The fact that an antiepileptogenic substance (or substances) also appears in CSF taken from cats which have developed seizures as a result of electroshock stimulation (ESh cats) is evidence that it may begin to be produced actually during the seizure period. From this point of view our results agree with those of a recently published study [8] in which seizures induced by Fluorotyl were found to be weakened by CSF taken from rats exhibiting single generalized seizures. However, the appearance of antiepileptic properties of the CSF is not linked with the seizure process itself, as the authors cited above suggest. Our investigations show that the anticonvulsant properties of the CSF are due to activity of the antiepileptic system, which is activated during the seizure process and participates in its suppression, or even causes this suppression. This conclusion is supported by the fact that the antiepileptic properties of the CSF in cats subjected to electrical stimulation, of kindling type, of an antiepileptic structure (the cortex of the vermis cerebelli) are more marked than in ESh cats with a seizure syndrome.

The results given above show that the antiepileptic substance discovered does not possess species specificity. Whatever its nature, the important point is that it is endogenous in origin and is the result of activity of the antiepileptic system and is one of the mechanisms whereby its effects are realized.

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CHANGES IN CYCLIC NUCLEOTIDE LEVELS AND LYSOSOMAL ENZYME ACTIVITY IN THE GASTRIC MUCOSA OF RATS WITH EXPERIMENTAL ULCERATION

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UDC 616.33-002.44-092.9-07:616.33-018.73-008.931+616.33-018.73-008.939.633

KEY WORDS: ulceration; lysosomes; cyclic nucleotides.

The development of ulcers of the gastric mucosa may be linked with the damaging effect of hydrolases [2], released from lysosomes into the cytosol after labilization of their membranes [3, 10, 12], on cellular structures. Meanwhile the stability of the lysosomal membranes largely depends on cyclic nucleotide levels [13]. In ulceration both elevation of the cAMP level in the gastric mucosa [5] or its lowering may be observed [6].

The aim of this investigation was to study changes in levels of cyclic nucleotides (cAMP and cGMP) and their ratio during the development of ulcers in the gastric mucosa under the influence of catecholamines. Acid phosphatase and proteinase activity also was investigated in the lysosomal fraction and the fraction of enzymes remaining in the supernatant after ultracentrifugation of mucosal homogenates. The choice of model of ulceration was determined by the fact that hyperactivation of adrenergic processes by an important factor in the development of ulcers of the gastric mucosa [1, 7].

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Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 106, No. 8, pp. 149-151, August, 1988. Original article submitted July 10, 1987.

