Protective Effects of Lithium on Sumatriptan-Induced Memory Impairment in Mice

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Abstract- Lithium is a drug used for the treatment of bipolar disorder. It has several mechanisms of action, and recently it is shown that lithium can antagonize the 5-HT1B/1D serotonin receptors. Sumatriptan is a 5-HT1B/1D receptor agonist used for the treatment of cluster headaches and migraine which might cause memory impairment as a potential side effect. In this study, effects of lithium on sumatriptan-induced memory impairment have been determined in a two-trial recognition Y-maze and passive avoidance tests. Male mice weighing 25-30 g were divided into several groups randomly. In Y-maze test, effects of lithium (1,5,10,20,40,80 mg/kg) and sumatriptan (1,5,10 mg/kg) were assessed on memory acquisition, then lithium (0.1,1,10 mg/kg) and sumatriptan (1,10 mg/kg) were studied in passive avoidance test. Effects of lithium (1mg/kg) on sumatriptan (10 mg/kg)-induced memory impairment were studied in both of tests. The present study demonstrated that sumatriptan impaired memory in Y-maze and passive avoidance tests ($P<0.05$, $P<0.01$, respectively). Lithium did not show any significant effect on memory function compared to saline-treated control group in both tests ($P>0.05$), but significantly reversed sumatriptan-induced memory impairment in Y-maze and passive avoidance tests ($P<0.001$, $P<0.05$, respectively). It is concluded that lithium reverses the sumatriptan-induced memory impairment probably through 5-HT1B/1D receptors antagonism.

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Keywords: Lithium; Sumatriptan; 5-HT1B/1D; Spatial recognition memory; Mice

Introduction

Sumatriptan is a 5-HT1B/1D receptor agonist (1). Since this receptor is coupled to Gi (2,3), studies have shown that stimulation of these receptors reduces the release of neurotransmitter (4-6). This drug with the same mechanism reduces the release of calcitonin gene-related peptide (CGRP) (7).

Considering the fact that sumatriptan decreases the release of various neurotransmitters, it is likely to cause memory impairment. Several studies have shown that part of the therapeutic effects of lithium may be due to inhibitory receptors 5-HT1B/1D (8-10). Perhaps part of the effects of lithium on memory is due to 5-HT1B/1D receptor antagonism (11), so the aim of the present study was to evaluate the effects of lithium on sumatriptan-induced memory impairment in a two trial recognition Y-maze test and passive avoidance in mice.

Materials and Methods

Housing and handling of the animals

The animals were handled in accordance with the criteria outlined in the Guide for the Care and Use of Laboratory Animals (NIH US publication 86–23 revised 1985). NMRI mice (Pasteur institute Tehran, Iran), 6-8 weeks of age, were kept in a controlled environment (23±2 °C, 50±5% humidity) under a 12-h light/dark cycle (light on 08:00-20:00) and had free access to a standard pellet chow and tap water throughout the study. Each mouse was used only once, and each mouse was used once and each treatment group comprised of 8-12 animals. Animals were excluded if they remained immobile during the test, or they resisted swallowing the drug and threw it out.

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Chemicals and drugs

Sumatriptan used in this study were purchased from Sigma-Aldrich (St. Louis, MO, USA), and lithium was purchased from Merck (Darmstadt, Germany). All drugs were freshly diluted in physiological saline. Lithium and sumatriptan were administrated intraperitoneally and subcutaneous, respectively

Y-maze task

The Y-maze is a simple two-trial recognition test for evaluating spatial recognition memory. It is based on the innate tendency of rodents to explore novel environments (12). It consists of three horizontal arms (40 cm long, 3 cm wide walls and 12 cm high) symmetrically disposed at 120° to each other. Each arm had different clues for distinction from each other. The Y-maze test comprised two trials separated by a 1 h inter-trial interval. In the first trial (training), which lasted 10 min, each mouse was placed at the end of the start arm and was allowed to explore only two arms (including the start arm), with the third arm (novel arm) being blocked. After 1 h, in the second trial (retention), the mouse was placed back in the maze, at the same start arm with free access to all three arms, being allowed to move freely during an 8 min period. The number of arm entries and exploration time in each arm were recorded using a video tracking software (EthoVision, Noldus, The Netherlands) for each mouse over an 8 min period. The total number of arm entries and distance moved were measured as indexes of locomotors activity to rule out the interference of changes in motility with the parameters of learning and memory. To avoid the presence of olfactory trials, maze arms were thoroughly cleaned between tests.

