REGULATION OF ISOPROTERENOL-INDUCED SALIVARY GLAND HYPERPLASIA IN YOUNG AND OLD MICE BY SUBSTANCES AFFECTING SEROTONINERGIC AND DOPAMINERGIC SYSTEMS

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A marked decline of immune responses is known to take place in old animals, and it is based on a deficiency of T helper cells and an increase in the number of T suppressor cells in old age [7, 9], which leads to a decrease in the proliferation of antigen-sensitive cells and their delay in the G_1 phase of the cell cycle [10]. A similar decrease in the mitotic index and the formation of a G_1/S block are characteristic of all other types of tissue in old animals [13], and in particular, this causes abrupt changes in the dynamics of cell proliferation induced by any agents in old animals, including a change in isoproterenol-induced hyperplasia of the salivary glands in old rats and mice [5].

At the same time, it has been shown that the immune response is under the reciprocal influence of the serotoninergic and dopaminergic systems of the brain; activation of the former, moreover, leads to inhibition of the immune response on account of T suppressor activation, whereas activation of the latter leads to stimulation on account of an increase in the number of T helpers [2]. Since activation of the serotoninergic systems of the brain [11] and inhibition of the dopaminergic systems [8], are observed in old age, these changes may determine changes in immune reactivity during aging.

The participation of T lymphocytes in the regulation of proliferation of tissues of any type, not only lymphoid [1, 3, 4], demonstrated in recent years, suggests that the changes in the serotoninergic and dopaminergic systems of the brain observed in old age may bring about a generalized decline in the mitotic index in old age.

The aim of this investigation was to study the effect of substances modulating serotoninergic and dopaminergic structures on induction of hyperplasia of the salivary glands by isoproterenol in young and old mice.

EXPERIMENTAL METHOD

Experiments were carried out on 220 female BALB/c mice aged 3 and 15 months. Hyperplasia of the salivary glands was induced by injection of isoproterenol in physiological saline subcutaneously in a dose of 5 mg/10 g body weight [6]. The reactions were read 16, 22, 30, 40, and 48 h after injection of the drug, taking into account the weight of the submandibular and parotid glands, isolated en bloc, and the intensity of incorporation of ^{3}H-thymidine, injected intraperitoneally in a dose of 1 μCi/g body weight 1.5 h before sacrifice of the animals, into the gland tissue. The salivary gland tissue was minced in 10% TCA, and the acid-insoluble residue obtained after three washings was dissolved in 0.1 N NaOH and standardized for absorption of UV light at 260 nm. The results were expressed in percent of values obtained in animals receiving an injection of physiological saline.

To activate their serotoninergic mechanisms, the mice were given a subcutaneous injection of 50 mg/kg of serotonin in Freund's incomplete adjuvant 1 h before an injection of isoproterenol, and to activate their dopaminergic structures, 200 mg/kg of L-dopa in physiological saline was injected subcutaneously at the same time before injection of isoproterenol and 2.5 and 8 h after its injection.

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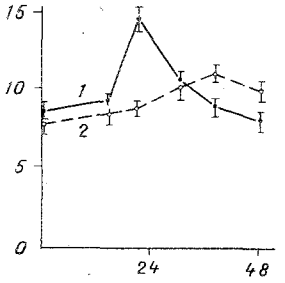

Fig. 1

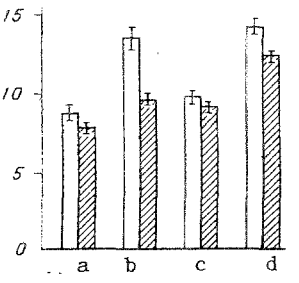

Fig. 2

Fig. 1. Time course of change in weight of submandibular and parotid salivary glands in young (1) and old (2) mice receiving injections of isoproterenol. Abscissa, time of recording (in h); ordinate, relative weight of salivary glands (in mg/g body weight).

