THE POSSIBLE EFFECTS OF B-ADRENERGIC BLOCKERS ON THE IMMUNOLOGICAL REACTIONS

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INTRODUCTION

B-adrenergic blocking agents have received major attention because of their utility in the management of cardiovascular disorders (Prichard et al., 1980). Furthermore, it was reported that some patients suffering from rheumatoid arthritis or other connective tissue disorders had improved following propranolol therapy for co-existent hypertension or angina pectoris (Moore et al., 1978).

Fleir (1971) reported that, the human peripheral lymphocytes have adrenergic sensitivity corresponding to alpha and beta receptors; alpha-adrenergic stimulation associated with augmentation, and beta with inhibition of lymphocyte transformation. Also lymphoid tissue is known to possess a high content of norepinephrine presumably related to its sympathetic

(Hadden, 1971). Furthermore, B-adrenoceptor blockers, may have immunomodulatory properties. Such a possibility was suggested by animal studies showing that propranolol can inhibit mitogenic activation of lymphocytes (Anderson et al., 1981), and can enhance antibody production in mice (Nakazawa et al., 1976).

The present study was conducted to assess the effects of beta-adrenergic blockers, propranolol and pindolol on the immune response in immunized mice with sheep red blood cells (SRBCs), also they were compared with hydrocortisone as a standard immuno-suppressive agent and all were compared with immunized control mice. The test drugs have different pharmacological properties to declare if these different properties

have a role in the possible immunological effects or not.

Material and Methods

Animals Used and Drug Treatment :

Mice used throughout the study were divided into five groups, the first group served as unimmunized control group, consists of 7 mice and each animal received sterile saline intraperitoneally (I.P) daily for 3 consecutive days in doses of 0.3, 0.4 and 0.6 ml respectively. The second group of 7 mice served as immunized control one and each animal received only the antigen (SRBCs 5% in RPMI medium) I.P. for 3 consecutive days in dose of 0.3, 0.4 and 0.6 ml. respectively. The other three groups for the 3 test drugs, the 3rd group for receiving hydrocortisone hemisuccinate in the dose of 40 mg/kg body weight I.P. for 5 consecutive days, the 4th group for receiving propranolol in the dose of 2 mg/kg B.Wt. I.P. for 5 consecutive days and the 5th group for receiving pindolol in the dose of 2mg/kg B.Wt I.P. for 5 successive days. Each one of the last three groups was subdivided into 3 subgroups each contained 7 mice. The 1st subgroup for giving the test

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drug before antigen immunization, the 2nd subgroup for giving the test drug with antigen simultaneously and the 3rd subgroup for giving the test drug after antigen immunization.

Sample Collection and Preparation :

After decapitation of animals the blood was collected and put in incubator at 37°C for one hour then centrifuged to separate the serum for determination of total serum immunoglobulins and immunoglobulin G(IgG). The serum kept frozen until assay.

The spleens were aseptically removed from mice then each spleen was placed in 5 ml. sterile RPMI 1640 medium containing foetal calf serum 10% and penicillin streptomycin 2%. These spleens were prepared for plaque forming cells assay.

Methods Used :

The methods which were chosen to assess the immunological effects of test drugs were.

(i) Quantitative estimation of immunoglobulins :

The method was the single radial immunodiffusion technique described by Fahey and McKelvey (1965) and

Mancini et al., (1965), for quantitative estimation of total globulin and IgG.

(2) Plaque forming cells (PFcs) Technique :

This Technique for detecting the antibody forming cells numbers in spleen representing the cellular immune response. This Technique was devised by Jerne et al., (1963) and Fauci and Pratt (1976).

RESULTS

I- Effect of The Test Drugs on The Serum γ globulin and Immunoglobulin G (IgG) in Sensitized Mice :

As illustrated in tables (1, 2 and 3) and figures (1 and 2) there was a highly significant increase in serum γ globulin and IgG levels in sensitized control group as compared with unsensitized control group.

(A) Effect of hydrocortisone :

As shown in table (I) and Figures (1 and 2) the administration of hydrocortisone hemisuccinate before, with or after antigen immunization produced a very highly significant reduction of the mean γ globulin and IgG levels ($P < 0.001$) as compared with sensitized control group.

(B) Effect of propranolol :

As illustrated in table (2) and Figs. (1 and 2), the administration of propranolol produced a highly significant reduction ($P < 0.01$) of γ globulin and significant reduction ($P < 0.05$) of IgG level when it was given before immunization and produced a highly significant reduction of both γ globulin level ($P < 0.01$) and IgG level ($P < 0.005$) when it was given with antigen simultaneously. But when it was given after immunization it produced significant reduction of both γ globulin and IgG level ($P < 0.05$) as compared with the immunized control group.

