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INVESTIGATING THE SEROTONERGIC SYSTEM'S ROLE IN THE OCCURRENCE OF LITHIUM-PILOCARPINE-INDUCED SEIZURES

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Abstract
The mechanism of lithium's psychoactive effects has not yet been clarified. However, the change in the endogenous chemical mediator systems of the brain is significant in the occurrence of its effects. Several interactions of lithium with muscarinic responses have been reported. In this regard, the mechanism enhancing convulsions induced by muscarinic agonists might be related to the mechanism of its psychoactive effects. It has been recommended that lithium might directly affect cholinergic neurotransmission or potentiate the effects of pilocarpine by affecting other chemical mediator systems. Owing to the significant role of the serotonergic system in the initiation, development, and suppression of seizures in various epilepsy models in this study, the present system investigates the occurrence of lithium-pilocarpine-induced seizures. The results suggest that pretreatment with some compounds affecting the serotonergic system such as cyproheptadine (0.2-0.8 mg/kg), propranolol (0.5-1 mg/kg), and fluoxetine (2-10 mg/kg) can suppress seizures induced by lithium-pilocarpine. However, destructing and even enhancing this system with para-chlorophenylalanine (150mg/kg) for three consecutive days before lithium), 5,7-Dihydroxytryptamine (200 µg per animal), and fenfluramine (55mg/kg) do not affect this type of seizure.

Keywords: Psychoactive drugs, Lithium-pilocarpine, Seizures, Serotonergic system

1. Introduction
Lithium has been used effectively to treat mental disorders for more than 40 years.[1,2] Complex and different effects of lithium have been reported.[3]However, the mechanism that causes its therapeutic or toxic effects has not been clarified yet.[1,4]This problem becomes more complex, especially with the wide range of clinical effects of lithium.[5] For example, lithium is effective in the treatment of treatment-resistant depression. It is also effective in the long-term prophylaxis of manic-depressive illness.[1] In other words, this combination relieves both mania and depression, which are two opposite stages.[2]Owing to the significant role of the central serotonergic system in the etiology of mental disorders,[1] much attention has been paid to the association of this system with the mechanism of action of lithium. Based on previous studies, lithium potentiates the convulsive response to cholinomimetic agents such as pilocarpine, aerocholine, and physostigmine.[6]

The results suggest that this potentiating effect is almost exclusive to the response of cholinomimetics.[6]The selective proconvulsant effect of lithium had drawn the attention of studies to investigate the site of action responsible for this response.[6] Lithium might directly potentiate cholinergic-mediated currents or affect systems that change cholinergic activity. According to the observations, none of the direct effects of lithium are applied through presynaptic cholinergic. Pretreatment with lithium increases the power of pilocarpine in causing seizures by 20 times. Also, lithium suppresses the development of seizures induced by pentylenetetrazole-kindling. Acute administration of lithium reduces seizure susceptibility in a dose-dependent manner in kindled rats. Unlike kindled rats, lithium has very weak anticonvulsant power in non-kindled animals.[6,7]

The results suggest that lithium might be useful in the treatment of particular forms of epilepsy and epileptic brain disorders.[7]Reports suggest that the acute consumption of lithium up to 5 meq/kg in the kindling epilepsy model does not change the threshold limit of subsequent discharges and the seizure severity. In other words, in the Kindle hippocampal epilepsy model, lithium showed little convulsive effect after acute administration.[6]Lithium also exacerbates the convulsive effect of morphiceptine, a selective opioid on the mu receptor.[6] The anticonvulsant effect of serotonin has been shown in several epilepsy models.[7] Serotonergic cell bodies in the raphe nucleus and its pathways have an inhibitory role in several behaviors. Several reports suggest an increase in HT and SHIAA in the CNS after taking anticonvulsant drugs such as valproic acid.[8,9]

