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The involvement of noradrenaline, 5-hydroxytryptamine and acetylcholine in imipramine-induced seizures in mice

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Abstract. The influence of some noradrenergic, 5-hydroxytryptaminergic and cholinergic agents on imipramine-induced seizures were investigated in mice. DL-threo-3,4-dihydroxyphenylserine (DOPS) and pargyline significantly potentiated imipramine-induced seizures. Phentolamine and prazosin significantly attenuated seizures elicited by imipramine and significantly attenuated the seizure-enhancing effect of DOPS. α-Methyl-p-tyrosine and reserpine significantly attenuated seizures induced by imipramine. Disulfiram significantly protected mice against imipramine-induced seizures. However, DOPS significantly potentiated seizures induced by imipramine in disulfiram-pretreated animals. Clonidine effectively protected mice against imipramine-induced seizures. Idazoxan, on the other hand, significantly protentiated seizures induced by imipramine and significantly antagonised the protective effect of clonidine against the seizures. 5-HTP, PCPA, cyproheptadine, mianserin, ketanserin and trazodone did not affect imipramine-induced seizures to any significant extent. Physostigmine antagonised seizures induced by imipramine while atropine significantly potentiated the seizures, and significantly attenuated the protective effect of physostigmine against the seizures. These data suggest that enhancement and attenuation of central noradrenergic and cholinergic neurotransmissions respectively, and not 5-HT mechanisms, may underlie imipramine-induced seizures in mice.
Key words. Imipramine; seizures; noradrenergic, serotoninergic and cholinergic mechanisms.

Convulsions are a widely reported side effect of the tricyclic antidepressant agent, imipramine[1–4], although the mechanism by which imipramine induces seizures is still not clear. The convulsant properties of imipramine and other tricyclic antidepressant agents have been attributed to the inhibition of serotonin (5-HT) re-uptake at the synaptic cleft. According to Westheimer and Klawans[5], increased concentrations of serotonin at striatal interneuron sites produce myoclonic jerks. However, Trimble et al.[6] reported that enhanced serotonin tone protects against seizures. Imipramine has also been reported to inhibit neuronal uptake of noradrenaline (NA)[7] which leads to its accumulation at the synapse. The role of noradrenaline in seizures has been well studied although the data available are, in general, conflicting. Both the stimulation and inhibition of the noradrenergic system have been shown to have convulsant and anticonvulsant effects[8–11]. Imipramine also has anticholinergic properties[12], and physostigmine has been used to reverse coma and other central nervous system complications, including convulsions, induced by tricyclic antidepressant poisoning[13]. In view of these findings, the present study has examined the involvement of noradrenergic, serotoninergic and cholinergic mechanisms in imipramine-induced seizures in mice.

Materials and methods

Animals. Male albino mice (inbred in the Animal House, University of Zimbabwe) weighing 20–25 g were used throughout this study. The mice were housed in groups of eight per cage and maintained on tap water and food ad libitum. A daily 12 h light cycle was maintained with lights switched on at 0700 h and off at 1900 h. Eight mice per dose of drug were used in the study. Each animal was used for one experiment only.

Drugs. The following drugs were used: imipramine hydrochloride (Sigma Chemical Co.), DL-threo-3,4-dihydroxyphenylserine (DOPS, Sigma Chemical Co.), phentolamine hydrochloride (Sigma Chemical Co.), clonidine hydrochloride (Sigma Chemical Co.), prazosin hydrochloride (Varichem Lab., Zimbabwe), idazoxan hydrochloride (Sigma Chemical Co.), reserpine (Sigma Chemical Co.), tetraethylthiuram disulfide (Disulfiram, Sigma Chemical Co.), pargyline hydrochloride (Sigma Chemical Co.), 5-hydroxy-DL-tryptophan (5-HTP, Sigma Chemical Co.), alpha-methyl-DL-p-tyrosine methylester hydrochloride (AMPT, Sigma Chemical Co.), cyproheptadine hydrochloride (Sigma Chemical Co.), DL-p-chlorophenylalanine (PCPA, Sigma Chemical Co.), mianserin hydrochloride (Sigma Chemical Co.), ketanserin (Sigma Chemical Co.), trazodone hydrochloride (Sigma Chemical Co.), atropine sulphate (Geddes Ltd, Zimbabwe) and physostigmine salicylate (Eserine, Sigma Chemical Co.). All were dissolved in physiological saline except the following: PCPA was suspended in Tween 80 and ketanserin diluted in a minimum amount of 0.1 M tartaric acid after which both were separately

