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ACTION OF CYSTEAMINE, AN ULCEROGENIC AGENT, ON GLUTATHIONE AND GLUTATHIONE-DEPENDENT ENZYME LEVELS IN THE GASTRODUODENAL MUCOSA OF RATS

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KEY WORDS: cysteamine; rat gastrointestinal trace; glutathione

Clinical and experimental studies have shown that the mucous membrane of the gastrointestinal tract, like the liver, contains high concentrations of glutathione and a broad spectrum of glutathione-dependent enzymes, which help to inactivate toxic compounds, lipid peroxidation (LPO) products, intracellular intermediates, drugs, and so on [5, 11, 14]. It has also been suggested that an unusually high level of reduced glutathione in the gastrointestinal mucosa may be a very important factor protecting the cells against the action of ulcerogenic agents [7, 9].

The aim of this investigation was to study the possible connection between the degree of activity of glutathione-dependent enzymes and the concentration of reduced and oxidized forms of glutathione in the mucous membrane of different parts of the gastroduodenal zone and the action of cysteamine, a specific ulcerogenic agent.

EXPERIMENTAL METHOD

Experiments were carried out on 120 female Wistar rats weighing 160-180 g. An experimental model of duodenal ulcer (DU) was produced by a single subcutaneous injection of cysteamine (from Fluka, Switzerland) in a dose of 30 mg/100 g, by the method in [13]. Under thiopental anesthesia the mucous membrane was removed from different parts of the stomach (fundus and antrum) and from DU, 2 weeks after injection of the compound, fixed in liquid nitrogen, and kept until use at −70°C.

Glutathione peroxidase activity was revealed by the method in [6] and glutathione reductase was determined in the modification of Gerasimov et al. [2]. Glutathione-S-transferase activity was studied with the aid of 1-chloro-2,4-dinitrobenzene as substrate [12].

Concentrations of reduced and oxidized glutathione were measured spectrofluorometrically [4]. Protein was determined by Lowry's method [10].

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TABLE 1. Effect of Cysteamine on Activity of Glutathione-Dependent Enzymes and on Glutathione Level in Different Parts of the Gastroduodenal Mucosa of Rats (M ± m)

Parameter studied	Control			Cysteamine		
	gastric fundus	gastric antrum	DU	gastric fundus	gastric antrum	DU
Glutathione peroxidase, nmoles/min/mg protein	148,6±13,27	158,7±16,7	28,3±2,9	92,4±6,8	83,5±6,9	10,4±0,8
Glutathione-S-transferase, nmoles/min/mg protein	109,5±6,2	128,6±8,8	298,4±18,6	64,4±5,2	45,9±3,7	71,0±5,8
Glutathione reductase, nmoles/min/mg protein	35,5±2,2	48,6±4,8	65,3±8,7	18,6±1,2	20,2±1,8	18,1±1,75
Glutathione, μmoles /g tissue, reduced	5,98±0,25	9,8±0,45	3,06±0,08	3,32±0,3	4,26±0,42	0,9±0,09
oxidized	0,29±0,08	0,75±0,09	0,3±0,01	0,406±0,05	1,43±0,12	0,87±0,08

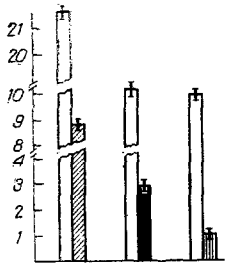

Fig. 1. Effect of cysteamine on ratio between levels of reduced and oxidized forms of glutathione in gastroduodenal mucosa of rats. Unshaded columns — control, obliquely shaded — gastric fundus, black column — gastric antrum, vertically shaded column — DU.

