ADRENERGIC MECHANISMS OF ADAPTIVE RESPONSE FORMATION IN DIFFERENT TISSUES

A. M. Dygai, O. Yu. Zakharova, T. I. Fomina, and E. D. Gol'dberg

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The involvement of different organs and systems in the formation of the nonspecific resistance of an animal to stress is connected with the development of a combination of morphological and functional changes in them, known as the "systemic structural trace" [5]. One of the triggering links in the chain of stress reactions at cellular and tissue levels in this case is activation of the sympathetic nervous system [6, 7]. The systemic catecholaminergic innervation and the existence of adrenergic receptors on many regulatory cells [8, 9] enable the sympathetic nervous system to have both a direct and an indirect influence on function and metabolic activity of the cellular structures of the body during stress. In particular, we know that under influences simulating stress (injection of isoproterenol) induction of cell proliferation in the submandibular gland of rats and mice takes place by migrating T lymphocytes [2]. During a study of the effect of peripheral adrenergic structures on reactivity of hepatopoietic tissue it was shown that injection of an α-adrenoblocker abolished, whereas injection of a β-adrenoblocker delayed the development of the characteristic hyperplastic response of the bone marrow to immobilization stress [3]. The effect of peripheral β-adrenoreceptor blockade on proliferative activity of other tissues was investigated by the writers in a model of immobilization, using the β-adrenoblocker propranolol.

EXPERIMENTAL METHOD

Experiments were carried out on 90 male (CBA × C57BL/6)F_1 mice immobilized for 10 h. Immediately before and 5 h after the beginning of immobilization the animals were given a subcutaneous injection of propranolol (Obsidan) in a dose of 5 mg/kg [3]. At various times after immobilization the mice were killed after preliminary (2 h beforehand) intraperitoneal injection of ^{3}H-thymidine in a dose of 1 MBq per mouse. The submandibular salivary gland, kidneys, and part of the liver and small intestine were removed and fixed in 12% formalin solution, embedded in paraffin wax, after which histologic sections 5 μ thick were cut for preparing autoradiographs [4]. The proliferative activity of the tissues was studied by determining the percentage of labeled enterocytes in the crypts, epithelial cells of the renal tubules, acinar regions and efferent ducts of the salivary gland, and hepatocytes and binuclear cells in the periportal zones of the liver. The significance of differences in the parameters in the samples was assessed by the nonparametric Wilcoxon–Mann–Whitney test.

EXPERIMENTAL RESULTS

The experiments showed that immobilization for 10 h caused the proliferative activity of most tissues studied to increase. For instance, a significant increase in incorporation of label into small intestinal enterocytes was observed from the first through the third and on the 6th day of investigation (rising to a peak of 143.7% on the 6th day – up to 143.7% of the initial level on the 3rd day; Fig. 1). A biphasic proliferative reaction also was discovered for the epithelium of the renal tubules, with an increase in the index of labeled nuclei on the 3rd and 6th days of the investigation (up to 186.7 and 200% of the initial level respectively).

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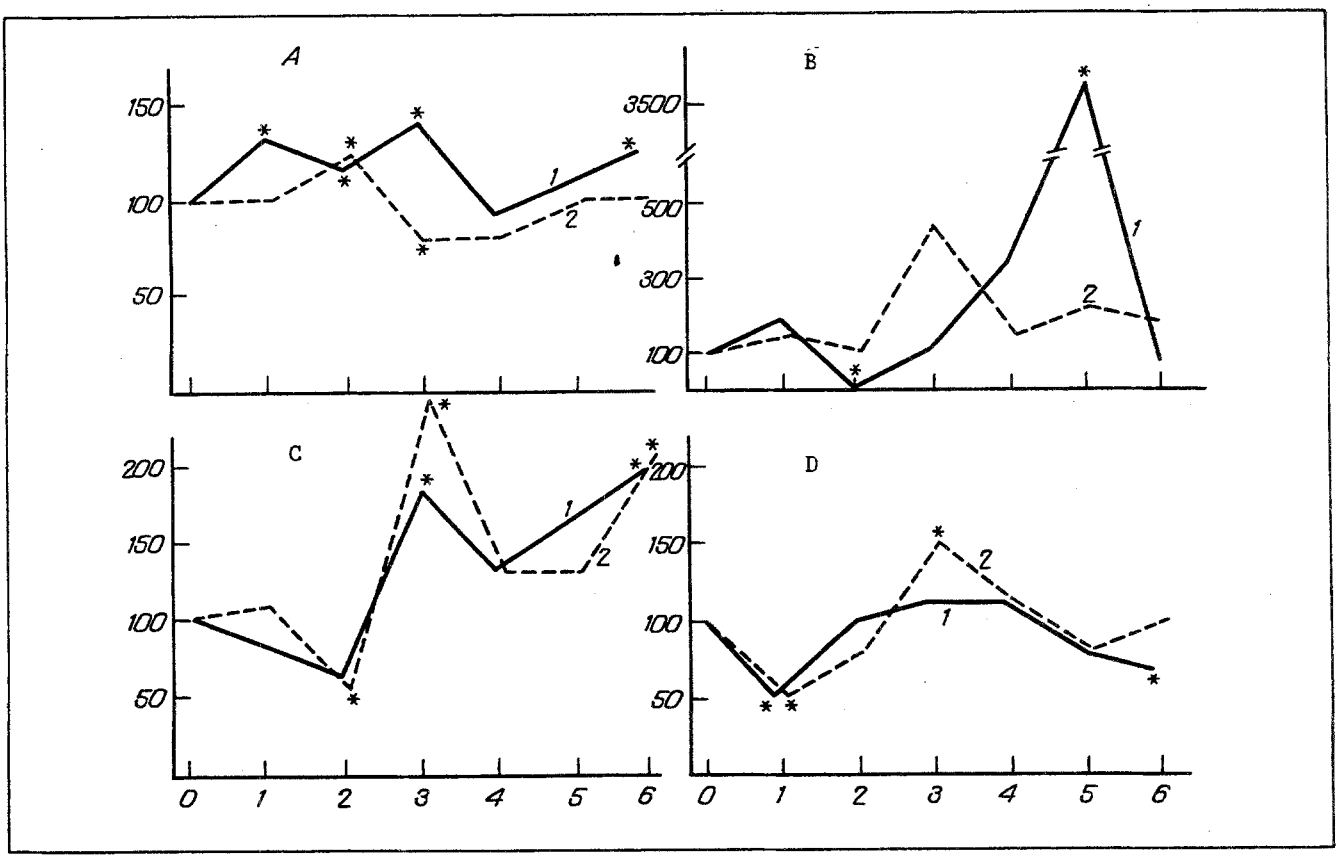