(C) Effect of pindolol :

As illustrated in table (3) and Figs (1 and 2), the administration of pindolol produced a very high reduction of γ globulin level ($P < 0.001$) and significant reduction of IgG level ($P < 0.05$) when it was given before and with antigen immunization. But, when it was given after immunization, produced highly significant reduction of γ globulin level ($P < 0.005$) and significant reduction of IgG ($P < 0.05$) as compared with sensitized control group.

II- Effect of The Test Drugs on Plaque Forming Cells (PFcs) in Spleen of Sensitized Mice .

DISCUSSION

1- Effect of Test Drugs on The Serum & Globulin and IgG Levels in Sensitized Mice With SRBCs :

There was highly significant increase in serum & globulin and IgG levels in the sensitized control group immunized with SRBCs (Sell et al, 1970). The response to antigenic stimulation is in itself a dynamic process, possibly involving a change in adrenergic receptor number and/or quality. It was reported that after initial immunization a decrease in T-cell beta-adrenoceptor binding sites occurred followed by an increase in B-adrenoceptor binding sites late in the immune response (Strom and Carpenter, 1980). Furthermore, Sanders and Munson (1984) reported that foreign antigen could evoke neurotransmitter release and subsequent action on immunocompetent cells.

(A) Effect of Hydrocortisone :

In the present study, hydrocortisone produced very highly significant reduction of both α globulin and IgG levels in mice immunized with SRBCs when it was given either before, with or after antigen immunization. In general, in vivo administered corticosteroids tend to suppress B-lymphocyte function as measured by immunoglobulin serum levels (Butler and Rossen,

(A) Effect of hydrocortisone :

As shown in table (4) and Fig.(3), the administration of hydrocortisone before, with or after antigen immunization produced a very highly significant reduction of the mean PFCs % ($P < 0.001$) as compared with the mean PFCs % in the sensitized control group.

(B) Effect of propranolol :

As shown in table (5) and Fig.(3), the administration of propranolol before antigen sensitization produced non significant reduction of the PFCs%, but the administration of drug with or after antigen immunization produced a very highly significant reduction of PFCs% count as compared with the sensitized control group ($P < 0.001$).

(C) Effect of pindolol :

As shown in table (6) and Fig.(3), the administration of pindolol before antigen immunization produced non-significant reduction of PFCs % count, but produced a very highly significant reduction PFCs % count as compared with the sensitized control group ($P < 0.001$).

1973).

In the present study, hydrocortisone produced the best reduction in γ globulin and IgG levels when it was given with antigen simultaneously. This effect is supported by Taniguchi and Tada (1971) who reported that cortisone treatment before immunization showed temporary accelerated antibody formation, whereas treatment during antigen immunization was moderately suppressive. Also Malinodan et al., (1970) reported that cortisone elicit its maximum suppressive activity when administered just prior to antigen.

(B) Effect of Propranolol :

In the present study the best result was obtained when the drug was given with antigen concurrently. Furthermore, it is clear from the previous data that this immunosuppressive effect is less than those of propranolol.

The immunosuppressive effects of propranolol could be attributed to effect of propranolol on the B-adrenergic receptors on murine lymphocytes which is stimulated with antigen to produce antibodies representing all five major immunoglobulin classes (Strom and Corptenter, 1960 and Sell et al., 1970). Furthermore, the increase

of norepinephrine levels in spleen of mice after SRBCs immunization in vivo shares in the antibody response (Besedovesky et al., 1979 and Sanders & Munson, 1984). So propranolol by blocking B-adrenoceptors can prevent the subsequent events. This explanation is supported by Bennes et al., (1968) who reported that propranolol reduced antibody formation more than tenfold when it is given 5 days before antigen injection in rats and it produced marked depression of cAMP level in spleen of sensitized mice.

In addition, the suppressive effect of propranolol may be due to its membrane-stabilizing effect where it appears to block action potentials in conducting tissue by a series of events, which in turn hyperpolarizes the membrane through the effect of free Ca^{+2} on K^{+} fluxes (Porzig, 1975 and Szasz et al., 1977). This changes in the ionic environment around critical sites could mediate the inhibition of lymphocyte capping by propranolol, where the capping of membrane molecules provides a useful model for detecting the transduction across the cell membranes of signals generated by antigen binding indicating active response of the cell (Ashman, 1973 and 1980).

