INFLUENCE OF β-ADRENOCEPTOR ANTAGONISTS ON SPONTANEOUS RATE AND ON FORCE OF CONTRACTION OF ISOLATED RABBIT ATRIA

KUSHAL PAL SINGH*

Department of Pharmacology,
All-India Institute of Medical Sciences, New Delhi - 110 029

(Received on July 11, 1983)

Summary : The influence of β-adrenoceptor antagonists on the spontaneous rate and on force of contraction of the myocardium was studied independently on spontaneously beating right and electrically driven isolated left atria of rabbit. On spontaneous rate, practolol had sympathomimetic effect only, N-isopropylmethoxamine (IMA). had both sympathomimetic as well as depressant effects, whereas alprenolol, procinolol, bunolol and H 35/25 had depressant effects only in higher concentrations. The order of potency was procinolol > bunolol > alprenolol > H 35/25 > and IMA. On the contractions of isolated left atria, all β-adrenoceptor antagonists produced concentration--dependent depressant effect. In relation to procinolol, these agents were 5-125 times less potent for depressing the contractions of left atria by 15% and the order of β-potency was procinolol > alprenolol > bunolol = H 35/25 > IMA > and practolol.

The present results indicate that the depressant effects of β-adrenoceptor antagonists on spontaneous rate of right atria and on contraction of isolated left atria are not related to each other.

Key words : β-adrenoceptor antagonists, isolated rabbit atria, sympathomimetic activity, depressant activity

INTRODUCTION

Besides the classical effects expected of β-adrenoceptor blockade, many β-adrenoceptor antagonists also exhibit sympathomimetic as well as variable myocardial depressant effect (1,3,4). In the the present study the sympathomimetic and depressant effects of some β-adrenoceptor antagonists were studied seperately using spontaneously beating and electrically driven isolated rabbit atria under comparible experimental conditions. The purpose of this was to determine the influence of β-adrenoceptor antagonists independently on spontaneous rate and on force of contraction by avoiding the secondary changes that may occur in force of contractions due to change in frequency (2,5,9). Such comparison has not been reported earlier with these antagonists.

MATERIAL AND METHODS

Both right and left rabbit atrial preparations were set up in two identical tissue baths

* Corresponding address : R-11/159, New Rajnagar, Ghaziabad - 201 002

containing oxygenated Kreb's bicarbonate solution at a temperature of 37.0±01°C, as described earlier (10,11). Left atrial preparations were electrically driven through bipolar platinum electrodes using a Grass S4 stimulator to deliver square wave pulses (0.3 ms; 2 Hz; strength, 15-25 V, which was 50% above threshold). Right atria were allowed to beat spontaneously. Contractions of both the atria were recorded simultaneously on Grass Model 7 Polygraph.

After stabilization of the spontaneous atrial rate and force of contraction, the effects of β-adrenoceptor antagonists were studied in cumulative fashion. Successive doses to make concentrations 3 times the previous one in bath were added at 10 min intervals. The statistical analysis was carried out by student 't' test for paired samples.

Hydrochloride salts of racaemic form of practolol (I.C.I., U.K.), procinolol (Roussel Ucalf, Paris,), bunolol (Warner-Lambert, N.J.), N-isopropylmethoxamine (IMA) (Burroughs Welcomes, U.S.A.), alprenolol and H 35/25 (A.B. Hassale, Sweden) were used in the present study.

RESULTS

Isolated right atria : The mean resting rate of spontaneously beating right atria was 199±6 beats/min (23 observations). The maximal effects of a concentration of β-adrenoceptor antagonist developed slowly in 5-10 min; the depressant effect was completely reversible after repeated washes.

Fig. 1 shows that 3 X 10^{-9}M concentration of practolol (5±1.37 beats/min) and IMA (7±2.57 beats/min) had significant ($P<0.05$) sympathomimetic activity. whereas other β-adrenoceptor antagonists were devoid of sympathomimetic activity. Practolol (even 10^{-4}M) had no depressant effect. All other β-adrenoceptor antagonists produced concentration-dependent but variable depressant effects upon the spontaneous atrial rate above concentration of 10^{-6}M. Curve for the depressant effect of procinolol exhibited a steeper slope in comparison to other β-adrenoceptor antagonists. The order of potency of these β-adrenoceptor antagonists for depressing the spontaneous atrial rate by 15% was Procinolol>bunolol>alprenolol>H 35/25>and IMA (Table I).

