E-ISSN:2454-9894 P-ISSN: 2454-9886
International Archives of
BioMedical and Clinical Research
(An Official Publication of "Ibn Sina Academy of Medieval Medicine & Sciences")
WWW.IABCR.ORG

Original Article

Role of Beta Blockers on Adrenaline Induced Leukocytosis in Rabbits

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ABSTRACT

Background: *Plasma Leukocytosis is known to occur in a variety of clinical conditions viz. infections, inflammations and collagen disorders. Apart from these many physiological factors like heat, solar radiation and high altitude also causes leukocytosis. It has been reported that even corticosteroids can cause leucocytosis which is usually polY morphonuclear leucocytosis. Adrenaline administered by various routes like I/M, I/V and S/C is also known to cause a rise in blood leukocytes. It has been reported that even corticosteroids can cause leukocytosis, which is usually polymorphonuclear leukocytosis. Since catecholamines have been implicated in the release of polymorphs from bone marrow into blood in the glucocorticoids induced leukocytosis, this could be a likely mechanism. If so then adrenergic receptors may be mediating this release. Attempt will be made to characterize these adrenergic receptors by studying the effect of some beta blockers on adrenaline induced Leukocytosis.* ***Materials and Methods:*** *The study was conducted in conscious albino rabbit. The rabbits were divided into 3 groups with 6 rabbits in each group beta blockers used in the study were propranolol (0.5mg/kg) and atenolol (0.5mg/kg). Cell counts before drug administration served as control values. Adrenaline was used in the dose of 200microgram/kg.* ***Result:*** *Group1- significant rise in total leukocytes count in the form of 2 peaks, first occurring at 1hr with 21.85% rise and 2nd at 4hr with 41.89 % rise, at 2hr rise was not significant. At 24hr the counts came back to normal values Group2- significant fall in TLC at 1hr +1.2% and at 4hr +5% while at 2hr +2.4%. The fall in TLC at 24hr was insignificant.Group3- significant fall in TLC at 1hr +1.5% and at 4hr +10.2% while at 2hr +7.94%. The fall in TLC at 24hr was insignificant.* ***Conclusion:*** *The beta-blockers Propranolol and Atenolol successfully blocked the rise in blood leukocyte counts induced by Adrenaline which shows that Adrenaline induced leukocytosis occurs through the activation of beta-adrenoreceptors.*

Key words: *Beta Blockers, Adrenaline, Leukocytosis.*

INTRODUCTION

Plasma leukocytosis is known to occur in a variety of clinical conditions viz. infections, inflammations and collagen disorders. Apart from these many physiological factors like heat, solar radiation and high altitude also causes leukocytosis. Strenuous exercise, pain, nausea and vomiting also cause a marked increase in blood leukocytes. It is the redistribution of leukocytes between the marginating and circulating pools that leads to leukocytosis in these conditions. It has been reported that even corticosteroids can cause leucocytosis which is usually polY morphonuclear leucocytosis. These changes can be attributed to decreased efflux of neutrophils from the blood and increased polymorph release from bone marrow into peripheral circulation. Catecholamines have been implicated in this action of glucocorticoids. Adrenaline administered by various routes like I/M, I/V and S/C is also known to cause a rise in blood leukocytes. This rise may reflect a shift leukocytosis or may be due to increased released of leukocytes from bone marrow into the peripheral circulation. It has been reported that even corticosteroids can cause leukocytosis, which is usually polymorphonuclear leukocytosis. Since catecholamines have been implicated in the release of polymorphs from bone marrow into blood in the glucocorticoids induced leukocytosis, this could be a likely mechanism. If so then adrenergic receptors may be mediating this release. Attempt will be made to characterize these adrenergic receptors by studying the effect of some beta blockers on adrenaline induced leukocytosis.

Access this article online	
Website: www.iabcr.org	Quick Response code
DOI: 10.21276/iabcr.2016.2.3.27	

Received:18.08.16| **Revised**:22.08.16| **Accepted**:30.08.16

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MATERIALS AND METHODS

The study was conducted in conscious albino rabbits of either sex weighing between 1-1.5kg after taking approval from the Institutional Animal Ethical Committee (IAEC) according to the guidelines for the purpose of control and supervision of experiments on animals (CPCSEA). They were fed with commercial pellet diet and water ad libitum. The rabbits were divided into 3 groups with 6 rabbits in each group. Blood samples were collected from ear vein of each rabbit. The TLC of rabbits included in this study ranged from 4000-7000 cumm.

Beta blockers used in the study were propranolol (0.5mg/kg) and atenolol (0.5mg/kg). Cell counts before drug administration served as control values. Adrenaline was used in the dose of 200microgram/kg. These drugs were obtained from Candilla Pvt. Ltd. and Cipla Pvt. Ltd.

Adrenaline was injected subcutaneously while beta-blockers were injected intraperitoneally. Adrenaline was injected half hour after beta-blockers.

Total Leucocyte Count was done by conventional method using neubar's chamber.

Group-1- was treated with Adrenaline at dose of 200microgram (mcg)/kg.

Group-2- was treated with both Adrenaline 200mcg/kg & Propranolol 0.5mg/kg.

Group-3- was treated with both Adrenaline 200mcg/kg and Atenolol 0.5mg/kg.