Moreover, it has been shown that the brain serotonin in genetically epilepsy-prone rats (GEPRs) is lower than normal,[3,10-12]and drugs that increase synaptic serotonin in the CNS suppress these seizures.[10,12]Fluoxetine, a selective serotonin reuptake inhibitor, suppresses seizures in GEPRs in a dose-dependent manner.[9,12]Additionally, other antidepressants such as imipramine, amitriptyline, doxepin, and desipramine o show anticonvulsant effects in a dose-dependent manner.[12]Reports also suggest that the increase in serotonin-induced by carbamazepine might be involved in its anticonvulsant effect.[10,13]

Several reports suggest that the peak anticonvulsant effect of these agents is associated with the peak concentration of serotonin,[10,12]and the discharge of the serotonergic system with PCPA reduces their anticonvulsant effect.[10,12,14]Moreover, it has been shown that sound-induced epileptic seizures in ethanol-deprived alcoholic rats are alleviated by low doses of 5-HT3 antagonist ondansetron and tropisetron.[15]Intra-hippocampal injection of 8-OH-DPAT, 5-HT1A agonist significantly increases the subsequent discharge threshold in hippocampal partial seizures and reduces the focal following discharge time. It explains the strong anticonvulsant effect of 8-OH-DAT in local administration and a reason for the inhibitory role of 5-HT1A receptors in causing hippocampal seizures.[16]

However, intra-ventricular injection of 300 µg of 5.7-DHT in rats causes seizures.[17] Reports suggest that the degradation of central indoleamine neurons by 5.7-DHT significantly increases the dose of P-DDT to cause myoclonic seizures in 50% of rats. It indicates the weakening effect of 5.7-DHT in the myoclonic model of P, P-DDT.[18]It has also been observed that serotonin-immunoreactivity decreases in the rostral and caudal levels of the neostriatum in rats that had generalized tonic-clonic seizures. However, it remains unchanged in the neocortex. Moreover, the level of reduction in the serotonin in the neostriatum in seizures induced by hyperthermia is significantly higher than in seizures induced by pilocarpine. These results suggest that serotonin levels changed depending on the type of seizure model and a more detailed regional analysis is necessary to determine the mechanism of seizures.[19]

Studies on animals suggest that lithium applies complex effects on serotonin. These effects differ depending on the brain region, the duration of treatment, and the sub-group of the serotonin receptor group.[20] Several researchers have investigated the effect of lithium on the rate of synthesis of serotonin. Generally, an increase in the rate of synthesis has been reported.[21-23]A study reported the highest level of increase in the rate of serotonin synthesis in the parietal cortex and caudate nucleus. However, it does not have a significant effect on the rate of serotonin synthesis in the pineal gland.[21]

In animals, lithium increases the synthesis and turnover of serotonin in presynaptic neurons.[1] A part of it occurs by increasing the reuptake of the precursor of tryptophan and serotonin synthesis.[22]Serotonin release also increases, especially in the hippocampus.[1,22,24,25]

Lithium reduces the sensitivity of postsynaptic HT2-5,[22]and 5-HT1 receptors in the striatal and hippocampal cortex. Also, lithium causes desensitization of presynaptic serotonin neuroreceptors in the rat hippocampus and thus increases the release of serotonin.[26]A study examined the acute effects of lithium on central serotonin in certain areas of the brain. In the mentioned study, the level of serotonin increased one hour after lithium consumption in all areas except the olfactory bulb.[27]In humans, lithium increases the 5-HT metabolite concentration in the cerebrospinal fluid.[2,20]It also increases the reuptake of serotonin by platelets,[2] and neuroendocrine responses to 5-HT agonists by lithium.[2,21]

Generally, the results suggest that a part of the anti-depressant properties of lithium is through increasing the serotonin system function.[2,28-32] Reports suggest that chronic use of lithium in rats increases serotonin and its metabolite HIAA-5 in the hypothalamus. Also, acute administration of lithium increases the level of extracellular 5-HT in the hippocampus and lateral hypothalamus to the same extent.[33]Lithium reduces HT-5 binding and the degree of inhibition of [3H] forskolin-stimulated adenylyl cyclase by 5-HT in the hippocampus, and [H3] ketanserin binding and 5-HT-stimulated IP formation in the cortex,[28]and increases serotonergic system response to amphetamine in the lateral hypothalamus.[31]

Studies have shown that the prolactin response to tryptophan after long-term use (more than 3 weeks of lithium) does not cause any change in depressed patients. However, the administration of lithium during the same period in healthy samples increased the prolactin response to tryptophan. In other words, the homeostatic responses of the HT-5 system to long-term use of lithium in patients with mental disorders are different from healthy samples.[17] Given what was stated above, the present study investigates the role of the serotonergic system in the occurrence of lithium-pilocarpine-induced seizures.

