THE EFFECT OF LITHIUM AND CALCIUM ANTAGONISTS ON BRAIN LIPID PEROXIDE AND GLUTATHIONE LEVELS IN MICE

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SUMMARY

The effect of lithium chloride and calcium antagonists (nifedipine and diltiazem) on brain lipid peroxide and glutathione levels were investigated in mice.

When nifedipine and diltiazem were administered separately brain lipid peroxide levels did not change, but nifedipine and diltiazem administration together with lithium chloride led to a significant decrease in the brain lipid peroxidation stimulated by lithium chloride.

Key Words: Lithium chloride. Calcium antagonists. Brain. Lipid peroxides. Glutathione.

INTRODUCTION

Lithium is the first drug which has been used widely in the treatment of manic depressive disorders (1). Long-term lithium therapy produces some neurotoxic effects (2,3). It has been proposed that lithium stimulates brain lipid peroxidation both in vitro (4,5) and in vivo (6), and that the formation of lipid peroxides can be the major factor in its neurotoxic action (4-6).

Because of its narrow therapeutic index, a new drug has been searched for as an alternative to lithium in the treatment of manic depressive disorders. Among these, calcium antagonists have drawn attention in recent years. It has been reported that calcium antagonists are as effective as lithium in manic depressive illness (7,8). On the other hand, it has been established that calcium antagonists have an in vitro antioxidant effect (9,10). However, their in vivo effects on lipid peroxidation and antioxidant system are not clear.

For this reason, we have planned to investigate the effect of lithium chloride and calcium antagonists (nifedipine and diltiazem) on brain lipid peroxidation and glutathione levels when they are administered separately or together.

MATERIALS AND METHODS

BALB/c mice of average weight of 25 g were used. For acute treatments, the animals were divided into 6 groups of 8 mice each;

a) Group 1: Saline-treated mice

b) Group 2: The mice were given intraperitoneally 4 mmol/kg of lithium chloride and they were killed, 2,4,6,12 and 24 hours after treatment.

c) Group 3 and 4: 10 mg/kg nifedipine or 10 mg/kg diltiazem were administered intraperitoneally and the mice were killed 2 hours after the injections.

d) Group 5 and 6: 4 mmol/kg lithium chloride and 10 mg/kg nifedipine or 10 mg/kg diltiazem were given intraperitoneally and the mice were killed 2 hours after treatment.

For chronic treatments, 2 mmol/kg/day lithium chloride was given to the mice intraperitoneally for 10 days. At the end of this period, 10 mg/kg nifedipine or diltiazem were given to the mice together with the last lithium chloride dose, and the mice were killed 2 hours after the last injection.

The mice were killed by decapitation, and whole brains were rapidly dissected. They were washed and homogenized in cold 1.15% KCl with a glass-Teflon homogenizer to make up a 10% homogenate (w/v). Brain lipid peroxide levels were determined according to the method of Ohkawa et al. (11). The breakdown product of 1,1,3,3-tetraethoxypropane was used as standard. Brain glutathione levels were measured with 5,5 -dithiobis- (2-nitrobenzoate) at 412 nm according to Ellman (12).

RESULTS

As shown in Table I, lipid peroxide levels were found to be increased 2,4,6 hours after lithium chloride administration compared to controls, but no significant difference was observed in brain lipid peroxide levels 12 and 24 hours after treatment (Table I). The highest value for brain lipid peroxide levels was observed 2 hours after treatment. When single doses of nifedipine and diltiazem were administered separately, brain lipid peroxide levels did not change, but nifedipine and diltiazem administration together with lithium chloride led to a significant decrease in the brain lipid peroxidation stimulated by lithium chloride (Table II).

Table I. The effect of lithium chloride (LiCl) on the brain lipid peroxide (malondialdehyde MDA) and glutathione levels in mice (Means±SD; n=8 each).

