EFFECT OF β-ADRENORECEPTOR BLOCKADE ON CELL DIVISION IN THE CORNEAL AND LINGUAL EPITHELIUM IN ALBINO RATS SUBJECTED TO CHRONIC HYPOXIA

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The writers showed previously that hypoxia has a more profound action on epithelial cell division than to cause reactive inhibition of mitosis, which is a property of ordinary stressors [2]. Short-term inhibition of mitotic activity immediately after the end of exposure to hypoxia was followed by its stimulation, due to activation of DNA synthesis. Stimulation of cell division was interpreted by the writers as a compensatory process, aimed at restoring tissue homeostasis, disturbed as a result of cell death during hypoxia. The increase in the frequency of pathological mitoses under these circumstances was regarded as a cellular manifestation of disadaptation [3]. Among harmful factors in stress a definite role evidently belongs to hypersecretion of catecholamines [7, 9]. Whatever the case, according to data in the literature [8] β-adrenoreceptor blockade in emotional-painful stress prevents the development of structural changes affecting DNA.

It was interesting to assess the character of changes in cell division in the epithelium of rats exposed to hypoxia and subjected to β-adrenoreceptor blockade.

EXPERIMENTAL METHODS

Experiments were carried out on noninbred male albino rats weighing 170-210 g. Chronic hypoxia was induced by keeping the rats for 4 h daily in a pressure chamber at an "altitude" of 9000 m for 1 week. Histological sections and autoradiographs for the study of mitotic activity and DNA synthesis in the corneal and lingual epithelial cell nuclei by high-resolution autoradiography were prepared by methods described previously [3].

Propranolol (East Germany), in a dose of 5 mg/kg body weight, was used a β-blocker. The drug was injected intraperitoneally before and after the "ascent" in order to induce long-term blocking of adrenergic structures [4, 5, 10]. After the "ascent" the effective dose of propranolol was maintained for 6 h by hourly fractional injections of half of the initial dose of the drug, allowing for its half-life [6]. Since, unlike the tongue, the cornea has no blood supply, the drug was also applied directly to it. The animals were killed 6 h after final exposure in the pressure chamber. All the animals were killed at 7 p.m.

Altogether 22 rats were used. The experimental results were subjected to statistical analysis by Student's test.

EXPERIMENTAL RESULTS

The results confirmed conclusions drawn from previous investigations regarding the compensatory character of changes in cell division during chronic hypoxia [3]. This can be seen from the activation of DNA synthesis in the two tissues studied (Tables 1 and 2). An increase in the number of DNA-synthesizing cells in the tongue was accompanied by an increase in the labeling intensity (LI). In the cornea there was only an increase in the index of labeled nuclei (ILN), and any increase in LI was not significant. A significant increase in the number of pathological mitoses (PM) was observed in both tissues studied: by twice in the cornea and by 2.6 times in the tongue.

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TABLE 1. Effect of β-Adrenoreceptor Blockade on Changes in Intensity of Cell Division in Corneal Epithelium of Albino Rats during Chronic Hypoxia (M ± m)

Exptl. conditions	DNA synthesis		ML, %	Ratio between phases of mitosis, %				PM level, %
	ILN, %	LI		prophase	metaphase	anaphase	telophase	
Control	73,3±7,9	22±1	12,2±0,8	12,2±0,7	59,3±1,1	8,0±0,6	20,5±0,9	8,5±0,6
Propranolol	85,8±7,2	19±2	13,9±1,2	14,9±0,8	50,0±1,1	7,5±0,6	27,6±1,0	7,9±0,6
Hypoxia	133,4±7,8*	26±2	14,6±2,6	19,8±0,9	57,9±1,1	6,0±0,5	16,3±0,8	17,1±0,8*
Hypoxia+ propranolol	81,4±5,2	16±2*	23,6±1,2*	18,0±0,6	48,1±0,8	9,8±0,5	24,1±0,7	13,1±0,6*

Legend. Here and in Table 2: *P < 0.05 compared with control.

