SHORT COMMUNICATION

POSSIBLE MECHANISM OF HYDROCORTISONE INDUCED EOSINOPOENIA

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Summary : Hydrocortisone (HC) injection in rabbits induced eosinopoenia (reduction in absolute eosinophil count) which could be successfully abolished by *beta*–adrenoceptor antagonists, a propranolol, sotalol, practolol and H 35/25 but not by *alpha*–adrenoceptor antagonist, phenoxybenzamine. Reserpine *per se* produced eosinopoenia followed by eosinophilia. However, reserpine pretreatment failed to abolish HC-induced eosinopoenia. It is suggested that the eosinopoenia is mediated through *beta*–adrenoceptors, which could not be differentiated into $Beta_1/Beta_2$–adrenoceptor subtypes as has been possible for other *beta*–adrenoceptor mediated responses.

Key words : hydrocortisone eosinopoenia reserpine *beta*–adrenoceptor

INTRODUCTION

Corticosteroids are known to alter the number of circulating white cells. A striking reduction in the number of lymphocytes and eosinophils in the peripheral blood is known to follow hydrocortisone (HC) administration. The mechanism of lymphopoenic action has been studied in detail (5) but the study of the mechanism of corticosteroid-induced eosinopoenia has not been attempted. Adrenaline is also known to induce eosinopoenia by its action on beta-adrenoceptors (12). It was, therefore, thought worthwhile to investigate the involvement of adrenergic mechanism in HC-induced eosinopoenia.

MATERIALS AND METHODS

The present study was conducted in conscious rabbits of either sex weighing between 1 to 2.5 *kg*. Each time 0.02 *ml* of blood sample was collected from ear vein to determine absolute eosinophil count (AEC) as described earlier (12). The control AEC was taken as 100% and the effect of drugs was expressed as percent of control AEC. Rabbits having an abnormally high AEC were excluded from the study. The AEC of rabbits included in the present study varied from 800 to 1000/mm^3 of blood which did not vary for more than 9% over a period of 4 hr of observation.

HC (2.5 to 7.5 *mg/kg* in propylene glycol) was injected subcutaneously (sc) to observe its effect on AEC. Propranolol (PPNL, 0. 5 *mg/kg*), sotalol (SOTL, 5 *mg/kg*), practolol (PRTL, 5 *mg/kg*), 1-(4'-methyl phenyl)-2-isopropylamino propanol (H 35/25, 2 *mg/kg*) and phenoxybenzamine (PBZ, 10 *mg/kg*) were given ip 1 hr before HC challenge. Catecholamine (CA) depletion was achieved by reserpine pretreatment (2.5 *mg/kg*, sc for 2 subsequent days).

RESULTS

Effect of HC on AEC : HC in graded doses (2.5, 5.0 and 7. 5 *mg/kg*, sc) was administered in groups of 5 rabbits each to observe its effect on AEC which was determined at one hourly interval for 4 hr and 24 hr. HC produced a dose-related varying degree of eosinopoenia which was maximum at 2 hr but the AEC did not come to control values after 24 hr. The typical eosinopoenic effect which persisted for over 24 hr obtained with 7.5 *mg/kg* dose is depicted in Fig. 1 and 2. Propylene glycol *per se* had no effect on AEC.