2. Materials & Methods

Lithium chloride and pilocarpine nitrate were obtained from Merck Company, methylscopolamine nitrate, para chlorophenylalanine methyl ester (PCPA), 5 and 7-dihydroxytryptamine creatinine sulfate (5.7-DHT), pentobarbital desipramine hydrochloride, and ketanserin was obtained from Sigma Company, and cyproheptadine hydrochloride, propranolol hydrochloride, and fluoxetine hydrochloride were obtained from our country. All drugs except 5.7-DHT were dissolved in saline and injected intraperitoneally (2ml/kg). However, methylscopolamine was injected subcutaneously (1ml/kg) and 5.7-DHT in 0.2% carrier (Saline+Vit.c) was injected through i.c.v. Male albino rats were obtained from the Pasteur Institute. They were selected in the weight range of 200-250 g. First, the rats anesthetized with pentobarbital (50mg/kg) were placed in the stereotaxic apparatus and DHT-15 9/10 (200) based on Paxinos& Watson's Atlas (1982) was injected into the lateral ventricle with specifications of L=1.4, V=3.4, and -0.8: AP by Hamilton syringe while bregma and lambda were placed at the same level (Flatscalp). To prevent the destruction of the adrenergic system, the animals were pretreated with desipramine (25 mg/kg) 30 minutes before 5.7-DHT. These animals were tested after 5 days and the recovery period.

2.1 Test conditions and sample size

All the research steps were conducted between 10:00 and 14:00. To adapt to the environmental conditions, the animals were placed in the laboratory environment 30 minutes before the start of the experiment. Each group included at least 6 rats and at least 2 rats were used as control. Lithium was injected 22 hours before pilocarpine in all animals. Each group of animals received the tested drug and the control rat received their carriers. Finally, each rat was used in only one experiment. Immediately after injecting the pilocarpine, the animal was left alone in the plexiglass chamber and its behavioral signs were monitored and recorded for 3 hours.

Injecting 1mg/kg of methylscopolamine 30 minutes before pilocarpine prevents the occurrence of symptoms of peripheral cholinergic stimulation. Behavioral changes after injecting pilocarpine include stereotypic movements and motor seizures. Stereotypic movements include oral movement, head bobbing, and tremors. Motor seizures include unilateral clonus or forelimb clonus, in which the

animal raises its one arm, bilateral clonus or rearing in which the animal raises both arms and sometimes falls from behind, consecutive seizures lasting more than 30 minutes, and HLTE (Hind-Limb Tonic Extension) in final stages. The rate of seizures and the start time of each of the above stages, and the mortality rate of animals up to 24 hours after pilocarpine injection were recorded.

2.2 Statistical calculations

Seizure and mortality rates were compared between the drug and control groups using the Fisher Exact Probability Test. Seizure onset time between these two groups was evaluated using the ANOVA test and student's t-test.

