OPIOID REGULATION OF GASTRIC AND DUODENAL AFFERENT REACTIONS IN THE EARLY STAGES OF ACUTE INJURY

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The phenomenon of "reversible deafferentation" observed in a number of investigations in the early period after acute injury to organs of such great functional importance as the heart, stomach, and duodenum, suggested that this type of response is a typical defensive reaction of the visceral organs, preventing the formation of a "pathological system" [1, 4]. It has been shown that an important role in modulation of the mechanisms of afferentation of the pathologically changed heart is played by opioid peptides [2]. However, the problem of the mechanisms of realization of this phenomenon as it affects the gastroduodenal complex has not yet been adequately discussed. Yet we know that the stomach and duodenum possess a powerful system for the production of endogenous opioids, which play an important role in the regulation of activity of the digestive system [5, 6]. It has also been shown that the action of opioids on gastric and duodenal function may be realized at different levels starting with the CNS and ending with direct interaction with opiate receptors of the tissue cells at the organ level [7].

In this investigation the role of opioid peptides in the formation of the "reversible deafferentation" of the gastroduodenal complex (GDC) was studied in the early stages after injury.

EXPERIMENTAL METHOD

Series of acute experiments were carried out on 45 adult cats weighing 2-3 kg, anesthetized with chloralose (40-50 mg/kg), curarized and artificially ventilated. Acute injury to the pyloric part of the stomach was reproduced by subaerosal injection of 0.2-0.3 ml of 10% neutral formalin solution through a specially introduced cannula. A catheter for administration of drugs with opioid activity also was fixed in the zone of presumed injury. In order to prevent leakage of the drugs into the peritoneal cavity the end of the catheter was covered with part of the greater omentum. Bipolar stimulating electrodes 5 mm in diameter were fixed in the region of the body of the stomach (BS), its pyloric portion (PP), and the duodenal bulb (DB). The operation wound was then closed in layers and without drainage. Afferent reactions of the components of GDC were judged by the amplitude of the initial phases of evoked potentials (EP) at foci of maximal activity (FMA) of the cortical representation of the parts of the stomach and duodenum [3] and in the centrum medianum (CM) of the thalamus. EP were recorded and analyzed by coherent averaging, using the "Multibasis" universal system (Biomedica, Italy). In the course of the experiments the animals' state was monitored by periodic recording of EP from the sciatic nerve. In individual experiments the right vago-sympathetic trunk was divided. In the remaining series the effect of opioid-active drugs (naloxone, moradol, and dalargin) on the formation of afferent reactions of the structures of GDC tested, was investigated. For this purpose, the formation of formalin-induced necrosis of the pyloric portion of the stomach was preceded by application of the above-mentioned drugs to the zone of necrosis in doses of 5-20 μg. The doses of the drugs were chosen so as to

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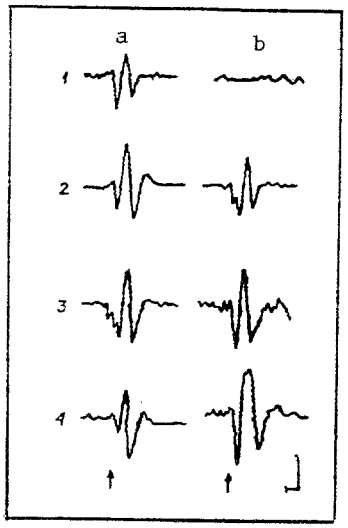

Fig. 1. EP recorded in cerebral cortex in response to electrical stimulation of intact and injured BS, against the background of action of opioidactive drugs: a) EP in cerebral cortex at end of experiments; b: 1) 5 min after injury to BS, 2) 5 min after injury to BS preceded by injection of naloxone; 3) 5 min after injury to BS preceded by injection of moradol; 4) 5 min after injury to BS after injection of dalargin. EP recorded in response to 10 presentations of stimulus. Calibration: 50 μV, 20 msec.

avoid any systemic action on account of the resorptive effect. After the background data and of data relating to the assumed peak of action of the drugs (after 15-20 min), formalin solution was injected subserosally and, 5-7 min later, EP were recorded in the cerebral cortex (and in CM of the thalamus). All the experiments were conducted on fasting animals 12-14 h after the last meal.

