EFFECT OF LIGANDS OF OPIOID RECEPTORS ON DNA SYNTHESIS AND HISTAMINE CONCENTRATION IN THE GASTRIC MUCOSA AND BLOOD OF ALBINO RATS

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The writers showed previously that ligands of opioid receptors (β-endorphin, naloxone, dalargin — a synthetic analog of Leu-enkephalin) activate proliferative processes in the lingual epithelium of albino rats [5]. Dalargin is nowadays regarded as one of the most promising antiulcer preparations [2]. It has been shown to stimulate regeneration in other tissues also [3]. An important component of regeneration is the proliferative activity of cells, and an essential role in the development and healing of gastric and duodenal ulcers has been ascribed to changes in histamine metabolism [10, 12, 13].

The aim of this investigation was to study the effect of ligands of opioid receptors on DNA synthesis in the gastric epithelium and on the histamine concentration in the stomach and blood.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred albino rats weighing 170-220 g. β-Endorphin ("Serva," West Germany), naloxone (Endolaboratories," USA), and dalargin (synthesized in the Laboratory of Peptide Chemistry, All-Union Cariologic Scientific Center, Academy of Medical Sciences of the USSR, by Dr. Chem. Sci. M. I. Titov) were injected intraperitoneally in doses of 0.1 ml of a 2×10^{-9} M solution of the ligand per 100 g body weight. Control animals were given an equal volume of isotonic NaCl solution. The animals were killed by decapitation 24 h after injection of the preparations. An intraperitoneal injection of 0.6 μCi/g of ^{3}H-thymidine was given to the animals 1 h before sacrifice. The specific activity of the ^{3}H-thymidine was 84 Ci/mmole. Pieces of the gastric fundus were fixed in a mixture of ethanol and acetic acid (3:1). Autoradiographs were prepared and the index of labeled nuclei (ILN, %) and labeling intensity (LI, mean number of tracks above the nuclei) were determined by methods described previously [1]. Histamine was determined in blood and homogenates of the gastric fundus by the method in [14], in the modification [4], by a spectrofluorometric method ("Hitachi").

EXPERIMENTAL RESULTS

The study of the regenerative potential in the gastric mucosa showed that dalargin and β-endorphin significantly increase the number of DNA-synthesizing nuclei by 1.5-1.6 times (Table 1). Injection of Leu-enkephalin and naloxone caused no changes in DNA synthesis. In the experiments performed previously naloxone had a stimulating effect on DNA synthesis in the epithelium of the tongue and cornea [5, 6].

The results of investigation of the histamine concentration in the stomach showed that Leu-enkephalin and its stable synthetic analog dalargin caused a significant increase in the histamine concentration in the gastric tissue whereas naloxone reduced its level significantly. No significant changes were observed under the influence of β-endorphin.

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TABLE 1. Effect of Ligands of Opioid Receptors on DNA Synthesis and Histamine Concentration in Gastric Mucosa and Blood

Ligands of opioid receptors	DNA synthesis in gastric epithelium		Histamine concentration	
	ILN, %	LI, number of tracks above nuclei	in stomach, μmoles/g	in blood, μmoles/g
Control	14,4±1,1	27,2±1,7	0,104±0,006	23,9±1,7
Dalargin	21,0±2,1*	26,9±1,1	0,137±0,013*	1,6±0,3*
Leu-enkephalin	11,2±1,8	22,3±2,1	0,142±0,016*	36,8±1,9*
β-endorphin	21,2±2,0*	29,6±2,3	0,096±0,013	29,6±1,2*
Naloxone	12,5±1,1	21,0±2,3	0,078±0,006*	34,8±3,3*

Legend. $p < 0.05$ compared with control.

The study of the histamine concentration showed that β-endorphin, leu-enkephalin, and naloxone evoked a similar reaction: a significant increase in the blood histamine concentration by 1.5-1.6 times. Dalargin caused a sharp decrease (by almost 15 times) in the histamine concentration.

