone for withdrawal induction were employed. SCH 23390 (0.01, 0.02 and 0.05 mg/kg) as a D1 dopamine receptor antagonist and sulpiride (20, 40 and 80 mg/kg) as a D2 dopamine receptor antagonist were able to prevent withdrawal signs precipitated by naloxone (5 mg/kg). Pretreatment of animals with lithium (600 mg/l) for 7, 14, 21 and 28 days, increased jumping induced by naloxone in morphine dependent animals. SCH 23390 did not show any significant alteration on the jumping response in animals pretreated with lithium for 28 days, but the inhibitory effects of sulpiride was significantly decreased in animals received lithium for 28 days. It is concluded that postreceptor mechanism (s) may be involve in the interactions of lithium with dopaminergic system in alteration of naloxone-induced jumping in morphine dependent animals.

Keywords: Lithium; Morphine; Dopamine; Jumping; Withdrawal; Dependence.

Introduction

The diversity of drug types capable of attenuating opiate abstinence suggests that withdrawal syndrome may be modulated at multiple sites involving a variety of neurotransmitter system (1).

Although many central neurotransmitter systems have been implicated, there is now considerable evidence that chronic administration of opiates, particularly of morphine to rodents, which results in the development of physical dependence, is associated with attenuates in the activity of brain dopaminergic neurons (2). Also it has been reported that chronic treatment with morphine is associated with the development of behavioral supersensitivity mediated by dopamine receptors (3, 4). Enhancement of behavioral response to apomorphine as a dopamine receptor agonist also has been reported in rats treated with human β-endorphin (5). On the other hand opposite results, in which either no change or even decreased sensitivity of dopamine receptors in morphine dependent

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rats have been noted, are reported by some investigators (6).

Dopamine receptors have now been classified into D1-like and D2-like subtypes (7). The application of homology screening technique has also led to the charachterization of three other dopamine receptors, which are D3, D4 and D5 (7). These findings certainly have, medical implications. For example most of what is known about dopamine agonists' and antagonists' action has to be reevaluated in view of the existence of the different dopamine receptors. Dopamine D1 receptors were described to be linked functionally to adenylyl cyclase, unlike D2 receptors (7, 8). In addition it has been shown that D1 and D2 dopamine receptors may interact with the inositol phospholipid signaling pathway (9-11). Lithium is an effective drug in the treatment of manic-depressive disorder. Despite the wide spectrum of data collected in these largely biochemical studies, no study has adequately explained the mechanism of the clinical action of lithium. However, there is increasing evidence that lithium exerts its therapeutic action by interfering with polyphosphoinositides metabolism and prevention of inositol recycling by an uncompetetive inhibition of inositol monophosphatase (12). The interactions between lithium with phosphoinositide pathways and dopaminergic agents have been shown in our previous works (13, 14).

A number of behavioral studies point to an interaction between lithium and opioid analgesics. Lithium administration to rodents may potentiate or reduce the analgesic effects of opioids (15-17), increase sensitivity to naloxone (18), increase or decrease morphine-induced hyperactivity (15,19) and reduce self-administration of morphine by addicted rats (20).

Tulunary et al. (21) and Mannisto and Saarnivaara (1972) (22) found that acute administration of lithium increased the analgesic action of morphine, whereas Saarnivaara and Mannisto (16) failed to show any potentiation of acute lithium administration on morphine analgesia. Chronic administration of lithium significantly antagonized the antinociceptive effect of morphine in mice (16). On the other hand, lithium has been shown to increase the antinociception caused by morphine in rats (15, 17).

The present work was designed to study the effects of acute and chronic administration of lithium on jumping induced by naloxone in morphine-dependent mice.

Experimental

Animals

Male albino mice (20–25 g) were used throughout the experiments, and were maintained on standard conditions of food, water, light (12 h/day) and temperature (25±2°C). Each animal was used once only.

