CHANGES IN THE NUCLEIC ACID AND CYCLIC AMP CONTENT IN NEUROGENIC DYSTROPHIES OF THE STOMACH

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A decrease in the RNA content was found in the stomach tissue of rats following degenerative changes in the organ induced by injury to the duodenum. A sharp fall in the cyclic AMP level in the gastric mucosa of rabbits was found under the same experimental conditions. The role of these changes in the mechanism of development of destructive and metabolic disturbances during the formation of neurogenic dystrophies caused by extraordinary stimulation is analyzed.

KEY WORDS: dystrophic changes in the stomach, nucleic acids, cyclic AMP.

Extraordinary stimulation of the nervous system causes destructive changes in the gastric mucosa. Under these circumstances mitotic activity of the cells is depressed [6] and protein synthesis is inhibited, which is reflected in a decrease in the uptake of labeled amino acids into the gastric mucosa [1].

Numerous investigations conducted in the writers' department have shown that the onset of dystrophic changes in the internal organs is connected with the disturbance of the regulatory influences of the nervous system and, in particular, of its sympathetic division, which perform a trophic function. The sudden exhaustion of catecholamines under the conditions of extraordinary stimulation lies at the basis of the profound metabolic and destructive changes in the tissues.

In the investigation of the mechanism of development and repair of neurogenic injuries of the internal organs caused by extraordinary stimulation, it is essential to take into account the role of the genetic apparatus, exerted through the DNA–RNA–protein system, for this is the most important intracellular mechanism determining the transformation of functional activity of the cell during exposure to various factors.

Metabolic changes in the tissues are closely linked with the genetic apparatus of the cells, the modification of which by nervous and hormonal factors may lead to induction and repression of so-called "key" enzyme system which perform an adaptive function under the conditions of extraordinary stimulation.

Recent investigations have shown that cyclic 3'5'-adenosine monophosphate (AMP) participates in the processes of transcription and translation and is an intermediary in the metabolic effect of most mediators and hormones. Cyclic AMP affects both the activity of many of the enzyme systems of the cell through the corresponding cyclic AMP-dependent protein kinases, and also the synthesis of enzyme and other proteins through its participation in the conversions of nucleic acids.

The object of the present investigation was to study the content of nucleic acids and cyclic AMP following neurogenic injury to the gastric mucosa, which under normal conditions is characterized by intensive proliferative processes and by a high level of protein resynthesis.

EXPERIMENTAL METHOD

Dystrophic injury to the gastric mucosa was produced by stimulation of interoceptors by the application of Pean's forceps to the pyloro–duodenal region for 10 min in rats and rabbits starved for 24 h [5]. The animals were killed 3 h later and tissue was taken for investigation. The DNA content was determined in homogenates of the rats stomach by the method of Schmidt and Thannhauser, and RNA was determined in homogenates

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TABLE 1. DNA, RNA, and Cyclic AMP Content in Stomach Tissue in Neurogenic Lesions Caused by Trauma to the Duodenum (M ± m)

Index studied	Species of animal and type of tissue	Control group	Experimental group	Number of experiments
DNA, μg P/g wet weight of tissue	Rat, homogenate of stomach	344,0±10,5	339,0±8,2	5
RNA, μg P/g wet weight of tussie	The same	390,1±6,8	327,0±2,1	7
RNA, μg P/ mg protein	Rat, microsomal fraction of stomach tissue	53,6±1,7	41,8±1,6	6
Cyclic AMP, nmoles/g wet weight of tissue	Rabbit, gastric mucosa	1,00±0,15	0,31±0,06	6

and the microsomal fraction of the rat stomach by a spectrophotometric method [15]. The cyclic AMP level was determined in the gastric mucosa of the rabbits by an enzymic method [14].