and appropriately reconstituted with physiological saline. All drugs were administered intraperitoneally (i.p.) in a volume of 1 ml per 100 g body weight of animal. Control animals received equal volume injections of the appropriate vehicles which included saline and Tween 80 or tartaric acid diluted in saline. Fresh drug solutions were prepared on the days of the experiment. The drug pretreatment times prior to the administration of imipramine were 20 min (physostigmine), 30 min (5-HTP, phentolamine, atropine), 45 min (clonidine), 1 h (cyproheptadine, mianserin, ketanserin, prazosin, idazoxan), 2 h (trazodone), 3 h (pargyline), 6, 4 and 2 h i.e., three times (disulfiram), 17 h (α-methyl-p-tyrosine), 21 h (reserpine) and 24 h (DOPS, PCPA). The pretreatment times as well as the doses used were established in our laboratory, except those of disulfiram which were as described by Maj et al.[14].

Convulsant activity assessment. The modification of the method of Vellucci and Webster[15] was used to assess the convulsant activity of imipramine. The animals were kept singly in transparent perspex cages (25 cm × 15 cm × 15 cm) for 30 min to habituate them to their new environment before drug treatment. After treatment with imipramine, the mice were observed for seizures for a period of 30 min. The latency of tonic convulsions and the proportion of animals convulsing were recorded. Animals that did not convulse within 30 min period of observation were regarded as not convulsing. The behaviour of animals prior to the onset of convulsions was also noted. The control experiments were carried out concurrently with the test experiments. All experiments were carried out between 0800 h and 1300 h in a quiet room with an ambient temperature of 23 ± 1°C.

Table 1. Convulsant effect of imipramine in mice

Imipramine (mg/kg, i.p.)	No. convulsed/ no. used	Latency of tonic convulsion (min) Mean ± SEM	
50	0/8	-	-
65	0/8	-	-
72.5	3/8	10.67	0.72
80	4/8	10.50	0.43
95	7/8	9.29	1.91
110	8/8	9.13	1.35
125	8/8	6.63	0.81
140	8/8	4.88	0.62

Statistical analysis. The data on the latency of tonic seizures were compared by Student's t-test whereas the analysis of the number of animals convulsing was done using the Chi-squared test.

Results

Convulsant effect of imipramine (table 1). Imipramine (50–140 mg/kg, i.p.) dose-dependently elicited tonic seizures in mice (table 1). The seizures induced by imipramine persisted for about 8 min, after which all of the animals recovered fully. The control vehicles did not affect the gross behaviour of mice or the convulsant effect of imipramine.

Effects of DOPS, prazosin and phentolamine on imipramine seizures (table 2). DOPS (2–8 mg/kg, i.p.) effectively shortened the onset of tonic seizures induced by imipramine (125 mg/kg, i.p.). 8 mg/kg (i.p.) of DOPS significantly shortened the onset of seizures elicited by low doses (72.5 mg/kg, i.p.) of imipramine and significantly increased the number of animals convulsing. Both prazosin (1–2 mg/kg, i.p.) and phentolamine (5–10 mg/kg, i.p.) reduced the proportion of mice con-

Table 2. Effects of dihydroxyphenylserine (DOPS), prazosin and phentolamine on imipramine seizures in mice

Doses (mg/kg, i.p.) Imipramine	DOPS	Prazosin	Phentolamine	No. convulsed/ no used	Latency of tonic convulsion (min) Mean ± SEM	
125	0	0	0	8/8	7.88	1.08
125	2	0	0	8/8	4.75**	0.38
125	4	0	0	8/8	4.63**	0.25
125	8	0	0	8/8	3.75****	0.23
72.5	0	0	0	3/8	9.67	1.36
72.5	8	0	0	7/8°	5.86^{+}	0.68
125	0	0.5	0	8/8	8.50	0.59
125	0	1	0	7/8	11.14**	0.37
125	0	2	0	5/8	13.00**	1.50
125	8	2	0	7/8	7.60^{++}	0.60
125	0	0	2.5	8/8	8.25	0.79
125	0	0	5	6/8	11.00*	0.67
125	0	0	10	6/8	12.33***	0.27
125	8	0	10	8/8	6.13^{++}	0.45