Induction of morphine dependence

For induction of morphine dependence, the mice were treated subcutaneously with morphine three times a day (10 a.m., 1 p.m. and 4 p.m.) for three days, and the doses of morphine were 50, 50 and 75 mg/kg respectively (23). The higher daily dose, injected at 4 p.m., was aimed at minimizing any overnight withdrawal. On day 4 they received a last dose of morphine (50 mg/kg, 10 a.m.). Groups of mice, each containing 10 animal, were animals of 10 mice were chosen randomly for the experiments.

Measurement of withdrawal syndrome

Physical dependence was inferred if a withdrawal syndrome could be precipitated with the opioid receptor antagonist, naloxone. Groups of mice were tested for the occurrence of jumping after 10 injections of morphine or saline. Two hours after the last administration of morphine animals were given naloxone (5 mg/kg) intraperitoneally and placed individually in a glass cylinder (28 cm diameter, 30 cm height). The number of jumps was recorded 2 min after naloxone injection for a period of 60 min. The mean±S.E.M. of the number of jumpings was determined for 10 mice.

Drugs

The following drugs were used: morphine HCl (Mac Farlan Smith Ltd. England), SCH 23390 (R-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-tetrahydro-3-methyl-5-phenyl-1H-3-benzazepine-7-ol-maleate; Research Biochemical Inc. U.S.A), sulpiride (Sigma, England), naloxone HCl (Sigma, England), lithium HCl (Merck, Germany). The drugs were dissolved in distilled water, except SCH 23390

which was dissolved in one drop of lactic acid and sulpiride which was dissolved in one drop of acetic acid and then diluted with distilled water. All the drugs were injected intraperitoneally except morphine HCl which was administered subcutaneously. The drugs were given in a volume of 5 ml/kg and 2 ml/kg for intraperitoneal and subcutaneous injections respectively. Also all the drugs were prepared immediately before injection. SCH 23390 and sulpiride were administered 30 min and 90 min before naloxone.

Chronic lithium experiments

For chronic administration, LiCl at a dose of 600 mg/l was dissolved in drinking water and rats received LiCl for periods of 7, 14, 21 and 28 days. Control animals received tap water (13, 14, 37, 38).

Determination of whole blood lithium level

Lithium measurement was made after 0, 7, 14, 21 and 28 days of lithium treatment. Animals were sacrificed by decapitation, and blood was collected from the heart into siliconized tubes. The amount of lithium present in whole blood was measured according to the method of Hisayasu et al. (24). Blood samples were treated by triton-x 0.05 (v/v) to lysis of erythrocytes. Flame atomic absorption spectrophotometer (Shimadzu, model 600-AA) was used for the detection of total lithium concentration.

Table 1. Effects of dopamine receptor antagonists SCH 23390 and sulpiride on naloxone-induced jumping in morphine-dependent animals.

Treatment (mg/kg)	Jumps/60 min Mean±S.E.M.
Saline (5 ml/kg)	39.75±5.30
SCH 0.01	30.83±8.07
SCH 0.02	23.50±4.15
SCH 0.05	10.00±2.45*
Saline (5 ml/kg)	44.83±7.30
Sulpiride 20	8.17±3.59**
Sulpiride 40	2.00±1.81**
Sulpiride 80	8.17±4.31**

Statistical analysis

Statistical analysis of the data was preformed with an analysis of variance (ANOVA) followed by Newman-Keuls test. Differences with $P<0.05$ was considered statistically significant.

Result and Discussion

Effects of D1 dopamine receptor antagonist SCH 23390 and D2 dopamine receptor antagonist sulpiride on naloxone-induced jumping in morphine-dependent mice

Table 1 shows that when different doses of either SCH 23390 (0.01, 0.02 and 0.05 mg/kg, i.p.) or sulpiride (20, 40 and 80 mg/kg, i.p.) were injected 30 and 90 min before naloxone (5 mg/kg, i.p.) injection respectively, a significant

