Mechanism for the Inhibition of Contractile Activity of the Gastric Antrum and Pylorus in Rabbits during Psychogenic Stress

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Psychogenic stress in rabbits (fixation to a frame) was accompanied by the inhibition of contractile activity of the gastric antrum and pylorus. These changes persisted during blockade of muscarinic receptors, nicotinic receptors, α_2-adrenoceptors, and β_1/β_2 adrenoceptors. A stress-induced decrease in gastric motor activity was mediated by the nonadrenergic noncholinergic mechanism. It resulted from the influence of a hormonal stress factor on the stomach, which was probably realized through nonadrenergic inhibitory neurons of the enteric nervous system.

Key Words: *psychogenic stress; contractile activity of the stomach*

Stress has an inhibitory effect on evacuation function of the stomach [8]. Our previous studies revealed that psychogenic stress is accompanied by a decrease in contractile activity (CA) of the gastric antrum and pylorus in rabbits [1], which is consistent with published data [6]. According to current concepts, the stress-induced changes in motor activity of the gastrointestinal tract are related to central activation of the sympathetic and parasympathetic autonomic nervous system and neurons of the myenteric plexus, release of catecholamines from the adrenal medulla, and influence of corticotropin-releasing hormone, urocortins, thyrotropin-releasing hormone, and other hormonal factors, including regulatory peptides (*e.g.*, vasopressin and glucagon-like peptide-1).

Here we studied the role of nicotinic receptors, muscarinic receptors, and α- and β-adrenergic and α_2-adrenergic cholinergic mechanisms in the stress-induced decrease in CA of the stomach.

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MATERIALS AND METHODS

Chronic experiments were performed on male rabbits weighing 2.5-3.0 kg. Bipolar loop electrodes were implanted to 6 animals (according to the requirements for abdominal operation). Electrodes were implanted into the subserous layer of the gastric antrum and pylorus. The study was conducted 10-12 days after surgery. The animals had free access to food and water during this period. Myoelectric activity (MEA) of the stomach was recorded on an ERG-16s encephalograph (time constant 0.1; write speed 7.5 mm/sec; sensitivity 250 mV; 1-cm deviation of the writing point).

After recording of baseline MEA, the rabbits were fixed by their limbs to a frame in the supine position to induce psychogenic stress. The stress response in rabbits is manifested in a sharp increase in heart rate [2] and elevation of adrenocorticotropic hormone, corticosteroids, epinephrine, and norepinephrine in blood plasma [3,7].

The effect of stress exposure on CA of the stomach was studied under control conditions (5 tests), blockade of muscarinic receptors (0.5 mg/kg methacin, 5 tests), nicotinic receptors (7 mg/kg

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TABLE 1. ICA of the Gastric Antrum and Pylorus under Stress Conditions before and after Blockade of α_2-Adrenoceptors and β_1/β_2-Adrenoceptors and Nonselective Blockade of α-Adrenoceptors, Muscarinic Receptors, and Nicotinic Receptors ($M \pm m$)

Type of blockade, portion of the stomach		Baseline	Stress exposure			
			phase 1		phase 2	
			abs.	Δ, %	abs.	Δ, %
Control (n=5)	antrum	5.5±1.0	0.9±0.3**	-83	3.1±0.2*	-44
	pylorus	15.8±1.3	7.0±1.0***	-56	12.7±1.1	-20
α_2-Adrenoceptors (n=5)	antrum	2.5±0.4	0***	-100	1.5±0.5	-40
	pylorus	12.9±1.3	0.9±0.4***	-93	3.2±0.8***	-75
β_1/β_2-Adrenoceptors (n=5)	antrum	10.4±1.2	1.9±1.3***	-82	5.9±0.8**	-43
	pylorus	16.9±1.6	9.1±1.1***	-46	14.5±1.3	-14
Nonselective blockade, α-adrenoceptors (n=6)						
	antrum	1.5±0.5	1.3±0.3	-13	2.0±0.4	+33
	pylorus	6.7±1.5	5.7±0.8	-15	9.9±1.0	+48
Muscarinic receptors (n=5)	antrum	3.2±1.0	0.2±0.2*	-94	1.8±0.7	-44
	pylorus	11.5±1.2	4.6±1.0**	-60	9.2±1.3	-20
Nicotinic receptors (n=6)	antrum	6.4±2.0	0*	-100	0.9±0.5*	-86
	pylorus	8.3±1.8	1.4±0.5**	-83	6.1±1.5	-27