Isolated left atria : In control experiments, the twitch tension (0.88±0.7 g-wt) that developed due to contraction did not alter during 2 hr period. Like the effect on spontaneous atrial rate, the effect of a concentration of a β-adrenoceptor antagonist on the force of contraction developed slowly in 5-10 min. However, the depressant effects of practolol, IMA and H 35/25 only were reversible after repeated washes.

Fig. 2 shows that all β-adrenoceptor antagonists produced concentration-dependent depressant effects on the force of contraction. No sympathomimetic effect was observed with these antagonists except that practolol (3×10^{-10} M) had a sympathomimetic effect (7.5 ± 2.92 g-wt %; $P = < 0.05$). The order of potency of these β-adrenoceptor antagonists for depressing the force of contraction of isolated left atria by 15% was procinolol > alprenolol > bunolol = H 35/25 > IMA > and practolol (Table I).

The contractions of atria were completely abolished in 4 out of 6 experiments of procinolol (3×10^{-5}M), 3 out of 8 experiments of alprenolol (3×10^{-5}M) and in 2 out

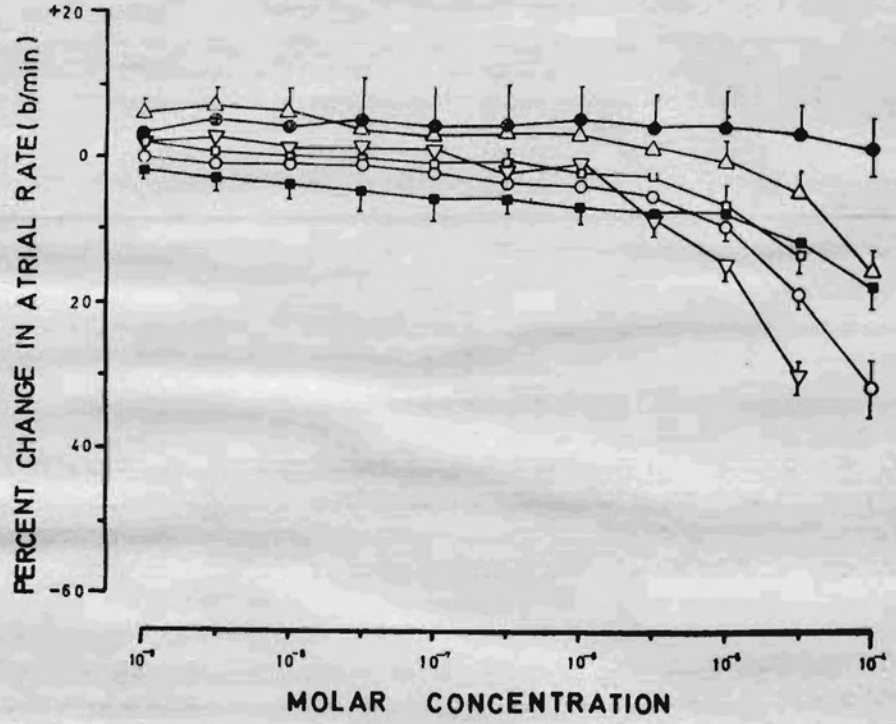

Fig. 1 : Effects of β-adrenoceptor antagonists on spontaneous rate of isolated right atria of rabbit. Values are means from experiments as shown below. (vertical lines indicate S.E.M.)

●—●	Practolol	(n=5)
△—△	IMA	(n=6)
■—■	H 35/25	(n=6)
□—□	Alprenolol	(n=7)
O—O	Bunolol	(n=6)
▽—▽	Procinolol	(n=5)

of 6 experiments of bunolol (10^{-4}M). Higher concentrations of β-adrenoceptor antagonists except practolol could not be employed because they either induced irregularities in rhythms or the tissue became inexcitable.