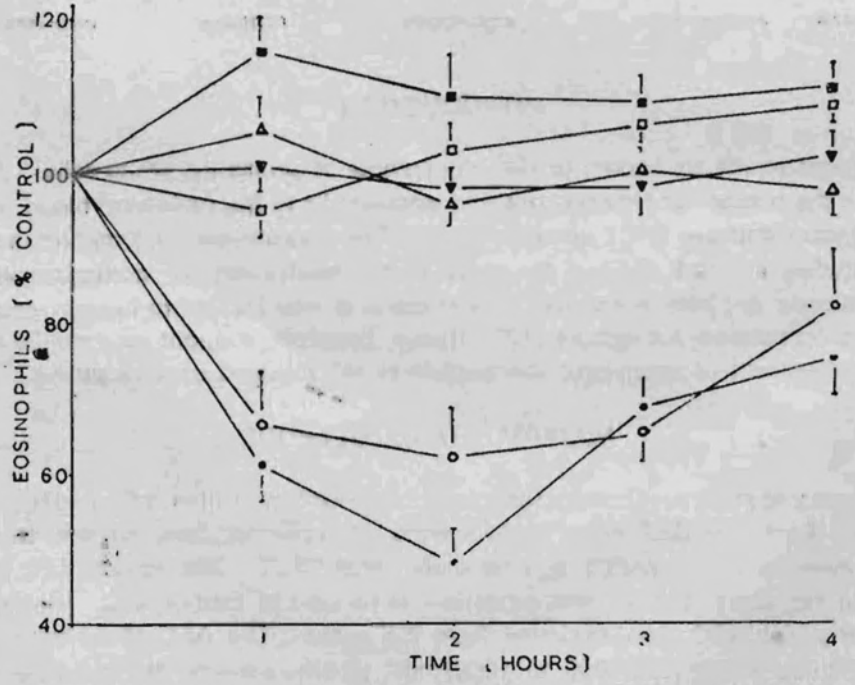

Fig. 1: Effects of adrenoceptor antagonists, PPNL (□), SOTL (■), PRTL (▲), H 35/25 (▼) and PBZ (O) on HC (●) induced eosinopoenia.

Effect of adrenoceptor antagonists on HC-induced eosinopoenia : Beta-adrenoceptor blockade was achieved in 4 groups of rabbits (5 in each) by PPNL, PRTL, SOTL or H 35/25 pretreatment 1 hr before injecting HC. HC (7.5 *mg/kg* sc) failed to induce eosinopoenia in these treated rabbits but there was varying degree of eosinophilia (except with H 35/25). PBZ treatment did not modify eosinopenic response to HC. The results are depicted in Fig. 1. The *beta*-blockers *per se* produced varying degree of eosinopoenia while PBZ produced eosinophilia (Fig. 3).

Effect of reserpine on HC-induced eosinopoenia : Reserpine (2.5 *mg/kg,* sc) was administered for two consecutive days to deplete CA stores. The first injection of reserpine produced eosinopoenia which was similar in magnitude to that produced by HC excepting that there was marked eosinophilia instead of eosinopenia at 24 hr. The eosinophilia persisted on the third day also. HC challenge in these CA-depleted animals produced persistent eosinopoenia which was much more marked than that observed in untreated control animals (Fig. 2).

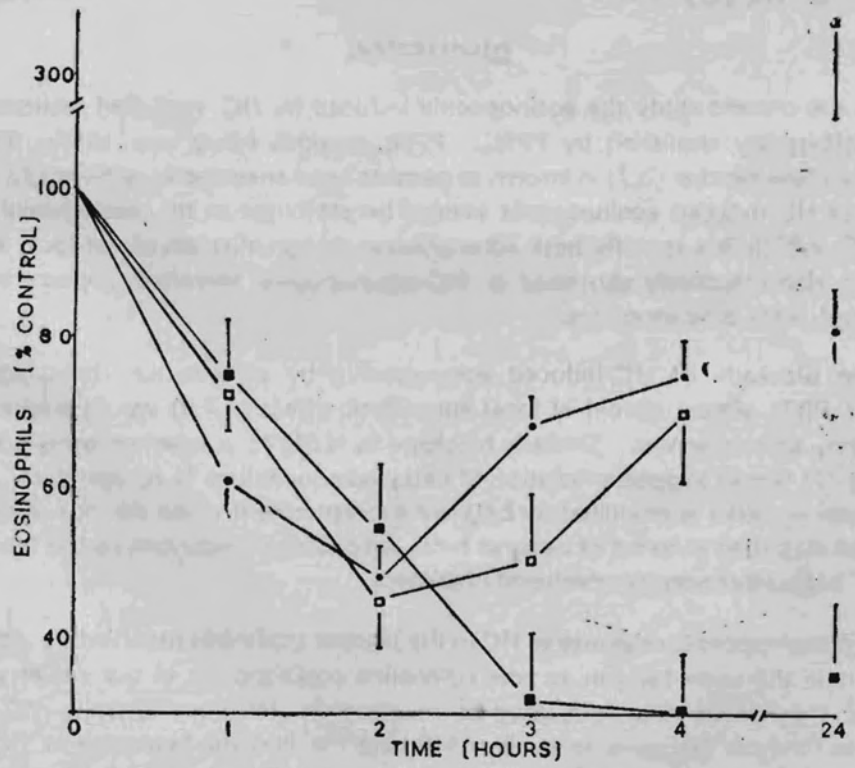

Fig. 2: Effects of reserpine *per se* (□) and reserpine pretreatment (■) on HC (●) induced eosinopoenia.

