Reaction of Adrenal Medulla to Extreme Factors of Various Nature

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Experiments on mice show that primary decrease in the catecholamine content in the adrenals 6 h and 1-2, and 4 days after immobilization stress is followed by catecholamine accumulation in the adrenal medulla. Practically the same dynamics within days 1-4 is observed after administration of a high dose of 5-fluorouracil; however, the restoration of the initial catecholamine level in mice treated with the cytostatic takes more than in stressed animals. These data suggests that high doses of 5-fluorouracil induce nonspecific activation of the sympathoadrenal system, presumably leading to adaptation to cytotoxic effects of 5-fluorouracil.

Key Words: *catecholamines; adrenals; 5-fluorouracil; immobilization stress*

Activation of the sympathoadrenal system (SAS) is the major endocrine shift in stress [4]. It manifests itself as enhanced catecholamine secretion in the adrenal medulla and sympathetic nerve endings and as elevated catecholamine concentration in biological fluids [8] proportionally to the intensity and duration of stress [6,9]. There is evidence that general organism reactivity and functional state of SAS change against the background of cytostatic treatment [11].

The SAS is the main determinant of adaptation to adverse environmental and internal factors [7]. In light of this, it seems interesting to find out some general reactions of SAS to extreme factors of various nature. The aim of the present study was to compare the reaction of the adrenal medulla to immobilization stress and treatment with a high dose of 5-fluorouracil (5-FU).

MATERIALS AND METHODS

Experiments were carried out on 95 random-bred male mice weighing 18-20 g. The animals were either immobilized for 6 h in a supine position with fixed extremities or given a single intraperitoneal injection of 5-FU in a dose of 0.5 MPD (maximum permissible dose, 114 mg/kg). The mice were sacrificed by cervical dislocation under ether anesthesia 6 h and 1-8 days after the challenge. The content of epinephrine and norepinephrine was determined by chromaffin reaction [3]. To this end the adrenals were treated with 5% potassium chromate and bichromate (1:9) for 2 days. Photometry of stained cryostate sections was performed using a Univar cytophotometer (Reichert). The data were processed statistically using the Student's t test.

RESULTS

Histochemical visualization of biogenic amines showed 3 stages in the dynamics of the adrenal catecholamine content in mouse subjected to immobilization stress (Table 1). A decrease in the catecholamine concentration observed after 6 h and 1-2 (to 52-82%) and 4 days (to 76% of the initial value) was followed by a considerable rise of this parameter on day 6 of the experiment (by 27% in comparison with the initial level). In other words, the reaction of the chromaffin tissue to stress consists in the release of catecholamines involved into the formation of sustained adaptation of different tissues [7], followed by compensatory up-regulation of their synthesis. The

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TABLE 1. Intensity of Catecholamine-Specific Histochemical Reaction (Arbitrary Optical Density Units) in Adrenals of Random-Bred Mice at Different Terms After Immobilization and 5-FU Treatment ($X \pm m$)

Time	Immobilization	5-FU treatment
Before challenge	0.197±0.004	0.197±0.004
6 h	0.152±0.008*	0.157±0.009*
1 day	0.102±0.005**	0.114±0.009**
2 days	0.162±0.007*	0.164±0.009***
3 days	0.186±0.014	0.185±0.010
4 days	0.149±0.006**	0.162±0.007*
5 days	0.205±0.007	0.177±0.003***
6 days	0.250±0.008**	0.244±0.008*
7 days	0.189±0.005	0.247±0.011**
8 days	0.194±0.005	0.208±0.006

Note. *$p<0.01$, **$p<0.001$, *$p<0.02$ in comparison with the initial level (before treatment), *$p<0.01$, **$p<0.001$ in comparison with immobilized mice.

described processes are consistent with neurohormonal changes characteristic of adaptation (resistance) to extreme stimuli [6,9].

Of interest is the fact that the dynamics of epinephrine and norepinephrine content in adrenal chromaffin cells during the first 4 days after injection of 5-FU in a dose of 0.5 MPD practically did not differ from that observed in animals subjected to 6-h immobilization (Table 1). This parameters decreased 6 h and 1-2 and 4 days after the challenge. This can be attributed to enhanced secretion of catecholamines, since 5-FU has no toxic effects of the adrenals, vegetative ganglia, and sympathetic nervous system [5]. Moreover, 5-FU-induced stimulation of SAS accompanied by elevation of the catecholamine content in the blood and urine has been previously shown [11].

Some differences in the adrenal level of catecholamines under our experimental conditions were noted on days 5-8 (Table 1). These differences consisted in prolonged release and delayed accumulation of the transmitters in 5-FU-treated mice in comparison with animals subjected to immobilization. For instance, on day 5 the studied parameter significantly decreased, while on day 7 it increased in comparison with both intact mice (catecholamine content constitutes 90 and 125% of the initial value, respectively) and the stress-control (to 86 and 130%, respectively). The presence of afferent and efferent nerve fibers forming reflex arches in different tissues enables coordinated functioning of executive and neuroendocrine organs [2]. It was hypothesized that afferent nerve fibers susceptible to "the growth pressure" are present in the hemopoietic tissue [12]. It seems likely that opposite biological effects of 5-FU and immobilization stress, namely, the long-term pronounced hypoplasia of actively proliferating tissues in the first case [5] and burst hyperplasia in the second case [1] are responsible for the above-described differences in the reaction of chromaffin tissue to the studied extreme factors.

Of importance also is a similar pattern of changes in the catecholamine concentration in the adrenal medulla in response to different extreme influences. Our findings suggest that treatment with high doses of 5-FU triggers nonspecific activation of SAS, contributing to the dynamics of postcytostatic repair processes in cell systems, for instance, in hemopoietic tissue [10]. Analogous activation of SAS was also observed in experiments with other cytostatics (L-asparaginase and cyclophosphamide) [11].

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