Note. *p<0.05, **p<0.01, and ***p<0.001 compared to the baseline.

benzohexonium, 6 tests), β_1/β_2 adrenoceptors (1 mg/kg propranolol, 5 tests), and α_2-adrenoceptors (1 mg/kg yohimbine, 5 tests), and nonselective blockade of α-adrenoceptors (0.5 mg/kg dihydroergotoxin, 6 tests). Test compounds were injected subcutaneously.

MEA was analyzed quantitatively during two 30-min periods after the start of stress (phases 1 and 2 of the response). CA was evaluated from the index of contractile activity (ICA). ICA was calculated as the product of the number of trains of action potentials over 40 sec and average amplitude of trains of action potentials over 40 sec (mm). This index was expressed in arbitrary units. The column "baseline" in Table 1 represents the following parameters: control series, mean values of ICA over 30 min before stress exposure; and series with receptor blockade, mean values of ICA for CA of the stomach after treatment with the corresponding antagonist of adrenoceptors or cholinoceptors (30 min before stress exposure).

The results were analyzed by means of Origin 6.1 software. We calculated the arithmetic mean

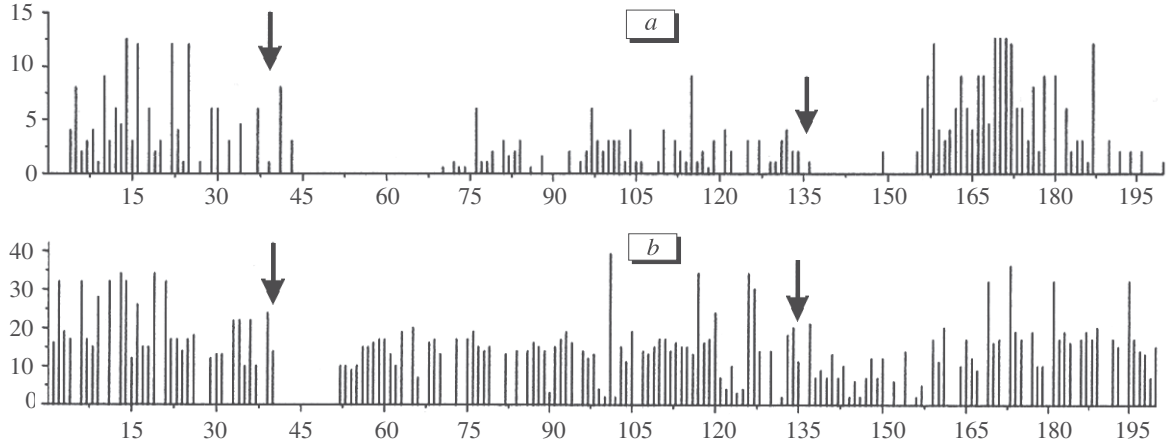

Fig. 1. ICA of the gastric antrum (*a*) and pylorus (*b*) during psychogenic stress. First arrow: start of stress; second arrow, cessation of stress. Here and in Figs. 2 and 3: abscissa, order numbers of 40-sec intervals in MEA recording; ordinate, ICA.

