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Behavioral and Neurochemical Alterations After Lithium–Pilocarpine Administration in Young and Adult Rats: A Comparative Study

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DE BRUIN, V. M. S., M. M. F. MARINHO, F. C. F. DE SOUSA AND G. S. B. VIANA. *Behavioral and neurochemical alterations after lithium–pilocarpine administration in young and adult rats: A comparative study.* PHARMACOL BIOCHEM BEHAV **65**(3) 547–551, 2000.—Pilocarpine and lithium–pilocarpine can induce seizures and brain damage in adult rats. However, manifestation of cerebral lesions seems to be an age-related phenomenon suggesting that maturational states of neurocircuitry may be involved. We have studied behavior changes, cerebral histopathology, and muscarinic and dopaminergic receptors density in rodents subjected to lithium–pilocarpine treatment. Wistar rats, at two different ages (21 days and 2 months), were treated with pilocarpine (15 mg/kg, SC), lithium (3 mEq/kg, IP), atropine (50 mg/kg, IP) and the combination of lithium to pilocarpine. Histopathologic studies showed that younger animals were more resistant to the development of cerebral changes and there was a preferential involvement of the striatum (Wilcoxon $p = 0.02$) as opposed to more generalized areas in adult animals such as hippocampus and neocortex. Lithium treatment induced an upregulation of muscarinic receptors at both ages, and this effect was reversed in younger animals after pilocarpine administration. Lithium also induced an upregulation of dopaminergic receptors in the striatum at both ages ($p < 0.05$), and this effect was not reversed after pilocarpine administration. Our data confirm that young animals show less brain damage after lithium–pilocarpine, and main alterations in dopaminergic receptors density occur in young and older animals after treatment with lithium and lithium combined to a low dose of pilocarpine. © 2000 Elsevier Science Inc.

Pilocarpine Lithium Striatum Hippocampus D_2-receptor Epilepsy

HIGH doses of the muscarinic cholinergic agonist, pilocarpine, or lithium pre-treatment followed by low doses of pilocarpine result in behavioural changes, seizures and widespread brain damage in adult rats (8,18,20,23,24,32,35,36,37). Both treatments result in status epilepticus and death in younger animals. However, in the latter group, brain tissue examination demonstrates less intense cerebral damage suggesting that histopathological changes are an age related phenomenon (6,17).

Age-related susceptibility to pilocarpine treatment might be connected to selective maturation of neural systems essential to epileptogenesis and brain damage. Cerebral monoaminergic neurons appear precociously, and can already be detected during the embrionary period (18th day) in rats, while immunoreactivity to cholinergic system markers (CAT) is not observed until the second or third week of postnatal life (1,9).

It is well demonstrated that convulsions induced by pilocarpine and lithium–pilocarpine can be blocked by prior use of atropine, consistently with the involvement of the cholinergic system. It is not established whether other neurotransmitters play a role in maintenance of convulsions and development of cerebral changes. To detect the preferential involvement of cholinergic and dopaminergic systems in the lithium–pilocarpine-induced convulsive model, we studied behavior changes and cerebral density of muscarinic and D_2 dopaminergic receptors in young and adult rats.

METHOD

Treatment of Animals

Male Wistar rats (150–200 g; 2 months old) were submitted to five sets of experiments to be described. One group was

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treated with pilocarpine (15 mg/kg, SC, P); another one received lithium chronically (3 mEq/kg, IP, 7 days) and in the eighth day a single dose of pilocarpine (15 mg/kg, SC, LP), and a third group, treated with lithium–pilocarpine, received atropine (50 mg/kg) 30 min before administration of pilocarpine (LAP). Other two experiments were performed using separate groups, treated either with a single dose of atropine (50 mg/kg, A) or with lithium (3 mEq/kg, 7 days, L). Younger animals (40–50 g, 21 days old) were submitted to the same treatments (P, LP, LAP, L, A). Control groups received saline. Animals were closely observed for behavioral changes immediately after the last injection during the initial 30 min and then at 1-h intervals for 12 h. Twenty-four hours after the last treatment, brains from animals were removed for histopathological or binding studies.