0007-4888/88/0008-1085$12.50

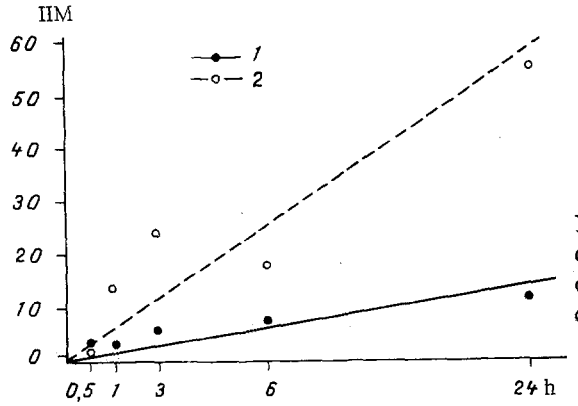

Fig. 1. Increase in IIM after injection of noradrenalin (1) or adrenalin (2) at different times after injection of catecholamines.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred rats of both sexes weighing 180-210 g. Before the experiments began the rats were deprived of food for 24 h but allowed unrestricted access to water. The rats were then given an intraperitoneal injection of adrenalin in a dose of 2.0 mg/kg or noradrenalin in a dose of 5.0 mg/kg. The animals were killed 5, 10, and 30 min and 1, 3, 6, and 24 h after injection of catecholamines. The stomach was then removed, opened along the lesser curvature, and the area (in mm^2) of the lesion of the mucosa estimated per animal in the group: the index of involvement of the mucosa (IIM). The mucosa was then separated from the submucosa, weighed, and divided into two parts: concentrations of cyclic nucleotides were determined in one part, the lysosomal fraction was isolated from the other part [8]. Cyclic nucleotide concentrations were determined by radioimmunoassay, using kits of Czechoslovak origin for determination of cAMP and cGMP. The results were expressed in pmoles/mg wet weight of mucosa. After isolation of the lysosomal fraction, activity of acid phosphatase and proteinases was determined [9] in the lysosomal fraction and in the unsedimented enzyme fraction. The significance of changes in the parameters studied was estimated by the use of the nonparametric tests [4].

EXPERIMENTAL RESULTS

Injection of adrenalin and noradrenalin into the experimental animals was followed by the development of erosions and ulcers in the gastric mucosa in 80-100% of cases, in agreement with data in [15]. The value of IMM reached a maximum 24 h after injection of adrenalin and 6 h after injection of noradrenalin (Fig. 1). Ulcers of the mucosa developed against a background of destabilization of the lysosomal membranes, expressed as lowering of the resistance of the membranes to the procedure of isolation of the lysosomal fraction and as increased release of enzymes from the lysosomes into the unsedimented enzyme fraction (Table 1). Under these circumstances, as increase in enzyme release from the lysosomes took place before the development of well defined lesions of the mucosa. A study of the cAMP level in the initial periods (0-30 min) after injection of noradrenalin showed a significant rise of the cAMP level in the mucosa after 5 min, but later, toward 30 min after injection, it returned and continued to fall from a long time thereafter (Table 2). The cAMP level remained low until 24 h after injection of noradrenalin. The cGMP level fell after injection of noradrenalin, returned to normal 1 h after injection, but exceeds the steady-state level 3-6 h after injection. By 24 h the cGMP level in the mucosa was back to normal (Table 2). Thus in the initial period before any changes were observed in IIM, and during the period of rise of IIM, opposite changes were found in the cAMP and cGMP levels in the gastric mucosa. As a result of cAMP/cGMP ratio increased in the initial period (until 1 h after injection of noradrenalin) and was sharply reduced after 3-6 h, due to the fall in the cAMP level and a rise in the cGMP level. The cAMP/cGMP ratio also was depressed 24 h after injection of noradrenalin. A significant fall of the cAMP level in the mucosa was observed after a transient rise (after 5 min) in the experimental animals after injection of adrenalin also. Fluctuations of the cGMP level after injection of adrenalin were less marked than after injection of noradrenalin (Table 2).

In connection with the results described above, an important fact is that destabilization of lysosomal membranes found during catecholamine-induced ulceration takes place against the background of a sharp decline in the cAMP content of the gastric mucosal tissue, for we know that cAMP may have a stabilizing effect on lysosomal membranes [11, 13, 14], whereas

TABLE 1. Changes (in % of control) in Enzyme Activity of Lysosomal Fraction and Unsedimented Enzymes of Gastric Mucosal Homogenates at Different Times after Injection of Noradrenalin and Adrenalin

Parameter		Time, h			
		1	3	6	24
Injection of noradrenalin					
AP	LS	142*	65*	58*	89
	UE	107	167**	136*	110*
PA	LS	121	78*	62*	82
	UE	98	140*	154**	126*
Injection of adrenalin					
AP	LS	124*	78	68*	84
	UE	108	182*	165*	129*
PA	LS	118	96	48*	76*
	UE	99	120	138*	140**

Legend. AP) Acid phosphatase; PA) proteolytic activity (pH 3.5); LS) lysosomal fraction; UE) fraction of unsedimented enzymes. *p < 0.05, **p < 0.01 compared with control.