TABLE 2. Effect of β-Adrenoreceptor Blockade on Changes in Intensity of Cell Division in Lingual Epithelium of Albino Rats Exposed to Chronic Hypoxia

Exptl. conditions	DNA synthesis		MI, %	Ratio between phases of mitosis, %				PM level, %
	ILN, %	LI		prophase	metaphase	anaphase	telophase	
Control	83,8±5,5	20,1	11,5±1,3	10,2±1,4	56,3±2,2	9,2±1,3	24,3±1,9	8,4±1,3
Propranolol	122,6±14,9*	16±3	11,0±1,6	19,2±1,9	52,9±2,4	10,6±1,5	17,3±1,8	10,4±1,5
Hypoxia	130,9±6,2*	24±1*	18,4±2,8*	10,4±1,1	58,5±1,8	10,1±1,1	21,0±1,5	22,1±1,5*
Hypoxia+ propranolol	99,4±9,5	17±1	12,8±1,5	13,6±1,4	54,7±2,1	15,8±1,5	15,9±1,5	11,4±1,3

Injection of propranolol itself caused no significant changes in cell division in the corneal epithelium. ILN and LI, as well as the mitotic index (MI) and the PM level, in animals receiving the drug were the same in the control. In the lingual epithelium, a significant increase in ILN took place under the influence of propranolol, but LI remained unchanged. Although MI in the lingual epithelium did not exceed the control values, the increase in the number of prophases is evidence of commencing stimulation of cell division. No significant changes in the PM level in either the tongue or the cornea were produced by propranolol. The reasons for the different effects of propranolol on cell division in the corneal and lingual epithelium require experimental analysis.

In rats exposed to chronic hypoxia β-adrenoreceptor blockade led to normalization of ILN in the cornea and tongue. LI in the cornea was significantly lower than in the control, MI was restored to normal only in the lingual epithelium, whereas in the corneal epithelium a significant increase in MI in these experiments could arise without additional application of propranolol to the tissue. Under hypoxic conditions, reactivity of dividing cells to propranolol eivdently depends on the type of epithelium and the concentration of the drug in the tissue. This also required experimental analysis.

It must be emphasized in particular that β-adrenoreceptor blockade during hypoxia reduced the PM level in the cornea and lowered this cellular parameter of disadaptation in the tongue to the control level.

The ability of propranolol to weaken or prevent the rise in the number of PM during hypoxia may be interpreted as evidence of its protective action manifested at the cellular level. The normalization of the parameters of DNA synthesis in the cornea and tongue during β-adrenoreceptor blockade in rats exposed to hypoxia is also interpreted in the same light. Injection of propranolol evidently alleviates the harmful action of hypoxia, reduces cytolysis, and thereby removes the leading factor stimulating cell division. This hypothesis requires further experimental confirmation.

LITERATURE CITED

1. I. A. Alov, Cytophysiology and Pathology of Mitosis [in Russian], Moscow (1972).
2. S. V. Vdovenko, in: Clinical and Functional-Morphological Aspects of Adaptation to Natural and Production Conditions in the Far-Eastern Region [in Russian], Khabarovsk (1982), pp. 118-120.
3. S. V. Vdovenko and S. S. Timoshin, Byull. Éksp. Biol. Med., No. 8, 86 (1983).

4. P. A. Vunder, V. P. Vunder, and T. A. Andronova, Byull. Éksp. Biol. Med., No. 11, 1373 (1976).
5. P. D. Gorizontov, O. I. Belousova, and Yu. I. Zimin, Byull. Éksp. Biol. Med., No. 11, 20 (1974).
6. V. V. Zakusov (ed.), Clinical Pharmacology [in Russian], Moscow (1978), pp. 36-58 and 90-91.
7. F. Z. Meerson, Adaptation, Stress, and Prophylaxis [in Russian], Moscow (1981).
8. F. Z. Meerson et al., Vopr. Med. Khim., No. 2, 115 (1982).
9. S. S. Timoshin, "Effect of stressors on cell division in the albino rat corneal epithelium," Author's Abstract of Doctoral Dissertation, Moscow (1982).
10. J. W. Black et al., Br. J. Pharmacol., 25, 577 (1965).
11. W. S. Bullough, Life Sci., 16, 323 (1975).