

THE EFFECT OF LITHIUM ON THE INOTROPIC EFFECT OF OUABAIN AND MANIFESTATION OF ARRHYTHMIA IN GUINEA-PIG ATRIA

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Abstract—Exposure of the guinea-pig whole atria to lithium (1 and 5 mM) produced a reduction of inotropic response to ouabain. The inhibitory effect of lithium (1 mM) was slight, whereas lithium (5 mM) significantly reduced the response of the preparations to ouabain (2 and 3 μ M). Lithium (1 and 5 mM) did not modify the inotropic response to 2 and 3 μ M of ouabain in electrically stimulated guinea-pig left atria. Lithium was not able to modify the capacity of ouabain to produce arrhythmia. The extent of contribution of the ouabain-like effect of lithium to our results could not be assessed, thus, an interaction between ouabain and lithium seems unlikely. Acta Medica Iranica 33 (3&4): 79-82; 1995

Key words: ouabain; atria (guinea-pig); lithium

INTRODUCTION

Lithium is widely used for the treatment of psychotic disorders although its mechanism of action is not yet clear. However, it has been reported that lithium inhibits the release of neurotransmitter from adrenergic nerve terminals of guinea-pig atria (1). On the other hand, it has been reported that lithium promotes catecholamine secretion from the adrenal gland of the cat, a process dependant on the concentration of the intracellular calcium. It has been suggested that lithium accumulates in the cells and can partially substitute sodium in the Na^+ - Ca^{++} countertransport system at the plasma membrane of the chromaffin cell (2). Cardiac glycosides such as ouabain increase the intracellular concentration of Ca^{++} by inhibiting Na^+ - K^+ ATPase (3). In this regard it seems that lithium can mimic the action of cardiac glycosides. Sperling et al (4) reported that long-term lithium therapy may be associated with cardiac arrhythmia but they mentioned no clear cause for this property and did

not clarify whether this was related only to lithium or other concomitantly used psychotic drugs were also involved. This study was carried out to investigate the effect of lithium on the inotropic effect of atria and to clarify whether it produces arrhythmia.

MATERIALS AND METHODS

A total of 36 albino guinea-pigs weighing approximately 500 g were sacrificed by a blow on the head and exsanguination. The hearts were removed rapidly, the auricles were dissected out in a physiologic solution (Tyrode or modified Krebs, depending on the experiment) and suspended vertically in isometric conditions under an appropriate tension (1 g for whole atria and 0.8 g for left atria) in a 20 ml glass chamber. For the experiments on the left atria, Tyrode solution was used and a tension of 0.8 g was exerted (1). The left atria were stimulated by pulses of 4 volts and 1 ms duration at a frequency of 240/min through two pointed electrodes. For the experiments on the whole atria, modified Krebs solution was used and a tension of 1 g was exerted. The temperature of the bathing solution was 37° C and the PH was 7.4. The composition of the Tyrode solution in mM was as follows: NaCl, 115; KCl, 4.7; CaCl_2 , 3.6; MgSO_4 , 1.2; KH_2PO_4 , 1.2; NaHCO_3 , 25; and Glucose, 10. The composition of the modified Krebs solution in mM was as follows: NaCl, 118; KCl, 4.7; CaCl_2 , 2.6; MgCl_2 , 1.2; NaH_2PO_4 , 1; NaHCO_3 , 25; Glucose, 11.1; EDTA, 0.004; and Ascorbic acid, 0.11 (5). The solution was oxygenated with a gas mixture of 97% O_2 and 3% CO_2 . Isometric contractions were recorded with an isometric transducer and displayed on DMR-4B physiograph (Narco Biosystem Inc.).

To avoid artifacts evoked by dissection, an equilibration period of 30 min was allowed before the control isometric developed tension (IDT) in mg, was determined. Thereafter, lithium or sucrose was added and left in contact with the preparation for 30 min.

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Mean tension values (in mg) were recorded after equilibration (zero time) and 30 min after addition of lithium or sucrose (before addition of ouabain). The latter values were considered as the absolute initial control tension. The maximal magnitude of IDT observed after ouabain was compared with that of initial controls (considered as 100%) and expressed as percent changes. The drugs used were ouabain (Sigma Co.) and LiCl (Merck Co.).

RESULTS

The positive inotropic effect of different concentrations of ouabain upon the isolated whole atria pretreated with different concentrations of lithium

The magnitude of the positive inotropic responses to ouabain 2×10^{-7} M was reduced significantly by Li^+ 5 mM ($P < 0.01$) while Li^+ 1 mM had no significant effect (Fig. 1). Li^+ 5 mM significantly reduced the magnitude of the positive inotropic responses to ouabain (3×10^{-7} M) ($P < 0.01$) but lithium 1 mM had no significant effect on this marker (Fig. 2).

Lithium at doses of 1 and 5 mM did not change the dose of ouabain required for manifestation of arrhythmia (Table 1).

