EFFECT OF HYPOXIA ON CELL DIVISION IN THE CORNEAL AND LINGUAL EPITHELIUM OF ALBINO RATS

S. V. Vdovenko and S. S. Timoshin

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The writers showed previously that repeated exposure to severe stress causes activation of cell division: the number of mitoses increases and DNA synthesis is stimulated in the corneal epithelium. The level of pathological mitoses rises substantially under these circumstances [5]. The object of the present investigation was to study the character of the effect of repeated exposure to hypoxia on cell division.

EXPERIMENTAL METHOD

Experiments were carried out on 96 male albino rats weighing 170-200 g. The model of hypoxia consisted of daily "ascent" of the animals in a pressure chamber to an altitude of 9000 m for 4 h, for 7 days. The pressure in the chamber was reduced in steps at the rate of 4-5 m/sec. Processes of cell division were studied immediately after the final exposure and again 3, 6, and 24 h later. The animals were killed at 7 p.m. Histological preparations and autoradiographs were obtained and the mitotic index (MI), level of pathological mitoses (PM), mitotic index after injection of colchicine (MIC), index of labeled nuclei (ILN), and labeling index (LI) were calculated by methods described previously [2]. The values of MI, MIC, and ILN were expressed in pro mille, and the level of PM as a percentage of the total number of dividing cells. Since we were unable to obtain satisfactory autoradiographs of the corneal epithelium after intraperitoneal injection of ^{3}H-thymidine in a dose of 0.6 μCi/g ILN and LI were determined only in the lingual epithelium, immediately after "descent" and 3, 6, and 24 h later. The PM level was calculated only in total preparations of the corneal epithelium. As an indicator of development of a general adaptation syndrome the plasma concentration of 11-hydroxycorticosteroids (11-HCS) was used [4]. The experimental results were subjected to statistical analysis by Student's method.

EXPERIMENTAL RESULTS

Hypoxia induced the development of a stress reaction. This was shown by elevation of the 11-HCS level by 1.6 times after 3 and 24 h. The study of cell division showed that the corneal and lingual epithelium reacts similarly to repeated exposure to hypoxia (Table 1). Immediately after hypoxia, MIC of the corneal and lingual epithelium decreased by 10, 5, and 2 times respectively. The absence of a decrease in MI in the lingual epithelium at this time was probably due to lengthening of the duration of mitosis itself. This inhibition reflects a stereotyped reactive inhibition of mitosis during stress, due to intensified secretion of adrenocortical hormones [6-9]. Simulation of cell division processes took place in both types of tissue 3 h after the end of exposure: MIC in the cornea and tongue was increased by 2.2 and 1.5 times respectively, and MI in the cornea was increased by 2.6 times. The absence of any significant change in MI in the lingual epithelium evidently indicates shortening of the duration of mitosis itself. After 6 h no difference in the values of MI and MIC for both types of tissue could be observed in the control and experimental animals. A significant increase in MI and MIC was observed both in the cornea and in the tongue 24 h after the final exposure in the pressure chamber. At all times of investigation the PM level was 3 times higher. Under these circumstances the number of "bridges" — pathological mitoses connected with changes in the chromosomes themselves — was increased in the cornea of the

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TABLE 1. Effect of Hypoxia on Proliferation in Corneal and Lingual Epithelium of Rats (M ± m)

Time of investigation	Cornea			Tongue			
	MI, ‰	PM, %	MIC, ‰	MI, ‰	MIC, ‰	ILN, ‰	LI
Immediately after stay in pressure chamber	1,4±0,3*	21,9±2,6*	2,3±0,4*	13,5±1,3	15,2±1,4*	67,8±5,9	26,8±1,7*
3 h later	25,8±1,0*	23,8±1,3*	53,6±6,3*	14,1±2,0	44,2±3,8*	158,2±6,5*	25,2±1,1*
Control	10,1±1,7	7,4±0,6	24,1±2,9	11,3±1,7	30,3±2,5	89,1±8,9	19,3±1,8
6 h later	14,3±2,3	19,4±0,6*	33,3±4,4	5,8±0,7	19,3±1,6	130,9±6,2*	24,2±1,3*
24 h later	26,1±3,5*	18,6±1,0*	59,1±4,7*	14,9±1,0*	36,5±2,1*	128,8±15,9*	21,8±1,8
Control	13,6±1,3	6,1±0,9	35,3±3,6	5,0±0,5	17,5±1,2	83,8±5,5	19,7±1,1

Legend. *P < 0.05 compared with control; LI) number of tracks above nucleus.

experimental animals. No significant changes could be found in the ratio between the phase of mitosis in the experimental animals compared with the control. However, the presence of anaphase delay in the cornea after 3 h must be noted. This phenomenon (a combination of anaphase delay with "bridges") was described by the writers in other types of severe stress [2]. It was reproduced in cell culture after inhibition of RNA synthesis [1, 11]. The results of autoradiographic analysis demonstrate poststress stimulation of cell division. A significant increase in ILN, accompanying an increase in LI took place after 3 and 6 h. Poststress activation of cell division is evidently the result of shortening of the life span and acceleration of the turnover of cells in the mitotic cycle as a result of their mass death [10]. In the present experiments activation of DNA synthesis is interpreted as the structural trace of adaptation [3]. Elevation of the PM level in these experiments is evidence of the incompleteness of adaptation and is interpreted as the structural trace of disadaptation.

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