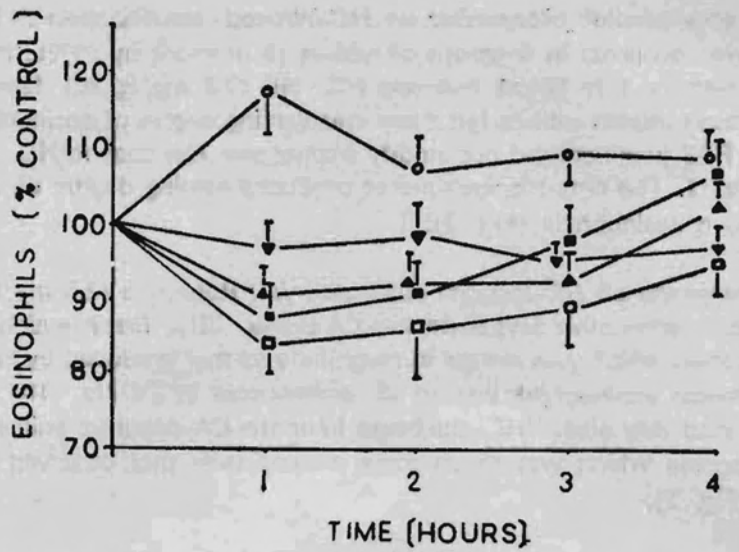

Fig 3: Effects of adrenoceptor antagonists, PPNL (□), SOTL (■), PRTL (▬) H 35/25 (▽) and PBZ (○) on AEC.

DISCUSSION

In the present study the eosinopoenia induced by HC remianed unaltered by PBZ but was effectively abolished by PPNL. PPNL besides being one of the most potent nonselective *beta* blocker (3,7) is known to possess local anaesthetic activity (2). However, blockade of HC-induced eosinopoenia cannot be attributed to its local anaesthetic effect since SOTL which is a specific beta-adrenoceptor antagnonist devoid of local anaesthetic effect (13) also effectively abolished it. HC-eosinopoenia, therefore, appears to be mediated through beta-adrenoceptors.

The blockade of HC-induced eosinopoenia by a selective $beta_1$-adrenoceptor antagonist, PRTL almost devoid of local anaesthetic effect (1,4,9) would suggest involvement of $beta_1$-adrenoceptors. Similarly blockade by H 35/25, a selective $beta_2$-adrenoceptor antagonist (7) would suggest mediation of $beta_2$-adrenoceptors. It is, therefore, concluded that HC-eosinopoenia is mediated by beta-adrenoceptors but these are not well differentiated to be classified in terms of $beta_1$ or $beta_2$-adrenoceptor subtypes as has been possible for other beta-adrenoceptor mediated responses.

The eosinopoenic response to HC in the present study was modified by adrenoceptor antagonists in the same fashion as was adrenaline eosinopoenia in our earlier study (12). Adrenergic mechanism therefore, may be involved in HC-eosinopoenia. HC is known to facilitate lipolytic response to cyclic AMP and the lipolytic response to HC has also

been shown to be related to the level of sympathomimetic amine (5). This type of role of HC acting in concert with other regulatory forces has been termed "permissive" by Ingle (6). In the present study also adrenergic mechanism could be involved in a similar fashion. An other way of involvement of adrenergic mechanism could be through release of CA by HC. Then the eosinopoenia should be abolished by CA depletion. However, in the present study reserpine treatment failed to prevent eosinopoenic response. The failure could be due to incomplete depletion of CA from certain sites. Adrenal medulla is one such site (10). Potentiation of eosinopoenic response by reserpine treatment could be due to development of supersensitivity at the sites of action of HC which are depleted of CA stores by reserpine. Initial eosinopoenia by reserpine alone may be explained in terms of CA releasing action of reserpine and subsequent eosinophilia in terms of CA depletion at sites responsible for eosinopoenic (destruction/migration from peripheral circulation) action.

Further studies are required to locate the beta adrenoceptors mediating eosinopoenia and to find out the fate of eosinophils which disappear from peripheral circulation. The eosinophils may be migrating to bone marrow as has been shown by demonstrating the presence of a large number of eosinophils in the bone marrow following dexamethasone injection in rats (11). However, the possibility that steroids induce the synthesis of a protein that in turn, acts to inhibit various cellular functions (8) as has been suggested for lymphopoenic action of corticosteriods, cannot be ruled out. Cyclic AMP may be involved in the synthesis of such a protein and that may clearly explain the eosinopoenic actions of CA and HC and blockade of the action by beta-adrenoceptor antagonists.

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