Effects of the drugs were monitored by doing Total Leukocyte Count at 1hr, 2hr, 4hr & 24hr interval after drug administration.

RESULTS

Table 1: The Effect of Adrenaline on Blood Leucocytes:

GROUPS	Percent change in Total Leucocyte Count			
	0 hr	1 hr	2 hr	4 hr
1	100	124.85 ±6.2	118.31 ±5.6	141.89 ±8.7
2	100	101.2 ±4.7	102.4 ±5.9	105.01 ±7.3
3	100	101.5 ±5.21	107.9 ±8.01	110.2 ±6.4

Adrenaline injected subcutaneously

Group 1- significant rise in total leukocytes count in the form of 2 peaks, first occurring at 1hr with 21.85% rise and 2nd at 4hr with 41.89% rise. at 2hr rise was not significant. At 24hr the counts came back to normal values.

Group 2- significant fall in TLC at 1hr +1.2% and at 4hr +5% while at 2hr +2.4%. the fall in TLC at 24hr was insignificant.

Group 3- significant fall in TLC at 1hr +1.5% and at 4hr +10.2% while at 2hr +7.94%. The fall in TLC at 24hr was insignificant.

The results were statistically analysed using unpaired Student's t test and presented as mean ± SEM. P values were calculated referring to appropriate tables.

DISCUSSION

In Plasma leucocytosis which form a strong defence mechanism against stressful situation tend to rise in blood whenever the body is exposed to any stressful stimulus. This stressful stimulus which may be physical, chemical or biological tends to trigger this release through activation of sympatho-adrenal discharge whenever massive amount of endogenous catecholamines such as adrenaline and noradrenaline are liberated. It is basically the action of catecholamines which results in marked blood leucocytosis. Daughaday WH et al 1948, Dougherty TF, Frank JA 1955 and Benschop RJ et al1966 have shown that adrenaline induced subcutaneously produces blood leucocytosis. Srivastava et al 1985 have found the rise in blood leucocytes through older sympathomimetic agents such as salbutamol and isoprenaline as well and have suggested the involvement of beta-adrenoreceptors for the involvememnt of leucocytes from bone marrow into circulation. In our study also we have found marked rise in blood leucocytes by subcutaneous injection of 200micro/g/kg of adrenaline in the rabbits. This leucocytosis was observed in 2 phases. The early one occuring at 1 hr and the later one at 4 hr. similar type of biphasic response was seen by Dougherty TF, Frank JA 1955 and Benschop J et al 1996 also, who found the first peak in about ½-1hr and the delayed response at 4hr. The variation in the early response in our study could be due to variation in the dose of adrenaline employed. In delineating the mechanism of this adrenaline induced leucocytosis we have employed beta adrenergic receptor blockers and observed their per se effect on blood leucocytes as well as their effect on leucocytosis induced by adrenaline. In our study we used both selective beta-blocker (atenolol) and non-selective beta-blocker (propranolol) and it is significant to note that both the beta-blockers produced a fall in blood leucocyte counts and prevented the rise in leucocyte count induced by adrenaline. This suppressive response was more marked at 2hr when the rise in blood leucocyte by adrenaline was less but was also seen significantly at 1hr and 4hr when the rise was more marked. Sympathetic nervous system characterstics play a prominent underlying role in acute cellular immune system activation. (Mills PJ et al., 1995). Both alpha and beta receptors are involved in mobilisation of lymphocytes whlie neither has any specific role in mobilisation of neutrophils. (Gader and Cash 1975). In catecholamine induced leucocytosis, the changes in lymphocyte circulation seem to be mainly mediated via activation of beta-2 adrenoreceptors, whereas granulocyte increases involve alpha-adrenoreceptors stimulation. (Landman et al 1981). Beta receptor subtypes have been demonstrated on immature rabbit bone marrow erythroblasts. (Setchenska MS, et. Al.., 1986). In vitro studies have shown that marrow erythroid colony growth is enhanced by beta adrenergic agonists. (Brown JE, Adamson JW, 1777). Adrenergic regulation of interleukin -1(IL-1) and IL-3 production by bone marrow cells under immobilization stress has been studied in mice. It was

found that beta-adreno blocker (propranolol) inhibited IL-3 production (main cytokine for granulopoesis). Thus, adrenergic structures take an active part in regulation of IL-1 and IL-3 production by haemopoiesis inducing microenvironment bone marrow cells. Also beta-adrenoreceptors blockers inhibited the post cytostatic reparation of erythro and granulopoesis. (Khlusov et. Al., 1993). Haden et al 1970 have demonstrated beta adrenergic receptors on lymphoid accessory cells. The nature of beta adrenoreceptors appears to be beta-2 metoprolol does not block the increase in exercise induced circulating T cells which is blocked by non-selective beta blocker, propranolol. (Murray et al 1992).

CONCLUSION

The beta-blockers Propranolol and Atenolol successfully blocked the rise in blood leukocyte counts induced by Adrenaline which shows that Adrenaline induced leukocytosis occurs through the activation of beta-adrenoceptors.

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How to cite this article: Rehman S, Lata S, Naim F, Chauhan D S. Role of Beta Blockers on Adrenaline Induced Leukocytosis in Rabbits. Int Arch BioMed Clin Res. 2016;2(3):107-109. DOI: 10.21276/iabcr.2016.2.3.27

Source of Support: Nil, **Conflict of Interest:** None