The best results when the drug

regard the comparison with hydrocortisone, the effect of pindolol was so strong that it reduced $\times$ globulin level to a level below those of the unimmunized group but it did not reach to the level produced by hydrocortisone.

The immunosuppressive effect of pindolol may be due to its B-adrenoceptor blockage and this explanation is the same as with propranolol, but pindolol is devoid of membrane stabilizing action. The suppressive effect of pindolol on serum $\times$ globulin was more than those of propranolol and this may be due to its intrinsic sympathomimetic activity. So pindolol can modulate the antibody response by its agonist effect like norepinephrine and epinephrine, this explanation can be supported by Benner et al., (1968) who reported that epinephrine reduced antibody formation and by Pearlman (1971) who stated also that epinephrine inhibit antibody formation *in vitro*.

II- Effect of The Test Drugs on Plaque Forming Cells Count in Spleen of Sensitized Mice With SRBCs :

The count of PFCs% in spleen of sensitized control group was 34.33% after 5 days from the first dose of antigen (SRBCs). The evaluation of serum antibody response to erythrocyte at

was given with antigen simultaneously because the most immunosuppressive agents are effective if used either immediately before the antigen administration or during the induction phase of immune response (Makinodan et al., 1970), also after initial immunization a decrease in T-cell beta-adrenoceptor binding sites occurs followed by an increase in B-adrenoceptor binding site late in the immune response, (Strom and Carpenter, 1980).

(C) Effect of Pindolol :

In the present study, the administration of pindolol either before or concurrent with antigen produced a very highly significant reduction of $\times$ globulin level and significant reduction of IgG level, but produced a highly significant reduction of $\times$ globulin and significant reduction of IgG when it was given after antigen immunization. From the previous data, it is obvious that pindolol produced more suppressive effect on $\times$ globulin level than the effect of propranolol, but its effect on IgG level was more or less similar to propranolol effect. This declared that pindolol can effect more immunoglobulin classes, for example IgM, other than IgG level because its effect on total $\times$ globulin level was obviously more than its effect on IgG alone. As

the cellular level is possible with the hemolytic plaque technique. The technique as described initially by Jerne et al., (1963) enumerates only cells releasing high hemolytic efficiency IgM antibodies, IgM PFcs reach maximum numbers on days 4-5 from the first dose of antigen (Pierce et al., 1971) while IgG PFcs usually are detected later and reach maximum numbers later than do IgM-PFcs (Sell et al., 1970).

This antigenic stimulation of IgM-PFcs may be attributed to B-adrenoceptors stimulation in spleen cells and due to sympathetic neurotransmitter release and subsequent action on immunocompetent cells. This view can be supported by Besedovsky et al., (1979) who reported that after SRBCs immunization in vivo, the level of norepinephrine in the rat spleen is increased. Moreover, the B-adrenoceptors have been identified to be the receptor responsible for the enhanced IgM antibody response produced by norepinephrine in mouse spleen cells immunized by SRBCs in vitro (Sanders and Manson, 1984). Also cAMP enhances antibody formation in vivo and in vitro where it increases the number of antibody forming splenic cells in mice immunized

with SRBCs (Hadden et al., 1979 and Strom and Carpenter, 1980).

A) Effect of Hydrocortisone :

In the present study, hydrocortisone produced a very highly significant reduction of PFcs count % in mice immunized with SRBCs when it was given either before, with or after immunization.

Corticosteroids, following in vivo administration, produced redistribution of the circulating peripheral leucocytes with increased numbers of neutrophils and decreased numbers of monocytes, lymphocytes and eosinophils. Moreover, lymphocyte with Fc receptor for IgM are exquisitely sensitive to the redistribution effect in vivo corticosteroids. Furthermore both in vivo and in vitro corticosteroids can alter the complex regulatory balance of helper and suppressor influences as well as alter both accessory and effector cells function (Cupps et al., 1982).

In general, corticosteroid impaired cellular immunity through inhibiting the migration of T-cells to the site of antigen disposition and blocking the local interaction between lymphocytes and monocytes (Parillo and Fauci, 1979).

B) Effect of Propranolol :

In the present study, the adminis-

Strom & Carpenter, 1980), so propranolol through its B-adrenergic blockade effect on splenic cells and by marked depression of cAMP level in spleen of sensitized mice can exhibit its suppressive action on immune competent cells in spleen.

C) Effect of Pindolol :

In the present study, the administration of pindolol before immunization produced non-significant reduction of PFCs count % in sensitized mice. This effect can be explained as mentioned before with effect of propranolol.

