EFFECTS OF MAGNESIUM ON ISOLATED RABBIT ATRIA*

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Summary : The cardiac effects of magnesium were studied on 40 spontaneously beating rabbit atria at 37°C. Magnesium administered in doses of 30, 60, 120 and 240 *mmol* elicited dose dependent negative inotropic and chronotropic responses. Larger doses above 240 *mmol* caused complete atrial arrest. Further it was observed that propranolol with magnesium became more effective in blocking the positive chronotropic and inotropic responses to isoprenaline. The finding is interesting and suggestive that magnesium could be employed either alone or in combination with propranolol in treatment of arrhythmias which are non-responsive to propranolol.

Key words : magnesium adrenoceptors arrhythmia

INTRODUCTION

Magnesium ion has long been known to produce several effects on cardiovascular system viz hypotension (3, 5, 7, 11), bradycardia (2, 3), prolongation of intraventricular conduction time (14) and reversal of digitalis induced arrhythmias (12, 13, 14). In contrast to above, certain workers (6, 9) reported hypotension alongwith tachycardia instead of bradycardia after magnesium administration. Ellis and Vincent (4) found that perfusion medium with high concentration of magnesium arrested guinea pig heart, which was not stimulated by epinephrine. However, Abe and Masayosi (1) observed that epinephrine increased the force of contraction of magnesium depressed frog and rabbit ventricular strips. Similarly other workers (3) reported that magnesium (20 *mmol*) reduced force of contraction by 85% but in such depressed hearts epinephrine produced greater stimulation, than in the normal hearts.

Recent studies (1, 3, 8) in relation to interaction of magnesium and adrenergic amines on heart provided the curiousity to investigate any relationship between magnesium

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and adrenoceptors in isolated rabbit atria, as these agonists act via adrenoceptors and magnesium modifies their action.

MATERIALS AND METHODS

This study was conducted on 40 rabbits of either sex weighing between 1 to 1.5 *kg*. The animal was stunned by sharp blow to the back of the neck. The heart was immediately removed and placed in oxygenated Tyrode solution. The atria were carefully isolated, avoiding injury to S.A. node and were mounted in Dale's organ bath. The Tyrode solution in organ bath was continuously bubbled with a gas mixture of 95% oxygen and 5% carbondioxide. The pH was kept constant at 7.43 and temperature was maintained at 37±0.5°C. Spontaneous contractions of atria were recorded on a smoked kymograph paper at slow speed using Starling's lever with 0.5 *gm* tension and 5 times magnification.

The following drugs were used :—

Isoprenaline hydrochloride (Unichem Lab.), Propranolol hydrochloride (Inderal, I.C.I.), Magnesium chloride. The experiments were carried out under the following groups;

Group I (8 rabbits) : Effect of increasing doses of magnesium (30 to 240 *mmol*) was observed on chrono and inotropic responses of rabbit atria. Then after each dose of magnesium effect of equimolar calcium was observed.

Group II (16 rabbits) : The responses to various concentrations of isoprenaline (10^{-9} to 10^{-6} *mol*) were observed before and after the treatment of atria with ;

(a) Magnesium (30 to 240 *mmol*).

(b) Magnesium (60 *mmol*) and equimolar calcium.

Group III (16 rabbits) : Concentration response of isoprenaline (10^{-9} to 10^{-6} *mol*) were recorded before and after administration of ;

(a) Propranolol (0.02, 0.2 and 2 μ*mol*).

(b) Propranolol (0.02 μ*mol*) and magnesium 30 *mmol*).

Isotonicity of the bath solution was maintained throughout the experiment by addition or substraction of dextrose.

Statistics :— All the values were presented as mean ± SE. Levels of significance was calculated by student's 't' test at 95% level of confidence.

RESULTS

Primary cardiac actions of magnesium and effect of equimolar calcium on magnesium depressed atria Group I :

In this group increasing doses of magnesium (30 to 240 *mmol)* produced a dose dependent reduction in rate and amplitude of atrial contraction. Magnesium in concentrations of 30, 60, 120, 240 *mmols* reduced the atrial inotropic responses to 87.5±0.74%, 62.2±0.82%, 21.25±0.3% and 12.5±0.7% respectively doses above 240 *mmol* produced complete atrial arrest while in the presence of magnesium and equimolar calcium inotropic responses were reduced to 94.3±0.6, 87.1±1.2, 21.2±0.46, 18.2±0.86 (Table I, Fig. I).

