Gastric Mucosal Lesions Caused in Rats of Different Strains by Emotional Stress, and the Protective Effect of Interleukin 1β

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Acute emotional stress results in damage to gastric mucous membranes in August, Wag, and particularly Wistar rats. The damage is less severe in rats preinjected with interleukin 1β into a lateral ventricle of the cerebrum.

Key Words: *emotional stress; interleukin 1β; brain; gastric lesions*

It has been established that individual sensitivity to stress agents depends on genetic factors [5], the state of stress-limiting systems [2], and on the stability of mechanisms by which self-regulation of particular functional systems is effected [3].

Rats of different strains differ in their sensitivity to emotional stress (ES). In terms of cardiovascular parameters, for example, Wistar and Wag rats are more resistant to acute ES than August rats, but are more prone to develop gastric lesions in response to such stress [1,4]. Interleukin 1β (IL-1β), being a transmitter of the acute phase of stress reactions [7], stimulates the secretion of CRF, ACTH, corticosterone, and β-endorphin. On the other hand, its injection into a lateral cerebral ventricle was found to prevent or diminish gastric damage in acute ES [10,11]. This protective effect was due to the central action of IL-1β as it did not occur when the interleukin was injected intraperitoneally in the same doses and was only observed after much higher intravenous doses.

In this comparative study we evaluated the sensitivity to acute ES in three strains of rats with genetically determined differences in resistance to stressful situations and measured the effects of IL-1β injected into a lateral cerebral ventricle on the severity of gastric lesions induced by acute ES in rats of these strains.

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MATERIALS AND METHODS

For the study, male rats of the strains August (196.1±4.1 g; n=19), Wistar (180.4±11.2 g; n=16), and Wag (268±13.9 g; n=13) were used. They were kept in cages, 4 animals in each, at 20-22°C (daylight hours from 3:45 to 21:15) with free access to food and water.

Five days before the tests, a guiding steel cannula 3 mm long and 0.8 mm in diameter was implanted under Nembutal anesthesia (40 mg/kg body weight) into the skull bone of each rat 1 mm rostral to the lambda and 1 mm to the right of the sagittal suture. The cannula was so positioned that it neither made contact with the brain tissue nor penetrated into the cavity of the lateral ventricle. Its outer end was fixed with protracryl. Four days after cannula implantation, the behavior of the rats was assayed in the open field test.

On the 5th day after the implantation, IL-1β or physiological saline was injected in the lateral ven-

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TABLE 1. Effect of Acute Stress on the Mean Number and Overall Extent of Gastric Lesions. The Values are Means±SD

Rat strain	Mean number of lesions		Mean extent of lesions, mm	
	Saline, 10 μl	IL, 100 ng/10 μl saline	Saline, 10 μl	IL, 100 ng/10 μl saline
August	0.67±0.33 2.60±0.24	0.33±0.21 1.20±0.58	1.00±0.46 10.88±4.24	0.63±0.34 9.34±6.38
Wistar	1.00±1.00 3.00±0.00	0.50±0.50 2.50±0.29	0.93±0.93 23.32±4.50	1.40±1.21 17.25±3.49
Wag	0.00±0.00 2.25±0.48	0.00±0.00 1.60±0.40	0.00±0.00 7.55±2.88	0.00±0.00 10.72±3.83

Note. Numerator – control animals; denominator – stressed animals.

tricle through the guiding cannula by means of a Hamilton microsyringe (USA) whose needle was introduced to a depth of 3 mm from the brain surface.

The rats of each strain were divided into four groups. Rats of group 1 were injected with IL-1β (100 ng in 10 μl saline) and exposed to acute ES, rats of group 2 were injected with IL-1β in the same dose and then returned to their cages, while those of groups 3 and 4 received saline (10 μl) instead of IL-1β and were then acutely stressed (group 3) or returned to their cages (group 4). Human recombinant IL-1β (activity 3×10^7 U/μl) obtained from the Institute of Immunology was used.