Recognition of the novel arm from the other two familiar arms is considered as a memory improvement effect. Mice which distinguish the unfamiliar arm show exploratory behavior, so they spend more time and enter more frequently to the novel arm in comparison with the other familiar ones.

Passive avoidance task

Passive avoidance apparatus was consisted of a two identical compartments (20×20×20 cm), illuminated and non-illuminated boxes (Borj Sanat Company, Tehran, Iran), separated by a guillotine door. The illuminated compartment contained a 40W bulb, and the floor of the non-illuminated compartment was composed of 2 mm stainless steel rods spaced 1 cm apart. During the training trial, each mouse was placed in the lighted compartment, and when the mouse entered the dark compartment the door closed, and the mouse received an inescapable electric shock (0.5 mA, 1 s). The test trial was done 24 h after the training trial; in this step, the mouse was again placed in the lighted compartment and the latency time to enter the dark compartment was measured. If the mouse did not enter the dark chamber within the cut-off time (300 s), it was assigned a latency value of 300 sec (13).

Experimental design

Y-maze

Mice were administered different doses of lithium (1,5,10,20,40,80 mg/kg) intraperitoneally 60 min before the training trial. In another group, sumatriptan (1,5, and 10 mg/kg) 30 min the training trial was administrated subcutaneously, and the third group was co-administrated lithium (1 mg/kg) and sumatriptan (10 mg/kg) 60 min and 30 min before training trial, respectively.

Passive avoidance

In the first group, different doses of lithium (0.1,1, and 10 mg/kg) were injected intraperitoneally 60 min before the training trial. In the second group, sumatriptan (10 mg/kg) 30 min before the training trial was administrated subcutaneously, and the third group was co-administrated lithium (1 mg/kg) and sumatriptan (10 mg/kg) 60 min and 30 min before training trial, respectively.

Statistical analysis

Statistical analyses were carried out using GraphPad Prism 5 software (San Diego, CA, USA). The results are presented as mean ± S.E.M. Differences among treatment groups were considered as between-group factor, whereas differences in arm entries and exploration time for each special treatment were considered as a within-group factor. Each of between-group differences in the determination of exploration time and number of arm entries in Y-maze was assessed with multivariate analysis of variance (ANOVA) and Tukey's post-hoc test. The non-parametric ANOVA using a medians test was applied to analyze the result of passive avoidance data. Moreover, one-way ANOVA was used to determine the within-group differences in locomotor activities, and *P* values less than 0.05 were considered statistically significant.

Results

Y-maze test

Injection of different doses of lithium could not alter

the time spent in the novel arm, significantly (P>0.05, Figure 1).

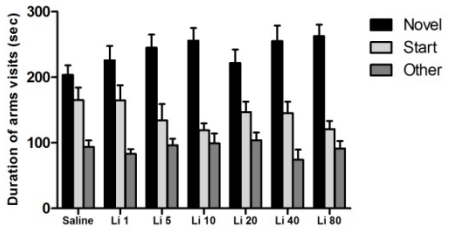

Figure 1. Time spent in the various arms of the groups receiving lithium

Sumatriptan at a dose of 10 mg/kg could reduce the time spent in the novel arm, compared to saline group (P<0.05, Figure 2).

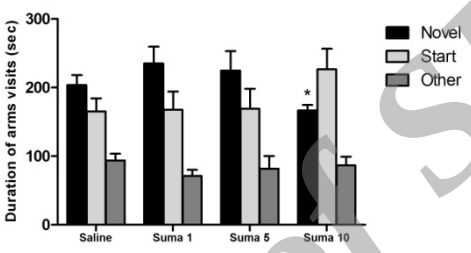

Figure 2. Time spent in the various arms of the groups receiving sumatriptan
The significant difference with the corresponding arm of the saline group, *:P<0.05.