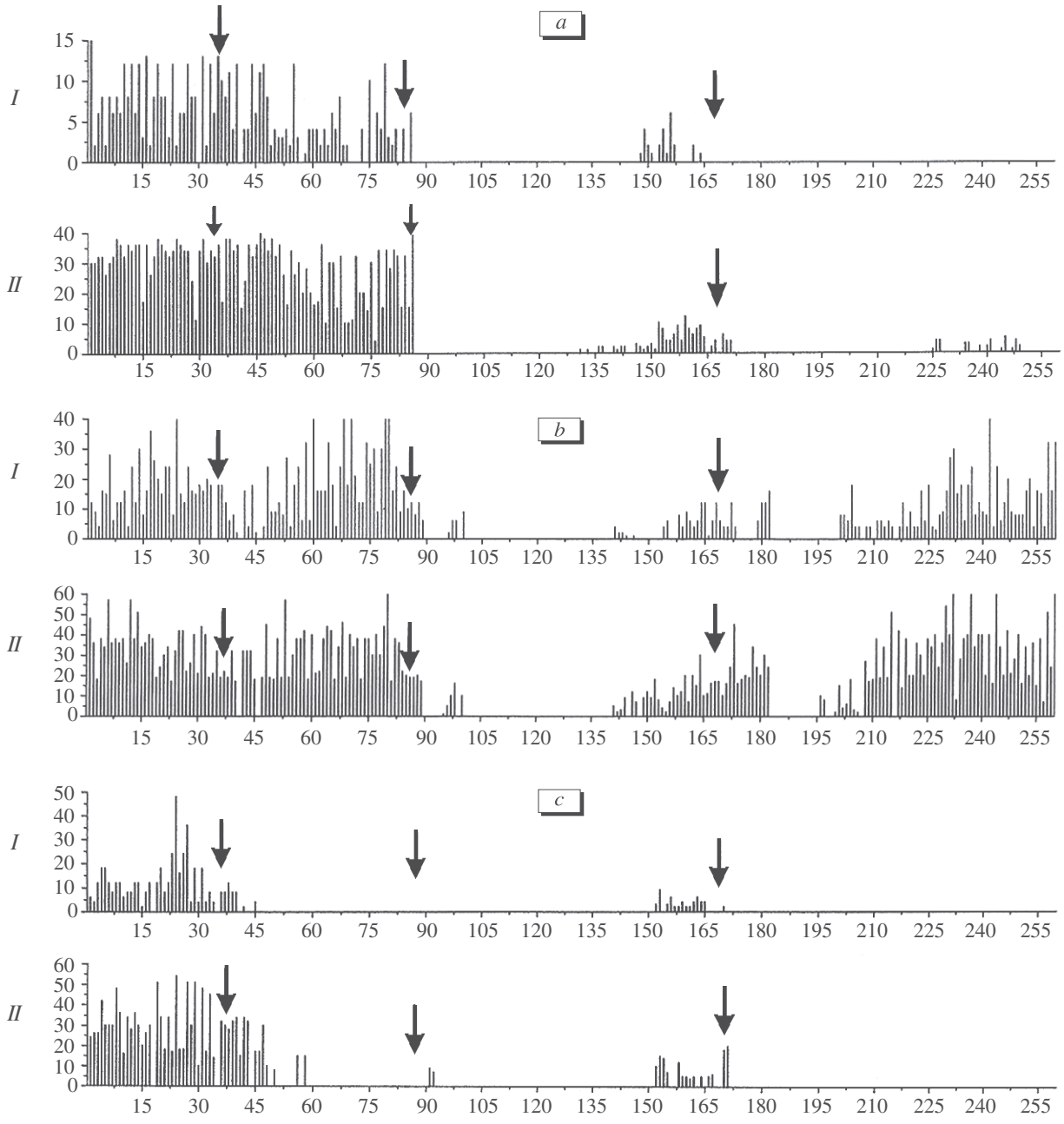

Fig. 2. ICA of the gastric antrum (*I*) and pylorus (*II*) during psychogenic stress upon blockade of α_2-adrenoceptors (*a*) and β_1/β_2-adrenoceptors (propranolol, *b*) and nonselective blockade of α-adrenoceptors (dihydroergotoxin, *c*). Here and in Fig. 3: first arrow, subcutaneous injection of antagonist; second arrow, start of stress; third arrow, cessation of stress.

and standard error of the mean. The significance of differences between mean values in independent samples was evaluated by analysis of variance (ANOVA).

RESULTS

Stress was followed by the inhibition of CA (Fig. 1; Table 1). ICA of the gastric antrum and pylorus decreased by 83 and 56%, respectively, in phase 1 of the response. The mean value of ICA in both portions of the stomach remained low in phase 2 of the response.

