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The Role of Histamine in the Initiation of the Posttraumatic Regeneration of the Submandibular Gland in Rats

A. V. Denisov

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It is found that both a stimulative and an inhibitory effect on histamine receptors retard the initiation and development of the posttraumatic regeneration of the submandibular gland. The selective blockade of H2 receptors does not lead to a compensatory hypertrophy of the paired gland.

Key Words: *salivary glands; histamine receptors; regeneration*

The large salivary glands are organs with weak reparative regeneration. Anatomically these organs are rich in mast cells, which are situated close to each acinus and undergo massive degranulation in trauma (sialotomy). Many drugs [6] administered intravenously cause histamine release from mast cells to the blood. The process of posttraumatic regeneration is a determined program [5], the fulfillment of which depends on the initial state of the organism and initiation factors [1,3]. The most common opinion is that the role of histamine is of a dual nature in the processes of proliferation depending on the dose [8-12].

The aim of the present investigation was to study the role of histamine in the initiation of the posttraumatic regeneration of the submandibular gland (SMG). For this purpose the effect of endogenous histamine was either increased by means of exogenous histamine or decreased due to the selective blockade of H_1 or H_2 histamine receptors at the moment of trauma of the gland, after which the result of developing hypertrophy was assessed.

Department of Pathophysiology with a Course in Clinical Immunology, Stomatology Faculty, N. A. Semashko Medical Institute of Stomatology, Moscow. (Presented by D. S. Sarkisov, Member of the Russian Academy of Medical Sciences)

MATERIALS AND METHODS

Experiments were carried out on 109 outbred rats of both sexes weighing 150-300 g. Sialotomy was performed under combined anesthesia produced by i. p. administration of hexenal at 75 mg/kg and local infiltration of 2% novocain in the neck region. Then 1/3 of the right SMG was resected from the side of the lower pole through a medial incision of the neck skin and muscles. The bleeding was stopped by tamponade and interrupted sutures were put on the wound. A week later the animals were sacrificed with a lethal dose of hexenal. The body was then weighed and both SMG and the thymus were isolated. The organs and resected gland were dried at 110°C to achieve of a constant mass. The result of reparative regeneration was assessed based on the determination of the resected weight, the weight of the gland at sacrifice, and the theoretical weight calculated according to a formula [2]. The percent of SMG regeneration and the percent change of paired gland weight were determined from these values.

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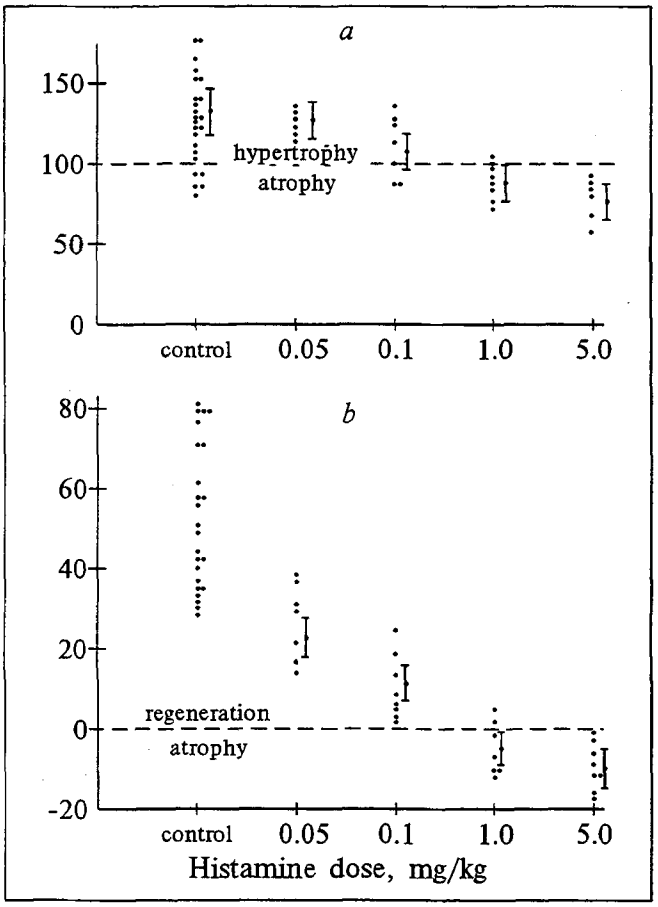

Fig. 1. Course of reparative regeneration in the damaged (*a*) and contralateral (*b*) glands against the background of histamine excess (7th day of experiment). Ordinate: *a*) value of SMG regeneration, %; *b*) value of hyper– or hypotrophy of the contralateral (intact) gland, %. Points signify the individual values: the arithmetic mean with its standard deviation are given nearby ($X \pm SE$).