Histopathological Studies

For histopathological analysis, brains previously fixed in formalin 10% had an initial cut at the level of the optic nerve; coronal slices were sequentially obtained at intervals of 1 mm, and sections were stained with hematoxylin & eosin and cresyl violet for light microscopy. The degree of brain damage severity was defined along a percent scale of 0 (none) to 100 (total) within each structural area examined by light microscopy (100×) and previously defined to be reliable for morphological analysis (4,31). Animals were defined as having brain damage if one or more structures showed at least 50% involvement. Structures routinely examined were hippocampus, striatum, neocortex, entorhinal cortex, amygdaloid nucleus,. and thalamus, and assessed according to Paxinos and Watson (29).

Determination of Muscarinic Receptor Numbers

For binding assays, animals were dissected on ice and cerebral areas (hippocampus and striatum) were immediately frozen at −20°C. Receptor numbers were measured through binding assays with a 10% homogenate prepared (w/v) in 150 mM sodium phosphate buffer, pH 7.4 at 4°C using [^{3}H]-*N*-methylscopolamine, [^{3}H]-NMS, (85 Ci/mmol, New England Nuclear, Boston, MA), according to Dombrowski et al. (11). Total homogenates (80–160 μg protein) were incubated in a buffer containing 2.35 nM of [^{3}H]-NMS in final volume of 0.2 mL. After incubation, at 37°C for 30 min., reaction was terminated by filtering the incubation mixture through Whatman GF/B filters. Filters were then washed five times with 4 ml of ice-cold saline, dried at 60°C and placed in vials with 3 ml of a toluene-based scintillation fluid. Radioactivity was measured with a Beckman scintillation counter at a counting efficiency of 48%. Specific binding was calculated as total minus nonspecific binding in the presence of atropine (12.5 μM), and results were expressed as femtomoles per milligram of protein. Protein was determined according to Lowry et al. (22) using bovine serum albumin as standard.

Determination of Dopaminergic Receptor Numbers

Methods described by Meltzer et al. (25) and Kessler et al. (21) were used for determination of D_2 receptors with the specific ligand [^{3}H]-spiroperidol (114.0 Ci/mmol). Total homogenates (80–160 μg protein) were incubated in 50 mM of Tris-HCl buffer, pH 7.4, containing 5 μM of mianserin to block serotonergic receptors and 17.3 nM of ^{3}H-spiroperidol in a final volume of 0.2 ml. Specific binding was defined as total minus nonspecific binding carried out in the presence of 100 μM dopamine. After incubation at 37°C for 60 min, experiments proceeded as described in the case of muscarinic binding.

RESULTS

Behavioral and Histopathological Studies

Peripheral cholinergic reactions, such as miosis, piloerection, chromodacriorrhea, diarrhea, and stereotyped movements (continuous sniffing and paw licking) were observed in all animals at both ages, after P and LP treatment. A few animals from the LP treated group, of both ages, developed convulsions, status epilepticus, and death (Table 1). In the younger group, a small number of animals died after the treatment with lithium for 7 days (11%). After pretreatment with atropine (LAP), all behavioral changes seen after lithium–pilocarpine administration were blocked. Atropine or lithium alone did not induce any effects in either age group.

Cerebral histopathological changes are expressed in Table 2. Animals treated with lithium, atropine, or saline only did not show alterations, and were not listed. Brain lesions were characterized by neuronal loss, vacuolar degeneration, and gliosis as previously described (8). Older animals treated with LP had more brain damage (50%) than younger ones (18%)

TABLE 1

BEHAVIORAL ALTERATIONS IN 2-MONTH AND 21-DAY-OLD RATS TREATED WITH PILOCARPINE AND THE COMBINATION OF LITHIUM PLUS PILOCARPINE

	Behavior alteration (%)						
Age/Treatment	PCS	Tremors	SM	Conv.	SE	% Death	% No. Animals
2-Month-Old							
P	100	0	100	0	0	0	42
LP	100	12	100	9	9	9	64
21-Day-Old							
P	100	0	100	0	0	0	38
LP	100	6	100	6	6	6	32

