DEPRESSANT EFFECT OF PROPRANOLOL ON THE ISOLATED DIAPHRAGMATIC TISSUE OF RAT

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Abstract

The effect of propranolol on the electric stimulation of rat isolated diaphragm shOwed the depression of its isometric force of contraction. This depressant effect of propranolol on the rat isolated diaphragm was produced in doses much higher than the doses required for the beta adrenergic receptor blocking activity. Isoprenaline showed no effect on the rat isolated diaphragm and it did not antagonise the depressant effect of propranolol on the tissue. Thus depression of the rat isolated diaphragm by propranolol is not related to its beta— receptor blocking activity and as it is propranolol at high doses, it does not seem to contribute significantly to the bronchospasm produced by the administration of propranolol (JPMA 38 183, 1988).

INTRODUCTION

The use of beta adrenergic blocking agents produce respiratory distress in certain individuals, especially in patients suffering from bronchial asthma or chronic obstructive bronchopulmonary disease.[1-3] The effects of propranolol, oxprenolol and practolol on the isolated diaphragm of rat, stimulated electrically to produce isometric twitch response, was studied and it was observed that all these drugs produced depression of the isometric force of contraction of the rat's isolated diaphragm[4]. In another study, the effects of isoprena. line and propranolol on the isolated diaphragm of rat in response to maximal tetanic stimulation, were observed. Propranolol caused the depression of the maximal force of contraction, whereas isoprenaline had no such effect. It was also observed that inhibition by propranolol could not be overcome by increasing the intensity or duration of electrical stimulation. Pretreatment with isoprenaline and d-tubocurarine did not alter the response to propranolol on the rat diaphragm was not mediated through beta receptors, or by the inhibition of the neuromuscular transmission. In the same study atenolol was observed to produce minimal depressant effect on the force of contraction of rat diaphragm. It was concluded that propranolol decreased the force of contraction of isolated diaphragm of rat by a mechanism related to stabilization of excitable membranes.[5]

As beta adrenergic blocking agents are widely prevailed drugs specially in cardiovascular diseases, in certain individuals these lead to troublesome and even fatal respiratory distress.

The present study was designed to see the mechanism of their action on the rat's isolated diaphragm because this effect may contribute significantly to the respiratory distress induced by the administration of beta adrenergic blocking agents.

MATERIAL AND METHODS

Male and female albino rats weighing from 150 - 200 gm were used in this study. Diaphragm was dissected out after the animals were killed by a blow on its head. A strip of 4X20 m.m size was prepared by the method of Drazon et al. (3983)[5]. The base of the strip consisted of the diaphragm attached to a part of rib margin and apex included a portion of the central tendon. Strings were tied to

all three angles of the strip and it was then tied to the rod bearing the electrodes of the electric square wave stimulator in such a way that basal portion of the strip was in complete contact with the electrodes. Tissue was then transferred to the tissue bath containing oxygenated Kreb's solution kept at 32°C. The apex of the strip was then tied to the force displacement transducer with the help of its thread. The tissue was kept at a tension of 250 mg and it was allowed to equilibrate for 30 minutes. During this operation the nutrient fluid was changed 2 — 3 times. The Kreb's solution contained 10 ug/lit. of d-tubocurarine to block the neuromuscular transmission. After the period of equilibration, records were taken on the polygraph for a period of about one minute. The bath fluid was changed once more and a set of control record was taken. After changing the bath fluid, the tissue was incubated with 10^{8}M propranolol for 10 minutes, and a record was taken. The bath fluid was changed twice and then the procedure was repeated with 10^{6}M, propranolol. The same procedure was repeated with 10^{-6}M, 10^{5}M, 10^{4}M and 10^{-3}M of propranolol.

RESULTS

Propranolol caused depression of the contractile response of isolated diaphragm to electrical stimulation. The mean values of the magnitude of contraction produced by the isolated diaphragm before treatment with propranolol were 21 .2 ± 1.83, 24.3 ± 2.59, 16.5 ± 2.15, 23.5 ± 1.83, 24.5 ± 2.20 and 20.5 ± 2.09 m.m. The percent response calculated from the mean values was 71.14, 81.54, 56.71, 78.85, 82.21 and 68.79 percent, respectively.

The mean values of the amplitude of contraction in isolated diaphragm of rat pretreated with l08M of propranolol was 25.8 ± 2.42 m.m. The mean value of the magnitude of contraction in tissue pretreated with 10^{7}M, 10^{-6}M, 10^{5}M, 10-4 M and 103M concentration of propranolol were 22.3 ± 2.42, 24.9 ± 1.88, 27.0 ± 3.43, 15.6 ± 2.36 and 6.2 ± 1.21 m.m. respectively. The percent response calculated from the mean values was 86.57, 74.83, 83.55, 90.60, 52.34 and 20.80 percent, for 10^{-8}M, 10^{-7}M, 10^{6}M, 10^{-5}M, 10^{4}M and 10^{-3}M concentration of propranolol respectively. The P — value for the results of 10^{8}M to 10^{5} M concentrations of propranolol was more than 0.05, while the P-value calculated for 10^{-4}M and 10^{3}M concentrations was less than 0.05.

Thus the results of the experiments were not significant for concentrations of propranolol varying from 10^{8}M to 10^{-5}M, while with 10^{-4} M and 10^{3}M of propranolol, the results were significant (Figure).

