RELATIONSHIP BETWEEN THE ANALGESIC AND ULCEROGENIC ACTION OF CYSTEAMINE*

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In previous investigations the writers found that certain structural analogs of the enkephalins have a protective action on the duodenal mucosa, preventing the development of duodenal ulcers induced by administration of cysteamine* in rats [1, 2]. At the same time, endogenous opioids and, in particular, enkephalins, are known to play a key role in the regulation of pain sensitivity [3].

The aim of this investigation was to study relations between the effect of cysteamine on the pain threshold and its ulcerogenic action.

EXPERIMENTAL METHOD

In the experiments of series I the effect of a single injection of cysteamine on the pain threshold was evaluated in 45 male Balb/C mice weighing 22-25 g. The pain threshold was measured by the method in [4], by measuring the time before withdrawal of the tail during continuous temperature stimulation, using an analgesia testing apparatus from "Hugo Sachs Elektronik" (West Germany). After measurement of the initial pain threshold, all the mice received a subcutaneous injection of cysteamine (from Fluka, Switzerland) in a dose of 350 mg/kg [1, 2], dissolved in 0.1 ml of physiological saline. The animals of group 1 received no further medication. Simultaneously with cysteamine the mice of group 2 received an injection of naloxone (from "Endo Labs," USA) in a dose of 1.5 mg/kg, and the mice of group 3 received the same dose of naloxone 60 min after injection of cysteamine. Pain thresholds were measured after 60, 120, and 180 min.

In the experiments of series II the effect of a single injection of cysteamine on the pain threshold of male Wistar rats (weighing 180-200 g) and the value of the original pain threshold for the development of experimental duodenal ulcers were determined. Animals receiving physiological saline formed the control group. After measurement of the original pain threshold by the method in [4], the rats were given an intramuscular injection of cysteamine in a dose of 350 μg/kg in physiological saline. Pain thresholds were redetermined 90 and 180 min and 24 h after the beginning of the experiment. The animals were then decapitated, and the state of the duodenal mucosa was examined with a binocular loupe. When the animals were divided into groups, a special ulcer index, defining the severity of the lesion (expressed in points) and frequency of lesions [2], was determined. The mean area of the ulcers also was determined for each group.

EXPERIMENTAL RESULTS

The pain threshold of the mice rose and remained consistently high 60 min after injection of cysteamine (Table 1). Naloxone, an antagonist of opiate receptors, almost completely blocked the analgesic effect of cysteamine. Delayed injection of naloxone also abolished analgesia induced by cysteamine, but this effect did not arise until 120 min after injection of the opiate antagonist.

Cysteamine also caused definite analgesia in rats (Table 2). The pain threshold was raised by 62% after 3 h. The analgesic effect was still present, although weaker, after 24 h.

*2-Aminoethanethiol.

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TABLE 1. Changes in Threshold of Pain Sensation in Mice under the Influence of Cysteamine (M ± m)

Group of animals	Pain threshold, sec			
	time after injection of cysteamine, min			
	0	60	120	180
1 (15)	2,83±0,11	3,99±0,20*	4,02±0,31*	4,07±0,34*
2 (15)	2,97±0,12	3,27±0,19	3,39±0,22	3,20±0,32
3 (15)	2,72±0,06	3,83±0,21*	3,60±0,30*	3,09±0,21*

Legend. Here and in Table 2 asterisk indicates $P < 0.05$ compared with initial value; number of animals given in parentheses.

TABLE 2. Changes in Threshold of Pain Sensation in Rats under the Influence of Cysteamine (M ± m)

Substance injected	Pain threshold, sec			
	time after injection of substance, h			
	0	1½	3	24
Physiological saline (10)	6,06±0,39	6,72±0,70	6,63±0,62	6,92±0,31
Cysteamine, 350 μg/kg (15)	5,55±0,52	7,98±0,70*	9,01±1,11*	6,99±0,39*

TABLE 3. Dependence of Severity of Lesion In Duodenal Ulcer Induced by Cysteamine on Pain Threshold in Rats (M ± m)

Pain threshold	Ulcer index	Severity of lesion, points	Area of lesion, mm^2
Under 5.5 sec	2,85	1,43±0,37	1,66±0,52
Over 5.5 sec	4,57	2,57±0,20*	6,74±1,55*

Legend. *$P < 0.05$. Number of animals in groups was seven.

Depending on the initial level of the pain threshold the animals were divided into two groups (above or below the average initial pain threshold of 5.5 sec; one animal died in the course of the experiment). Ulcer formation was much more intensive in rats with a low initial pain threshold: The severity of the lesion was significantly increased and the area of the ulcers was increased fourfold (Table 3).

Under the influence of cysteamine a considerable and lasting lowering of sensitivity to pain was thus observed in both mice and rats. Since the analgesic effect was blocked by naloxone, a specific antagonist of opiate receptors, it can be concluded that this effect is realized through the endogenous opioid system.

The facts on the analgesic action of cysteamine described above do not, at first glance, agree with data obtained previously showing the marked protective action of endogenous opioids and their synthetic analogs in an experimental model of cysteamine-induced duodenal ulcer [1, 2]. Currently, however, views on the opioid system are in the stage of accumulation of facts and are constantly being added to. The presence of a series of subpopulations of opiate receptors, through which different and often antagonistic effects of opioids are mediated, has been demonstrated in the body [5]. The impression is gained that the analgesic effects of opiate ligands in the CNS are realized mainly through the population of new-receptors [9]. Meanwhile, the writers previously demonstrated that morphine, a typical agonist of μ-receptors,

does not possess any marked antiulcer properties [2]. Correlation thus does not exist between the analgesic and antiulcer action of opioids, which suggests the presence of different receptor pathways for the realization of these effects.

Finally, the presence of considerable quantities of opioid peptides in peripheral tissues and, in particular, in the organs of the gastrointestinal tract [7, 8], suggests that peptides have special functions that are exhibited at the periphery, and which differ sharply from their central effect, as was recently confirmed in relation to central and peripheral effects of opioids on the development of experimental stress-induced gastric ulcers [6].

Changes in the endogenous opioid system are thus probably one stage in the pathogenesis of experimental duodenal ulcer induced by injection of cysteamine. The more precise determination of the character of this phenomenon will give a clearer idea of relations between central and peripheral opioid influences on the development of duodenal ulcer.

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