EXPERIMENTAL RESULTS AND DISCUSSION

Stimulation of the receptor zone of the pyloro–duodenal region caused injury to the gastric mucosa with the development of discrete punctate ulcers. Data obtained by determination of the DNA, RNA, and cyclic AMP content in the stomach under the conditions described above are given in Table 1. A significant decrease in the RNA level both in the homogenates and in the microsomal fraction of the stomach tissue was observed 3 h after injury, whereas the DNA content remained unchanged. The cyclic AMP content in the gastric mucosa of the rabbits fell sharply to 30% of the control level.

During the development of neurogenic dystrophies arising as a result of extraordinary stimulation, the RNA level in the stomach tissue thus falls considerably; this evidently may indicate insufficiency of the genetic processes in this pathological entity.

The discovery of genetic disturbances in particularly important, for it is at the genetic level that the processes of resynthesis of protein structures responsible for the plastic function of the tissues and processes of energy formation, responsible for supplying the necessary energy in the form of ATP, are coordinated [10]. As the writers showed previously, during extraordinary stimulation of the organism, leading to dystrophic changes in the internal organs, the incorporation of labeled amino acids into proteins of the gastric mucosa and also into the ribosomal fraction of the liver cells is delayed [9]. Meanwhile the energy resources in the tissues are severely depleted. Stimulation of the duodenal receptor zone led to a fall in the creatine phosphate level in the stomach by 50% or more and a decrease of 20% in the ATP content. Considering the decrease in the RNA level, the disturbance of protein synthesis and the severe energy deficit in the neurogenically damaged tissues suggest that under these conditions the closely linked processes of functioning of the genetic apparatus and structural and energy metabolism are disturbed.

Investigations in the writers' department have shown that metabolic and destructive changes during the development of dystrophic phenomena are connected with the disturbance of the trophic function of the sympathetic nervous system and a deficiency of noradrenalin in the tissues, as well as a deficiency of cyclic AMP, an intermediary in the action of catecholamines on metabolism. The quantity of noradrenalin is reduced by several times in dystrophic lesions of the stomach caused by electrical stimulation of animals and also by traumatization of the duodenum [2, 8]. Besides exhaustion of the noradrenalin content, the cyclic AMP level in the gastric mucosa also was sharply reduced 3 h after stimulation of the duodenum (Table 1). The writers also found correlation between the fall in the cyclic AMP and noradrenalin levels during the development of neurogenic lesions of the myocardium [7]. Judging from recent observations, cyclic AMP plays a direct part in the realization of genetic information in cells, through its influence on the phosphorylation of histone and nonhistone proteins, on synthesis of messenger RNA, and also on other genetic processes [3, 12, 13]. Accordingly, the sharp decrease in the cyclic AMP level found in the stomach in dystrophic lesions of that organ can evidently play an important role in the development of genetic disturbances and of the metabolic and destructive changes connected with them.

It can thus be concluded from these results that during the development of neurogenic dystrophies caused by extraordinary stimulation changes take place in the genetic apparatus of the cells, and are accompanied by a disturbance of the synthesis of protein structures, including enzyme proteins. This conclusion is confirmed by data obtained in the writers' laboratory on the prevention of changes in glucose-6-phosphate dehydrogenase activity in the neurogenically damaged myocardium by actinomycin D, an inhibitor of RNA synthesis.

Pharmacological action on the DNA–RNA–protein system can activate the synthesis of tissue proteins and repair processes under conditions of neurogenic damage and can bring about a favorable therapeutic effect. As has been shown in the writers' laboratory, administration of orotic acid, a precursor of synthesis of pyrimidine nucleotides, considerably accelerates the healing of ulcers of the gastric mucosa [4]. The substance ethimizole which, as the writers have shown, leads to an increase in the cyclic AMP content in the tissues [11] and to marked acceleration of energy-forming processes, has an activating effect on regenerative processes in the gastric mucosa affected by dystrophic changes.

The establishment of a genetic link in the chain of pathological processes leading to disturbance of tissue nutrition is important, in the investigation of the mechanism of development and repair of neurogenic dystrophies of the internal organs caused by extraordinary stimulation, for the goal-directed use of pharmacological agents aimed at normalizing structural and energy metabolism in the damaged tissues.

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