EXPERIMENTAL RESULTS

Cysteamine lowered the activity of all glutathione-dependent enzymes tested and also the concentration of the reduced form of glutathione, whereas the level of the oxidized form of glutathione rose (Table 1). These changes were observed in all parts of the gastroduodenal zones investigated, although they differed in severity, and were manifested to the greatest degree of the duodenal mucosa, i.e., the zone affected by ulcers. Even the activity of glutathione peroxidase, one of the enzymes most resistant to injury, was greatly disturbed after injection of cysteamine. For instance, in the mucosa of the gastric fundus it was reduced by 1.5 times, in the antrum by 1.9 times, and in the mucosa of DU by 2.7 times. The main function of glutathione peroxidase is known [1] to be the detoxication of all kinds of peroxides (organic and inorganic), and a sharp fall in the activity of this enzyme leads to injury to the membranes, disturbance of homeostasis and, ultimately, death of the cell.

The function of glutathione-S-transferase, another very important detoxicating enzyme, was depressed more than any other parameter studied, and particularly so in the duodenal mucosa (by 4.2 times compared with the control). This is a particularly interesting discovery, for we know that glutathione-S-transferase is an enzyme which is able to detoxicate any toxic substance entering the body and cell or formed in them [3].

Lowering the activity of glutathione reductase, an enzyme maintaining the reduced form of glutathione, a very important substrate and coenzyme of all glutathione-dependent enzymes, was also important. Hence it is clear that disturbance of the function of this enzyme leads to a shift in the ratio between reduced and oxidized forms of glutathione, leading inevitably to activation of LPO [15]. As will be clear from the data described, the activity of this enzyme in the zone of ulcer formation was reduced by 3.6 times compared with the control.

Under the influence of cysteamine the concentration of the reduced form of glutathione increased considerably whereas the level of its oxidized form rose. The change in the ratio between these two forms of glutathione is clearly shown in Fig. 1: the greatest shift was observed in the duodenal mucosa.

Thus injection of cysteamine leads to a significant disturbance of the function of the system of glutathione and glutathione-dependent enzymes, which is one of the most important protective systems of cells. The selectivity of the harmful action of cysteamine on the duodenal mucosa, leading to ulcer formation, makes this pathological model most appropriate for the study of the mechanisms of pathogenesis of peptic ulcer as a whole.

Data indicating that exposure to various injurious factors may lead to a fall in the concentration of SH-compounds, of which the most important is reduced glutathione, have recently been published. For instance, it has been shown that injury to the gastric mucosa of rats induced by ethanol is closely connected with a marked fall in the reduced glutathione concentration in the mucosa [8]. Injection of prostaglandin E_2, or of one of the compounds containing SH-groups, before administration of ethanol considerably reduced erosion formation, whereas injection of substances blocking the formation of compounds with SH-groups (N-ethylmaleimide), including glutathione, caused weakening of the protective properties of the gastric mucosa. Accordingly the authors cited postulated that glutathione and other SH-compounds may influence the structure and formation of protective mucus in the stomach.

It can thus be concluded from analysis of data in the literature and the results of our own investigations that the system of glutathione and glutathione-dependent enzymes plays an important role in the mechanisms of pathogenesis of ulcer formation in the gastroduodenal zone.

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BIOSYNTHESIS OF PREGNANCY-SPECIFIC β_1-GLOBULIN IN RATS IN VIVO

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KEY WORDS: pregnancy-specific β_1-globulin; radioimmunodiffusion; placenta

Pregnancy in man and mammals is accompanied by the appearance of pregnancy-associated antigens in the blood stream, in the composition of α- and β-globulins. In rats during pregnancy α_1- and α_2-globulins [2, 5], α-fetoprotein [5], and pregnancy-specific β_1-globulin (PSG) [3, 4, 9] have been identified.

PSG in rats is the analog of human trophoblast-specific β_1-glycoprotein (TSG) [6]. Similar analogs also have been found in the blood serum of several other mammals [11-13]. TSG was found in the blood serum of pregnant women [6, 15], and later in the blood serum of patients with trophoblastic tumors [7, 15]. TSG, synthesized by cells of the syncytiotrophoblast [8], is now considered to be a reliable marker of pregnancy and of trophoblastic tumors [15].

The aim of this investigation was to determine the site of synthesis of PSG during pregnancy in rats.

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