There is no general agreement in the literature on the role of histamine in adaptation of the gastric mucosa to unfavorable influences. According to data in [9] positive correlation exists between the intensity of ulcer formation in the rat stomach under the influence of cysteamine and the histamine concentration in the mucosa. In patients with gastroduodenal ulcers the histamine concentration is raised in the blood and also in the zone of the ulcer [10]. On the other hand, it was observed in [12, 13] that the histamine concentration in the gastric mucosa of patients with peptic ulcer is 30% lower than in normal individuals. The process of ulcer healing is accompanied by an increase in the histamine concentration in the mucosa. Vagotomy, which facilitates ulcer healing, also leads to an increase in the histamine concentration in the mucosa [13]. The authors cited consider that the fall in the histamine level in the mucosa promotes disturbance of the microcirculation, whereas an increase within certain limits improves the circulation in the stomach. Accordingly, data [7] showing changes in the microcirculation in the rat mesentery following injection of dalargin are interesting. An increase in vascular permeability and diapedesis of leukocytes, which took place in those experiments, may be partially explained by an increase in the histamine concentration, which was observed in the present experiments also. According to the author cited [7], the spectrum of changes induced by dalargin in the microcirculation leads to more rapid repair processes in the tissues. Another important mechanism explaining the efficacy of dalargin is its ability to stimulate proliferative processes. The writers showed previously that dalargin can stimulate DNA synthesis by its direction action on cells [6]. Evidently a definite role in stimulation of proliferative processes in the gastric mucosa in response to injection of dalargin is played by an increase in the histamine concentration. According to views expressed in [11], histamine is a local mitogen. Data on stimulation of enterocyte proliferation under the influence of histamine are given in [15]. The character of the effect of histamine on proliferation depends on the dose of the compound; a stimulating effect is mediated through cGMP accumulation in the cell [8]. However, it has to be pointed out that Leu-enkephalin, causing an increase in the histamine concentration in the stomach, had no effect on DNA synthesis. In our previous experiments, injection of Leu-enkephalin had no effect on proliferative processes. β-Endorphin, like dalargin, activated DNA synthesis in the gastric mucosa but caused no change in the histamine concentration.

The ability of dalargin to activate proliferative processes in the stomach and to increase the histamine concentration in the mucosa simultaneously, while reducing the blood histamine concentration, distinguishes it from the other ligands of opioid receptors which we studied. It is perhaps this property which lies at the basis of its therapeutic efficacy.

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EFFECTOR MODELING OF THE ACTION OF GABA—RECEPTOR-COMPLEX LIGANDS. FUNCTIONAL INTERACTION OF THE HYPOTHETICAL ALCOHOL RECEPTOR AND OTHER SUBUNITS OF THE COMPLEX

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Introduction of ethanol (E) into the body modifies the pharmacologic effects of exogenous ligands of the GABA-receptor—ionophore complex (GABA-RC) [7, 9], and in particular, it potentiates the action of 1,4-benzodiazepine (BD) derivatives [7]. Aliphatic alcohols (AA) have been shown to affect the binding parameters of barbiturate (BB) antagonists by synaptosomes [8] and conductance of the chloride ionophore of GABA-RC [5]. One suggested explanation is that the GABA-RC possesses in its structure a binding site or sites for E or AA, namely the hypothetical E receptor [2], with an influence on the conformational state of the complex.

The aim of the investigation was to determine the character of interaction of alcohols with the hypothetical AA-subunit of the complex and to determine its functions in a structural and functional model of interaction of GABA-RC and its ligands.

EXPERIMENTAL METHOD

Experiments were carried out on female CBA mice weighing 18-22 g. Animals of the control groups and 30 min after internal administration of 0.01% solution of AA (methanol, ethanol, propranol, n-butanol, isoamyl alcohol, and n-heptanol, 0.75-8 g/kg) received an intravenous (into the caudal vein) injection of solutions of bicuculline (BC; 0.01%), bemegride (BM) and picrotoxin (PC; 0.5%), and metrazol (ME; 1%), and the minimal effective doses of the convulsant inducing clonicotonic convulsions (DCTC) and tonic extension (DTE) were recorded [1, 2]. Thiosemicarbazide (TS; 6-20 mg/kg) was injected intraperitoneally into the control animals and, 30 min after injection of E, the probability of onset of clonicotonic convulsions (CC) and tonic extension (TE) was recorded. The experimental results were analyzed by algorithms given in [4].

EXPERIMENTAL RESULTS

The writers showed previously that during intravenous infusion of convulsants (L_c) which are exogeneous ligands of GABA-RC, the minimal effective doses inducing rapidly reversible effects in mice (responses of integral biosystem) are determined by doses (concentrations in the biophase of action) of anticonvulsant compounds (L_a) such as BB and BD [1, 2]. To determine the type of interaction of L_a, L_c, and GABA-RC, in experiments in vivo, the fundamental issue [1] is determination of the final (under conditions of reception of L_a and L_c) state of the receptor-

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