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ABILITY OF LIGANDS OF OPIATE RECEPTORS (ENDORPHINS AND EXORPHINS) TO INHIBIT GASTRIC JUICE SECRETION IN DOGS

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It is now reasonably well established that the opioid peptides, ligands of opiate receptors, can modify the functions of the digestive system, including the formation of gastric secretion. However, available evidence on the direction of the secretory effects is contradictory and ambiguous [1, 2, 4, 5]. As a rule investigations of this kind have involved the study of properties of natural compounds of enkephalins, namely leucine- and methionine-enkephalins.

Data on the effect of several opioid peptides of both endogenous and exogenous origin on the acidity of the gastric juice are summarized in this paper. The following synthetic endogenous peptides were studied: γ-endorphin, Des-Tyr-γ-endorphin, and Tyr-D-Ala-Gly-Phe-NH_2-(pNO_2), and activity of the peptide formed by peptic hydrolysis of milk — synthetic casomorphine 1-5 (Tyr-Pro-Phe-Pro-Gly) also was determined [3]. The preparations listed above were obtained in the Laboratory of Peptide Synthesis, All-Union Cardiologic Scientific Center, Academy of Medical Sciences of the USSR, by the classical methods of peptide chemistry.

EXPERIMENTAL METHOD

Experiments were carried out on eight hungry mongrel dogs weighing 16-20 kg, in which gastric fistulas were formed by Basow's method. Gastric acid secretion was stimulated by pentagastrin (PG; from Serva, West Germany), in a dose of 1 μg/kg/h, and in some experiments opiate receptors were blocked by the specific antagonist naloxone (from Narcan, USA) in a dose of 100 μg/kg. The peptides for study were injected after a constant volume of gastric juice had been established after administration of PG. Most of them were used in a stable dose of 30 μg/kg/h, but casomorphine was given in doses increasing by a factor of 10 after each hour of the experiment — 1, 10, and 100 μg/kg/h respectively (10 μg/kg/h is equimolar with 30 μg/kg/h for the other preparations). At the end of perfusion of solutions containing peptides, injection of pure PG was continued for a further hour. The technique of these experiments did not differ in principle from that used previously and it was described in more detail in earlier publications [1, 2]. The results were subjected to statistical analysis by Student's test. Differences were considered significant at a 95% level ($P < 0.05$).

EXPERIMENTAL RESULTS

Data on the action of opioid peptides on gastric secretion in dogs are summarized in Table 1. Injections of most of the opioid peptides studied, whether of endogenous or of exogenous origin, caused considerable inhibition of secretion of gastric juice, as shown by a decrease in the volume of juice secreted and in the rats of HCl production. Comparison of the effectiveness of the antisecretory action of the various preparations showed that casomorphine in a dose of 10 μg/kg/h had the greatest inhibitory potential: the rate of HCl production

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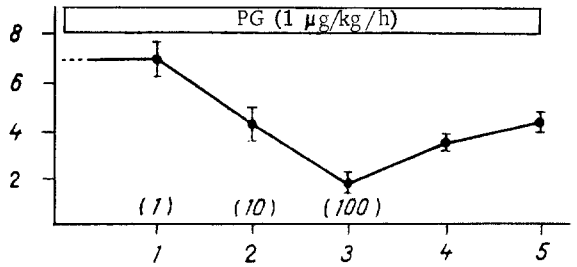

Fig. 1. Effect of increasing doses of casomorphine on acid production. Abscissa, time (in h); ordinate, rate of HCl production in meq/30 min). Numbers in parentheses give doses of casomorphine (in μg/kg/h).

TABLE 1. Rate of HCl Production (in meq/30 min) in Dogs with Gastric Fistula after Injection of Opioid Peptides Combined with Perfusion with PG

Preparation	Dose	Duration of experiment, h				
		1	2	3	4	5
γ-Endorphin	0, 30, 0 μg/kg/h	6,6±0,8 (100%)	2,0±0,3* (31%)	3,6±0,4* (55%)	—	—
γ-Endorphin + naloxone	0, 30, 0 μg/kg/h + 100 μg/kg	6,6±0,8 (100%)	6,0±0,7 (90%)	6,0±0,6 (90%)	—	—
Des-Tyr-γ-endorphin	0, 30, 0 μg/kg/h	4,8±0,5 (100%)	1,5±0,3* (31%)	3,6±0,4 (75%)	—	—
Des-Tyr-γ-endorphin + naloxone	0, 30, 0 μg/kg/h + 100 μg/kg	4,8±0,5 (100%)	2,4±0,5* (50%)	4,8±0,3 (100%)	—	—
Tyr-D-Ala-Gly-Phe-(pNH_2)	0, 5, 0 μg/kg/h	5,2±1,1 (100%)	6,0±2,0 (115%)	5,8±1,6 (111%)	—	—
Casomorphine	0, 1, 10, 100, 0 μg/kg/h	6,9±0,8 (100%)	4,2±0,7* (61%)	1,8±0,4* (26%)	3,5±0,2* (51%)	4,3±0,4* (63%)
Casomorphine + naloxone	0, 1, 10, 100, 0 μg/kg/h + 100 μg/kg	8,1±1,9 (100%)	8,7±1,8 (107%)	7,6±1,5 (93%)	—	—