The administration of pindolol either with antigen or after immunization produced a very highly significant reduction of PFCs count % in sensitized mice. Also those effects as previously mentioned may be attributed to its B-adrenergic blockade action and its intrinsic sympathomimetic effect. The effect of pindolol is more or less similar to the propranolol effect, also the suppressive effects of both pindolol and propranolol were less than the effect of hydrocortisone as standard immunosuppressive agent.

Propranolol administration with or after the beginning of immunization exhibited a very highly significant reduction of the mean PFCs count %. Since Besedovsky et al., (1979) have reported that after SRBCs immunization in vivo, the levels of norepinephrine in the rat spleen is increased and Sanders and Munson (1984) have reported that B-adrenoreceptors have been identified to be the receptors responsible for the enhanced IgM antibody response produced by norepinephrine in mouse spleen cells immunized by SRBCs in vitro, furthermore, cAMP increases the numbers of antibody forming splenic cells in sensitized mice (Hadden et al., 1979 and

predicted. immunosuppressive effect can not be late in the immune response, so its increase in B-adrenoreceptor binding sites occurs, followed by an increase in T-cell B-adrenoreceptor binding sites after initial immunization a decrease in T-cell B-adrenoreceptor binding sites occurs, followed by an increase in B-adrenoreceptor binding sites

Table (1) : Effect of hydrocortisone hemisuccinate on serum γ globulin and IgG levels (mg/100ml) in sensitized mice (7 animals in each group).

	CONTROL GROUPS		TEST GROUP		
	unsensitized group	Sensitized group	1 st subgroup	2 nd subgroup	3 rd subgroup
Mean of γ globulin.	1268.33 $\pm$ 176.229	1600 $\pm$ 223.696	845.00 $\pm$ 142.056	737.50 $\pm$ 129.10	773.33 $\pm$ 133.533
$\pm$ S. D.	-	$\bar{P} < 0.01$	$P < 0.001$	$P < 0.001$	$P < 0.001$
Mean of IgG	790.000 $\pm$ 126.39	1066 $\pm$ 154.96	670.71 $\pm$ 136.669	642.14 $\pm$ 118.77	700.00 $\pm$ 106.26
$\pm$ S. D.	-	$\bar{P} < 0.005$	$P < 0.001$	$P < 0.001$	$P < 0.001$

P : Significance of difference between the means of the test drug and the sensitized control group.

$\bar{P}$: Significance of difference between the means of the sensitized control group and unsensitized control group.

Table (2) : Effect of propranolol as serum γ globulin and IgG levels (mg/100ml) in sensitized mice (7 animals in each group).

	CONTROL GROUPS		TEST GROUP		
	unsensitized group	Sensitized group	1 st subgroup	2 nd subgroup	3 rd subgroup
Mean of γ globulin.	1268.33 $\pm$ 176.229	1600 $\pm$ 223.696	1296.66 $\pm$ 99.33	1305.0 $\pm$ 115.368	1296.66 $\pm$ 171.30
$\pm$ S. D.	-	$\bar{P} < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.05$
Mean of IgG	790.000 $\pm$ 126.39	1066 $\pm$ 154.96	860.714 $\pm$ 157.75	801.42 $\pm$ 152.6	872.85 $\pm$ 149.13
$\pm$ S. D.	-	$P < 0.005$	$P < 0.05$	$P < 0.005$	$P < 0.05$

P : Significance of difference between the means of the test drug and the sensitized control group.

$\bar{P}$: Significance of difference between the means of the sensitized control group and unsensitized control group.

Table (3) : Effect of pindolol on serum γ globulin and IgG levels (mg/100ml) in sensitized mice (7 animals in each group).

	CONTROL GROUPS		TEST GROUP	
	unsensitized group	Sensitized group	1 st subgroup	2 nd subgroup
Mean of γ globulin.	1268.33 $\pm$ 176.229	1043.33 $\pm$ 140.80	1026.66 $\pm$ 148.413	1163.33 $\pm$ 215.37
$\pm$ S. D.	-	$P < 0.01$	$P < 0.001$	$P < 0.001$
Mean of IgG	790.000 $\pm$ 129.39	1066 $\pm$ 154.96	860.71 $\pm$ 142.89	862.14 $\pm$ 135.45
$\pm$ S. D.	-	$P < 0.005$	$P < 0.05$	$P < 0.05$
P : Significance of difference between the means of the sensitized control group and unsensitized control group.				

