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EFFECT OF HALOPERIDOL ON DISTRIBUTION OF FUNCTIONALLY DIFFERENT CELLS IN IMMUNOCOMPETENT ORGANS

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Activation of the serotoninergic system by administration of the amine itself and of substances affecting its metabolism, has been shown to cause suppression of the immune response of IgM and IgG [9]. The same effect may also be achieved by administration of haloperidol (HP) [14], a specific blocker of dopamine receptors, whereas activation of the dopaminergic system [2] leads to stimulation of the immune process.

The action of serotonin on immunogenesis has been found to be due to a redistribution of cell populations possessing suppressor activity in both central and peripheral immunocompetent organs [4].

The object of this investigation was to study the principles governing the distribution of lymphocytes when the immune response is depressed by HP, i.e., during inhibition connected with another (dopaminergic) amine system, in order to determine the basis of suppression of immune responses during blockage of that system.

EXPERIMENTAL METHOD

Experiments were carried out on CBA mice aged 2 months in a system of syngeneic cell transfer: cell suspensions from intact (control) and HP-treated animals were transplanted into lethally irradiated recipients (800 R) together with sheep's red blood cells (5×10^6). Spleen cells were transplanted in a concentration of 40 million cells per mouse, cells of other organs in a concentration of 10 million per mouse. The donors received a single injection of HP in doses of 5 and 12 mg/kg subcutaneously in physiological saline 2 h before removal of the organs.

The intensity of the immune response in the recipients was determined in the spleen by the number of rosette-forming cells (RFC) on the 5th day after immunization [5]. IgM- and IgG-RFC were differentiated by their sensitivity to 2-mercaptoethanol [13].

EXPERIMENTAL RESULTS

Transplantation of spleen cells alone and also together with lymph node cells from donors receiving HP in a dose of 5 mg/kg stimulated the recipients' immune response compared with the control. Whereas in the first case stimulation was due to an increase in the level of both IgM-RFC and IgG-RFC, addition of lymph node cells caused the increase to be chiefly confined to the IgG-RFC (Fig. 1A). Meanwhile, combined transplantation of spleen and bone marrow cells from animals receiving HP revealed a marked decrease in rosette formation in the recipients on account of both types of RFC compared with this parameter when a similar cell suspension obtained from intact donors was injected. Simultaneous transplantation of spleen and thymus cells from donors receiving HP did not change the total RFC level in the recipients compared with the control, but did cause it to decrease compared with transplantation of spleen cells alone from these donors. In this situation, there was a sharp decrease in the number of IgM-RFC and an increase in the number of IgG-RFC.

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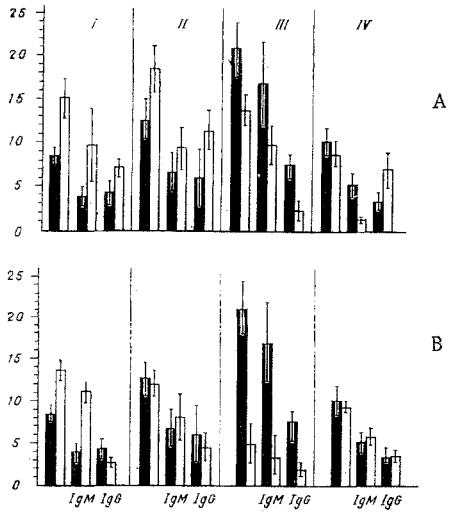

Fig. 1. Primary immune response in recipients on 5th day after immunization with sheep's red blood cells (5×10^6) and transplantation of cells from intact donors (black columns) and animals receiving HP (unshaded columns). Ordinate, number of RFC ($\times 10^3$ cells), I) spleen, II) spleen + lymph nodes, III) spleen + bone marrow, IV) spleen + thymus. A) HP 5 mg/kg; B) HP 12 mg/kg.