Legend. *) significance of differences from initial value at 95% level ($P < 0.05$). Doses of opioid peptides relate to each hour of the experiment.

was reduced by 75% compared with its initial value. Rather less, but also very considerable inhibition of acid production was observed after perfusion with γ-endorphin and Des-Tyr-γ-endorphin in a dose of 30 μg/kg/h, (in both cases by 69%; $P < 0.05$). The experiments revealed resumption of the rise in the level of secretion after termination of administration of solutions of the opioid peptides but during continued perfusion with PG (Table 1).

Of all the preparations studied only Tyr-D-Ala-Gly-Phe-NH_2-(pNO_2) caused no change in either the quantity or the rate of formation of HCl ($P > 0.05$).

In a separate series of experiments the action of increasing doses of casomorphine on acid production was studied. Maximal inhibition of acidity occurred after injection of casomorphine in a dose of 10 μg/kg/h. Increasing the dose to 100 μg/kg/h also depressed the secretion of gastric juice, but by a substantially lesser degree (Fig. 1).

A single intravenous injection of naloxone (100 μg/kg) virtually abolished the inhibitory effect of γ-endorphin and casomorphine (Table 1), but caused virtually no change in the level of inhibition when Des-Tyr-γ-endorphin was used.

These experiments thus showed that the opioid peptides studied cause marked inhibition of gastric juice secretion stimulated by PG. Of all the preparations tested, casomorphine, γ-endorphin, and Des-Tyr-γ-endorphin gave an inhibitory action on the formation of gastric secretion. Tyr-D-Ala-Gly-Phe-NH_2-(pNO_2) caused no significant changes in the level of gastric secretion, possibly due to the presence of a nitro group in its structural formula.

Blocking the inhibitory action of most of the test preparations on secretion by additional administration of the opiate receptor antagonist naloxone (Table 1) is evidence that the antisecretory effect of these peptides is mediated through specific opiate receptors. Meanwhile the absence of blocking of the inhibitory effect when Des-Tyr-γ-endorphin was used could indicate the presence of other mechanisms, for we know that in the absence of N-terminal tyrosine, interaction between ligands and opiate receptors does not take place [6].

The results of the present investigation, showing that opioid peptides can inhibit gastric acid secretion confirm the writer's previous findings of analogous effects following administration of leucine- and methionine-enkephalins [1, 2], and they also agree with the result of experiments on dogs when initial stimulation of secretion was induced by food [4].

Meanwhile the present investigation confirmed once again our hypothesis on the physiological inhibitory activity of peptides in small doses only, which was demonstrated in the case of casomorphine, when an increase in the dose of the compound to 100 μg/kg/h significantly reduced the inhibition of HCl secretion. A similar effect was observed by the writers previously when testing activity of methionine-enkephalin [2]. Furthermore, this result may explain the possibility of stimulation of gastric secretion by the use of opioid peptides in increasing doses [5].

Opioid peptides of both endogenous and exogenous origin thus have a considerable inhibitory action on gastric secretion, and this is further confirmation of the importance of the study of their role in the regulation of gastric secretory processes.

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CHARACTERISTICS OF THE ENDOCRINE SYSTEM OF RATS DIFFERING IN INCLINATION FOR VOLUNTARY ETHANOL CONSUMPTION

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Administration of a single and repeated doses of ethanol causes marked and varied changes in the function of several endocrine organs both in man and in experimental animals [3-6]. On this basis an endocrine nature of certain etiologic and pathogenetic factors of alcoholism has been postulated [7, 9]. However, when standard models of experimental alcoholism are used it is impossible to differentiate between primary etiologic endocrinopathies and secondary hormonal disturbances caused by ethanol administration.

The possibility of selecting animals with a constitutional inclination for voluntary ethanol consumption from the general population of noninbred rats goes some way toward solving the problem of whether endocrine disturbances are the result of development of alcoholism or whether individual variability in hormonal status can be regarded as one of the primary factors provoking the development of this disease. Accordingly animals predisposed and not predisposed to voluntary consumption of ethanol were used as models with which to study the function of

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