TABLE I : Showing inotropic (1NO) and chronotropic (CHR) responses of isolated rabbit atria to :

(A) Mg alone (30 – 240 mM)
(B) Mg (30 – 240 mM) + equimolar calcium

	Percent Reduction ± SEM Mg M mol							
	30		60		120		240	
	1NO	CHR	1NO	CHR	1NO	CHR	1NO	CHR
A	87.5 ±0.74	75 ±0.2	62.2 ±0.82	62.5 ±0.2	21.15 ±0.3	10 ±0.9	12.5 ±0.7	3.1 ±0.9
B	94.3 ±0.6	87.6 ±0.2	87.1 ±1.2	62.6 ±1.1	21.2 ±0.46	20.3 ±0.8	18.3 ±0.86	12.1 ±1.1

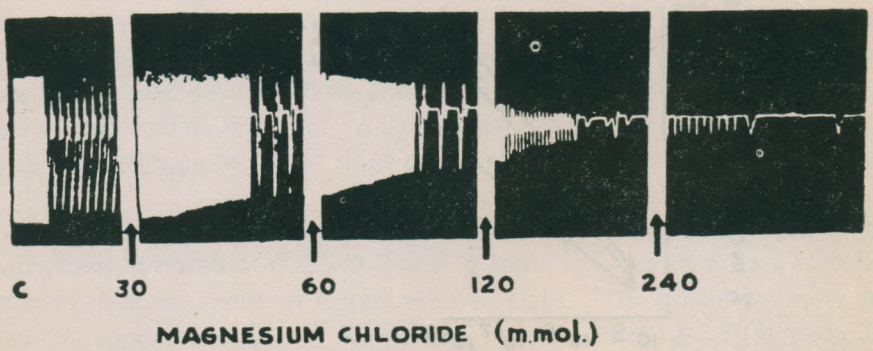

Fig. 1 : Kymographic tracings showing the effect of different concentrations of magnesium chloride on atrial responses.

Similarly atrial chronotropic responses in the presence of magnesium 30, 60, 120 and 240 *mmols* were reduced to 75±0.2%, 62.5±0.27%, 10±0.9% and 3.1±0.9% respectively while in the presence of magnesium and equimolar calcium chronotropic responses were reduced to 87.6±0.2%, 62.6±1.1%, 20.3±0.8%, and 12.1±1.1.

Effect of magnesium on atrial responses to beta agonist isoprenaline (Group II). The concentration response curves of isoprenaline are shown in Fig. 2 and 3, Table II. Isoprenaline (10^{-6} *mol*) produced 91.1±1.5% and 517.7±10.83% increase in chrono and inotropic responses respectively. These responses were reduced by administring different concentrations of magnesium. So magnesium (240 *mmol*) reduced the chrono

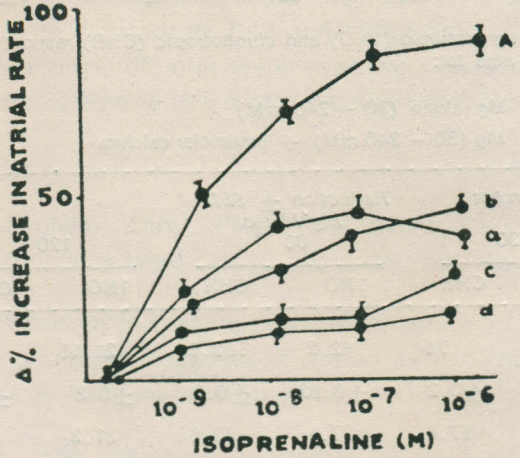

Fig. 2 : Concentration response curve of isoprenaline (*mol*); control (A), After administration of magnesium 60 *mmol* (B), 120 *mmol* (C), 240 *mmol* (D) and magnesium 60 *mmol* + equimolar calcium(a).

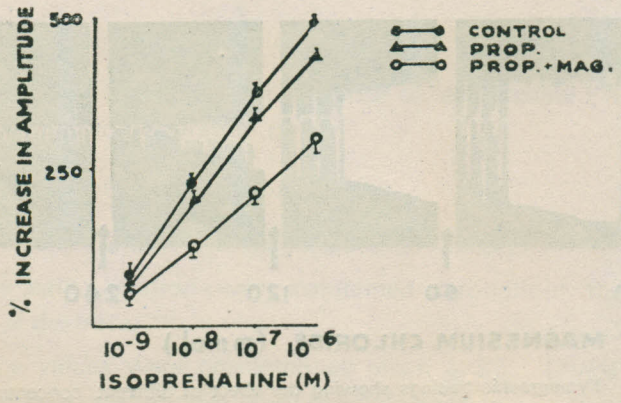

Fig. 3 : Concentration response curve of isoprenaline (*mol*) after propranolol alone and after propranolol 0.02 UM + magnesium (30 mM).

TABLE II : Showing positive inotropic responses of Isoprenaline (10^{-9} – 10^{-6} M) in isolated rabbit atria.

a - Control, b– to c– in presence of magnesium 30, 60, 120 mM F in presence of 60 mM magnesium with equimolar calcium.