3. Results

Injecting pilocarpine (15 mg per kilogram of body weight) 22 hours after receiving lithium (6 mEq per kilogram of body weight) in all control rats caused seizures and death (Table 1). Immediately after injecting pilocarpine, the stereotypic movements started and the animals experienced motor seizures for about 30 minutes. Injecting cyproheptadine (0.2, 0.4, 0.8 mg/kg) 30 minutes before pilocarpine dose-dependently ($P<0.001$) prevented seizures and mortality (Table 1). Injecting Ketanserin (1mg/kg 20 minutes before pilocarpine) did not have a significant effect on the evaluated parameters (Table 1). Injecting propranolol (1mg/kg and 0.5) 30 minutes before pilocarpine could prevent seizures and mortality dose-dependently ($P<0.001$) (Table 1). Injecting 5- and 7-dihydroxytryptamine (200/10g) 5 days before receiving lithium did not affect the occurrence of seizures and mortality (Table 2). Injecting fluoxetine (2 and 10 mg/kg) 30 minutes before pilocarpine could prevent seizures and mortality dose-dependently ($P < 0.01$) (Table 1). Injecting Fenfluramine (5mg/kg) 30 minutes before pilocarpine did not affect the occurrence of seizures and mortality induced by lithium-pilocarpine (Table 1). Injecting para-chlorophenylalanine (PCPA) (150mg/kg) for three consecutive days before receiving lithium could not significantly prevent seizures and mortality (Table 1). Injecting 7.5-dihydroxytryptamine 5 days before pilocarpine (50-150mg/kg) could not intensify the convulsive effect of pilocarpine (Table 3). There was no significant difference between the two groups receiving the drug and its carrier in animals suffering from seizures regarding the onset time of seizures (Tables 1 and 2). Moreover, in these animals, seizures were associated with a complete pattern including stereotypic movements, tonic-clonic, status epilepticus, falling, rearing, forelimb clonus, and HLTE. The factors that prevented the occurrence of seizures did not show an effect on stereotypic movements.

TABLE 1. The effect of cyproheptadine, ketanserin, propranolol, fluoxetine, fenfluramine, and PCPA on the rate of seizures and mortality induced by lithium.

Drug	Dose mg/kg	Number	Injection time	Motor seizures %	Lethality	Motor seizure latency (mean ± S.E.M)
Saline		6		100	100	27.2±7.3
Cyproheptadine	0.2	9		55.5	55.5	27.6±8.9
Cyproheptadine	0.4	6		44.4*	44.4*	31.5±8.8
Cyproheptadine	0.8	6		0***	0***	
Saline		4		100	100	28.3±2.1
Ketanserin	1	6		83.3	83.3	28.2±5.1
Saline		6		100	100	28.5±6.3
Propranolol	0.5	6		66.6	66.6	35±3
Propranolol	1	6		0***	0***	
Saline		6		100	100	28.2±5.4
fluoxetine	2	6		83.3	50	38±15.8
fluoxetine	10	6		16.6**	16.6**	31±0
Saline		4		100	100	27.7±5.6
Fenfluramine	5	6		100	100	25.5±6.3
Saline		6		100	100	28.5±6.2
PCPA	150	9		77.7	77.7	38.8±16.1

Table 1 shows the effect of cyproheptadine, ketanserin, propranolol, fluoxetine, fenfluramine, and PCPA on the rate of seizures and mortality induced by lithium-pilocarpine and the onset time of seizures in all animals received lithium chloride (6 meq/kg) 22 hours before pilocarpine (15mg/kg). The rates of seizures and mortality were compared between the two groups receiving the drug and its carrier using the Fisher Exact probability test.
*P<0.05; ** P< 0.01; ***P< 0.001
The onset time of seizures has been compared between the two groups receiving the drug and its carrier using ANOVA and student's t-test.

TABLE 2. The effect of 5, 7-dihydroxytryptamine (5, 7-DHT) on the rates of seizure and mortality.

Drug	Dose g/rat	Number	Injection time	Motor seizures %	Lethality	Motor seizure latency (mean ± S.E.M)
Saline		4	5 days before lithium	100	100	25.5±1.3
5, 7-DHT	200	6	5 days before lithium	100	100	24.5±6.2

Table 2 compares the effects of 5 and 7-dihydroxytryptamine (5,7-DHT) on the rate of seizure, mortality, and onset time of seizure induced by lithium-pilocarpine in rats pretreated with desipramine its carrier using the Fisher exact probability test. Seizure onset time was compared between two groups using a student's t-test.

TABLE 3. The effect of 5 and 7-dihydroxytryptamine (5,7-DHT) on the rate of seizure and mortality.

Drug	Dose g/rat	Number	Injection time	Motor seizures %	Lethality
Saline		4	5 days before pilocarpine	0	0
5, 7-DHT	200	6	5 days before pilocarpine	0	0

Table 3 shows the effect of 5 and 7-dihydroxytryptamine (5,7-DHT) on the rate of seizure and mortality induced by the administration of different doses of pilocarpine alone (50-150mg/kg) in rats pretreated with desipramine.