Table (4) : Effect of Hydrocortisone Hemisuccinate on the plaque forming cells in spleen of sensitized mice (7 animals in each group and subgroup).

	CONTROL GROUP		TEST GROUP	
	Sensitized group	1 st subgroup	2 nd subgroup	3 rd subgroup
Mean $\pm$ S. D.	34.33% $\pm$ 2.87	15.33% $\pm$ 2.732	13.71% $\pm$ 1.70	19% $\pm$ 1.73
P	-	< 0.001	< 0.001	< 0.001
P : Significance of difference between the mean of the test drug and the sensitized control group.				

Table (5) : Effect of propranolol on plaque forming cells in spleen of sensitized mice (7 animals in each group and subgroup).

	CONTROL GROUP	TEST GROUP		
	Sensitized group	1 st subgroup	2 nd subgroup	3 rd subgroup
Mean $\pm$ S. D.	34.33% $\pm$ 2.87	32.33% $\pm$ 7.174	17.85% $\pm$ 3.33	21.66% $\pm$ 2.58
P	-	N. S.	< 0.001	< 0.001

P : Significance of difference between the mean of the test drug and the sensitized control group.

Table (6) : Effect of pindolol on plaque forming cells in spleen of sensitized mice (7 animals in each group and subgroup).

	CONTROL GROUP	TEST GROUP		
	Sensitized group	1 st subgroup	2 nd subgroup	3 rd subgroup
Mean $\pm$ S. D.	34.33% $\pm$ 2.87	31.66% $\pm$ 2.42	20.5% $\pm$ 1.378	22.42% $\pm$ 2.93
P	-	N. S.	< 0.001	< 0.001

Fig. (3): Effect of Hydrocortisone, Propranolol & Pindolol on plaque forming cells of spleen in sensitized mice.

Fig. (1): Effect of Hydrocortisone, Propranolol & Pindolol on serum IgG level in sensitized mice.

Fig. (2): Effect of Hydrocortisone, propranolol & pindolol on serum IgG level in sensitized mice.

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الملخص العربى

التأثير المحتمل لمثبطات المستقبلات الادرينالينية من نوع بيتا فى التفاعلات المناعية لحيوانات التجارب

أجرى هذا البحث لدراسة تأثير بعض مثبطات المستقبلات الادرينالينية من نوع بيتا مثل البروبرانولول والبندولول على التفاعلات المناعية فى الفئران المستحثة مناعياً وذلك بحقنها بكرات الدم الحمراء من الأغنام ومقارنة هذين العقارين بالهيدروكورتيزون كمثبط قياسى للجهاز المناعى.

وقد احتوى البحث على خمسة مجموعات من الفئران :

المجموعة الأولى : تشتمل على الفئران التى لم تستحث مناعياً.

المجموعة الثانية : تشتمل على الفئران التى استحثت مناعياً وذلك بحقنها بكرات الدم الحمراء من الأغنام فى الغشاء البروتونى.

المجموعة الثالثة :

تشتمل على ثلاث مجموعات فرعية :

مجموعة (أ) : تم حقنها بالهيدروكورتيزون لمدة خمسة أيام ثم أستحثت مناعياً.

مجموعة (ب) : تم حقنها بالهيدروكورتيزون لمدة خمسة أيام مع حثها مناعياً فى نفس الوقت.

مجموعة (ج) : تم حقنها بالهيدروكورتيزون لمدة خمسة أيام بعد حثها مناعياً.

المجموعة الرابعة : تشتمل أيضاً على ثلاث مجموعات فرعية مثل المجموعة الثالثة تماماً مع إعطاء

البروبرانولول بدلاً من الهيدروكورتيزون.

المجموعة الخامسة : تشتمل أيضاً على ثلاث مجموعات فرعية مثل المجموعة الثالثة مع إعطاء البندولول

بدلاً من الهيدروكورتيزون.

وقد تم معرفة التأثير المناعى لهذه العقاقير بتعيين معدل التغير فى كمية الجلوبيولينات المناعية الكلية

والنوعية من نوع "ج" وأيضاً تعيين معدل التغير فى عدد الخلايا الليمفاوية المكونة للأجسام المضادة فى الطحال.

وقد أوضحت نتيجة البحث الآتى :-

١- وجد أن حقن الهيدروكورتيزون فى الغشاء البروتونى أحدث انخفاضاً له دلالة احصائية ملحوظة جداً

فى كمية الجلوبيولينات المناعية الكلية والنوعية من نوع "ج" وعدد الخلايا الليمفاوية المكونة للأجسام