TABLE 2. Changes in Cyclic Nucleotide Concentration (in pmoles/mg tissue) in Gastric Mucosa of Rats at Different Times after Intraperitoneal Injection of Noradrenalin and Adrenalin

Time after injection	Noradrenalin			Adrenalin		
	cAMP	cGMP	cAMP/cGMP	cAMP	cGMP	cAMP/cGMP
0 min	0,58	0,06	9,6	0,50	0,06	8,3
5 min	1,25**	0,028**	44,6***	1,80**	0,05	36,0**
10 min	0,71	0,05	14,2	0,67	0,057	11,7
30 min	0,34*	0,056	6,1*	0,29*	0,112*	2,6**
1 h	0,26**	0,04	6,5**	0,08**	0,04	2,0**
3 h	0,14**	0,08	1,8**	0,10**	0,04	2,5**
6 h	0,21**	0,14*	1,5**	0,16**	0,106	1,5**
24 h	0,13**	0,065	2,0**	0,29**	0,06	4,9**

Legend. *p < 0.05, **p < 0.01, ***p < 0.001 compared with initial concentration.

the lowering of the cAMP level may contribute to destabilization of lysosomal membranes [13]. Another factor causing further destabilization of the lysosomal membranes may be elevation of the cGMP level [14], which was observed in the case of noradrenalin, and also the absence of any marked change in its level in the mucosa, but in the presence of a sharp fall in the cAMP level, which in both cases leads to an increase in the cAMP/cGMP level, but it is during this time when this ratio is rising that erosions and ulcers are observed to develop in the gastric mucosa.

The results are thus evidence that under the influence of catecholamines, injected intraperitoneally, erosions and ulcers are observed to develop in the gastric mucosa of the experimental animals, which is preceded by destabilization of the lysosomal membranes and increased release of liposomal enzymes into the cytoplasm of the cells. Destabilization of the lysosomal membranes takes place against the background of a fall in cAMP concentrations, of considerable duration and magnitude, in the cells of the gastric mucosa. An essential role in the distribution of stability of the lysosomal membranes observed in the present experiments may be played both by profound inhibition of cAMP formation and the fact that it takes place against the background of a relatively small change in cGMP level in the mucosa falls in the phase of ulcer formation. This may be a pathogenetically important feature and one cause of destabilization of the lysosomal membranes, and in turn, it induces the next chain of pathological reactions leads to the development of ulceration of the mucosa [2].

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IMMUNOMEDIATED INDUCTION OF HYPERLIPOPROTEINEMIA

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UDC 616.153.915-008.61-092:612.017.1.064

KEY WORDS: immunodepression; immunostimulation; lipids; hyperlipoproteinemia.

The concept of metabolic immunodepression postulates that immunity is dependent on lipid and carbohydrate metabolism [2]. The mechanism of this dependence is determined by the immunoregulatory properties of lipoproteins: the inhibitory action of low-density and very low-density lipoproteins (LDL and VLDL, respectively) on immunocompetent cell function [5]. It has also been observed that immunization and virus infections lead to hyperlipidemia, which is transient and is independent of the fat content in the diet and the nature of the sensitizing agent [3, 9-11].

The aim of this investigation was to study dependence of immunocompetence of the body on hyperlipidemia and, second, dependence of lipid and lipoprotein metabolism on the state of the immune system during both immunodepression and immunostimulation.

EXPERIMENTAL METHOD

Hyperlipidemia was induced experimentally in male C57BL/6 mice. Control mice were kept on an ordinary diet whereas the experimental animals were given egg yolk ad libitum. The blood sera of the mice were tested on the 10th day after the beginning of the experiment. At the same time lipophoid cells isolated from the mouse spleen were investigated. The well-known model of virus-induced Rauscher leukemia [1] was used as the model of acquired immunodeficiency. To study the lipid profile during antigenic stimulation, experimental models of the formation of an immunocomplex lesion of the glomeruli in mice in situ by preliminary sensitization, and also in the presence of a raised level of circulating immune complexes

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Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 106, No. 8, pp. 151-153, August, 1988. Original article submitted August 12, 1987.

 0007-4888/88/0008-1088$12.50