4. Discussion

Based on previous studies, lithium potentiates the convulsive response to cholinomimetic agents such as pilocarpine, aerocholine, and physostigmine.[34,35]The results show that this potentiating effect is almost exclusive to the cholinomimetic response.[35]The selective proconvulsant effect of lithium has resulted in studies investigating the site of action responsible for this response.[35]Lithium may directly potentiate cholinomimetic-mediated currents or affect systems that modulate cholinomimetic activity. According to the observations, none of the direct effects of lithium are applied through presynaptic instead of postsynaptic cholinergic. Reports suggest that lithium increases the turnover of acetylcholine in the rat brain. When it is administered with pilocarpine, it causes a further increase in acetylcholine in the cortex and hippocampus. Also, lithium potentiates seizures induced by cholinesterase inhibitors.[35]
Results have shown that the choline reuptake inhibitor, hemicholine-3 weakens lithium-pilocarpine-induced seizures. Also, lithium does not have major direct impacts on muscarinic receptors. The observed effects on secondary messenger production are due to cholinomimetics.[35]Since many studies and reports show the role of the serotonergic system in the development and suppression of seizures in various epilepsy models, this study investigates the role of this system in lithium-pilocarpine-induced seizures. Animal studies have shown that lithium applies agonistic effects on the serotonergic

system.[2]For example, the synthesis of HT in presynaptic neurons is increased by lithium. It is partially due to the increase in the reuptake of tryptophan, the precursor of 5-HT synthesis.
Moreover, lithium increases the release of SHT, especially in the hippocampus.[2] Also, serotonin increases the firing rate of cortical neurons,[36]since the activation of 2-receptors causes the transmission of a stimulating message.[37]First, the antagonists of this receptor were used. Cyproheptadine could suppress lithium-pilocarpine-induced seizures dose-dependently. However, ketanserin did not show any specific effect in this regard. Cyproheptadine blocks SHT2C-5 receptors with a slightly lower affinity than HT2A-5,[37] in the serotonergic system. SHT2C-5 receptors are structurally and pharmacologically very similar to HT2A-5 receptors. Some of the effects attributed to HT2A-5 are mediated by SHT2C-5. Since the more specific HT2A antagonist ketanserin,[37]has no seizure-suppressing effect, cyproheptadine controls seizures through the SHT2C-5 receptor block.
SHT2C-5 receptors are significantly found in the striatum and substantia nigra regions of the brain involved in the development of epileptic discharges.[37] Additionally, the stimulation of these receptors activates phospholipase C (PLC), accumulates inositol phosphates, increases diacylglycerol (DAG), and thus increases the activity of the protein kinase PKC (C).[37] Several reports suggest that lithium causes the discharge of inositol and the accumulation of inositol phosphates by inhibiting inositol monophosphatase (IMPase). It also increases DAG and the activity of PKC in the brain.[38]PKC potentiates at least a part of the effects of SHT2C-5. Also, PKC activity causes seizures by v.i.c injection of phorbol esters in rats.[38]
Cyproheptadine is also known as a muscarinic antagonist.[37]There is a possibility that its anti-cholinomimetic effect is involved in suppressing seizures. However, such justification seems unlikely since this combination does not affect stereotypic movements suppressed only by anti-cholinomimetic agents. Previous reports suggest that HT1B-5 receptor block by cyanopindolol leads to the suppression of seizures induced by high doses of pilocarpine.[39] Our study revealed that the HT1B-5 antagonist propranolol can inhibit lithium-pilocarpine-induced seizures dose-dependently. The affinity of propranolol for HT1B-5 receptor (PA2 = 9.6) is lower than cyanopindolol (PA2 = 8.2).[37] However, according to the results of this report, the effective dose of propranolol (1 mg/kg) to suppress lithium-pilocarpine-induced seizures is lower than the effective dose of cyanopindolol (8 mg/kg) to inhibit seizures induced by high doses of pilocarpine.[39]Thus, it can be stated that lithium binding increases the affinity of the dopamine D1 receptor to be an antagonist.[37]
The results suggest that the selective destruction of the central serotonergic system by i.c.v. injection of the neurotoxin DHT-7/5 in rats pretreated with desipramine[36] can control seizures induced by lithium pilocarpine. This issue suggests that the block of 5-HT1B receptors in the cholinergic nerve endings[39]by propranolol is involved in suppressing seizures. Propranolol is a non-selective antagonist of β-adrenoceptor receptors. However, since beta-adrenergic receptors are more peripheral, the effect of blocking these receptors in suppressing seizures seems unlikely. It has been clarified that some regions of the brain receive inhibitory serotonergic nerve fibers from serotonergic nuclei, and serotonin inhibits electrical responses in the neurons of these regions.[36,40]
It has been also shown that serotonin has anticonvulsant effects in several epilepsy models,[41] so the peak of the anticonvulsant effect of fluoxetine and other antidepressants such as imipramine, doxepin, and amitriptyline in genetically epilepsy-prone rats (GEPRs) is associated with the peak of serotonin concentration, and the discharge of the serotonergic system with PCPA reduces the anticonvulsant effect of these agents. The 5-HT1B receptor is negatively coupled with adenylyl cyclase and its stimulation inhibits the production of cAMP. Reports suggest that lithium reduces the inhibition of cAMP production induced by serotonin.[38]In other words, lithium probably increases the production of cAMP and subsequently intracellular reactions through this receptor in response to the agent that its blockage is responsible for inhibiting the effect of lithium in intensifying the convulsive power of pilocarpine.
Propranolol also with a relatively lower affinity blocks the 5-HT1B receptor[37] and the blockade of this receptor may be effective in the suppression of lithium-pilocarpine-induced seizures. However, the possibility of this mechanism is weaker since it has been reported that the stimulation of the HT1A-receptor 5 by intra-hippocampal injection of 8-OH-PAT, the selective agonist of this receptor, shows