Fig. 2. Changes in response of salivary glands in young (unshaded columns) and old (shaded columns) mice to isoproterenol against the background of injection of serotonin and dopamine. Ordinate, relative weight of glands (in mg/g body weight). a) Control animals, b) response to isoproterenol (22nd hour of administration), c) response to isoproterenol together with injection of serotonin, d) response to isoproterenol together with injection of dopamine.

TABLE 1. Effect of Serotonin and Dopamine on Isoproterenol-Induced Proliferation of Salivary Gland Cells and Number of Activated Splenic Lymphocytes in Old Mice

Experimental conditions	Incorporation of ^3H-thymidine, cpm/g body body weight	Number of activated splenic lymphocytes ($\times 10^6$) with a density of under 1.070
Intact mice (control)	124±34	3,7
Injection of isoproterenol	210±17*	5,6
Injection if isoproterenol and serotonin	154±22	4,7
Injection of isoproterenol and dopamine	445±35**	7,7

Legend. *$P < 0.05$, **$P < 0.01$ compared with control.

The numerical results were subjected to statistical analysis by Student's t test.

EXPERIMENTAL RESULTS

After injection of isoproterenol into the mice the weight of their salivary glands increased by 1.7-2 times compared with the control; this is known [6] to be the result of induction of proliferation of the gland cells with hyperplasia of the gland. The responses in young and old mice differed significantly: In young animals there was a rapid increase in weight of the glands, the reaction reaching its maximum 22 h after injection of the drug, and this was followed by rapid atrophy, with restoration of the original weight by the 2nd day of the investigation; in old animals the peak of the response was shifted to later times, with a decrease in the absolute weight of the gland attained (Fig. 1).

After injection of substances simulating excitation of serotoninergic and dopaminergic structures of the brain changes were observed in the reactivity of the salivary gland tissue to isoproterenol (Fig. 2). There was a significant decrease in the attained weight of the glands in response to injection of isoproterenol when serotonin was given, and an increase when the dopaminergic structures were activated. Under these circumstances, a greater degree of enhancement of the response of the glands was observed in old mice, in which the response to isoproterenol accompanied by injection of dopamine came close in its intensity to the response of young mice which had not received dopamine; the peak of the response in old animals under these conditions was observed, just as in young animals, at the 22nd hour of action of isoproterenol.

Restoration of reactivity in old animals was achieved on account of activation of proliferation of the salivary gland cells (Table 1).

To assess the effect of the drugs on the lymphoid system, activation of which was demonstrated in the course of isoproterenol-induced hyperplasia of the salivary glands in mice and rats [2], an approach based on the isolation of activated lymphocytes, which are larger and have a lower specific gravity [12], was used. It will be clear from Table 1 that the number of these lymphocytes, isolated 4 h after injection of isoproterenol into old animals, was greatly increased in mice receiving dopamine, but reduced in mice receiving serotonin.

Excitation of serotoninergic structures thus inhibits, whereas excitation of dopaminergic structures stimulates (like its effect on immune reactions [3]) the response of mice to isoproterenol. Since the action of these substances was accompanied by a corresponding simultaneous decrease and increase in the number of active splenic lymphocytes which, as the writers have shown [2], are responsible for induction and for restriction of proliferation of salivary gland cells, it can be concluded that the action of serotonin and dopamine is mediated through its effect on the lymphoid system.

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BONE FORMATION IN BONE MARROW ORGAN CULTURES

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Evidence that osteogenic precursor cells are present in bone marrow has been obtained in heterotopic transplantation experiments. Fragment of bone marrow, when transplanted in diffusion chambers, form bone tissue [2, 6], and if transplanted beneath the renal capsule, they form bone marrow organs in which bone, osteogenic cells, and colony-forming stromal mechanocytes of the medullary cavity are of donor origin [3, 5]. Osteogenic cells also are present in suspensions of bone marrow cells. If the latter are transplanted in diffusion chambers, bone and cartilage are formed [6, 9], and transplantation of 10^5 bone marrow cells beneath the renal capsule leads to the formation of a heterotopic bone marrow organ [4].

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