An increase in the dose of HP to 12 mg/kg stimulated the IgM-immune response only when spleen cells were transplanted (Fig. 1B). Meanwhile, compared with the control, no changes were found in the intensity of the immune response in animals receiving spleen and lymph node cells or spleen and thymus cells from donors receiving this dose of HP. However, if in the last case the value of the immune response is compared with that following transplantation of spleen cells only, the total number of RFC was found to be reduced on account of a sharp fall in the intensity of the IgM-response. Simultaneous transplantation of spleen and bone marrow cells from donors receiving HP in a dose of 12 mg/kg revealed the same general rules as when the drug was given in a dose of 5 mg/kg, but the inhibition was more marked as regards both the total number of RFC and the IgM-RFC, whereas the value of IgG-RFC was practically the same.

It can be concluded from these findings that a redistribution of cell populations takes place in unimmunized animals under the influence of HP. Suppressor cells from the spleen and lymph nodes (but in a dose of 12 mg/kg from the spleen only, for transplantation of lymph node cells from donors receiving HP in this dose did not cause stimulation) migrate into the bone marrow, injection of which, together with spleen cells, caused suppression of the immune response in the recipients. The possibility cannot be ruled out that the suppressing action of HP in a dose of 12 mg/kg was attributable not only to a redistribution of cell populations in the unimmunized donors, but also to functional properties such as proliferation of the immune lymphocytes, as other workers who have used high doses of HP also suggest [11]. Since a definite number of cell generations is necessary for development of the IgG-response [7], by contrast with the IgM-response, this suggests that production of this type of immunoglobulins is more sensitive to the action of HP (12 mg/kg). Under the influence of serotonin, moreover, a considerable increase in activity of the suppressor cells was observed in the spleen and thymus of immunized animals [3], and this may perhaps take place together with their redistribution under the influence of a large dose of HP.

The results are evidence of general rules governing the distribution of functionally different cells under the influence of HP and, as was shown previously, in response to elevation of the serotonin level [4]. They concern, first, an increase in the number mainly of IgM-RFC compared with the control in response to transplantation of spleen cells, and of IgG-RFC in response to combined transplantation of spleen and lymph node cells (for HP in a dose of 5 mg/kg only), and second, a decrease in the number of both types of RFC following injection of spleen and bone marrow cells. Consequently, two substances, serotonin and HP, whose inhibitory action is due to activation of the serotoninergic system, which inhibits immunogenesis, and a

corresponding blockade of the dopaminergic system, which stimulates immunologic reactions, cause a similar redistribution of functionally different cell populations. This distribution consists of an increase in the number of suppressors of the IgM- and IgG-response, migrating from the spleen and lymph nodes, which are depopulated of cells of this type, in the bone marrow.

It has been shown that the B cells of bone marrow possess suppressor activity [6]. It can accordingly be postulated that under the influence of HP, suppression of B cells is intensified, more especially because the presence of B suppressors has been demonstrated in the bone marrow of immunized mice receiving serotonin [3]. However, we know that in unimmunized animals in certain situations, such as during stress reactions [1] and in response to injection of hormones [8], T cells with helper activity may migrate into the bone marrow. At the same time, investigations have shown predominant migration of T suppressor cells from the spleen into the bone marrow of tolerant mice [12]. Consequently, depending on the character of neurohumoral action on the body and on its state, T cells migrating into the bone marrow may possess either a helper or a suppressor function. In light of the facts described above and of existing data on the greater migrating capacity of T cells than of B cells [15], it seems probable that in this case the suppressor cells are more likely to belong to the T population.

The results thus indicate that the action of a specific blocker of the dopaminergic system on immunogenesis is due, just as in the case of activation of the serotoninergic system, to redistribution of functionally different cells, namely, through migration of IgM- and IgG-suppressors into the bone marrow. Consequently, irrespective of whichever system inhibits immunogenesis, the inhibition is based on similar processes of cell migration.

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