As Figure 3 shows, the time spent in the novel arm of the group receiving coadministration of lithium and sumatriptan at doses of 1 mg/kg and 10 mg/kg respectively was significantly greater than the group receiving a dose of 10 mg/kg of sumatriptan alone (P<0.001). In this regard, the time spent in the start arm of the group injected with combination of lithium and sumatriptan at mentioned doses was significantly lesser than the group treated with a dose of sumatriptan (10 mg/kg) alone (P<0.01, Figure 3).

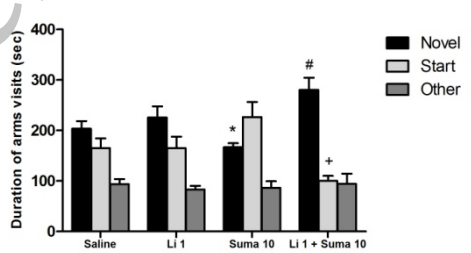

Figure 3. Time spent in the various arms of the lithium and sumatriptan co-administration group
The significant difference with the corresponding arm of the saline group, *: P<0.05. The significant difference with the corresponding arm of sumatriptan 10 group, #: P<0.001, +: P<0.01.

In the case of entry into each arm, all groups showed a significant difference in the percentage of novel arm entries compared with saline group (P<0.05, Figure 4).

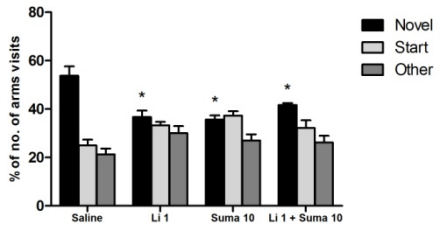

Figure 4. Percent of arm visits in different groups. The significant difference with the new arm of the saline group, *: $P<0.05$.

However, no significant differences were observed between groups in locomotor activity parameters including the total number of arm entries, and total distance moved in arms ($P>0.05$, Figure 5).

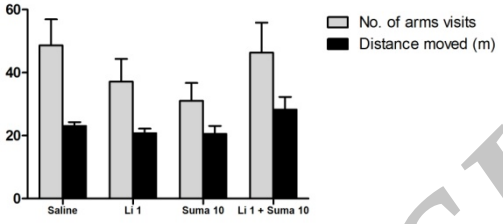

Figure 5. Locomotor activity in different groups

Passive avoidance test

Figure 6 demonstrates the effect of lithium on memory in step-through latency (STL). Different doses of lithium (0.1 mg/kg, 1 mg/kg, and 10 mg/kg) administered 60 min before training test did not show any significant difference in latency time in comparison with saline group ($P>0.05$, Figure 6).

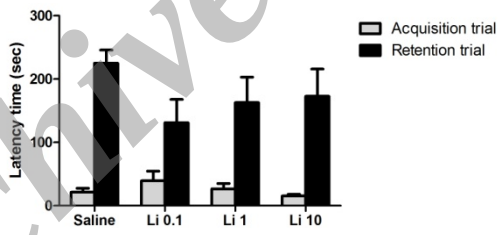

Figure 6. Step-through latency time in the acquisition of memory in the groups receiving lithium

In STL using the passive avoidance paradigm, sumatriptan (10 mg/kg) administered 30 min prior to a training session, significantly decreased the latency time compared with saline group ($P<0.01$, Figure 7).

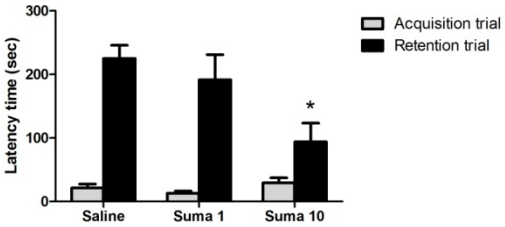

Figure 7. Step-through latency time in the acquisition of memory in the groups receiving sumatriptan
The significant difference with the latency of retention trial of the saline group, *: $P<0.01$

Demonstrating in Figure 8, lithium (1 mg/kg) administered 60 min before the training session, could reverse the sumatriptan-induced memory impairment in passive avoidance test (P<0.05), while it had no effect on latency time by itself (P>0.05, Figure 6).

