REDUCED BETA ADRENERGIC RESPONSIVENESS IN ISOLATED RABBIT ATRIA DURING HYPOTHERMIA

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Summary: Beta adrenergic agonist isoprenaline (8×10^{-6}M) produced a 500% increase in inotropic and 90% increase in the chronotropic responses of isolated rabbit atria at 37°C. On cooling the atria to 23°C, these responses were significantly reduced to 87% and 30% respectively. Similar results were obtained with adrenaline, but isoprenaline was more potent. The positive chronotropic and inotropic responses to isoprenaline were effectively blocked by propranolol and practolol at 37°C whereas at 23°C these beta blockers were unable to block even minor positive responses obtained by isoprenaline at this temperature. On the contrary at 23°C, phenylephrine (alpha adrenergic agonist) produced marked positive chronotropic and inotropic effects indicating enhancement of alpha adrenoceptor activity at lower temperatures. This also suggests that reduced beta receptor activity at lower temperature is not due to a generalised depression of adrenoceptors as a result of hypothermia. Rewarming of atria to 37°C restored the beta adrenoceptor responsiveness to previous level. It appears that ambient temperature is important in maintaining normal beta adrenergic activity of the atria.

Key words: adrenpceptors beta agonists hypothermia

INTRODUCTION

Several studies have shown that adrenoceptor properties can be altered qualitatively by change in metabolic activity of the tissue. The metabolism in turn can be changed by alteration in temperature and thyroid activity.

Reduced beta activity has been reported during hypothyroidism (5,7 and 9). Similarly hypothermia results in a low beta adrenergic responsiveness in frog (2, 8 and 12), toad (6), and rat heart (1,10). On the contrary certain workers (4,3 and 11) reported that beta adrenergic responsiveness is not altered by lowering the temperature.

Hence the present study was undertaken to elucidate the behaviour of beta adrenoceptors during hypothermia in isolated rabbit atria.

MATERIALS AND METHODS

The present study was conducted on 30 rabbits of either sex weighing between 1-1.5 *kg*. The animal was stunned by a blow to the back of the neck. The heart was repidly removed and placed in oxygenated tyrode solution. The atria were carefully isolated, avoiding injury to S.A. node and were mounted in Dale's bath. The tyrode solution in the organ chamber was continuously bubbled with a gas mixture of 95% oxygen and 5% carbon

dioxide. The pH of tyrode solution was kept constant at 7.43 and the temperature was maintained at desired level by a thermostatically controlled water bath. Each atrial preparation was tested with a particular adrenoceptor agonist and antagonist at 37°C. Then the temperature of the bath was lowered gradually by adding ice cooled water to 30°C and 230° C respectively. The atrial responses to agonist and antagonist were tested at these temperatures also. The preparation was then slowly rewarmed from 23°C to 37°C to observe the recovery of adrenoceptor activity. At each temperature spontaneous contractions of atria were recorded on a smoked kymograph paper at slow speed, using Starling's lever with 0.5 g tension and 5 times magnification.

The following drugs were used :

Adrenaline tartarate (May & Baker), Isoprenaline hydrochloride (Unichem), Phenylephrine hydrochloride (Sigma Lab.), Propranolol hydrochloride (Inderal, I.C.I.), Practolol (Practolar CIPLA), Phentolamine hydrochloride (CIBA) and Phenoxybenzamine hydrochloride (S.K.& F.). (All these drugs were added to bath in a volume of 0.5 *ml* after withdrawing equal amount of tyrode solution so as not to disturb the total volume). After the preparation had stabilized the increasing doses of the agonist were added cumulatively till a maximal response was obtained (10). The atrial preparations were then washed several times with fresh tyrode solution and allowed to become stable before testing the antagonist. The responses of the atrial preparation to test doses of agonist previously used were compared to those obtained after antagonist treatment at different temperatures. Percent change in rate and force of contraction of the atria was calculated, considering the control parameters as 100%. In those experiments where agonist was retested after the antagonist treatment, the second control was taken when the treated preparation had stabilized, at the desired temperature. These control responses were also considered at 100% for calculating the percent change in response.