Fig. 1. Time course of proliferative activity of cells of small intestine (A), liver (B), kidney (C), and submandibular salivary gland (D) in (CBA × C57BL/6)F_1 mice immobilized for 10 h after preliminary subcutaneous injection of propranolol (2) or of physiological saline (1). Abscissa, time of investigation after immobilization, days. Ordinate, per cent of labeled nuclei, per cent of background. Multiplication sign) difference from initial value significant at $p < 0.05$.

TABLE 1. Time Course of Number of Binuclear Hepatocytes (percent) in (CBA × C57BL/6)F_1 Mice Subjected to Immobilization for 10 h after Preliminary Administration of Propranolol or Physiological Saline (X, p)

Time of investigation, days	Physiological saline	Propranolol
Before immobilization	17,1	17,1
1	13,4	11,9
	>0,05	<0,05
2	11,8	15,2
	<0,05	>0,05
3	10,3	13,3
	<0,05	>0,05
4	16,0	15,3
	>0,05	>0,05
5	16,4	10,9
	>0,05	<0,05
6	17,0	8,9
	>0,05	<0,05

The hepatocytes reacted to stress by a decrease in the number of binuclear cells on the 2nd and 3rd days of the experiment and in the percentage of labeled nuclei on the 2nd day of the experiment, followed by a 35-fold increase on the 5th day of the investigation (Table 1, Fig. 1). Conversely, in the epithelium of the secretory zones and efferent ducts of the submandibular salivary gland proliferative activity fell compared with initially on the 1st (by 50%) and 6th (by 33%) days after immobilization. Blockade of the peripheral β-adrenoreceptors in animals subjected to immobilization changed the character of the adaptive response of the tissues studied. For instance, the increase in proliferative activity of the enterocytes in mice receiving propranolol was delayed by 24 h compared with that in the control immobilized animals (Fig. 1). The second rise of this parameter did not take place in the group of mice receiving the drug. On the whole, the percentage of labeled enterocytes in this group on the 1st, 3rd, and 6th days was significantly lower than that in the control animals subjected to immobilization. The increase in proliferative activity of the epithelium of the renal tubules in mice receiving the β-adrenoblocker took place, just as in mice exposed to immobilization only, on the 3rd and 6th days, but under conditions of β-adrenoreceptor blockade this was preceded by significant inhibition of proliferative activity of the renal epithelium on the second day of the experiment (to 53% of the initial level). No increase in proliferative activity of the hepatocytes was observed in the liver of animals receiving propranolol, but the percentage of binuclear cells in this case was depressed on the 1st, 5th, and 6th days of the experiment compared with initially. An unexpected finding was that injection of the β-adrenoblocker stimulated the proliferative activity of cellular structures of the salivary gland on the 3rd day of the investigation (Table 1; Fig. 1).

Thus immobilization, as a rule, leads to an increase in proliferative activity of various tissues. The mechanisms of this phenomenon, which have been studied in detail previously in the case of hematopoietic tissue may perhaps be universal and may include activation of the sympathetic nervous system and the pituitary-adrenal system and associated migration of regulatory T lymphocytes into the tissues, as well as production of universal regulators of proliferation such as interleukin-1 and -3 by stromal and macrophagal cells [1]. Under these conditions blockade of the peripheral adrenergic structures did not abolish the development of adaptive changes in the tissues, but modified them: it delayed them and weakened their intensity in tissues with an initially high proliferative potential (small intestine and bone marrow), caused transient inhibition of proliferation (kidney), but preserved the response of the binuclear hepatocytes to the stimulus for division, reducing the intensity of DNA synthesis in the liver cells. The response of the cellular structures of the submandibular salivary gland to immobilization was atypical, in the light of the published data [2]. We know, however, that the character of the adaptive response depends on the intensity of the stressor. Our chosen model of stress perhaps had an inhibitory effect on proliferative activity of the tissue chosen for study because of its functional peculiarities. Meanwhile, the "weakening" of the intensity of the stressor taking place under the influence of propranolol led to stimulation of proliferation of the salivary gland epithelium.

The character of the adaptive response of different tissues is thus formed under the influence of adrenergic mechanisms. The influence of β-adrenergic structures in the situation we studied was evidently realized locally, and could be manifested as a change in functional activity of the regulatory cells, producing short-distance proliferative signals.

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