TABLE I : Molar concentrations of β-adrenoceptor antagonists having a 15% depressant effects upon the spontaneous rate and the force of contraction of isolated rabbit atria and the potency ratios.

Antagonists	*Force of contraction*		*Spontaneous rate*		*Relative potency Ratio***
	Conc. (M)	*Potency ratio**	*Conc. (M)*	*Potency ratio**	
Procinolol	2.5×10^{-9}	1	10^{-5}	1	40001 :
Alprenolol	1.0×10^{-8}	0.19	4.0×10^{-5}	0.25	3077 : 1
Bunolol	3.6×10^{-8}	0.07	2.0×10^{-5}	0.50	556 : 1
H 35/25	3.6×10^{-8}	0.07	5.6×10^{-5}	0.18	1556 : 1
IMA	7.2×10^{-8}	0.035	9.0×10^{-5}	0.11	1250 : 1
Practolol***	3.7×10^{-7}	0.008	..		

* Potency ratio in comparison to procinolol = 1.

** For depressing spontaneous rate and force of contraction by 15%.

*** Depressant effect was not observed even upto 10^{-4}M.

DISCUSSION

On the spontaneous rate, practolol had sympathomimetic effect only. The results are in agreement with those of Grodzniska and Gryglewski (3) on isolated guinea pig right atria and with those of Refsum and Landmark (8) on isolated rat right atria. Higher concentrations ($>10^{-6}$M) of other β-adrenoceptor antagonists had variable depressant effects.

On the contractions of isolated left atria, all β-adrenoceptor antagonists had concentration-dependent depressant effect. Unlike the earlier studies wherein, practolol was reported to have sympathomimetic effect only on the contractions of isolated rat left atria (8) and on travecular muscles of dogs (6), it produced concentration-dependent depressant effect on the contractions of electrically driven left atria in the present study. This agrees with the marked quinidine-like effect of practolol reported on isolated rabbit left atria (7).

On analysing and comparing the results obtained for the depressant effects of all β-adrenoceptor antagonists on spontaneous rate of right atria and on contractions of left atria (Table I) in relation to procinolol it appeared that except practolol, other β-adrenocep-

tor antagonists were 2-9 times less potent in depressing the spontaneous atrial rate whereas they were 5-30 times less potent in depressing the contractions of left atria. Though practolol failed to depress spontaneous atrial rate to any extent, it was 125 times less potent than procinolol in depressing the contractions of isolated left atria. In general, the β-adrenoceptor antagonists (except practolol) were 500-4000 times more potent

