The Professional Medical Journal
www.theprofesional.com

ORIGINAL PROF-2463

ADRENALINE;
THE EFFECTS IN PRESENCE OF BETA BLOCKER IN ISOLATED MAMMALIAN HEART

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Article received on:
14/03/2014
Accepted for publication:
15/10/2014
Received after proof reading:
15/12/2014

ABSTRACT… There is no doubt that the effects of the catecholamines of the heart are mainly due to the stimulation of β-adrenoceptors but in the mid 1960' s the first evidence was presented that a-adrenoceptors mediating positive inotrpoism exists also in the myocardium beside well established β -adrenoceptors. In our observation adrenaline shows a positive inotropic response. The response of adrenaline in presence of metoprolol (β1blocker) showed negative inotropic effect.

Key word: Adrenaline, B1 blocker, Metoprolol.

Article Citation: Baloch NK, Jafri N, Danyal A. Adrenaline; the effects in presence of beta blocker in isolated mammalian heart. Professional Med J 2014; 21(6):1157-1160.

INTRODUCTION

More than 40 year ago, Ahlquist 1948 noted that the functional responses of a variety of tissues to catecholamines could be separated into "alpha" and "beta" type based on the observed relative activities of several catecholamine derivatives in mammalian smooth muscle and myocardium. The evidence was based on 2 distinct rank orders of agonist potency for a variety of pharmacological responses, plus the ability to inhibit the vasoconstrictor or uterine contraction responses of the α group, with 3 different compounds. (dibenamine, ergotoxine, or tolazoline) that would later be termed α – blocking agents[1]. Subsequently, α- adrenoceptors have been divided into α-1 and α-2 subtypes based initially on anatomical location and later, more accurately, by rank order of potency of pharmacological agents, which inhibit or elicit response[2].

The β- adrenoceptors mediated responses could be classified as either β-1 or β-2, suggesting the existence of at least one additional β adrenoceptors subtype[3].The existence of two subtypes of the β-adrenoceptors is generally accepted[4]. Evidence has accumulated throughout the year for the existence of a β adrenoceptors that is insensitive to the commonly used antagonists.

The human β-3 adrenoceptors has recently been recombinant.β-1 adrenoceptors mediate increase in cardiac rate, force of contraction, stimulation of renin secretion, and relaxation of coronary arteries. β -2 adrenoceptors mediate smooth muscular relaxation. β -3 adrenoceptors mediate stimulation of adenylel cyclase in cells expressing the recombinant receptor[5].

This work was conducted in The Department of Pharmacology and Therapeutics' Basic Medical Sciences Institute, Jinnah Postgraduate Medical Centre, Karachi.

METHOD

In this study we used rabbits having weight of 0.75kg of either sex. In our vitro project, Ringer Locke physiological nutrient solution was used for retrograde perfusion to the isolated rabbit heart[6]. The composition of Ringer's Locke solution was:Nacl,45g; $NaHCO_3$ 1.0g; $C_6H_{12}O_6$ 5.0g; Kcl 2.1g; Cac12 1.6g and H_20 5000ml. Preparation and isolation of heart was based on Langendorff methods, described by Kitchen[7],1984 and Burn[8],1952.

For the preparation of isolated heart we first injected 0.5cc or 2500 IU of heparin intramuscularly and waited for 3-5 minutes. The rabbit was

then scarified 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[9].

Heart was coated with liquid paraffin to prevent drying. 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 Kitchen[7]1984. Drugs were administrated through the butterfly needle, which was connected with rubber tube near the aorta. The volumes of all injections were kept constant at 0.2 ml intervals of 10-20 minutes were allowed between successive injections.

RESULTS

As pre protocol the tissue was prepared and EC_{50} was evaluated. Five observations were taken of each dilution ranging form10^{-4} to 10^{-8}. The difference of amplitude on contractility of the isolated rabbit heart was evaluated from normal reading in comparison with the effect produced by individual drugs. The differences were evaluated on percentage basis. 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 observation.

