Differences in Behavioral Patterns and Resistance to Stress-Induced Gastric Ulceration between August and Wistar Rats Adapted and Unadapted to Hypoxia

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 128, No. 12, pp. 638-641, December, 1999
Original article submitted February 22, 1999

The incidence of gastric ulceration induced by acute emotional stress in Wistar rats is 3 times higher than in August rats, and the mean number of gastric ulcers in Wistar rats 6.3-fold surpassed that in August rats. Wistar rats predisposed to stress-induced ulceration displayed suppressed locomotor and exploratory activities in the open field test, while August rats had more stable behavioral patterns and enhanced exploratory activity after stress. Short-term preadaptation to hypobaric hypoxia for 6 days attenuated stress-induced gastric ulceration, whereas long-term adaptation (40 days) aggravated the severity of gastric ulcers in August and Wistar rats. The interstrain differences in stress-induced ulceration persisted after adaptation. The data suggest that these differences are related to genetically determined peculiarities of production and metabolism of NO and glucocorticoids in August and Wistar rats.

Key Words: *August and Wistar Rats; stress; ulcer formation; adaptation; behavior*

August rats are less resistant to stress-induced damages to the cardiovascular system than Wistar rats, which are assumed to be more resistant to emotional stress [9,13]. However, in stressed August rats the rise in blood concentration of creatine phosphokinase (marker of injuries) is less pronounced [8], and the primary immune response to sheep erythrocytes was greater than in stressed Wistar rats [11]. Therefore, various systems of the body have different genetically determined resistances to stress-induced damages. Here we studied gastric ulceration and behavioral changes induced by emotional stress in August and Wistar rats. The effect of preadaptation to hypobaric hypoxia (AH) possessing protective properties in stress [7] on stress-induced gastric ulceration was assessed.

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MATERIALS AND METHODS

Experiments were performed on 129 male August and Wistar rats weighing 250±30 and 300±50 g, respectively. In series I, stress-induced formation of gastric ulcers in intact rats and animals adapted to hypobaric hypoxia was studied. In series II, open field (OF) behavior of intact fasted or sated rats and stressed fasted rats was tested [14]. The rats deprived of food for 24 h were placed for 30 min into a standard cage (50×30×20 cm) filled with water (22°C, 15-cm layer) and covered with a grid (5 cm form water surface) [1]. The total length and area of gastric ulcers were assessed 1 h after stress. The OF behavior of each rat was tested for 4 min, and the numbers of peripheral and central ambulations (horizontal activity) and peripheral and central rearings with and without support (vertical activity) were recorded. Long-term and short-term AH were conducted in a hypobaric pressure chamber of the extract-and-influx type. Long-term AH was performed for 1, 2, 3, and 4 h at simulated alti-

0007-4888/99/0012-1213$22.00

tudes of 1000, 2000, 3000, and 4000 m above sea level on days 1, 2, 3, and 4-40, respectively (5 procedures a week, a total of 40 procedures). Short-term AH was conducted for 10, 20, and 30 min at a simulated altitude of 5000 m above sea level on days 1, 2, and 3, respectively (a total of 6 procedures); the course was repeated after 2 days. The animals were stressed on the next day after completion of AH. The results were analyzed by Wilcoxon—Mann—Whitney (behavior) and Student's *t* tests (ulceration).

RESULTS

The incidence of stress-induced gastric ulceration in August rats was lower than in Wistar rats (Table 1). Stress-induced gastric ulcers were found in 5 of 17 (29%) and in 11 of 14 (14%) unadapted August and Wistar rats, respectively (Table 1). The number of gastric ulcers per group and per stomach in Wistar rats was 5.2 and 6.3 times greater, respectively, than in August rats, and the area of ulcers in Wistar rats surpassed that in August rats. Thus, August rats were more resistant to stress than Wistar rats. These results are consistent with previously reported data showing that stress induced a less pronounced rise in blood creatine phosphokinase in August rats compared to Wistar rats [8].

Differences in the severity of stress-induced gastric ulcers between August and Wistar rats persisted after preliminary AH. Short-term AH produced stress-protective effects on gastric mucosa (Table 1), especially in August rats (only 1 small ulcer in only 1 animal). The total number of stress-induced gastric ulcers and their mean area per stomach in adapted Wistar rats 3-fold surpassed those in unadapted animals. Interstrain differences in the severity of stress-induced ulcers persisted after short-term AH: by contrast to August rats, Wistar rats had considerable gastric damages. Long-term AH did not prevent ulceration of the gastric mucosa, but even stimulated this process (Table 1). Stress caused gastric ulcers in 6 of 7 August rats underwent long-term AH, and in 5 of 17 unadapted animals; the total area of ulcers after long-term AH 3-10-fold surpassed that in unadapted animals. Interstrain differences in the degree of stress-induced gastric ulceration were also retained after long-term AH: Wistar rats developed more severe ulcers than August rats (Table 1).