RESULTS

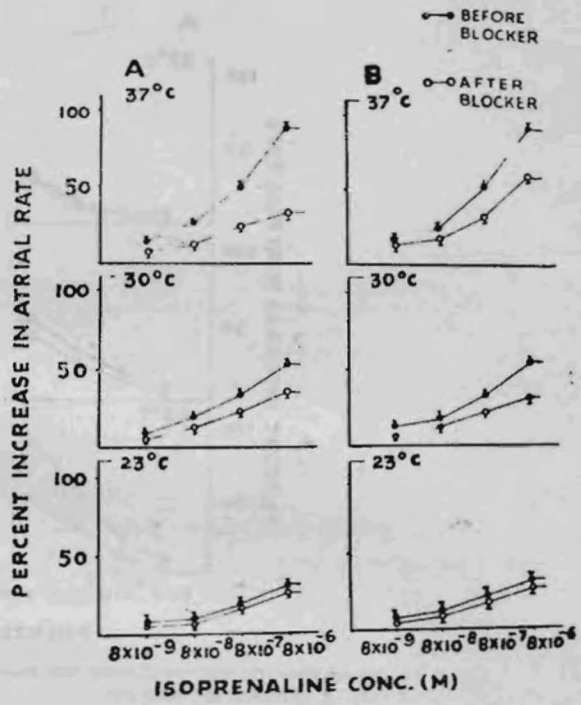
Beta agonist isoprenaline (8×10^{-6}M) produced a maximum positive chronotropic response of $90.1 \pm 4.32\%$ at 37°C which reduced significantly to $52.5 \pm 2.78\%$ and $28.7 \pm 1.68\%$ at 30°C and 230°C respectively ($P < 0.05$). Similarly the positive inotropic response to agonist was found to be $517.7 \pm 10.83\%$ at 37°C, while it was reduced to $87.2 \pm 4.77\%$ at 23°C. This reduction was statistically highly significant ($P < .001$). The responses to Isoprenaline were significantly blocked by propranolol (2 μM) at 37°C as shown by a marked shift to right of concentration response curves (Figs. 1 and 2). However, at 23°C none of the responses to isoprenaline were blocked by propranolol. Similarly practolol (18 μM) blocked the responses to isoprenaline at 37°C but it was ineffective in blocking any response to agonist at 23°C. The results obtained by another beta agonist adrenaline were similar to those obtained by isoprenaline but the latter was more potent.

Phenylephrine ($3x10^{-3}M$) produced maximum positive chronotropic and inotropic responses at 23°C. The alpha antagonists effectively blocked these responses (Figs. 2 and 3) as evident by a marked shift to right of concentration response curves.

Fig. 1 : Curves showing positive chronotropic response to increasing concentrations of isoprenaline (M) at different temperatures.

A — Before and after treatment with propranolol (2 μM)

B — Before and after treatment with practolol (18 μM)



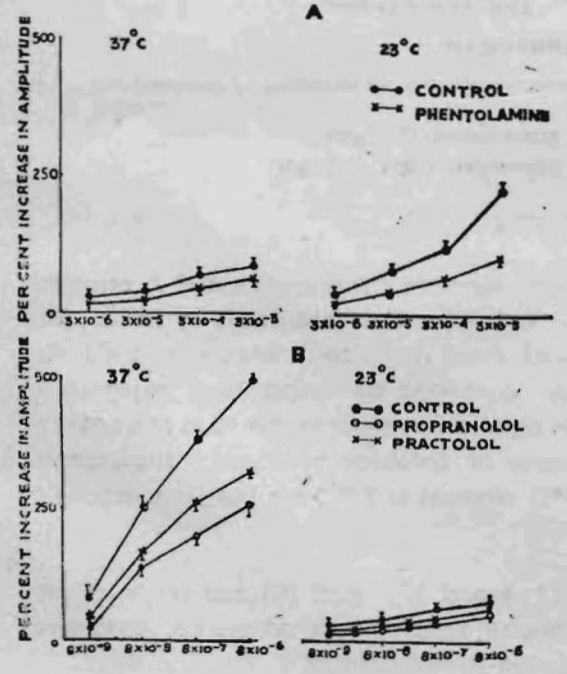


Fig. 2 : Curves showing positive inotropic response to increasing concentrations of the agonists at different temperatures before and after respective blockers.