	Percen change ± SEM		*Isoprenaline M*	
	10^{-9}	10^{-8}	10^{-7}	10^{-6}
A	333.3 ±7 62	450.2 ±10.86	473.1 ±4.08	517.7 ±10.83
B	198.2 ±3.2	310.6 ± 8.2	36.12 ±7.8	392.1 ±1.2
C	101.4 ±2.7	202.6 ± 0.82	258.2 ±3.3	296 ±7.16
D	82.1 ±0.82	150.6 ±10.9	230.1 ±5.7	250.3 ±5.25
E	51.2 ±7.5	82.3 ± 4.3	168.7 ±6.3	210.3 ±6.2
F	150.4 ±1.3	270.3 ± 3.2	196.1 ±8.7	302 ±6.8

and inotropic responses of isoprenaline to 18.6±3.5% and 210.4±6.12% respectively in rabbit atria. When similar doses of isoprenaline (10^{-6} *mol*) were administered in presence of magnesium (60 *mmol*) and equimolar calcium the positive chronotropic and inotropic responses were only 49.1±1.63% and 302±6.82% respectively. Still the stimulatory responses of isoprenaline were not of similar magnitude in the presence of magnesium and calcium as they were alone, when none of the ions were present in bath media.

Effect of magnesium on beta blockade (Group III); Pre-treatment of atria with propranolol in doses of 0.02, 0.2 and 2 *µmol* resulted in a dose dependent shift of concentration response curve of isoprenaline to right. The positive chrono and inotropic responses of isoprenaline (10^{-6} *mol*) were reduced to 54±2.01% and 90.4±5.83% respectively in presence of propranolol (2 *µmol*) This reduction was found to be statistically highly significant ($P<.001$) However, pretreatment of atria with propranolol

(0.02 *µmol*) reduced insignificantly ($P<0.05$) positive chrono and inotropic responses of isoprenaline (10^{-6} *mol*) to 89.3±2.84% and 510.7±12.3% respectively (Fig. 3). When propranolol (0.02 *µmol*) and magnesium (30 *mmol*) were administered together in the bath, there was a significant reduction ($P<.05$) in the positive inotropic response of isoprenaline to 54.3±0.82% and shift in concentration response curve to right (Fig. 3 and Table III).

TABLE III : Showing positive chronotropic responses of isoprenaline :
(A) Control.
(B,C,D) After pretreatment of 2, 0.2 and 0.02 UM propranolol and
(E) After 0.02 UM Prop and Mg 30 mM all values are represented as percent change ±SEM.

	Isoprenaline M			
	10^{-9}	10^{-8}	10^{-7}	10^{-6}
A	49.9 ±2.3	68.7 ±0.05	82.1 ±10.8	91.1 ±1.5
B	15.1 ±4.5	28.2 ±3.9	35.1 ±3.5	54.02 ±12.1
C	28.3 ±0.82	44.92 ±0.15	66.1 ±2.3	72.81 ±8.3
D	48.3 ±0.82	67.92 ±0.23	80.1 ±2.32	89.34 ±10.84
E	40.2 ±3.3	51.91 ±10.8	54.32 ±1.91	50.3 ±0.83

DISCUSSION

The experiments presented here have shown that magnesium has got marked depressant effect on atrial responses. This effect is dose dependent. Both inotropic and chronotropic responses were reduced by magnesium, the reduction in latter response being more marked. This is in confirmity with the observations of other workers (1, 2, 3, 7, 15). However, Hoff *et al.* (6) and Maxwell *et al.* (9) observed tachycardia instead of brady cardia after magnesium administration in dogs.

Isoprenaline failed to elicit an equal stimulation in magnesium depressed atria, as it did in the absence of magnesium. It suggests that magnesium has got a marked influence on adrenergic responses of rabbit atria. Our findings are in favour of Ellis and Vincent (4) who also observed failure of catecholamines to stimulate magnesium depressed

hearts. Contrary to above, certain workers (1, 3) reported that catecholamines produced greater stimulatory responses in hearts inhibited by magnesium pretreatment.

The decreased action of isoprenaline in presence of magnesium may be due to a fall in the calcium uptake by heart produced by magnesium. Kenneth and Douglas (7) have reported a magnesium calcium interaction at sarcolemmal membrane level and suggested that low levels of calcium are necessary for magnesium to elicit its responses. However, Arnold and Kollmeyer (2) reported depressant action of magnesium without any associated change in calcium levels.

In our study this appears to be unlikely since it has been found that calcium in equimolar concentration did not recover the atria depressed by high concentration of magnesium (240 *mmol*). However, calcium caused a partial recovery in function of atria depressed by smaller concentrations of magnesium (30–60 *mmol*). Similar results were obtained by Meltzer and Aver (10). Also, that in presence of both calcium and magnesium, isoprenaline could not produce an appreciable stimulatory response. Thus it appears that reduced calcium uptake by magnesium contributes partly in decreasing beta agonist activity. The depressant action may also be due to some other mechanism besides producing a decreased calcium uptake by heart.

It is possible that high concentrations of magnesium caused the depression of beta receptors by combining competitively with receptors sites. It was observed in our experiments that propranolol in small dosage of 0.02 *µmol* which produced almost insignificant blockade of stimulatory responses to isoprenaline, could shift its concentration response curve significantly to right in presence of lowest concentration of magnesium 30 *mmol* (Fig 3).

Thus the effect of high magnesium medium in supressing the myocardium is very similar to that produced by beta blockade but the explanation for this at cellular level remains unknown and needs further investigation.

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