*$p < 0.05$, **$p < 0.02$, ***$p < 0.01$, ****$p < 0.005$ vs imipramine (125 mg/kg) control, Student's t-test.
$^{+}p < 0.025$ vs imipramine (72.5 mg/kg), Student's t-test.
$^{++}p < 0.001$ vs DOPS (8 mg/kg) plus imipramine (125 mg/kg), Student's t-test.
$^{\circ}p < 0.01$ vs imipramine (72.5 mg/kg), Chi-squared test.

Table 3. Effects of clonidine and idazoxan on imipramine seizures in mice

Doses (mg/kg, i.p.) Imipramine	Clonidine	Idazoxan	No. convulsed/ no. used	Latency of tonic convulsion (min) Mean ± SEM	
125	0	0	8/8	6.75	0.74
125	0.25	0	8/8	11.25*	1.39
125	0.5	0	3/8°	13.00***	1.70
125	1.0	0	3/8°	14.67****	1.19
125	0	1	8/8	5.63	0.68
125	0	2	8/8	3.88**	0.48
125	0	4	8/8	3.38***	0.58
125	0.5	2	7/8$^{\blacksquare}$	7.29^{+}	1.02
72.5	0	0	3/8	11.00	1.41
72.5	0	2	8/8$^{\blacktriangle}$	6.88^{++}	0.82

*$p < 0.02$, **$p < 0.01$, ***$p < 0.005$, ****$p < 0.001$ vs imipramine (125 mg/kg) control, Student's t-test.
$^{+}p < 0.02$ vs clonidine (0.5 mg/kg) plus imipramine (125 mg/kg), Student's t-test.
$^{++}p < 0.001$ vs imipramine (72.5 mg/kg), Student's t-test.
$^{\circ}p < 0.05$ vs imipramine (125 mg/kg) control, Chi-squared test.
$^{\blacksquare}p < 0.01$ vs clonidine (0.5 mg/kg) plus imipramine (125 mg/kg), Chi-squared test.
$^{\blacktriangle}p < 0.005$ vs imipramine (72.5 mg/kg), Chi-squared test.

Table 4. Effects of alpha-methyl-para-tyrosine (AMPT), reserpine, pargyline, disulfiram and dihydroxyphenylserine (DOPS) on imipramine seizures in mice

Doses (mg/kg, i.p.) Imipramine	DOPS	AMPT	Reserpine	Pargyline	Disulfiram	No. convulsed/ no. used	Latency of tonic convulsion (min) Mean ± SEM	
125	0	0	0	0	0	8/8	7.25	1.00
125	8	0	0	0	0	8/8	4.00****	0.43
125	0	25	0	0	0	8/8	8.50	0.68
125	0	50	0	0	0	6/8	11.67****	0.73
125	0	100	0	0	0	5/8	12.60^{+}	0.78
125	0	0	5	0	0	8/8	9.25	0.74
125	0	0	10	0	0	8/8	9.75	0.79
125	0	0	20	0	0	8/8	10.75***	0.81
125	0	0	0	25	0	8/8	5.00	0.43
125	0	0	0	50	0	8/8	5.88	0.41
125	0	0	0	100	0	8/8	4.63*	0.47
125	0	0	0	0	3 × 50	3/8$^{\blacktriangle}$	12.33**	1.19
125	0	0	0	0	3 × 100	3/8$^{\blacktriangle}$	13.67****	1.19
125	8	0	0	0	3 × 50	6/8°	8.00^{++}	0.67

*$p < 0.05$, **$p < 0.025$, ***$p < 0.02$, ****$p < 0.01$, $^{+}p < 0.005$ vs imipramine control, Student's t-test.
$^{++}p < 0.05$ vs disulfiram (3 × 50 mg/kg) plus imipramine, Student's t-test.
$^{\blacktriangle}p < 0.05$ vs imipramine control, Chi-squared test.
$^{\circ}p < 0.05$ vs disulfiram (3 × 50 mg/kg) plus imipramine, Chi-squared test.

vulsing and significantly delayed the onset of imipramine seizures. However, low doses of prazosin (0.5 mg/kg, i.p.) and phentolamine (2.5 mg/kg, i.p.) did not affect the incidence or onset of imipramine seizures to any significant degree. The onset of imipramine seizures in the presence of DOPS (8 mg/kg, i.p.) was markedly delayed in either prazosin (2 mg/kg, i.p.) or phentolamine (10 mg/kg, i.p.)-pretreated animals.