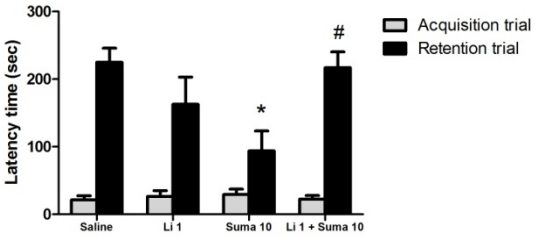

Figure 8. Step-through latency time in the acquisition of memory in lithium and sumatriptan co-administration group
The significant difference with the latency of retention trial of the saline group, *: P<0.01. The significant difference with the latency of retention trial of sumatriptan 10 group, #: P<0.05

Discussion

Alzheimer's disease is the most common cause of progressive intellectual failure in aged humans. Advancing age increases the risk of acquiring Alzheimer's disease. In the present study, we showed for the first time that administration of lithium (1 mg/kg) could reverse memory impairment induced by sumatriptan (10 mg/kg). To investigate the effect of drugs on memory acquisition, we used Y-maze task as a specific test of short-term spatial recognition memory and the passive avoidance task for the long-term memory status. Our findings showed that lithium could opposite the sumatriptan-induced memory impairment in both tests, whereas it was unable to exert any significant effect on memory by itself (Figures 1, 6).

Lithium is a drug commonly used for maintenance treatment of manic and unipolar and bipolar depression. Many studies have pointed out the dual effects of lithium on memory consolidation and destruction. Creson *et al*., in 2003 in a trial to assess short-term memory in dose-response fish studies, using different doses of lithium concluded that in all of these groups, varying degrees of memory impairment, but independently of the dose can be observed (14). Some other studies have also shown that lithium can cause memory impairment (15,16). A recent study by Honarmand *et al*., in 2014 reported that among different doses of lithium (5,10,20, and 40 mg/kg), the dose of 40 mg/kg of lithium could significantly impair the acquisition of spatial recognition memory in mice. Anyway, we did not show any significant effect of lithium on short-term and long-term memory in a wide range of lithium in both tests, which might attribute to ambiguous effects of lithium on memory.

Many experimental studies in animals, however, are contrary to the above mentioned. Tsaltas *et al*., in 2007 reported that lithium may increase spatial memory in rats (8). Inhibition of glycogen synthase kinase-3 (GSK-3) by lithium causes the accumulation of beta-catenin in the brain, which plays a role in memory consolidation (9,10).

Physiological, pathophysiological, and therapeutic roles of 5-HT systems in learning and memory are described frequently (17). Among 5-HT receptors, 5-HT1B/1D and 5-HT1A receptors are more related to memory (18,19). For instance, Malleret *et al*. reported that 5-HT1B receptor knock-out mice exhibit increased exploratory activity and enhanced spatial memory performance in the Morris water maze (20). Similarly, Meneses *et al*. showed that stimulation of presynaptic 5-HT1B/1D receptors impairs the consolidation of learning in male rats (19). In the present study, we showed memory impairment by a 5-HT1B/1D agonist, sumatriptan, which corroborates with previous experiments.

Schechter *et al*., have shown that 5-HT1B/1D receptor antagonists increase the performance and the signaling between neurons involved in the process of cognition and memory (21). Harder *et al*. also reported that the 5-HT1A receptor antagonists to prevent the process of memory loss in Alzheimer's disease (22). The results of these studies are in agreement with findings of the present study based on a memory corruption by sumatriptan, as well as the abolishment of this event by lithium.

Results of the present study implicate the regulatory effects of 5-HT1B/1D receptors in memory

performance, reflecting in impairment of memory by 5-HT1B/1D receptor agonist, sumatriptan. Based on this event, lithium as a 5-HT1B/1D receptor antagonist was anticipated to might potentiate memory performance, which was reported in aforementioned experiments (8,9). Anyway, though lithium could not show memory enhancement significantly, but obviously reversed sumatriptan-induced memory impairment in both tests.

According to the findings of the present study, inhibition of 5-HT1B/1D receptors by lithium might reverse memory deficits induced by 5-HT1B/1D receptor agonists such as sumatriptan. In other words, a part of the effects of lithium on memory is due to 5HT1B/1D receptor antagonism. However, to clarify this issue, further studies on the interactions of lithium with other 5HT1B/1D receptor agonists in animal models of memory seems necessary.

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