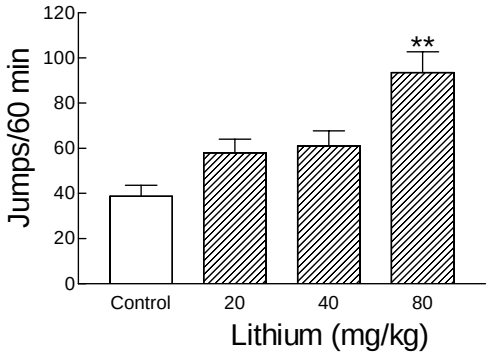

Figure 1. Effects of different doses of lithium on naloxone-induced jumping in morphine-dependent mice. Animals were treated subcutaneously with morphine three times daily (50, 50 and 75 mg/kg, respectively) for 3 days; The last dose of morphine (50 mg/kg) was injected on day 4; in order to develop dependence to morphine. Naloxone (5 mg/kg, i.p.) was injected 2h after administration of the last dose of morphine. Animals were administrated either saline (5 mg/kg, i.p.) or LiCl (20, 40 and 80 mg/kg, i.p.) acutely 60 min before naloxone (5 mg/kg, i.p.) injection. Naloxone was injected 2h after administration of the last dose of morphine. The frequency of jumping was recorded during 60 min after naloxone injection. Each point is the mean±S.E.M. of 10 animals. **P<0.01 different from control group.

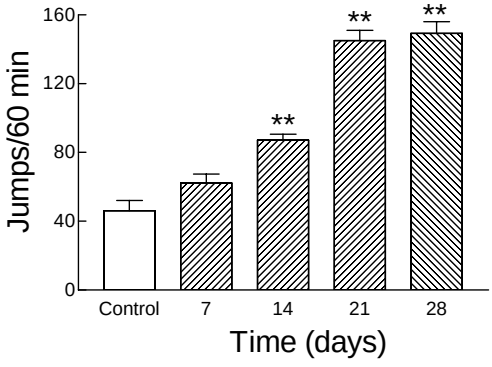

Figure 2. Effects of lithium pretreatment on naloxone-induced jumping in morphine-dependent animals. Animals were treated subcutaneously with morphine three times daily (50, 50 and 75 mg/kg, respectively) for 3 days; The last dose of morphine (50 mg/kg) was injected on day 4 in order to develop dependence to morphine. Naloxone (5 mg/kg, i.p.) was injected 2h after administration of the last dose of morphine. Lithium pretreated mice received LiCl (600 mgl^{-1}) in their drinking water for 7, 14, 21 and 28 days. Control animals received tap water. The frequency of jumping was recorded during 60 min after naloxone injection in each period. Each point is the mean±S.E.M. of 10 animals. **P<0.01 different from control group.

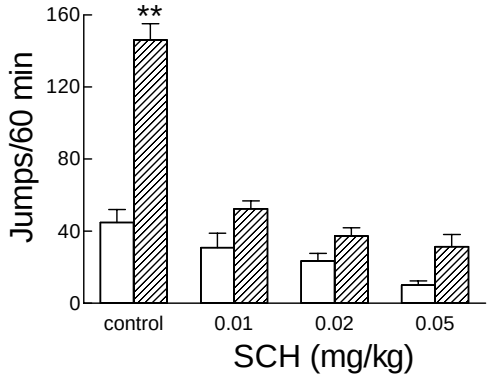

Figure 3. Effects of different doses of SCH 23390 on naloxone-induced jumping in chronic lithium pretreated (▨) and control (▭) mice. Animals were treated subcutaneously with morphine three times daily (50, 50 and 75 mg/kg, respectively) for 3 days; The last dose of morphine (50 mg/kg) was injected on day 4 in order to develop dependence to morphine. Naloxone (5 mg/kg, i.p.) was injected 2h after administration of the last dose of morphine. Chronic lithium pretreated animals received LiCl (600 mgl^{-1}) in their drinking water for a period of 28 days. Control mice received tap water. Animals were injected intraperitoneally with SCH 23390 (0.01, 0.02 and 0.05 mg/kg) 30 min before naloxone (5 mg/kg, i.p.) injection. The frequency of jumping was recorded during 60 min after naloxone injection. Each point is the mean±S.E.M. of 10 animals. **p<0.01 different from control group.