	LIPID PEROXIDE (nmol MDA/g tissue)		GLUTATHIONE (μmol/g tissue)	
Hours	Saline	LiCl	Saline	LiCl
2 h	324.2 ± 24.7	405.2 ± 27.2*	1.79 ± 0.22	1.77 ± 0.21
4 h	326.7 ± 22.8	386.7 ± 23.2*	1.83 ± 0.24	1.80 ± 0.23
6 h	330.2 ± 26.3	382.2 ± 26.7**	1.81 ± 0.21	1.79 ± 0.24
12 h	327.8 ± 29.3	335.5 ± 26.2	1.75 ± 0.23	1.76 ± 0.26
24 h	340.7 ± 30.1	320.0 ± 26.2	1.75 ± 0.25	1.78 ± 0.25

*p<0.001; **p<0.01 as compared to saline-injected controls.

On the other hand, we have observed a significant increase in brain lipid peroxide levels after 10 days of 2 mmol/kg/day lithium chloride administration. When 10 mg/kg nifedipine or diltiazem were given to mice together with the last lithium chloride dose, nifedipine, but not diltiazem, caused a decrease in the elevated brain lipid peroxide levels due to lithium chloride (Table III).

In addition, brain glutathione levels remained unchanged following these treatments (Table I, II and III).

DISCUSSION

Lithium is known to have neurotoxic effects (2,3). It has been proposed that lipid peroxidation may be involved in certain neurotoxic effects (4-6). However, lithium salts have been observed to have different effects on lipid peroxidation in in vitro models (5). It has been reported that lithium carbonate stimulates lipid peroxidation in rat cerebral cortex synaptosomes and kidney homogenates, while lithium chloride does not (5). However, in our present study, in contrast to these in vitro findings (5), the administration of lithium chloride caused an elevation in lipid peroxide levels in brain homogenates, similar to our previous results with lithium carbonate (6). These findings indicate that

Table II. The effect of lithium chloride (LiCl) and calcium antagonists (nifedipine and diltiazem) on brain lipid peroxidation and glutathione levels when they are administered separately or together (Means±SD: n=8 each).

	LIPID PEROXIDE (nmol MDA/g tissue)	GLUTATHIONE (μmol/g tissue)
Control	336.2 ± 23.4	1.76 ± 0.22
LiCl	405.2 ± 27.2*	1.79 ± 0.24
Nifedipine	331.8 ± 27.5	1.80 ± 0.26
Diltiazem	348.6 ± 24.4	1.81 ± 0.27
LiCl + Nifedipine	297.3 ± 30.5**,***	1.76 ± 0.21
LiCl + Diltiazem	309.0 ± 26.2**,***	1.77 ± 0.24

*p<0.001; **p<0.05 as compared to controls; ***p<0.001 as compared to LiCl-injected group.
The mice were killed 2 hours after the injections.

The stimulation of brain lipid peroxidation is due to lithium, not to the accompanying anions of the lithium salts.

It has been reported that calcium antagonists, drugs alternative to lithium, have antioxidant effects in vitro (9,10). However, we found that although nifedipine and diltiazem do not effect brain lipid peroxidation, they are able to prevent the increasing effect of lithium on brain lipid peroxidation.

In conclusion, the present findings suggest that lipid peroxidation may play a role in lithium neurotoxicity and that calcium antagonists may be used to prevent lithium toxicity caused by lipid peroxidation.

Table III. The effects of single doses of nifedipine and diltiazem on brain lipid peroxide and glutathione levels in mice chronically treated with lithium chloride (Means±SD)

		LIPID PEROXIDE (nmol MDA/g tissue)	GLUTATHIONE (μmol/g tissue)
Control	(n=8)	342.3 ± 26.9	1.75 ± 0.23
LiCl	(n=8)	426.3 ± 28.0*	1.78 ± 0.27
LiCl+Nifedipine	(n=8)	385.6 ± 26.3**,***	1.79 ± 0.28
LiCl+Diltiazem	(n=8)	410.1 ± 22.3*	1.80 ± 0.25

*p<0.001; **p<0.01 as compared to controls ***p<0.01 as compared to chronically LiCl-injected mice. The mice were killed 2 hours after the last injection.

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