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H_2 RECEPTOR ACTIVITY;
EFFECT IN ISOLATED RABBIT HEART

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ABSTRACT… Histamine can stimulate the heart by directly interacting with cardiac histamine receptors. In the present study we have investigated the H_2 receptor activity in isolated rabbit heart. Cimetidine, a specific H_2 receptor antagonist was used. The isolated heart was mounted in langendroff apparatus. The heart was perfused at a constant pressure with oxygenated Ringer's Locke solution. H_2 receptor antagonist produces negative inotropic effect in the presence of histamine. This indicates that H_2 receptors are present in rabbit heart, and plays a role in mediation of positive inotropic effect produced through CAMP by histamine.

Key words: Histamine.H_2 antagonist. Cimetidine.

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INTRODUCTION

The presence of histamine in large quantities in cardiac tissue is well documented[1]. The cardiovascular actions of histamine have been attributed to the activation of two different types of histamine receptor classified as histamine type H_1 receptors and type H_2 receptors[2,3].

It has been observed that histamine and its analogue posses a direct stimulatory effect on heart. Such compounds also increase the activity of cardiac adenylate cyclase and cardiac phosphorylase as well as increasing the adenosine 3'5' monophosphate[4,5,6,7]. Contraction or force development by smooth muscle cells depends by the elevation of Intracellular calcium in the myoplasm. This is caused by either release of I/C calcium from the storage sites like mitochondria, or entry of calcium via receptor operated channels[8].

METHOD

In this study we used rabbits having weight of 0.75 to 1.5kg of either sex. In our vitro project Ringer Locke physiological nutrient solution was used for retrograde perfusion to the isolated rabbit heart[9]. The composition of Ringer Locke solution was NaCl, 45g; $NaHCO_3$ 1g; $C_6H_{12}0_6$,5G; KCl 2.1G; $CaCl_2$, 1.6g; and H_2O, 5000ml.

Preparation and isolation of heart was based on Langendorff methods, described by kitchen[10], 1984, and Burn[11], 1952.

For the preparation of isolated heart we first injected 0.5cc or 2500 IU of heparin intravenously and waited for 3-5 minutes. The rabbit was then sacrificed by cutting the neck with a sharp surgical knife. The chest of animal was opened and heart with at least 1cm of aorta was removed as quickly as possible and placed in petri dish, which already contained the oxygenated Ringer Locke solution at room temperature. Heart was squeezed several times gently, to remove blood. Surrounding tissues of the heart were removed. Aorta was tied with steel cannula fixed with Langendorff apparatus[5].

Heart was coated with liquid paraffin to prevent drying[12]. Thread was attached to the tip of ventricle by heart clip and other end of thread was tied with transducer after passing the thread through two pullies. Transducer was connected with 7B Grass polygraph machine, which recorded the isolated heart activity on polygraph paper. Heart was perfused with oxygenated Ringer Locke solution and allowed to equilibrate 30-45 minutes[10].Drugs were administered through the butterfly needle, which was connected with rubber tube near the

aorta. The volume of all injections were kept constant at 0.2ml; intervals of 10-29 minutes were allowed between successive injections.

RESULTS

As per protocol the tissue was prepared and EC50 was evaluated. Five observations were taken of each dilution ranging from 104 to 108. The difference of amplitude on contractility of the isolated rabbit heart was evaluated from normal in comparison with the effect produced by individual drug.

The results were tabulated in descending order and median value was taken as EC_{50}.

The EC_{50} of individual dilution was used for further observations.

The observations of five responses of EC_{50} of histamine on amplitude of contraction were recorded. The mean value observe 1.54mm from normal as depicted in table- I. The observation of five responses of histamine EC_{50} with H_2 blocker (Cimetidine) were recorded as shown in table-II. the mean value of five observations of histamine compared with the mean value of five observation of histamine in the presence of H_2 blocker were compared as shown in table II. The difference showed a decrease from 1.54 to -4.11mm. This means that H_2 blocker produces a negative inotropic effect in the presence of histamine.

Amplitude in mm				
S/No	BD	AD	Diff	%Percent Diff
1	21.16	23.05	1.89	0.1
2	31.29	32.72	1.43	4.3
3	33.17	34.85	1.98	5.6
4	40.71	42.00	1.29	3.0
5	56.56	57.69	1.13	1.9
Mean	36.58	38.06	1.54	4.58

Table-I. The mean value of five observations of histamine

DISSCUSION

Our finding demonstrates that in isolated rabbit heart histamine induced changes in contractile force. It produces an inotropic effect at low dose

Amplitude in mm				
S/No	BD	AD	Diff	%Percent Diff
1	27.74	18.79	-8.95	-32.26
2	17.73	8.39	-9.34	-52.67
3	11.90	8.77	-3.13	-26.30
4	13	13.13	0.13	0.99
5	14.07	14.77	0.7	4.73
Mean	16.88	12.77	-4.11	-21.10

Table-II. The mean value of five observations of histamine in presence of H_1 blocker

and the effect was blocked by an H_2, receptor blocking agent. This observation suggests that the inotropic effect of histamine was due to H_2 receptor stimulation and that H_2 receptor were associated with cardiac adenylate cyclase activity. The enzyme is activated by histamine and cAMP increase in the whole heart prior to the increase in force of contraction when histamine is injected. All effects are blocked by H_2 blocker. Intracellular Ca^+ is closely regulated by sodium-calcium exchanger (NCX) and Ca^+ efflux is dependent on the I/C sodium (Na^+) concentration and trans- sarcolemmal Na^+ gradient[13]. Data from other observers also agree with our findings[14,15]. Histamine H_2 receptors are pivotal in mediating the increase in contractility elicited by histamine in the mammalian heart[5]. First phase of histamines positive inotropic effect is due to an increase in cytosolic calcium resulting from enhanced calcium released from the sarcoplasmic reticulum promoted by inositol phosphate. Hence the two histamine receptors types coupled to distinct signal transduction pathways which co-exist in heart muscle produces positive inotropic effect[16,17,18].

CONCLUSIONS

Our finding demonstrate that histamine produces positive inotropic effects. Whereas histamine in presence of H_2 blocker (Cimetidine) produces a negative inotropic effect. This suggests that H2 receptors are present in rabbit heart.

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