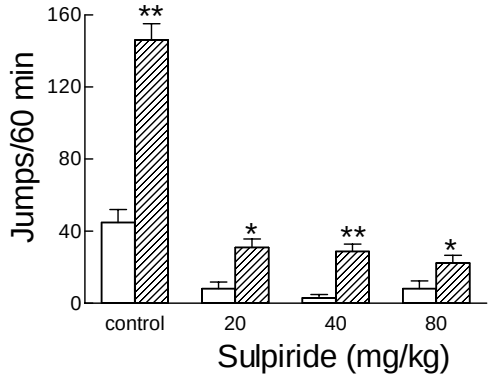

Figure 4. Effects of different doses of sulpiride on naloxone-induced jumping in chronic lithium pretreated (▨) and control (▭) mice. Animals were treated subcutaneously with morphine three times daily (50, 50 and 75 mg/kg, respectively) for 3 days; The last dose of morphine (50 mg/kg) was injected on day 4 in order to develop dependence to morphine. Naloxone (5 mg/kg, i.p.) was injected 2h after administration of the last dose of morphine. Chronic lithium pretreated animals received LiCl (600 mgl^{-1}) in their drinking water for a 28 days period. Control mice received tap water. Animals were injected intraperitoneally with sulpiride (20, 40 and 80 mg/kg) 90 min before naloxone (5 mg/kg, i.p.) injection. The frequency of jumping was recorded during 60 min after naloxone injection. Each point is the mean±S.E.M. of 10 animals. *P<0.05, **p<0.01 different from control group.

decrease in naloxone-induced jumping was observed in the treated animals.

Effects of acute and chronic lithium pretreatment on naloxone-induced jumping in morphine dependent mice

Lithium (20, 40 and 80 mg/kg, i.p.) or saline (10 ml/kg, i.p.) were injected 60 min before naloxone (5 mg/kg, i.p.) injection on the 4^{th} day. Intraperitoneal injection of a high dose of lithium (80 mg/kg) significantly increased naloxone-induced jumping in morphine-dependent animals (Figure 1). Single administration of lithium without naloxone did not elicit any response.

Pretreatment of animals with lithium (600 mg/l) in their drinking water increased the jumping induced by naloxone in morphine-dependent mice after 7, 14, 21 and 28 days. Significant differences were obtained in animals received lithium for 14, 21 and 28 days in comparison with the control group. The maximum response was observed after 28 days of lithium pretreatment (Figure 2).

Table 2. Whole blood lithium concentration after 0, 7, 14, 21 and 28 days of receiving lithium chloride (600 mg/l) in drinking water

Time (days)	Whole blood lithium concentration (µg/ml)
Control	1.36 ±0.19
7 days	4.11 ±0.5 **
14 days	29.89±0.01 **
21 days	26.99±0.13 **
28 days	9.81 ±0.23 **

Animals received lithium chloride (600 mg/l) for 7, 14, 21 and 28 days in theirdrinking water. Control groups received tap water. Each point is the mean±S.E.M. of 10 animals. **p<0.01 different from control group.

Effects of dopamine receptor antagonists on jumping induced by naloxone in animal pretreated with lithium for 28 days

Figure 3 shows that when different doses of SCH 23390 (0.01, 0.02 and 0.05 mg/kg, i.p.) were administered 30 min before naloxone in morphine-dependent animals which pretreated with chronic lithium for 28 days, the jumping response to naloxone was not changed significantly compared with their respective control group. However, administration of lithium (600 mg/l) in drinking water for 28 days significantly decreased the inhibitory effects of sulpiride (20, 40 and 80 mg/kg, i.p.) on jumping response to naloxone, compared with the corresponding control group (Figure 4).

Whole blood lithium concentration

the whole blood lithium concentrations after 7, 14, 21 and 28 days lithium was given in the

drinking water (600 mg/l), which are shown in table 2.