Effects of clonidine and idazoxan on imipramine seizures (table 3). Clonidine (0.25–1 mg/kg, i.p.) dose-dependently and markedly delayed the onset of tonic seizures induced by imipramine (125 mg/kg, i.p.). While low doses (0.25 mg/kg, i.p.) of clonidine did not affect the incidence of the seizure, higher doses (0.5–1 mg/kg, i.p.) significantly reduced the number of animals convulsing. On the other hand, idazoxan (2–4 mg/kg, i.p.) significantly shortened the onset of imipramine (125 mg/kg, i.p.) seizures. The protective effect of clonidine (0.5 mg/kg, i.p.) against imipramine seizures was antagonised by idazoxan (2 mg/kg, i.p.) which significantly increased the number of animals convulsing and hastened the onset of the seizures. Similarly, the incidence of seizures induced by low doses (72.5 mg/kg, i.p.) of imipramine were profoundly increased, and their onset hastened, by 2 mg/kg (i.p.) of idazoxan.

Effects of α-methyl-p-tyrosine, reserpine, pargyline, disulfiram and its interaction with DOPS on imipramine seizures (table 4). Higher doses (50–100 mg/kg, i.p.) of α-methyl-p-tyrosine reduced the number of animals

Table 5. Effect of 5-hydroxytryptophan (5-HTP) on imipramine seizures in mice

Doses (mg/kg, i.p.) Imipramine	5-HTP	No. convulsed/ no. used	Latency of tonic convulsion (min) Mean ± SEM	
125	0	8/8	6.50	0.64
125	2	8/8	6.75	0.79
125	4	8/8	7.50	1.46
125	8	8/8	6.88	0.48
125	16	8/8	6.50	0.79
125	32	8/8	7.38	1.08
125	64	8/8	6.63	0.77

convulsing and effectively delayed the onset of imipramine seizures. However, low doses (25 mg/kg, i.p.) neither affected the incidence nor the onset of the seizures. Low doses (5–10 mg/kg, i.p.) of reserpine did not affect the incidence or onset of imipramine seizures while higher doses (20 mg/kg, i.p.) significantly delayed the onset of the seizures. Pargyline (100 mg/kg, i.p.) significantly hastened the onset of imipramine seizures while low doses (25–50 mg/kg, i.p.) did not affect the incidence or onset of the seizures. Disulfiram (3 × 50 to 3 × 100 mg/kg, i.p.) effectively reduced the incidence and delayed the onset of imipramine seizures. DOPS (8 mg/kg, i.p.) significantly hastened the onset of imipramine seizures in disulfiram (3 × 50 mg/kg, i.p.)-pretreated animals.

Effects of 5-HTP on imipramine seizures (table 5). 5-HTP (2–64 mg/kg, i.p.) did not alter the incidence and onset of imipramine seizures. During the 30 min pretreatment period with 5-HTP, most of the animals moved about their cages with persistent head shakes.

Effects of PCPA, cyproheptadine, mianserin, ketanserin and trazodone on imipramine seizures (table 6). PCPA (100–400 mg/kg, i.p.), cyproheptadine (2–8 mg/kg, i.p.), mianserin (2–8 mg/kg, i.p.) ketanserin (2.5–10 mg/kg, i.p.) and trazodone (5–20 mg/kg, i.p.) did not affect the number of animals convulsing or the speed of onset of imipramine seizures to any significant extent. The head shaking seen with 5-HTP was also seen in animals pretreated with trazodone, especially at higher doses (20 mg/kg, i.p.).