The five responses of EC_{50} of adrenaline on amplitude of contraction were recorded. The mean value of adrenaline 0.61 mm observed from normal has been depicted in table I. The five responses of adrenaline with metoprolol were recorded and difference in amplitude of contraction was evaluated as shown in table II. Then mean value of adrenaline with metoprolol on amplitude of contraction compared with mean value of adrenaline. The difference shows a decrease from 0.61 to -1.15 mm. This means metoprolol decreases the amplitude of contraction in the presence of adrenaline.

Amplitude in mm	BD	AD	DIFF	%DIFF
1	34.96	35.15	0.19	0.5
2	31	31.6	0.66	2.0
3	26.15	26.93	0.77	2.8
4	24.64	25.48	0.84	3.2
5	23.42	24.00	0.58	2.4
Mean	28.03	28.64	0.61	2.18

Table-I. Mean of five observations of adrenaline EC_{50} on amplitude of contraction

No. of Observation	Amplitude in mm	BD	AD	DIFF	%DIFF
1	1	29.43	27.6	-1.93	-6.56
2	2	28.56	25.6	-2.94	-10.29
3	3	31.33	28	-3.33	-10.53
4	4	25.34	22.5	-2.84	-11.21
5	5	26.8	25.08	-1.42	-5.30
Mean	Mean	27.56	26.47	-1.15	-4.03

Table-II. Mean of five responses of adernaline EC_{50} in presence of EC_{50} of metoprolol on amplitude of contraction

DISCUSSION

There are nine subtypes of adrenoceptors (ARs) with distinct tissue expression and pharmacological properties: αIA, αIB, αID, α2A, α2B, α2C, β1, β2, β3[10].

The mechanical effects associated with α1-adrenoceptors stimulation are qualitatively different from these of β adrenoceptors. At physiological and elevated concentrations, norepinephrine, released from the sympathetic nerves, acts predominantly via the β1- adrenoceptors (β1-ARs) on ventricular cardiomyocytes, exerting positive inotropic and lusitropic responses. These effects are the result of β1- AR coupling to the GS protein family, which increases intracellular cyclic AMP levels through adenyl cyclase[11].

Epinephrine has a higher affinity for myocardial α1 adrenoceptors than for β adrenoceptors. Myocardial α- adrenoceptors mediated effects on cardiac force of contraction have been reviewed in isolated rabbit heart. Epinephrine and lower then need for β adrenoceptors stimulation. Unlike β adrenoceptors stimulation, myocardial α adrenoceptors does not increase adenyl cyclase activity or cyclic AMP levels.α1 adrenoceptors stimulation might exert its effects by GTP binding G protein - mediated activation of phospholipase which catalysis the hydrolysis of phosphatidyl inositol 4,5 biphosphate to inositol and 1,2 diacyclglycyerol; IP3 is released into the cytoplasm to mobilize calcium for stores, while diacyclglycyerol remains in the plasma membrane to activate protean kinase C. Epinephrine release atrial natriuretic peptide from isolated rat atria by α adrenoceptors stimulation but the physiological significance of this effect is questionable[12]. It has been proposed that α1 adrenoceptors might serve as a reserve mechanism to maintain myocardial responsiveness to catecholamines under conditions in which the β adrenoceptors are blocked, functionally antagonized, reduced in number, or uncoupled form its transudation pathway[13]. Chronic treatment with β adrenergic antagonist augments the number of myocardial α- adrenoceptors[14].

We have observed that adrenaline by producing its actions on adrenergic receptors produces positive inotropic effect on mammalian (rabbit) heart. Whereas adrenaline in presence of metoprolol (β1 blocker) produces negative inotropic effects due to alpha – receptor. This indicates that α and β adrenergic receptors are present in mammalian heart.

CONCLUSIONS

From our study it is confirmed that different receptors are working in myocardium. The response of adrenaline may change in the presence of beta antagonist which basically depends upon the concentration of antagonist.

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Never trust someone who lies to you.

Unknown