Involvement of dopaminergic mechanism in the withdrawal jumping in morphine dependency is well established. It implies that morphine activates dopaminergic pathways in amigdala, being a mesolimbic area (2). Dopamine is known to bind to separate receptor subtypes, named D1 and D2 (7). The present data indicated that the D1 dopamine receptor antagonist SCH 23390 (25) reduced the number of jumping responses induced by naloxone; It was also found that D1dopamine receptors were involved in the jumping episodes, which is in agreement with previous data (26). The D2 dopamine receptor antagonist, sulpiride (27), also decreased naloxone-induced jumping; this shows that D2 dopamine receptors are involved in jumping reflexes. Our data are in agreement with those obtained by Cerbo et al. (28), who showed that D2 dopamine agonists increase withdrawal jumping. These finding are in agreement with the hypothesis that dopamine is important in the rewarding effects of abused drugs and opioid withdrawal (29). However, other reports indicate that dopamine receptor activation causes an increase (30) or a decrease (31) in withdrawal jumping.

Recently some investigators showed that chronic, intermittent injections of morphine caused an increase in D3R mRNA in dopaminergic and dopaminiceptive regions of the rat brain (32).

The major finding of the present study is that acute and chronic lithium pretreatment in mice can increase naloxone-induced jumping. In acute administration of lithium the maximum response was achieved with high doses of lithium and in chronic lithium pretreated mice the maximum jumping was observed after 28 days of treatment. There is conflicting evidence concerning the effects of lithium alone and the effects of lithium on the action of morphine.

There is evidence that lithium can decrease the binding of opioid agonists to brain opiate receptors (33, 34) and thus subsequently change the jumping response of injected opioid antagonists.

The mechanism of development of physical dependence is a true cellular adaptive response that is associated with changes in second messengers related to calcium flux (1). On the other hand, lithium as well as morphine interact with the intracellular calcium content. Chronic exposure to opioids is associated with an elevation of intracellular calcium content (1), whereas lithium treatment leads to a decrease of intracellular calcium (12). Lithium treatment reduces the level of inositol stores in the brain through inhibition of inositol-1-phosphatase and this could interfere with the resynthesis of PIP2 and thus influence the signaling mechanism operating through the phosphoinositide system and reduce the intracellular calcium (12, 35, 36). Therefore, if the action of morphine is a result of the hydrolysis of phosphoinositides (37), the potentiation effects of lithium on jumping response could be accounted for, at least partially, by a lithium-induced perturbation of the phosphoinositide cascade in the brain.

Our previous works also have shown that lithium can affect the responses mediated by the second messengers of the phosphoinositide cascade (13, 14, 38, 39).

Administration of lithium for 28 days did not decrease the inhibitory effect of SCH 23390 on jumping induced by naloxone, but the inhibitory response of sulpiride was reduced.

The ability of sulpiride to strongly block opiate withdrawal, when compared to SCH 23390, suggests that D2 dopamine receptors may be primarily involved in the control of opiate withdrawal (26). Thus the alteration of sulpiride response in animals treated with lithium 28 days could be due to the greater more potency of sulpiride on blocking the opiate withdrawal. Also it is suggested that phosphoinositides pathway has a more important role in the function of D2 dopamine receptors than D1 dopamine receptors in morphine-dependent animals. In addition, in our studies the lithium-treated rats had a whole blood lithium concentration of 9.81±0.23 µg/ml after 28 days. Kanba et al. (40) have suggested that the lithium level required to affect adenylyl cyclase is higher than this level. Thus the reason that chronic lithium did not block the inhibitory effect of SCH 23390 on the jumping response may be due to the low level of lithium. Furthermore Marinho et al. (41) indicated a decrease of 32% in D2 receptors in animals treated with lithium. The decrease of D2 dopamine receptors is another possibility for changing the sulpiride response in 28 days lithium treated animals. The concentrations of

lithium were decreased after the 14th day. Wood et al. (42) reported the pharmacokinetic profile of lithium in rat, mouse and human. They found significant inter- and intra-species differences in the volume of distribution. Therefore, the falling of whole blood lithium concentrations after 14 days could be related to its movement from blood to tissues.

In conclusion, our results partially show a possible interaction of lithium, dopaminergic system and phosphoinositide cascade in alterations of jumping response induced by naloxone in morphine-dependent animals. There are, however, other proposed mechanisms for morphine, dopamine and lithium, which need not to occur by a common pathway of phosphoinositides. This requires futher studies for clarification.

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