Wistar rats were acutely treated with pilocarpine (15 mg/kg, SC, P). Lithium (3 mEq/kg, IP) was administered during 7 days (L7d) followed 24 h later by a single dose of pilocarpine (15mg/kg, SC) (LP). Animals were submitted to a 12-h observation time for six continuous periods of 1 h, 30 min after pilocarpine administration. PCS = Peripheral cholingergic signs; SM = stereotyped movements; SE = status epilepticus.

and, in both groups, atropine blocked lesions completely. Older animals treated with LP showed preferential damage in neocortex, entorhinal, and pyriform cortices, hippocampus, striatum, and substantia nigra (Table 2). Younger animals showed less cerebral changes and there was a preferential involvement of the striatum (Fig. 1) with relative preservation of other areas, such as, neocortex and hippocampus (Table 2).

Binding Studies

Results of [^{3}H]-NMS binding studies in hippocampus and striatum in 21-day- and 2-month-old rats are presented in Table 3. Two-month-old rats showed a muscarinic receptors upregulation in the hippocampus after administration of lithium and atropine alone (28 and 61%, respectively) or in combination with pilocarpine (48%) compared to controls. The same group presented an upregulation (19%) in the striatum after LAP treatment. Twenty-one-day-old rats showed an upregulation (19%) in the striatum, after lithium treatment, and this effect was blocked by pilocarpine.

Results of [^{3}H]-spiroperidol binding studies in hippocampus and striatum from 21-day- and 2-month-old rats are shown in Table 4. In the lithium-treated group, 2-month-old animals showed a dopaminergic receptors downregulation (24% decrease) in the hippocampus, while 21-day-old rats showed no alterations. Noteworthy, several changes were demonstrated in the striatum in both groups of rats, specially with younger ones. Thus, in 21-day-old rats, there was a 26% increase in receptors density compared to their controls, and this effect was maintained in the LP group (23% increase). Atropine alone caused a downregulation (15% decrease) in the striatum of younger rats. Also, in the 21-day-old-group, the association of LAP caused a significant decrease in receptors density when compared to controls (52%) and to the LP treatment (34%). Two-month-old rats, after lithium treatment, showed a decrease and a similar increase of around 24 % in hippocampus and striatum respectively, as related to controls, and the increase in striatum was blocked by pilocarpine.

TABLE 2

HISTOPATHOLOGICAL CHANGES IN BRAIN AREAS OF 21-DAY AND 2-MONTH-OLD RATS TREATED WITH LITHIUM (3 mEq/kg) FOR 7 DAYS AND PILOCARPINE (15 mg/kg) ADMINISTERED 24 h LATER (LP)

	Lesion Mean Score	
Brain Area	2-Month-Old Rats LP	21-Day-Old Rats LP
Frontoparietal cortex	21	6
Enthorinal cortex	30	6
Pyriform cortex	22	6
Amygdaloid nucleus	15	6
Corpus striatum	30	18*
Thalamus	24	6
Hippocampus	34	5
Paraseptal area	21	6
Sunstantia nigra	30	10
Total number of animals	8	11
Number of animals with lesions	4	2

Lesion severity was expressed as a mean score in a scale from 0 (no damage) to 100% damage within each structure. Brain damage was defined as present if there was at least 50% involvement of one or more brain areas.

*Wilcoxon test $p = 0.02$.

