Biochemical Pharmacology, Vol. 26, pp. 167 - 170. Pergamon Press, 1977, Printed in Great Britain.

PRELIMINARY COMMUNICATION

LITHIUM INHIBITION OF CYCLIC AMP ACCUMULATION INDUCED BY DOPAMINE IN ISOLATED RETINAE OF THE RABBIT

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(Received 5 November 1976; accepted 8 November 1976)

Lithium is used for the management of affective disorders[1], although its mechanism of action remains obscure[1]. Several lines of evidence suggest that the dopaminergic system is involved in mania[2] and possibly in schizophrenia[3]. We present here the first experimental evidence that in intact cells belonging to brain structures (retina), lithium can inhibit a dopamine-sensitive adenylate cyclase.

Materials and Methods.

The methods employed for the dissection and isolation of the rabbit retina and for the measurement of cyclic AMP have been described elsewhere[4]. A standard concentration of 0.1 mM dopamine (or dopamine-mimetic agents) was used in all experiments with drugs, since it has been previously found that at this concentration, a maximal accumulation of cyclic AMP is produced[4-6] Lithium was added in solution as the chloride salt before the final incubation (10 min, 35°).

Results and Discussion.

Figure 1 shows that more than 50 % inhibition of the dopamine effect was obtained when 5 mM lithium was present. Complete inhibition was achieved in the presence of 50 mM lithium. The range of effective concentrations of lithium is comparable to that used by other investigators, who have found a 80 % inhibition by 50 mM lithium of noradrenaline induced formation of cyclic AMP in slices of rat cerebral cortex[7]. Therapeutic concentrations of

lithium in human plasma can easely reach 2 mM during the treatment of acute mania with lithium salts[1,7]. At this concentration, a 27 % inhibition of the dopamine effect was also measured. In the latter experiments, absolute values of cyclic AMP concentrations in control-, dopamine- or dopamine plus 2 mM lithium-retinae were 18.5 ± 2.1(6), 57.1 ± 7.1(5) and 41.4 ± 3.3(5), respectively (pmol per mg protein, mean ± s.e.m., number of retinae in parenthesis).

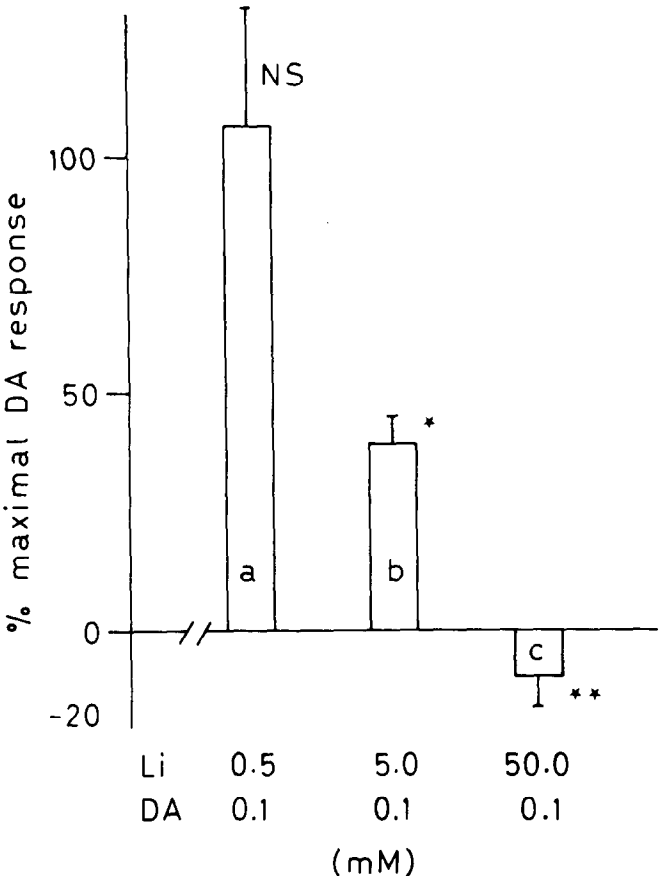
Inhibition by lithium of basal adenylate cyclase activity appears to be unlikely, since the absolute values of cyclic AMP in the presence of 0.5, 5 and 50 mM lithium (in the absence of dopamine) were not significantly different from basal values (i.e. in the absence of drugs). Column c (Figure 1) appears to indicate an inhibition of basal activity at 50 mM lithium concentration, as the percentage of maximal dopamine response is shown. However, the absolute values of cyclic AMP in the presence of both dopamine and lithium were not significantly different from basal values (no drugs). The specificity of the lithium effect is supported by similar experiments using dopamine-mimetic agents (Table 1). It is well established that N-methyl-dopamine (epinine) and apomorphine act at dopamine receptors of the CNS, which are different from either α- or β-adrenoceptors[8].

Table 1. Blockade by 50 mM lithium of the cyclic AMP production* induced by dopamine-like drugs in isolated retinae of the rabbit.

Drug, 0.1 mM	Drug-treated retinae		control retinae
	Without Li	With Li	
	a	b	c
epinine	60.7 ± 10.7(5)	19.8 ± 2.7(5)	20.4 ± 0.9(3)
apomorphine	79.6 ± 8.5(5)	20.9 ± 2.3(5)	17.2 ± 3.1(5)
ergometrine	23.4 ± 2.4(6)	16.1 ± 0.6(5)	14.8 ± 1.4(5)

*pmol per mg protein, mean ± s.e.m. The number of retinae is indicated in parenthesis. For each experiment, values given in column a are significantly different from values given in column b or c ($0.05 > P \geq 0.001$). No significant differences were found between values given in column b and values given in column c ($P > 0.05$).

Figure 1. The effect of lithium (Li) on stimulation of cyclic AMP production induced by dopamine (DA) in isolated retinae of the rabbit.



The increments of cyclic AMP production induced by dopamine alone in experiments a, b and c were 30.6 ± 3.0, 48.1 ± 10.5 and 26.9 ± 1.5 respectively (pmol per mg protein, mean ± s.e.m., n = 5) and normalised to 100 %. The same number of retinae (n = 5) were exposed to both Li and dopamine, for each experiment a, b and c. The increments of cyclic AMP production were then expressed as the percentage of the corresponding maximal dopamine response (ordinate).

* $P < 0.05$; ** $P < 0.001$; NS = not significantly different.

As for dopamine, the accumulation of cyclic AMP induced by 0.1 mM epinine or apomorphine is completely abolished by 50 mM lithium. Complete inhibition was also achieved when the stimulating agent is an ergot alkaloid, ergometrine. The latter drug belongs to a new class of potential dopamine-agonists[6]. It is conceivable that due to a high degree of structural specificity for agonist activity[3,9], all three agents would stimulate the same population of retinal dopamine receptors and that one of the cellular effects of lithium is a specific inhibition of dopamine-sensitive adenylate cyclase.

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Supported by SNSF (3.544.075). We thank Miss C. Blank for excellent technical assistance. We gratefully acknowledge the receipts of drugs from P. Laduron (Janssen Pharm.) and Sandoz AG.