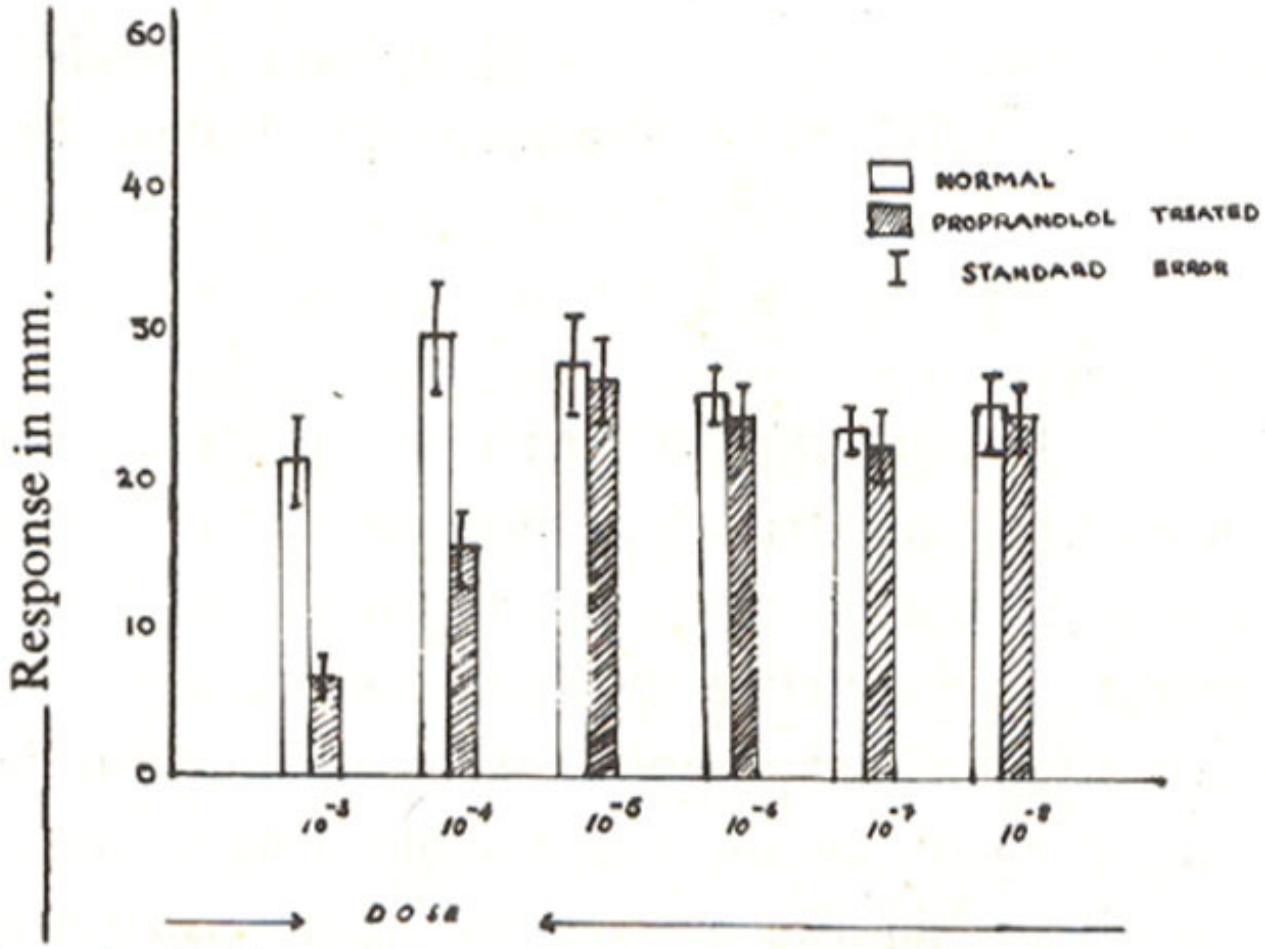

Figure 1. Effect of Electrical Stimulation on Normal and Propranolol treated isolated rat diaphragmatic tissues.

DISCUSSION

The results of the present study show the propranolol produced depression of the isometric force of contraction of the rat isolated diaphragm, which was induced by the electrical stimulation. From the results it is clear that the depressant effect is significant when the tissue is treated with 10^{-3} M and 10^{-4} M concentrations of propranolol. With lower concentrations of propranolol, no significant depression in the isometric force of contraction of diaphragm was observed in response to electrical stimulation. It has been shown that propranolol produces its beta receptor blocking effect even in concentration of 10^{8}M. This shows that the depressant effect of propranolol on the rat diaphragm is not related to its beta adrenergic receptor blocking activity, but it is because of some other mechanism.

Drazen et al. (1983) also showed that pro. pranalol produced depression of the rat isolated diaphragm in response to electrical stimulation, which was not altered by isoprenaline or d- ubocurarine. They concluded that the depressant effect of propranolol on the rat diaphragm was not due to its beta adrenergic receptor blocking activity, but was due to the membrane stabilizing effect of the drug[5]. As diaphragmatic depression produced by propranolol accrues at doses much higher than normally

employed for their beta receptor blocking activity, the respiratory distress produced due to their administration is not significantly contributed by their depressant effect on diaphragmatic contraction. When propranolol is used in high concentrations, its depressant effect on the movement of diaphragm may significantly contribute in the respiratory distress produced by the drug.

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