During 24 h prior to the tests, the rats were deprived of food while being given water ad libitum. Acute stress was produced by the method of Overmier *et al.* [9]: rats were placed in plastic tubes 16.5 cm in length and with an inner diameter of 5.5 cm and immersed in water (23°C) up to the xiphoid process for 2 h, after which they were held in ordinary cages for another 2 h and then decapitated. The thymus, adrenals, and spleen were removed and weighed. The stomach was removed, opened along the greater curvature, and washed; the number of lesions in the stomach was counted under a binocular microscope and their extent was measured (in mm) with an eyepiece micrometer. The severity of gastric damage in each rat was described in terms of the total number and overall length of lesions.

The results were evaluated by analysis of variance taking into account three factors: stress, the solution used (IL-1β or saline), and strain. For multiple comparisons, the LSD test was used. The numerical values appearing in Table 1 and in the text below are means with their standard deviations.

RESULTS

The acute stress increased significantly the number of gastric lesions ($F=47.3$; $p<0.0001$) and their overall length ($F=31.8$; $p<0.0001$) in rats of all three strains, but in Wistar rats both the number of lesions (LSD, $p<0.05$) and their overall length (LSD, $p<0.05$) were greater than in August and Wag rats (Table 1).

After the injection of IL-1β, the number of stress-induced gastric lesions was significantly lower in August rats (by 53.8%; $F=5.8$; $p<0.03$) while the decreases recorded for the other two strains did not reach the level of statistical significance.

IL-1β virtually did not affect the overall length of gastric lesions in any strain. This result agrees with the observation that quantitative estimates of the degree to which the gastric mucosa is lesioned in acute ES may vary [8].

The relative weight of the thymus decreased significantly by 50% ($F=9.8$; $p<0.02$) in both groups (IL-1β- and saline-treated) of acutely stressed Wag rats. No significant differences were detected for the August or Wistar rats.

For Wag rats, the two-factor analysis of variance revealed a significant effect ($F=25.9$; $p<0.001$) of IL-1b on the relative weight of the adrenals, which increased by 22.2% (LSD, $p<0.01$). The acute ES did not affect this parameter. The increase in adrenal weight after IL-1β injection presumably occurred because of an increased release of glucocorticoid hormones as a result of IL-1β-stimulated secretion of CRF and ACTH [6].

The ES factor did, however, have a significant effect on the relative weight of the spleen, which decreased by 23.3% ($F=8.4$; $p<0.011$) in August rats, by 28.5% ($F=7.6$; $p<0.02$) in Wistar rats, and by 22.9% ($F=12.5$; $p<0.01$) in Wag rats.

In summary, the acute ES caused damage to the gastric mucosa in August and Wag rats and to a still greater extent in Wistar rats, the damage being less severe after IL-1β injection into a lateral cerebral ventricle. The factors determining individual and genetic differences in resistance to acute ES among rats as well as the mechanisms through which IL-1β exerts its stress-protecting effect are subjects for further studies.

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Time Course of Serotonin in Platelets from Patients with Affective Disorders

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Temporal variations in platelet levels of serotonin were found to be significantly decreased in patients with endogenous affective disorders, particularly those with the bipolar type of manic-depressive psychosis. The time course of serotonin content in these cells was not affected by either the sex or the age of the patients. *In vitro* incubation with lithium oxybutyrate raised mean platelet serotonin levels and stabilized their fluctuation in platelets from healthy subjects but not in those from the mental patients.

Key Words: *serotonin; platelets; lithium; depression*

It has been established beyond doubt that the serotoninergic system plays a substantial role in the pathogenesis of affective disorders. The systems of secondary messengers in neurons and platelets, the mechanisms of serotonin release, uptake, and storage by these cells, and their receptors for serotonin and imipramine have a number of similar characteristics so that platelets may be used as a convenient model for the study of serotonin transport in health and in mental disorders [9].

The purpose of this study was to examine the time course of platelet serotonin in patients with affective disorders before and during treatment and the effect of lithium oxybutyrate on the serotonin concentration in these cells *in vitro*.

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MATERIALS AND METHODS

Temporal variations in platelet serotonin were examined in 16 patients with primary endogenous affective disorders, in 11 patients with a depressive syndrome in the framework of other mental disorders (neurosis or organic brain disease), and in 20 mentally healthy donors. The patients were examined on admission to the clinic before the initiation of pharmacotherapy (or during the 2-week period before admission if pharmacotherapy was not administered) and during remission. The depression in all cases was classified as pronounced (a mean score of 26.6 on Hamilton's scale).

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