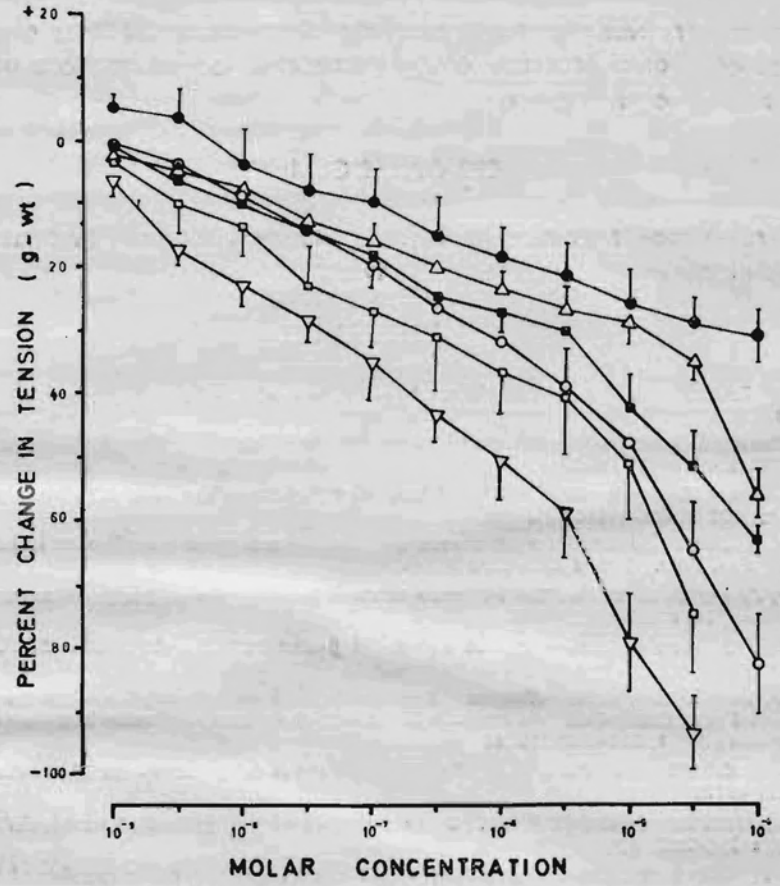

Fig. 2 : Effects of β-adrenoceptor antagonists on force of contraction of isolated left atria of rabbit. Values are means from experiments as shown below. (Vertical lines indicate S.E.M.)

●—●	Practolol	(n=5)
△—△	IMA	(n=6)
■—■	H 35/25	(n=6)
□—□	Alprenolol	(n=8)
O— O	Bunolol	(n=6)
▽—▽	Procinolol	(n=6)

in depressing the contractions of isolated left atria than the depressing spontaneous atrial rate. It is also apparent from Fig. 1 and 2 that the concentrations in which these agents had significant depressant effects on contractions of isolated left atria, had no depressant effect upon spontaneous atrial rate and their depressant effect appeared only in concentrations higher than 10^{-6}M.

Thus it appears from the present study that the depressant effects of β-adrenoceptor antagonists on spontaneous rate of right atria and on contractions of isolated left atria are not related to each other.

ACKNOWLEDGEMENTS

I am grateful to Dr. Pramod K. Gujaral, Former Associate. Professor of Pharmacology for his guidence and help during this work.

REFERENCES

1. Blinks, J. R. Evaluation of the cardiac effects of several beta adrenergic blocking agents. *Ann. N.Y. Acad. Sci.*, **139** : 673-685, 1967.
2. Dale, A. The relation between amplitude of contraction and rate of rhythm in the mammalian ventricle. *J. Physiol.*, **70** : 455-473, 1930.
3. Grodzinska, L. and R. Gryglewski. Action of beta adrenolytics on the isolated guinea pig atria. *Arch. int. Pharmacodyn.*, **191** : 133-141, 1971.
4. Koch-Weser, J. Direct and beta adrenergic receptor blocking actions of nethalide on isolated heart muscle. *J. Pharmac. Exp. Ther.*, **146** : 318-326, 1964.
5. Koch-Weser, J. and J. R. Blinks. The influence of the interval between beats on myocardial contractility. *Pharmacol. Rev.*, **15** : 601-652, 1963.
6. Nayler, W. G. Comparative partial agonist activity of β-adrenoceptor antagonists. *Brit. J. Pharmac.*, **45** : 382, 1972.
7. Paps, J. Gy. and E. M. Vaughan-Williams. A comparison of the antiarrhythmic actions of ICI 50172 and (−-) propranolol and their effects on intracellular cardiac potentials and other features of cardiac function. *Brit. J. Pharmac.*, **37** : 391-399, 1969.
8. Refsum, J. and K. Landmark. The actions of practolol on the isolated rat atrium. *Acta. Pharmac. et Toxicol.*, **31** : 97-106, 1972.
9. Rosenbleuth, A., J. Allanis and R. Rubio. Some properties of the mammalian ventricular muscle. *Arch. int. Physiol.*, **67** : 276-293, 1959.
10. Singh, K. P. Effect of alprenolol and N-isopropyl methoxamine on the pacemaker of the isolated rabbit atria accelerated by isoprenaline or histamine. *Int. J. Pharmac.*, **10** : 139-145, 1978.
11. Singh, K.P. Antagonism of isoprenaline or histamine induced positive chronotropic and inotropic effects by alprenolol. *Ind. J. Med. Res.*, **70** : 841-848, 1979.