The positive inotropic effect of different concentrations of ouabain upon the isolated left atria pretreated with different concentrations of lithium

Neither the magnitude of the positive inotropic responses to ouabain (2×10^{-7} M and 3×10^{-7} M) nor the dose of ouabain required for the manifestation of arrhythmia was changed in the presence of lithium (1 and 5 mM) (Figs. 3 and 4 and Table 2).

DISCUSSION

The results of the present study demonstrate that some concentrations of lithium are able to depress the isometrically developed tension to ouabain in guinea-pig atria. Exposure of the whole atria to lithium (1 and 5 mM) for 30 min produced a reduction of the ouabain response. The inhibitory effect of 1 mM lithium was slight, whereas 5 mM lithium significantly reduced the response of the preparation to 2×10^{-7} M ouabain. When the dose of ouabain was increased to 3×10^{-7} M, only 5 mM of lithium was able to inhibit the response to ouabain. These results are in good agreement with

previous findings obtained in electrically stimulated guinea-pig atria (1).

It has been reported that lithium is able to depress the cardiac response to sympathetic nerve stimulation in guinea-pig atria in a dose-dependent manner. The inhibitory effect of lithium was attributed to an action at prejunctional level (1). Lithium (1 and 5 mM) did not modify the inotropic response to 2×10^{-7} M and 3×10^{-7} M ouabain in electrically stimulated guinea-pig left atria. It

Table 1. Effect of lithium (1 and 5 mM) on the dose of ouabain required for induction of arrhythmia in the guinea-pig whole atria. Data are given as mean \pm s. e. of six experiments.

Experiment	Dose of ouabain required for induction of arrhythmia (μM)
Control (ouabain)	0.45 ± 0.042 (ns)
Lithium (1 mM)	0.47 ± 0.028 (ns)
Lithium (5 mM)	0.357 ± 0.02 (ns)

Table 2. Effect of lithium (1 and 5 mM) on the dose of ouabain required for induction of arrhythmia in the guinea-pig left atria. Data are given as mean \pm s. e. of six experiments.

Experiment	Dose of ouabain required for induction of arrhythmia (μM)
Control (ouabain)	0.72 ± 0.050 (ns)
Lithium (1 mM)	0.66 ± 0.042 (ns)
Lithium (5 mM)	0.70 ± 0.044 (ns)

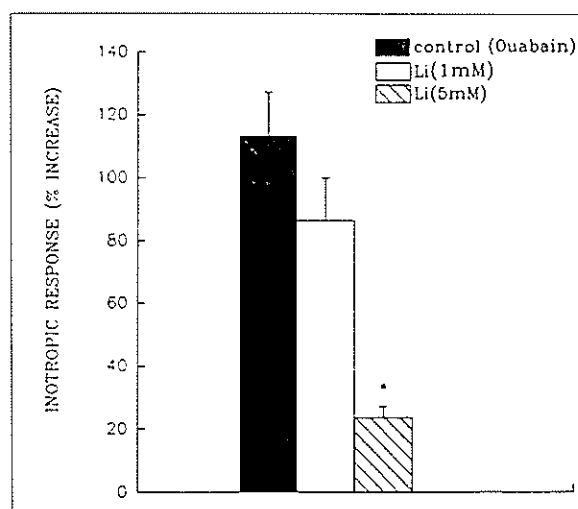


Fig. 1. Effect of lithium (1 and 5 mM) on the inotropic response to ouabain 2×10^{-7} M in the guinea-pig whole atria. Data are given as mean \pm s. e. of six experiments. Statistically significant differences from the control are indicated by (* $P < 0.01$).

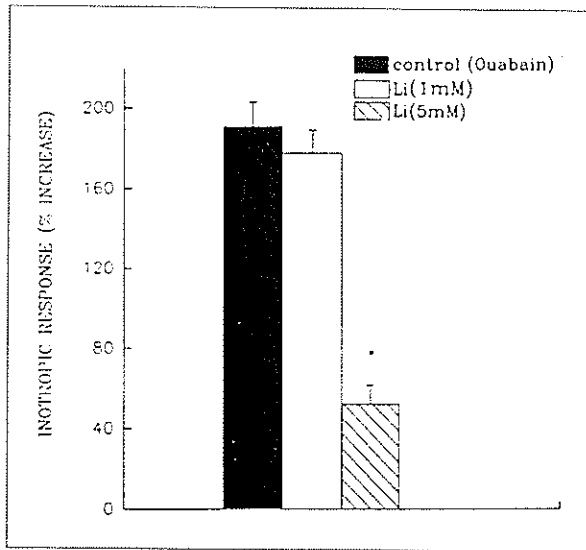


Fig. 2. Effect of lithium (1 and 5 mM) on the inotropic response to ouabain 3×10^{-7} M in the guinea-pig whole atria. Data are given as mean \pm s.e. of six experiments. Statistically significant differences from control are indicated by (* $P < 0.01$).