A — Phenylephrine

B — Isoprenaline

On rewarming the atrial preparations from 23°C a to 37°C, there was a complete recovery in 83% of atrial preparations within 2 hrs. Rest of the preparations also showed full recovery within four hrs.

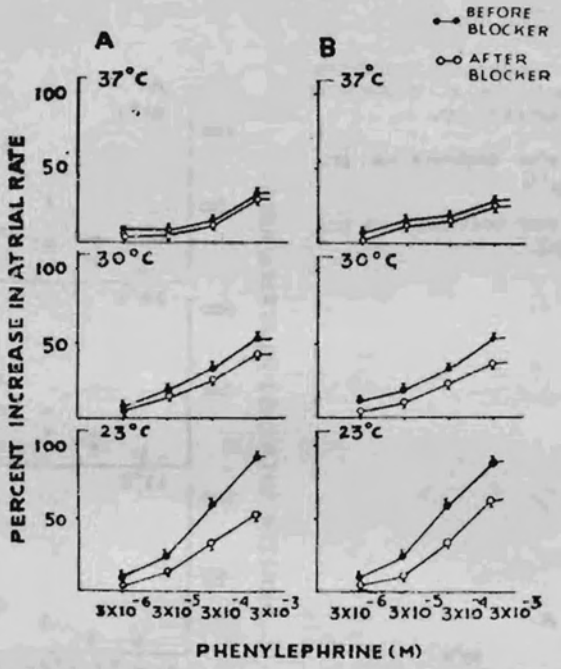


Fig. 3 : Curves showing positive chronotropic response to increasing concentrations of phenylephrine (M) at different temperatures.

A — Before and after treatment with phentolamine (5.3 μM)

B — Before and after treatment with phenoxybenzamine (6.5 μM)

DISCUSSION

The present study revealed that the beta agonists (Isoprenaline and Adrenaline) executed graeter positive chronotropic and inotropic effects on rabbit atria at 37°C. The cooling of the atria to 30°C and 23°C reduced these responses. Maximum reduction occured at 23°C. These results were further confirmed by using beta antagonists, propranolol and practolol. Both the antagonists significantly blocked the atrial responses to isoprenaline and adrenaline at 37°C. The degree of blockade produced, subsequently decreased with lowering of temperature to 30°C, whereas at 23°C the blocking actions of these antagonists were absent.

Similar results were reported in frog (2, 8 and 12), toad (6) and rat heart preparations (1 and 10) during hypothermia. Moreover, reduced beta adrenergic responsiveness was also observed in rats (5,7 and 9) during hypothyroidism.

However, in disagreement to these findings, Martinez and Mcneill (11), Benfey (3) and Caron and Lefkowtiz (4) reported no change in beta adrenergic responsiviness during hypothermia. This discrepancy presumably appears to be due to different experimental conditions.

Thus it appears that normally observed beta adrenergic responsiveness is reduced during hypothermia in rabbit atria. This may be an entirely temperature dependent reversible phenomenon, as by rewarming, the original response to beta agonists appeared again. Further, at 23°C phenylephrine (alpha adrenergic agonist) produced a marked positive chronotropic and inotropic effects, indicating an enhancement of alpha adrenoceptor activity at low temperatures. This observation would also suggest that reduced beta receptor activity is not due to a generalized depression of the adrenoceptors as a result of hypothermia. It seems that ambient temperature is important in maintaining normal beta adrenergic activity of the rabbit atria.

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