ICA of the gastric antrum and pylorus decreased by 100 and 93%, respectively, in phase 1 of the response under conditions of α_2-adrenoceptor blockade (Fig. 2, *a*; Table 1). The mean value of ICA in the gastric antrum and pylorus were below the baseline in phase 2 of the response (by 40 and 75%, respectively). ICA of the gastric antrum and

pylorus decreased by 94 and 60%, respectively, in phase 1 of the response under conditions of muscarinic receptor blockade (Fig. 3, *a*; Table 1). The mean value of ICA in the gastric antrum and pylorus remained below the baseline in phase 2 of the response (by 44 and 20%, respectively).

These data indicate that stress exposure during blockade of α_2-adrenoceptors and muscarinic receptors is followed by the inhibition of CA of the gastric antrum and pylorus (similarly to the control). Therefore, a decrease in CA of the gastric antrum and pylorus does not result from the influence of circulating catecholamines on α_2-adrenoceptors in cholinergic effector neurons of the enteric nervous system. This process is mediated by the nonadrenergic noncholinergic mechanism.

During blockade of β_1/β_2 adrenoceptors with propranolol, ICA of the gastric antrum and pylorus was shown to decrease in phase 1 of the response (by 82 and 46%, respectively; Fig. 2, *b*; Table 1). The mean value of ICA in both portions of the stomach remained low in phase 2 of the response (Table 1). These data indicate that stress exposure during blockade of β_1/β_2 adrenoceptors is followed by a decrease in motor activity of the gastric antrum and pylorus (similarly to the control). We conclude that a stress-induced decrease in motor activity of the gastric antrum and pylorus is not associated with the action of circulating catecholamines on inhibitory β-adrenoceptors in smooth muscle cells. Hence, this process is not mediated by the β-adrenergic mechanism.

α-Adrenoceptor blockade with dihydroergotoxin was accompanied by a significant decrease in CA of the gastric antrum and pylorus (by 84 and 73%, respectively). It should be emphasized that CA was undetected before the start of stress exposure (Fig. 2, *c*). Under these conditions, an inhibitory effect of stress on the stomach could not be manifested in the reduction of CA. However, motor activity was also suppressed during α-adrenoceptor blockade (as compared to the pre-blockade level; Fig. 2, *c*). The increase in CA during stress exposure was statistically insignificant (Table 1). Probably, α-adrenergic inhibition due to the effect of catecholamines on inhibitory α-adrenoceptors in smooth muscle cells does not contribute to a stress-induced decrease in CA of the gastric antrum and pylorus.

Our findings indicate that a decrease in CA of the gastric antrum and pylorus during psychogenic stress is not related to the action of circulating