Effects of physostigmine and atropine on imipramine seizures (table 7). Physostigmine (2–8 μg/kg, i.p.) alone did not induce seizures but dose-dependently reduced the number of animals convulsing and significantly delayed the onset of imipramine seizures. Similarly, atropine (1–4 μg/kg, i.p.) given alone did not elicit seizures. However, the speed of onset of imipramine seizures was significantly shortened by atropine (1–4 μg/kg, i.p.). In addition, atropine (2 μg/kg, i.p.) markedly increased the incidence and hastened the onset of seizures induced by low doses (72.5 mg/kg, i.p.) of imipramine. The protective effect of physostigmine (8 μg/kg, i.p.) against imipramine seizures was antagonised by atropine (2 μg/kg, i.p.) which increased the number of mice convulsing and significantly shortened the delay before onset of the seizures. Higher doses of physostigmine (32 μg/kg, i.p.) and atropine (15 μg/kg, i.p.) elicited seizures in some of the mice (results not shown) when given alone.

Discussion

The results of this study show that imipramine dose-dependently elicits seizures in mice. It is widely accepted that the pharmacological effects exerted by DOPS are due to noradrenaline directly formed from it in vivo[16].

Table 6. Effects of p-chlorophenylalanine (PCPA), cyproheptadine, mianserin, ketanserin and trazodone on imipramine seizures in mice

Doses (mg/kg, i.p.) Imipramine	PCPA	Cyproheptadine	Mianserin	Ketanserin	Trazodone	No. convulsed/ no. used	Latency of tonic convulsion (min) Mean ± SEM	
125	0	0	0	0	0	8/8	7.13	1.65
125	100	0	0	0	0	8/8	7.25	0.55
125	200	0	0	0	0	8/8	7.00	1.03
125	400	0	0	0	0	8/8	7.13	0.84
125	0	2	0	0	0	8/8	6.38	0.50
125	0	4	0	0	0	8/8	7.25	0.77
125	0	8	0	0	0	8/8	7.13	0.91
125	0	0	2	0	0	8/8	7.38	0.56
125	0	0	4	0	0	8/8	5.88	0.37
125	0	0	8	0	0	8/8	6.38	0.43
125	0	0	0	2.5	0	8/8	6.88	0.62
125	0	0	0	5.0	0	8/8	6.00	0.66
125	0	0	0	10.0	0	8/8	7.13	0.65
125	0	0	0	0	5	8/8	6.50	0.71
125	0	0	0	0	10	8/8	7.00	1.21
125	0	0	0	0	20	8/8	5.88	0.76

Table 7. Effects of physostigmine and atropine on imipramine seizures in mice

Doses Imipramine (mg/kg, i.p.)	Physostigmine (μg/kg, i.p.)	Atropine (μg/kg, i.p.)	No. convulsed/ no. used	Latency of tonic convulsion (min) Mean ± SEM	
125	0	0	8/8	6.25	0.46
0	2	0	0/8	-	-
0	4	0	0/8	-	-
0	8	0	0/8	-	-
125	2	0	8/8	8.63**	0.81
125	4	0	6/8	12.00***	0.82
125	8	0	4/8	14.50***	1.64
0	0	1	0/8	-	-
0	0	2	0/8	-	-
0	0	4	0/8	-	-
125	0	1	8/8	4.13*	0.78
125	0	2	8/8	3.50***	0.25
125	0	4	8/8	3.75***	0.34
125	8	2	6/8	7.17+	0.80
72.5	0	0	3/8	10.67	0.98
72.5	0	2	8/8°	7.38++	0.39

*$p < 0.05$, **$p < 0.025$, ***$p < 0.001$ vs imipramine (125 mg/kg) control, Student's t-test.
+$p < 0.005$ vs physostigmine (8 μg/kg) plus imipramine (125 mg/kg), Student's t-test.
++$p < 0.005$ vs imipramine (72.5 mg/kg), Student's t-test.
°$p < 0.005$ vs imipramine (72.5 mg/kg), Chi-squared test.

In this study, DOPS (2–8 mg/kg, i.p.) potentiated the seizures induced by imipramine. It is therefore probable that the seizure-potentiating effect of DOPS might be due to noradrenaline formed from it in vivo. According to Zsoter[17] and Rang and Dale[12], prazosin, a selective alpha-1 adrenoceptor antagonist and phentolamine, a nonselective alpha adrenoceptor antagonist, act by blocking the effects of noradrenaline at the alpha adrenoceptors. The present study shows that prazosin (1 – 2 mg/kg, i.p.) and phentolamine (5–10 mg/kg, i.p.) attenuated imipramine seizures and also profoundly attenuated the effect of DOPS on the seizures. These data indicate that activation of noradrenergic receptors may be involved in imipramine seizures. These results are in agreement with the observation of Wambebe et al.[18] who reported the proconvulsant and anticonvulsant effects of DOPS and phentolamine respectively against strychnine seizures in mice.