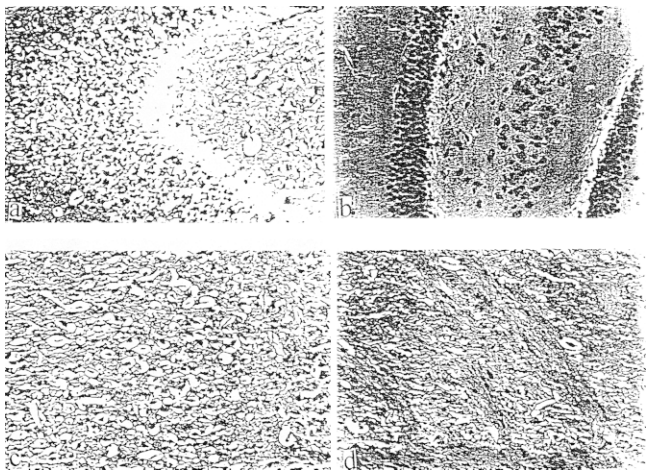

FIG. 1. Photomycrographs obtained by light microscopy of hippocampus and striatum of young (right) and adult (left) rats treated with lithium–pilocarpine (LP). (a) Hippocampus of LP-treated adult animal showing neuronal loss and vacuolar degeneration (cresyl violet, CV ×200). (b) Hippocampus of LP-treated young animal exhibiting normal appearance (HE ×100). (c) Striatum of adult rat, treated with LP, showing neuronal loss and vacuolar changes (CV ×200). (d) Neuronal loss and vacuolization of striatum of young rat treated with LP (HE ×100).

DISCUSSION

Several neurochemical systems are modified in the developing brain (14,16,19,33). Thus, during development, a decrease in muscarinic receptor density in the cerebral cortex (26,30) and a higher sensitivity of the M1 cholinergic receptor to cholinergic agonists have been described (27). Muscarinic receptors reach adult levels between 21 and 40 days of age (31); however, other studies detected muscarinic receptor numbers close to adult levels at 12–14 days of life in rat hippocampus (3). Other works show that, in both age groups, cholinergic activation is essential to initiate the convulsive process because atropine inhibited convulsions and brain damage. Ontogenic studies show an age-dependent difference in response of animals treated with pilocarpine (28,37).

In the present work, lithium chronically administered, atropine, and the association of lithium–atropine–pilocarpine produced an upregulation of muscarinic receptors in the hippocampus of adult rats. In younger animals, lithium pretreatment induced upregulation of muscarinic receptors in the striatum that was reversed by pilocarpine administration. Lithium also induced upregulation of dopaminergic receptors in the striatum of young and adult animals, and this effect was not reversed by pilocarpine administration in the younger group. In this latter group, the striatum was also the most compromised area, suggesting that lesion of this area is essential for epileptogenesis, as previously reported (2).

Sankar et al. (35), with the lithium–pilocarpine model of status epilepticus, provided evidence for the vulnerability of the immature brain to seizure-induced damage that bears features of the necrotic and apoptotic death. On the other hand, in adult rats, LP-induced status epilepticus produces neuronal

TABLE 3

EFFECTS OF LITHIUM, PILOCARPINE, AND ATROPINE ALONE OR IN ASSOCIATION ON [^{3}H]-NMS BINDING IN HIPPOCAMPUS AND STRIATUM FROM 21-DAY AND 2-MONTH-OLD RATS

	[^{3}H]-NMS (fmol/mg Protein)			
	2-Month-Old Rats		21-Day-Old Rats	
Group	Hippocampus	Striatum	Hippocampus	Striatum
Control	324.4 ± 26.2 (39)	427.2 ± 31.8 (14)	366.5 ± 28.2 (21)	386.2 ± 14.3 (21)
P	342.7 ± 18.7 (20)	351.5 ± 38.8 (16)	305.1 ± 23.1 (07)	373.7 ± 13.1 (10)
L	414.1 ± 29.9 (12)[a]	362.4 ± 32.2 (12)	346.1 ± 20.4 (10)	460.4 ± 35.5 (10)[a]
LP	323.5 ± 27.3 (16)	371.8 ± 30.4 (15)	300.6 ± 6.0 (06)	383.9 ± 11.8 (08)[b]
A	522.6 ± 48.1 (06)[a]	484.8 ± 41.9 (06)	335.4 ± 15.7 (08)	426.0 ± 28.6 (10)
LAP	482.5 ± 44.8 (06)[a,c]	508.8 ± 36.0 (06)[c]	363.3 ± 34.6 (07)	377.1 ± 22.5 (07)

Animals were acutely treated with pilocarpine (15 mg/kg, SC, P). Lithium (3 mEq/kg, IP, L) was administered for 7 days alone or followed 24 h later by a single dose of pilocarpine (15 mg/kg, SC, LP). Atropine (50 mg/kg, IP, A) was injected alone or 30 min before pilocarpine in the lithium–pilocarpine group (LAP). Results were expressed as mean ± SEM. Values in parentheses represent number of animals. For statistical analysis, ANOVA and Fisher post hoc test were used. [a],[b], and [c] were compared to controls, L, and LP, respectively ($p < 0.05$).

injury with the appearance of necrosis rather than apoptosis. The necrotic neurons show nuclear pyknosis, chromatin condensation, and internucleosomal DNA fragmentation (15).

