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ALLEVIATION OF STRESS AND GASTRIC ULCERATION BY GAMMA-HYDROXYBUTYRIC ACID

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The effect of preliminary administration of sodium hydroxybutyrate (GHBA) on activation of the adrenergic and pituitary-adrenal systems during emotional-pain stress and on the severity of gastric ulcers after the end of such stress was studied in experiments on rats. Preliminary administration of GHBA was shown to restrict excitation of the systems responsible for stress and to prevent the development of ulceration of the gastric mucosa. It can be suggested that activation of the GABA-ergic inhibitory system arising during stress is the sole mechanism of limitation of the stress reaction and of prevention of stress-induced injuries.

KEY WORDS: emotional-pain stress; noradrenalin; corticosterone; sodium γ-hydroxybutyrate; gastric ulcers.

Recent investigations have shown that in emotional-pain stress (EPS) marked activation of the inhibitory GABA-ergic system of the brain is regularly observed [3]. This activation is brought about in such a way that it must lead to an increase in the formation of a terminal metabolite of the GABA system in the brain – sodium hydroxybutyrate (GHBA), a substance which has now been shown to have a strong and direct inhibitory action [6]. It has accordingly been postulated that activation of the GABA-ergic system through the action of GHBA limits excitation of the adrenergic and pituitary-adrenal system in stress and thereby prevents stress-induced injuries to the internal organs.

To test this hypothesis, in the present investigation the effect of preliminary injection of GHBA on activation of the adrenergic and pituitary-adrenal systems during EPS and on the severity of gastric ulceration, which are usually observed after exposure to EPS, was studied.

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar rats weighing 180-200 g. EPS was evoked in the form of an anxiety neurosis by Desiderato's method [4] and it lasted 6 h. GHBA was injected subcutaneously in a dose of 100 mg/kg 30 min before EPS, and also 2 and 4 h after the beginning of EPS. Physiological saline was injected into the control animals at these same times.

The concentration of corticosterone in the adrenals, blood plasma, and heart was determined by chromatography on silica-gel columns [1]. The noradrenalin concentration in the adrenals and heat was determined by a fluorometric method [2]. The animals were decapitated for determination of corticosterone and noradrenalin 1 and 6 h after the beginning of EPS, and also 2 h after the end of EPS.

Ulcers observed in the gastric mucosa after EPS are the result of digestion of areas of the mucosa in which foci of ischemic necrosis occurred previously [5]. They were assessed quantitatively by measurement of the total length of the ulcers present in the stomach of rats killed at the end of a period of rest of 2 h after termination of EPS.

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TABLE 1. Effect of GHBA on Dynamics of Corticosterone and Noradrenalin Concentration during EPS (M ± m)

Experimental conditions (n = 10)	Corticosterone, μg%			Noradrenalin, μg/g tissue	
	plasma	heart muscle	adrenals	heart muscle	adrenals
Control	6,8±1,07	14,9±2,6	1018,0±324,0	0,70±0,06	117,1±13,9
EPS for 1 h	26,5±0,9*	67,2±8,2*	3287,5±158,3*	0,38±0,05*	65,5±14,2‡
GHBA +EPS for 1½ h	23,3±4,8†	30,3±2,6*	2533,0±221,8†	0,63±0,15	81,8±14,1
EPS for 6 h	24,3±1,8*	66,5±7,9*	2375,0±238,0†	0,36±0,08†	76,7±13,2‡
GHBA +EPS for 6½ h	11,9±1,8‡	32,1±4,6†	1415,0±267,0	0,57±0,09	128,9±18,6
EPS for 6 h + rest of 2 h	22,7±1,3*	24,0±2,3‡	2260,6±424,7‡	0,39±0,07†	109,8±10,5
GHBA + EPS for 6 h + rest of 2 h	13,8±1,2*	15,0±2,6	1371,9±354,0	0,70±0,04	99,2±17,6

*P < 0.001.

†P < 0.01.

‡P < 0.05.

EXPERIMENTAL RESULTS

The results given in Table 1 show that the doses of GHBA used significantly (by 50-67%) reduced activation of the stress-realizing systems.

The noradrenalin concentration in the adrenals 1 and 6 h after the beginning of EPS was reduced by 40 and 50 μg/g respectively, whereas in the heart it was reduced by almost half. Against the background of GHBA all these changes, evidence of increased catecholamine expenditure and activation of adrenergic regulation, were not significant, i.e., they were essentially prevented.

The model of EPS used led to the development of ulcers in the gastric mucosa of all animals without exception, with a mean length of the ulcers per stomach of 10.5 ± 1.1 mm. After preliminary injection of GHBA, 28% of the animals did not develop ulcers, and in the rest their mean length was 3.3 ± 1.4 mm, only one-third of that during EPS without GHBA.

Injection of GHBA thus limits excitation of the stress-realizing systems and so prevents ulceration of the gastric mucosa during EPS. This fact is in harmony with the view that activation of the GABA-ergic inhibitory system, developing in the brain during stress, is a natural mechanism of limitation of the stress reaction and of prevention of the pathological consequences of stress.

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