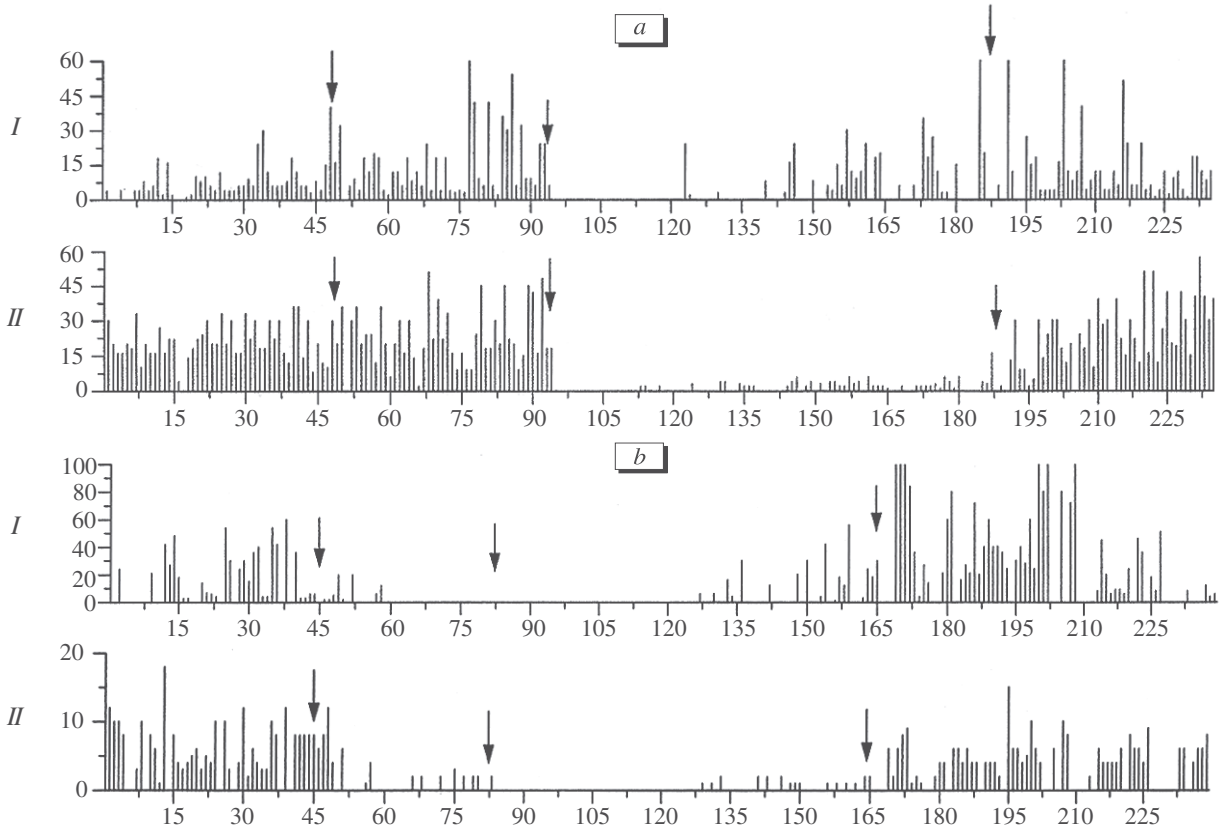

Fig. 3. ICA of the gastric antrum (*I*) and pylorus (*II*) during psychogenic stress upon blockade of muscarinic receptors (*a*) or nicotinic receptors (*b*).

catecholamines on presynaptic α_2-adrenoceptors in cholinergic neurons or inhibitory α-adrenoceptors and β-adrenoceptors in smooth muscle cells. This inhibition is not mediated by the adrenergic cholinergic or adrenergic mechanism.

The inhibition of CA in the gastrointestinal tract is primarily associated with activation of nonadrenergic inhibitory neurons in the enteric nervous system. This process involves such neurotransmitters as NO, VIP, and PACAP. This type of inhibition received the name "nonadrenergic noncholinergic inhibition". Stimulation of nonadrenergic inhibitory neurons is probably related to the neurogenic effect (realized via interneurons of the enteric nervous system) and action of hormonal factors.

Blockade of ganglionic transmission in the autonomic nervous system prevents the neurogenic stimulatory effect on nonadrenergic inhibitory neurons of the enteric nervous system. The stress-induced inhibition of CA of the gastric antrum and pylorus was observed during blockade of ganglionic transmission (*i.e.*, blockade of nicotinic receptors with benzohexonium; Fig. 3, *b*, Table 1). Therefore, a stress-induced decrease in CA of the stomach does not result from neurogenic stimulation of nonadrenergic inhibitory neurons. It may be suggested that the humoral stress factor serves as a stimulatory agent.

Much attention was paid to the role of neuroendocrine stress factors, corticotropin-releasing hormone, and urocortins I, II, and III in the regulation of motor function of the gastrointestinal tract [4,8]. Previous studies demonstrated that central or systemic administration of corticotropin-releasing hormone has an inhibitory effect on evacuation function of the stomach. These observed changes are similar to those revealed in stress [8]. Corticotropin-releasing hormone is the "first stress mediator", which has function of a humoral factor. This substance contributes to the nonadrenergic noncholinergic inhibition of gastric CA during psychogenic stress. Published data show that neurons of the enteric nervous system carry receptors for corticotropin-releasing hormone [8]. These data suggest that the stress-induced inhibition of CA of the gastric antrum and pylorus is related to the effect of corticotropin-releasing hormone on nonadrenergic inhibitory neurons in the enteric nervous system.

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