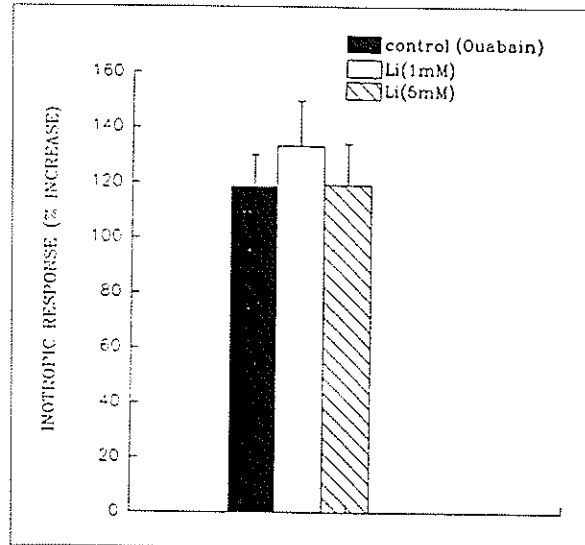


Fig. 4. Effect of lithium (1 and 5 mM) on the inotropic response to ouabain 3×10^{-7} M in the guinea-pig left atria. Data are given as mean \pm s.e. of six experiments.

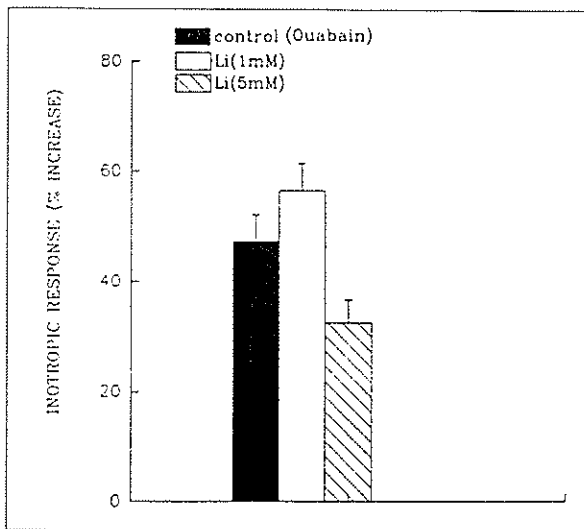


Fig. 3. Effect of lithium (1 and 5 mM) on the response to ouabain 2×10^{-7} M in the guinea-pig left atria. Data are given as mean \pm s.e. of six experiments.

has been previously shown that lithium (1 and 10 mM) produced a dose-dependent inhibition of cardiac response to field stimulation of the adrenergic nerve terminals without affecting myocardial contractility in electrically stimulated guinea-pig atria (1). However, this was not supported by our findings. Such discrepancy could arise from the species of animal and/or the stimulating procedure used.

It is generally accepted that the positive inotropic

influence of effective concentrations of cardiac glycosides varies with contractile frequency as a result of differences in the magnitude of contractile tension existing before the addition of glycoside (6). It has been suggested that ouabain acts upon the peak tension developed in isolated atria by two mechanisms: one, affected by the frequency of stimulation, appears to be subserved by adrenergic factors and is found with the higher concentrations of ouabain; the other, which is independent of the frequency of stimulation, dose not have a direct relationship with adrenergic processes and occurs with lower concentrations of ouabain (7). The findings show that low concentrations of ouabain (2 and 3 μ M) elicited an inotropic effect at the frequency used (4 Hz) are not sensitive to inhibition by lithium. It seems that the low concentrations of ouabain influenced contractile response in electrically stimulated guinea-pig atria. This did not appear to have a direct relationship with adrenergic processes. It has been shown that there is a relationship between the adrenergic nervous system and digitalis toxicity (8) and it has been claimed that agents which reduce adrenergic nervous activity also decrease the capacity of digitalis to produce arrhythmia (9). These observations were confirmed subsequently by Erlj and Mendez (10), Boyajy and Nash (11), Takagi et al (12) and by a series of studies by Roberts and his group (13,14,15,16). A direct effect of ouabain on sympathetic neural discharge was established in 1969 by McInain (17) and Gillis (18).

The close similarity between the secretory response on catecholamine release by both lithium and ouabain

has been reported (2) and suggested that lithium activates a $\text{Li}^+-\text{Ca}^{++}$ exchange mechanism leading to an increase of $[\text{Ca}]_i$ that subsequently promotes catecholamine secretion (2). However, the results in the present investigation with lithium were not in agreement with this hypothesis. Lithium was not able to modify the capacity of ouabain to produce arrhythmia. The preparations (whole and/or left atria) incubated with lithium did not show statistically significant increase in the sensitivity of the tissues to arrhythmogenic effect of ouabain. Therefore, the extent of the contribution of the ouabain-like effect of lithium to our results could not be assessed, thus, an interaction between ouabain and lithium seemed unlikely.

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