a few hours after clinical death from slow blood loss, a shift of fluid into the cellular sector took place in the initial stage of the postresuscitation period. This may perhaps be the reason why an increase in the cerebral flow in the early stages of the postresuscitation period due to administration of adrenergic drugs does not improve, but impairs the restoration of brain functions after long periods of clinical death [6]. Conversely, stabilization of arterial pressure and removal of the load from the venous system, by reducing the volume perfusion, help to produce some improvement in the course of recovery processes.

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EFFECT OF DOPAMINE AGONISTS AND ANTAGONISTS ON ENERGY RESOURCES OF THE RAT GASTRIC MUCOSA IN EXPERIMENTAL STRESS

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KEY WORDS: stress; gastric mucosa; dopamine receptors; adenine nucleotides; glycogen.

The writers showed previously [2, 3] that the antiulcerogenic action of metoclopramide is due to blocking of dopamine receptors in the CNS, which weakens the autonomic effect of stress-inducing stimulation, and not to the ability of metoclopramide to stimulate gastric and intestinal movement, as was hitherto considered [7]. This conclusion was based on an evaluation of the vulnerability of the gastric mucosa to attack by stress-inducing factors after preliminary administration of dopamine agonists and antagonists to animals. It was interesting to discover how the energy resources of the gastric mucosa change under these circumstances, in the light of Menguy's hypothesis [8, 11] that in stress induced by massive

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TABLE 1. Changes in Content of Adenine Nucleotides and Glycogen in Gastric Mucosa of Rats Treated with Metoclopramide and L-Dopa under "Social Stress" Conditions (M ± m)

Parameter		Control	Stress	Stress + metoclopramide (0.04 mg/kg)	Stress + L-dopa (60 mg/kg)	Stress + L-dopa + metoclopramide
ATP	mmoles/kg	0,92±0,08 (7)	0,34±0,06* (5)	0,45±0,04** (7)	0,27±0,01*,** (5)	0,27±0,04*,** (6)
ADP	mmoles/kg	1,37±0,14 (7)	0,55±0,12* (5)	0,73±0,12 (7)	0,36±0,13*,** (5)	0,96±0,11*,** (6)
AMP	mmoles/kg	2,01±0,21 (7)	1,49±0,12* (5)	1,26±0,12*,** (7)	0,39±0,1*,** (5)	1,58±0,13* (6)
ATP + ADP + AMP	mmoles/kg	4,3±0,2 (7)	2,38±0,09* (5)	2,44±0,1* (7)	1,02±0,07*,** (5)	2,81±0,1*,** (6)
Glycogen, mg/kg		1966,0±29,3 (5)	1772,5±19,3* (5)	1908,7±48,5** (8)	1792,5±44,9* (8)	1861,4±33,2** (7)

Legend. *P ≤ 0.05 compared with control, **P ≤ 0.05 compared with animals exposed to stress. Number of animals given in parentheses.

blood loss the cause of lesions of the gastric mucosa is an acute deficiency of the adenine nucleotide pool.

Biochemical investigations have shed considerable light on the role of ATP as the principal high-energy compound which determines the energy potential of the cell. ATP deficiency is known to be one cause of disturbance of vitally important processes in tissue [15]. According to some workers [13], the role of the glycolytic pathway of carbohydrate conversion is enhanced in various pathological states, and for this reason investigation of the glycogen content in tissues is important.

The aim of this investigation was to study changes in the content of adenine nucleotides and glycogen in rat stomach tissues under the influence of a threat-inducing factor and, against this background, administration of a blocker of dopamine receptors.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred albino rats of both sexes weighing 150-200 g in four series. Animals in series I were exposed to stress by the "social stress" technique devised by the writers [1], the basic principle of which is that hungry rats are kept for 24 h in perforated metal cartridges of diameter corresponding to that of the rat's body, and these cartridges were placed in a colony of unrestrained albino rats. The rats were then decapitated, the stomach removed, and an area of mucosa chosen for subsequent biochemical study.

In the experiments of series II, before being placed in the cartridges, the rats were given a subcutaneous injection of metoclopramide in a dose of 0.04 mg/kg. In the experiments of series III, 3 h before being placed in the cartridge, the rats were given L-dopa in a dose of 60 mg/kg by the intragastric route. The time of administration of L-dopa was chosen on the grounds that, as Franz [6] points out, absorption of L-dopa and its conversion into dopamine in the gastrointestinal tract take place in the course of 3 h. In the experiments of series IV, 3 h before the beginning of stress rats were treated with L-dopa, and immediately before being placed in the immobilizing cartridges, they were given metoclopramide. L-dopa and metoclopramide were given in the same doses as in the experiments of series II and III. From five to eight rats were used in each series of experiments.

The concentration of adenine nucleotides was determined in a homogenate of gastric mucosa by electrophoresis on No. F-1 paper followed by spectrophotometry, and expressed in mmoles/kg wet weight of tissue [14]; the glycogen content also was determined with the aid of anthrone reagent [5], and expressed in mg/kg wet weight of tissue.

EXPERIMENTAL RESULTS

The action of the stress-inducing factor caused a marked decrease in the concentrations of all three adenine nucleotides in the gastric tissue by 63.1, 59.9, and 25.9% respectively;

as regards the degree of this decrease they were arranged in the following order: ATP > ADP > AMP (Table 1). The total nucleotide level was lowered by 44.7%.