an anticonvulsant effect against hippocampal attacks. Also, lithium causes down-regulation of the 5-HT1B receptor, which potentiates the access to 5-HT1B for the blocking agent. Moreover, 5-HT1B receptors are found abundantly in the Pars reticulata region of the substantia nigra, which is involved in the mechanism of epileptic discharges.[37] Based on the reports, the 5-HT1B receptor is involved not only in the serotonergic nerve terminal but also in the control of the release of other chemical mediators such as acetylcholine and glutamate. In the present study, fluoxetine, a selective serotonin reuptake inhibitor, could effectively control lithium-pilocarpine-induced seizures and mortality dose-dependently. However, serotonin-releasing fenfluramine[20]did not have a specific effect in this regard. Lithium increases the releasable reserves of 5-HT and the response to fenfluramine increases during pretreatment with lithium[20]and fenfluramine probably causes the release of corresponding amounts of HT-5 at the synapse site. Also, fluoxetine inhibits the release of serotonin.[36] Hence, the difference in the synaptic concentration of serotonin is the reason for the difference in the observed effect. The results suggest that the selective destruction of the serotonergic system with DHT-7.5 or its discharge with PCPA cannot suppress lithium-pilocarpine-induced seizures. Also, the destruction of this system does not intensify the convulsive effect of pilocarpine (even with high doses of pilocarpine up to 150mg/kg). In other words, the destruction of the serotonergic system does not imitate the effect of lithium in intensifying the pilocarpine power. Thus, it can be stated that based on the previous reports, the serotonergic system is not the primary site of lithium's effect.[20] Its other effects are also significant in the process of enhancing the convulsive effect of cholinomimetics. This study shows the involvement of the central serotonergic system in the mechanism of action of lithium in intensifying the convulsive power of cholinomimetics. The results of this report suggest that pretreatment with some effective compounds in the serotonergic system such as cyproheptadine, fluoxetine, and propranolol can suppress lithium-pilocarpine-induced seizures. However, the discharge, destruction, or even strengthening of the serotonergic system, respectively, with PCPA, DHT-7.5, or fenfluramine has no effect on this type of seizure.

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