Stress control was performed by the thymus index (TI), calculated as the ratio between the dried organ weight (in mg) and the body weight (in g) in conventional units. Drugs affecting the histamine receptors were administered i. p. to rats 30 min prior to the operation. Histamine dehydrochloride (at 0.05; 0.1; 1; and 5 mg/kg) and the H_1 blocker mepyramide (10 mg/kg, Sigma) were diluted in saline; the H_2 blocker methiamide (10 mg/kg, Sigma) was dissolved in 0.1 N HCl and then the pH was adjusted to 7.0 using O.1 N NaOH. Statistical reliability of the results was assessed using the Student *t* test and the Fisher *F* test ($p<0.05$).

RESULTS

The time course of reparative regeneration after histamine administration was studied in the first experimental series (Fig. 1). One-factor analysis of variance of the results showed that 51±6% of all acting factors were taken into account in this experimental series ($p<0.01$). Nevertheless, the result obtained was conclusive, namely a single administration of the drug before SMG trauma resulted in a weakening of its reparative regeneration. Even the minimal dose studied (0.05 mg/kg) led to a twofold decrease of the SMG weight incremet (50±4% regenerates in the control and 26±4% in the experiment). A moderate negative correlation is obtained for SMG regeneration and histamine dose ($r=-0.505$; $p=0.01$). The regeneration program is controlled on the systemic level, which is why the intact contralateral gland is involved in the process and its hypertrophy is noted on the 7th day (129±6%). Analysis of variance showed that the majority of the factors (73%) involved in the development of hypertrophy were not revealed. Administration of histamine in small doses (0.05 and 0.1 mg/kg) did not change the course of hypertrophy. On the other hand, large doses of histamine (1 and 5 mg/kg) cause atrophy of SMG by 30-35% instead of its hypertrophy.

Stress was monitored by the TI value. It was found that thymus atrophy by 44% (0.534±0.037 c.u. in the control and 0.297±0.010 c.u. in the experiment) developed under the influence of sialotomy. The combination of SMG trauma with histamine administered in different doses boosted this process, this being maximally manifested when histamine was added in the maximal dose of 5 mg/kg, at which the thymus atrophied by 97% (TI=0.039±0.015, $p<0.01$).

In the second experimental series the drugs selectively blocking histamine receptors situated on smooth muscle cells (H_1) and glandular cells (H_2) were used. The results and statistical analysis of them are listed in Table 1. Sixty-five to 68% of all acting factors were taken into account in this experimental series. It was found that variation coefficient (ω) is greater than 100%, testifying that the results obtained are heterogeneous according to the laws of variational statistics. Based on this we divided the data obtained into two groups: the first consisted of rats with regenerating SMG and the second with developing SMG atrophy. It was found that weak regeneration (6% of resected weight on average) developed in 38% of animals with preliminary blockade of the H_1 receptors. "Systemic" hypertrophy of the contralateral gland significantly decreased by 20% simultaneously. The administration of the H_2 blocker induced regeneration in a greater number of rats (44%) and comprised only 13%. In addition, unlike in the foregoing group, "systemic" hypertrophy was completely absent (104±3%). The administration of H_1 or H_2 bloc-

kers did not cause a change of the TI value as compared to the first experimental series (0.296± ±0.040 for H_1 and 0.224±0.019 for H_2.)

Thus, a change of the conditions triggering reparative regeneration, appearing after unilateral sialotomy of SMG by a single stimulation or blockade of histamine receptors inhibits the development of regeneration. Since the hypertrophy reaction is found in the paired gland, there is a systemic effect. We think that the superficially similar manifestation, namely the inhibition of regeneration, induced both by stimulation and by blockade of histamine receptors, is different in its mechanism. Stimulation of H receptors causes the progressive inhibition of stimulation and thymus atrophy in parallel. Therefore, there has to be a common extrasystemic factor inhibiting anabolic processes in the tissues. In contrast, the thymus tissue reacts to the operation stress, but not to the administration of the drugs blocking H_1 or H_2 receptors. Two groups of animals are thus clearly defined, namely animals capable of regeneration and animals without the response to sialotomy. Blockade of secretory cell receptors (H_2) resulted in a systemic blockade not only of the regeneration process but also of compensatory hypertrophy. Therefore, the use of antihistamine drugs [7] in the complex pretreatment of patients may cause an aggravation of the reparative processes in glandular tissue.

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