Pargyline inhibits the enzyme monoamine oxidase, thereby elevating endogenous levels of all brain monoamines[19]. In this study, pargyline (100 mg/kg, i.p.) potentiated seizures induced by imipramine. This result disagrees with that of Lehmann[20] who observed that monoamine oxidase inhibitors protected mice against audiogenic seizures. The apparent discrepancy may possibly be due to the different seizure models used. It is, however, noteworthy that Amabeoku and Chikuni[21] reported the proconvulsant effect of pargyline against chloroquine-induced seizures in mice. According to Spector et al.[22] and Svensson and Waldech[23], α-methyl-p-tyrosine specifically depletes brain catecholamines by inhibiting the enzyme tyrosine hydroxylase. The present data show that α-methyl-p-tyrosine (50–100 mg/kg, i.p.) attenuated imipramine seizures. Similarly, reserpine, an adrenergic neurone blocking drug, which depletes monoamine stores by interfering with their uptake and storage[24], attenuated the seizures induced by imipramine. These results indicate that imipramine seizures may be mediated in part by a non-specific mechanism. However, disulfiram, which depletes brain noradrenaline by inhibiting dopamine-beta-hydroxylase which normally converts dopamine to noradrenaline[25], effectively protected mice against imipramine seizures. It is significant that DOPS, which is directly converted to noradrenaline in vivo[19], potentiated imipramine seizures in disulfiram-pretreated animals. These data further implicate noradrenaline in imipramine seizures. Clonidine, a selective alpha-2 adrenoceptor agonist[12], lowers noradrenaline levels peripherally and centrally by inhibiting its release. In the present study, clonidine (0.25–1 mg/kg, i.p.) effectively protected mice against seizures elicited by imipramine. It is possible that the anticonvulsant effect of clonidine may be a result of decreased levels of noradrenaline. It is not surprising therefore that idazoxan, a selective alpha-2 adrenoceptor antagonist[26], enhanced imipramine seizures and also antagonised the anticonvulsant effect of clonidine. These data further support the proposal that noradrenaline might be involved in imipramine-induced seizures in mice. The results essentially agree with the observations of Papanicolaou et al.[27] who reported the anticonvulsant effect of clonidine in rats, and Fletcher and Forster[28] who reported the proconvulsant effect of idazoxan in mice.

5-HTP is thought to exert its pharmacological effects via 5-HT formed from it by decarboxylation in vivo[29].

The present data show that 5-HTP (2–64 mg/kg, i.p.) did not have any significant effect on imipramine seizure. Similarly, trazodone, which accumulates 5-HT rather than noradrenaline at the synapse by inhibiting 5-HT uptake[30], did not alter imipramine seizures to any significant extent. PCPA blocks the activity of tryptophan hydroxylase, thereby inhibiting 5-HT synthesis[31]. In this study, PCPA (100–400 mg/kg, i.p.) did not affect seizures induced by imipramine. Furthermore, cyproheptadine and mianserin, both 5-HT receptor antagonists[12,32], and ketanserin, a selective 5-HT_2 receptor antagonist[33], did not modify imipramine seizures to any significant degree. These data indicate that 5-HT neurotransmission may not underlie imipramine seizures.

Physostigmine is a potent and competitive inhibitor of cholinesterases which break down acetylcholine, thus increasing the availability of acetylcholine[12]. The present data show that physostigmine (2–8 μg, i.p.) did not induce seizures in mice but effectively protected the animals against seizures induced by imipramine. This result is in agreement with the observation of Burk et al.[13] who reported the use of physostigmine in reversing certain central nervous system complications, including convulsions, induced by tricyclic antidepressant poisoning. Atropine, a competitive antagonist of acetylcholine at the muscarinic receptors[12], potentiated imipramine seizures and significantly antagonised the protective effect of physostigmine against the seizures. These data implicate cholinergic mechanisms in imipramine seizures.

In conclusion, while the data obtained in this study suggest the central noradrenergic and cholinergic neurotransmission may be involved in imipramine seizures, central 5-HT neurotransmission may not underlie imipramine-induced seizures in mice.

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