Although in 21-day-old rats our results suggest that striatum lesions may be essential for epileptogenesis, other areas are equally important in adult animals. Furthermore, D_2 receptors play an important role in the lithium–pilocarpine convulsive model-2.5.

Dopaminergic D_2 receptors reach adult levels at the 24th day of life (10), occurring at a very low level at birth and gradually increasing during the second week of life (7). It has been shown that although D_1 dopaminergic antagonists decrease, D_2 antagonists facilitate lithium–pilocarpine-induced convulsions in adult rats (2). In our study, lithium caused an increase of D_2 receptor density in the striatum from both young and older rats. Carli et al. (5) demonstrated that lithium chronic treatment altered striatal dopaminergic activity, suggesting that it directly or indirectly acts on G-protein coupled to dopaminergic receptors.

Brain damage following status epilepticus might be caused by glutamate release, and immaturity of glutamatergic system may be responsible for less severe histopathological changes observed after LP treatment in younger animals. Although our results point out to main alterations in dopaminergic receptors, more than one factor seems to be involved in the genesis of convulsions and brain damage induced by lithium–pilocarpine. Thus, Sankar et al. (34), studying the metabolism of GABA during status epilepticus in the developing rat brain, show that immature hippocampus is more capable of maintaining GABA synthesis in SE, at the earliest stages of development. This would, in part, explain the relative resistance of immature hippocampus to seizure spread and to certain types of seizure-induced damage, including that produced by a high dose of pilocarpine or the combination of lithium–pilocarpine (12,13).

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TABLE 4

EFFECTS OF LITHIUM, PILOCARPINE, AND ATROPINE ALONE OR IN ASSOCIATION ON [^{3}H]-SPIROPERIDOL BINDING IN HIPPOCAMPUS AND STRIATUM FROM 21-DAY AND 2-MONTH-OLD RATS

	[^{3}H]-Spiroperidol (fmol/mg Protein)			
	2-Month-Old Rats		21-Day-Old Rats	
Group	Hippocampus	Striatum	Hippocampus	Striatum
Control	375.7 ± 25.1 (10)	380.7 ± 27.3 (12)	330.8 ± 15.6 (23)	344.9 ± 17.0 (20)
P	318.0 ± 32.0 (08)	367.6 ± 27.7 (16)	374.2 ± 23.0 (07)	376.0 ± 25.0 (08)
L	284.7 ± 24.0 (12)[a]	473.8 ± 46.8 (11)[a]	337.7 ± 18.3 (08)	434.1 ± 13.7 (09)[a]
LP	348.2 ± 31.3 (13)	353.9 ± 34.7 (16)[b]	327.2 ± 24.3 (08)	425.4 ± 29.0 (08)[a]
A	396.7 ± 29.7 (06)	431.4 ± 30.3 (06)	354.3 ± 24.0 (10)	292.1 ± 16.7 (13)[a]
LAP	361.7 ± 38.9 (06)	363.3 ± 14.6 (06)	389.6 ± 19.1 (06)	282.0 ± 22.7 (09)[a,c]

Animals were acutely treated with pilocarpine (15 mg/kg, SC, P). Lithium (3 mEq/kg, IP, L) was administered for 7 days alone or followed 24 h later by a single dose of pilocarpine (15 mg/kg, SC, LP). Atropine (50 mg/kg, IP, A) was injected alone or 30 min before pilocarpine in the lithium–pilocarpine group (LAP). Results were expressed as mean ± SEM. Values in parentheses represent number of animals. For statistical analysis, ANOVA and Fisher post hoc test were used. [a],[b], and [c] were compared to controls, L, and LP, respectively ($p < 0.05$).

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