Sated August rats displayed lower horizontal activity, higher vertical activity, and more visits to the central zone in OF than sated Wistar rats (Table 2). Therefore, exploratory activity of August rats was more resistant to novel environmental conditions (OF). Food deprivation (weak stress) induced similar behavioral shifts in both rat strains: increased the number of visits to the central zone and stimulated vertical activity (especially Wistar rats). These results agree with the fact that fasted rats display high exploratory activity [14]. Strong emotional stress (water immersion in the cage) revealed marked interstrain differences in rat OF behavior. Wistar rats peripheral and central rearings (vertical activity) and central ambulations disappeared, which indicated a considerable anxiety reaction [14]. However, stressed August rats retained the behavioral pattern typical of intact animals and displayed even more central ambulations than intact animals.

Thus, August rats were highly resistant to gastric ulcer formation induced by emotional stress and displayed relatively stable behavioral pattern and enhanced exploratory activity in OF, while Wistar rats had severe gastric ulcers and characterized by suppressed locomotor and exploratory activities in OF after stress.

Stress-induced ulceration results from linear ischemic necroses of gastric mucosa caused by vasoconstriction due to enhanced release of catecholamines [2,12]. It was shown that suppressed production of the major vasodilator NO in the stomach (a local stress-protective factor) plays a key role in adrenergic vasoconstriction and ischemic injuries [15]. Thus, the higher resistance of August rats compared to Wistar rats to stress-induced gastric ulceration is probably due to more intense basal and poststress NO production [6].

TABLE 1. Stress-Induced Gastric Ulceration in August and Wistar Rats Unadapted (Control) and Adapted to Hypoxia ($M\pm\sigma$)

Parameters	August			Wistar		
	control (n=17)	STAH (n=9)	LTAH (n=7)	control (n=14)	STAH (n=8)	LTAH (n=7)
Number of rats with gastric ulcers (%)	5 (29)	1 (10)	6 (85)	11 (79)	6 (75)	6 (85)
Total number of ulcers per group	13	1	19	67	21	27
Total number of ulcers per rat	0.76±0.29	0.11±0.10*	2.7±0.28*	4.8±1.2	2.62±0.62	3.85±1.00
Total length of ulcers per stomach, mm	0.73±0.27	0.22±0.20*	4.1±1.28*	9.2±1.28	2.92±0.80*	16.82±6.5
Total area of ulcers per stomach, mm^2	0.23±0.08	0.11±0.1*	2.05±0.67*	5.94±1.71	2.00±0.70*	8.41±3.20

Note. STAH and LTAH: short-term and long-term adaptations, respectively. Differences between STAH, LTAH, and control group, and between August and Wistar rats are significant; *$p<0.05$ compared with the control.

TABLE 2. Effect of Stress on Behavior of August and Wistar Rats in Open Field Test

Locomotor activity	August			Wistar		
	Sated (23)	Fasted (5)	Food deprivation+ stress (5)	Sated (24)	Fasted (5)	Food deprivation+ stress (5)
Horizontal locomotor activity						
Total number of crossed squares	34.8	34.2	36.0	47.9°	47.6°	41.0°
Number of crossed central squares	5.0	12.3*	23.9*+	2.0°	7.1°	0°*+
Vertical locomotor activity						
Total number of rearings	22.2	27.8	22.8	9.9°	12.4°*	6.8°+
Number of rearings without support, %	24.0	18.0	28.9+	5.1°	16.0*	0°*+

Note. Significant differences: °compared with August rats, *compared with sated rats, and +compared with fasted rats. The number of animals is shown in parentheses.

It should be emphasized that August and Wistar rats have various basal and poststress activities of the hypothalamo-pituitary-adrenocortical system and, therefore, different blood concentrations of glucocorticoids preventing stress-induced ulceration [1]. It was shown that basal and poststress contents of glucocorticoids in the blood of August rats are much higher than in Wistar rats [8,13].

Enhanced gastric ulceration induced by stress after long-term AH (instead of the expected protective effect) can also be associated with changes in NO metabolism. Long-term AH suppressed the basal (by 2-3 times) and carbachol-induced NO production [3], which can potentiate stress-induced vasoconstriction in the stomach and, therefore, promote ulceration of the gastric mucosa. The mechanism of these changes in NO metabolism during AH remains unclear. Recent experiments on Wistar rats showed that long-term AH stimulated NO accumulation in the endothelium, and the rate of this process exceeded that of NO production [4]. These data suggest that the content of active NO in organs decreases under these conditions. The protective effects of short-term AH are probably associated with the fact that the initial stage of adaptation is accompanied by activation of stress systems and enhanced secretion of glucocorticoids [5], which protect gastric mucosa under stress conditions [10]. Moreover, NO accumulation does not dominate over NO production during short-term AH [4].

Thus, August rats predisposed to damages to the cardiovascular system induced by stress [9] are more resistant to stress-induced gastric ulceration and behavioral changes than Wistar rats. The data confirm our assumption that genetically determined resistance to stress is not universal, but rather specific for different systems of the body.

This work was supported by the Russian Foundation for Basic Research (grant No. 99-04-48823).

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