Administration of metoclopramide to rats before the beginning of exposure to the stress-inducing factor, in a dose which, according to previous investigations [2] had the maximal protective action against lesions of the gastric mucosa in rats, was accompanied by an increase in the ATP and ADP content in the stomach tissue compared with that in animals not receiving metoclopramide. Conversely, administration of the dopamine precursor L-dopa to the rats in a dose of 60 mg/kg aggravated exhaustion of adenine nucleotides in the stomach tissue. For instance, compared with the control the ATP and ADP concentrations were depressed by more than two-thirds, and the AMP concentration was only 19.4% of the control. The total nucleotide level under these circumstances was depressed by 4.2 times. After combined administration of L-dopa and metoclopramide, the action of L-dopa was weakened. The total nucleotide level rose twice as high as in animals of the previous series. The glycogen content in the gastric mucosa of rats exposed to stress was reduced by 10% ($P = 0.05$). Preliminary administration of metoclopramide increased this parameter in the direction of normal.

The data given on the effect of metoclopramide and L-dopa on the concentrations of energy-yielding adenine nucleotides in the gastric tissue of rats exposed to a combination of psychogenic and immobilization shock are in good agreement with the results of previous investigations [3], which showed that blocking central dopamine receptors by metoclopramide weakens, whereas their stimulation by L-dopa potentiates stress-induced damage to the rat gastric mucosa. At the same time these data contradict those of Menguy [8, 9], according to whom, of all stressors, it is only bleeding which causes this effect, and they confirm the results of Moreva [4], who observed a decrease in the ATP and creatine phosphate concentration in the tissues under the influence of widely different stress-inducing factors (stimulation of reflexogenic zones of the intestine, or hypothalamus), noradrenalin, reserpine, histamine, atophan, and butadione. All these facts indicate the universal character of disturbances of energy metabolism as a possible step in the pathogenesis of acute ulcer, leading through a deficiency of ATP and ADP to disturbance of working of the Na,K-pump and, accordingly, to death of the gastrocytes [9]. As Menguy [8, 9] considers, essentials for disturbance of energy homeostasis in the gastric mucosa are a reduced glycogen concentration in the gastric mucosa compared with other tissues and a predominant role of oxidative phosphorylation in restoration of the adenine nucleotide pool. The decisive role of oxidative phosphorylation in metabolism in the gastric mucosa and, in particular, in its fundal division, also is stipulated by Sato et al. [12]. In reviews of Menguy's article [8], Rosato and Smale also mentioned the great importance of the problem of "nutrition" of the mucosa in the pathogenesis of ulcer. Finally, Menguy himself showed in [11] that alpha-adrenoreceptor blockade by phentolamine significantly weakens the stress-inducing action of bleeding, and on that basis concluded that ischemia is the cause of the disturbance of energy metabolism in the gastric mucosa. However, according to data obtained by Moreva [4], histamine, which stimulates blood flow in the mucosa, and butadione, which does not change it, also cause lesions of the gastric mucosa in rats, accompanied by a decrease in the adenine nucleotide pool. Our own observations [3] show that the potentiating effect of L-dopa on stress-induced lesions of the gastric mucosa is also connected with an increase in vagal, but not sympathetic, tone, and this is not accompanied by ischemia.

Consequently, the problem of the cause of the energy depletion of the gastric mucosa at the intermediate level, under the influence of widely different factors requires further study. However, the data described above provide fresh confirmation of the role of excitation of central dopamine receptors in the pathogenesis of acute stress-induced gastric ulcer and of the protective action of the dopamine receptor blocker metoclopramide in psychogenic and immobilization stress.

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REGENERATION OF THE LIVER AT DIFFERENT PERIODS OF MONONUCLEAR INFILTRATION INDUCED BY ZYMOSAN GRANULES

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After injection of 2 mg of zymosan granules (ZG) into mice they are initially ingested by Kupffer cells (KC), which induces the development of focal, and later of diffuse, areas of mononuclear infiltration in the liver [4]. Regression of mononuclear infiltration is not complete until at least 2 months after injection of ZG. The areas of infiltration contain liver macrophages with high acid phosphatase activity. The course of reparative regeneration of the liver depends essentially on the reactivity of KC [1, 2].

The aim of this investigation was to discover how the liver, with areas of mononuclear infiltration, developing in response to activation of KC by ZG, regenerates.

EXPERIMENTAL METHOD

Experiments were carried out on 250 male (CBA × C57BL)F_1 mice weighing 18-22 g. ZG were injected intravenously into the experimental animals in a dose of 2 mg per animal in 0.5 ml of 0.85% NaCl. In the control, 0.5 ml of 0.85% NaCl was injected. Partial resection of the liver (PRL) by the method in [6] was performed under ether anesthesia between 9 and 10 a.m., 1 and 5 days and 2 months (series I, II, and III of experiments respectively) after injection of ZG. The animals were killed 24, 30, 36, 42, 48, 54, 60, 66, 72, and 96 h and 11 and 16 days after the operation. An intraperitoneal injection of 1 μCi of ^{3}H-thymidine/g body weight (specific radioactivity 20 Ci/mmole) was given to the mice 1 h before sacrifice. Liver sections, stained with hematoxylin and eosin, were coated with liquid photographic emulsion (Photographic Chemical Research Institute project) and exposed in darkness at 4°C for 3 weeks. To determine the mitotic index (MI) of the hepatocytes (in %) 5000 hepatocytes were counted in liver sections stained with hematoxylin and eosin. To calculate the index of labeled nuclei (ILN) of the hepatocytes (in %) 3000 nuclei were counted on autoradiographs. The percentage regeneration capacity of the liver was determined by the equation [5]:

$$\text{Percentage regeneration capacity} = \frac{P_1 - P_2}{P_3} \times 100\%,$$

where P_1 is the weight of the liver at sacrifice, P_2 the weight of the residual liver after PRL, and P_3 the weight of the part of the liver removed during resection.

The numerical results were subjected to statistical analysis by Student's t test.

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