PROTECTIVE ACTION OF ENDOGENOUS OPIOID PEPTIDES OF DIFFERENT ORIGIN AGAINST DUODENAL ULCER IN RATS

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During the last few years the writers have studied the effect of various opioid peptides and their synthetic analogs on experimental ulcer production in rats. Some of these peptides have been shown to have a marked protective action on the duodenal mucosa [1-3].

In the investigation described below the antiulcer action of a number of endogenous opioids – β-endorphin, γ-endorphin, Met-enkephalin, Leu-enkephalin, and dinorphine – which are formed in the body from the various high-molecular-weight precursors – pro-opiomelanocortin (β- and γ-endorphins), proenkephalin A (Met- and Leu-enkephalins), and proenkephalin B (dinorphine and Leu-enkephalin) [9], – was studied.

EXPERIMENTAL METHOD

Experiments were carried out on 495 male Wister rats weighing 180-220 g. Duodenal ulcer formation was induced by cysteamine hydrochloride (Fluka, Switzerland), which was injected subcutaneously in a single dose of 350 mg/kg. Administration of the test peptides began immediately after cysteamine was given, as four subcutaneous injections with intervals of 12 h between them. The rats were decapitated 48 h later, the stomach and duodenum were removed, and the state of their mucosa was evaluated visually. The severity of the ulcers (SU) in the duodenal mucosa was assessed in points [3]. The frequency of the ulcers (FU) in groups also was counted. For each group of animals a special ulcer index (UI) was determined by the formula UI = SU + 2FU. Animals which died before the results were read were disregarded when ulcer formation was evaluated (mortality was 22%).

Dinorphine 1-13 was obtained from Calbiochem (USA). All other peptides were synthesized in the Laboratory of Peptide Synthesis (Head, M. I. Titov), All-Union Cardiologic Scientific Center, Academy of Medical Sciences of the USSR.

The results were subjected to statistical analysis for SU by Student's t test, and for FU by Pearson's chi-square test. Differences were taken to be significant at the 95% level ($P < 0.05$).

EXPERIMENTAL RESULTS

The results are given in Table 1. The peptide β-endorphin prevented the development of duodenal ulcers, and the effectiveness of its action depended on dose. In the most effective dose (500 nmoles/kg) it reduced the UI by more than half. γ-Endorphin had much stronger antiulcer activity than β-endorphin. Its maximal effective dose was 10 times smaller, and in this dose γ-endorphin reduced UI more than sevenfold. With an increase in dose, the antiulcer activity of the peptide decreased. Met- and Leu-enkephalins had a moderate antiulcer action, depressing UI in a dose of 20 nmoles/kg by 30 and 39% respectively. A decrease in effectiveness with an increase in dose was observed for both peptides, but by a greater degree for Met-enkephalin. Dinorphine, used in a dose of 20 nmoles/kg, reduced UI by 3.5 times. In a dose of 200 nmoles/kg dinorphine had virtually no antiulcer action.

All endogenous opioid peptides tested thus possessed antiulcer activity to a greater or lesser degree. This effect is probably mediated by opiate receptors, for it is blocked by their specific antagonist naloxone [13]. All opioid peptides except β-endorphin are characterized by a phenomenon of "sliding" of the effect with

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TABLE 1. Effect of Endorphins, Enkephalins, and Dinorphine on Development of Experimental Duodenal Ulcers (M±m)

Substance	Dose, nmoles/kg	No. of animals	SU	FU	UI
Control	—	104	1,76±0,13	0,67	3,10
β-Endorphin	12	6	1,33±0,42	0,67	2,67
	50	28	1,00±0,24*	0,43*	1,86
	125	31	0,84±0,20*	0,39*	1,62
	500	22	0,86±0,29*	0,32*	1,50
γ-Endorphin	12	8	1,13±0,48	0,38	1,89
	50	14	0,29±0,16*	0,07*	0,43
	125	10	0,50±0,27*	0,20*	0,90
	500	10	0,80±0,33*	0,40	1,60
Met-Enkephalin	2	10	2,00±0,31	0,80	3,60
	20	34	1,18±0,19*	0,53	2,24
	200	21	1,57±0,25	0,71	2,99
Leu-Enkephalin	2	10	1,90±0,37	0,80	3,50
	20	33	1,00±0,20*	0,45*	1,90
	200	21	1,19±0,25*	0,52	2,23
Dinorphine	2	9	0,67±0,35*	0,33*	1,33
	20	9	0,44±0,29*	0,22*	0,88
	200	8	1,50±0,47	0,63	2,76

Legend. *P < 0.05 compared with the control.

an increase in dose, which was observed by the writers previously in a study of the antiulcer action of a synthetic enkephalin analog [2]. A similar change in pharmacological activity of opioids depending on dose has been observed by other workers also. It can be tentatively suggested that it is connected with complex interactions between opioids and different populations of opiate receptors [4]. Incidentally, all biosynthetic precursors of the peptides studied, namely pro-opiomelanocortin and proenkephalins A and B, have been found in large quantities in peripheral tissues and, in particular, in the gastrointestinal tract [6-8]. They may perhaps exert their activity not only by the endocrine, but also by the paracrine route. It can be postulated that during duodenal ulcer formation endogenous opioid peptides exert a synergic protective action on the duodenal mucosa. Because of this duplication of function, the necessary reserve of strength is created, and failure of one or even several protective mechanisms will not lead inevitably to the development of the pathological process. In a study of the role of these substances in the pathogenesis of diseases of the gastrointestinal tract, the whole spectrum of endogenous opiods must be studied, because changes in levels of one or two of them do not enable the state of the opioid system as a whole to be evaluated, especially if certain peptides have a common precursor.

One of the functions of endogenous opioids of different origin is therefore to protect the duodenal mucosa when exposed to ulcerogenic influences. Further investigations will show whether the sphere of their protective action is limited to pathological states of the digestive system. Very probably the cytoprotective effect of opioids is the basis of their physiological action on the viscera. This conclusion is supported by the absence of correlation between the analgesic (central) potential of the peptides studied [5] and their peripheral effects.

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