EXPERIMENTAL RESULTS

Recording of the background data revealed the following values of total amplitude of the initial phases of EP: in the cortex in response to stimulation of BS 184 ± 19.8, in PP 141 ± 12.4, in DB 150 ± 14.6; in CM in response to stimulation of BS 139 ± 11.4, in PP 111 ± 10.6, and in DB 123 ± 11.8 μV. The amplitude of EP 5 min after division of the vasosympathetic trunk in response to stimulation of all parts of the GDC studied, both in the cerebral cortex and in CM, increased on average by 15-20% [3]. The amplitude of the initial phases of EP 5 min after injection of formalin into the pyloric portion, was significantly reduced after truncal vagotomy compared with initially. In the cerebral cortex it was: BS 62 ± 6.3 μV, $p < 0.01$; PP 49 ± 5.1 μV, $p < 0.01$ (Fig. 1b, 1); in DB 53 ± 6.9 μV, $p < 0.01$. The same tendency for changes in amplitude of EP also was observed in CM of the thalamus. It was: BS 48 ± 6.1 ($p < 0.01$), PP 26 ± 3.4 ($p < 0.01$), and DB 57 ± 7.6 ($p < 0.05$) μV. However, 15 min after injection of formalin the amplitude of EP in the cerebral cortex and CM of the thalamus in response to stimulation of PS and DB increased up to values comparable with those found intially (BS 219 ± 17.5, 136 ± 15.7 μV; DB 155 ± 11.7 and 113 ± 10.8 μV respectively). During the same period the amplitude of EP in response to stimulation of PP of the stomach remained significantly depressed: in the cortex 63 ± 5.9 μV ($p < 0.05$), in CM 39 ± 6.2 μV ($p < 0.01$).

TABLE 1. Changes in Total Activity of Initial Phases of EP (in μV) in Response to Stimulation of Components of Gastroduodenal Complex during Reproduction of Formalin Necrosis in Pyloric Portion of Stomach, Preceded by Administration of Drugs with Analgesic Activity

Region of recording	Zone of stimulation	Initial data	15 min after injection of naloxone	5-7 min after injection of formalin	5 min after injection of moradol	5-7 min after injection of formalin	15 min after injection of dalargin	5-7 min after injection of formalin
FMA	BS	184±19,8	166±12,3	151±11,9	171±16,9	193±14,7	141±10,6	175±11,2
Cerebral cortex	PP	141±12,4	132±11,8	122±10,6	139±12,3	158±12,7	124±12,6	169±15,8
	DB	150±14,6	141±14,1	119±13,7	154±10,2	183±13,6	131±10,3	153±12,5
CM of thalamus	BS	139±11,4	148±13,5	129±15,9	143±11,8	106±9,5	133±11,5	141±12,7
	PP	111±10,6	122±14,8	104±12,6	129±14,3	141±13,7	107±7,4	149±9,8
	DB	123±11,8	141±7,6	153±11,2	117±6,7	138±11,3	123±9,6	157±14,3

Legend. No statistically significant differences between data were found.

Experiments to study the effect of drugs with opioid activity showed that in the doses tested they have little effect on the formation of afferent reactions evoked by stimulation of components of the intact GDC (Table 1). This follows from the fact that in no case did application of these drugs give rise to significant changes in amplitude of EP. A somewhat different picture was observed in a model of formalin necrosis preceded by the action of naloxone, moradol, and dalargin. Although in this case also there were no significant changes, in our view some general tendencies must be observed. For instance, injection of formalin into PP of the stomach, preceded by injection of naloxone, in most cases led to a decrease in the total amplitude of EP. Conversely, formalin necrosis, after preliminary application of moradol and, in particular, of dalargin was accompanied by a clear tendency for the amplitude of the initial phases of EP of the test structures to increase (Table 1).

The results shed some light on the mechanisms of modulation of the afferent reactions of the gastroduodenal complex in the intact state and against the background of acute injury. They confirm the view that the vagus nerve system is involved in the control of afferent reactions of visceral organs. At the same time, the results show that involvement of the vagus nerves is not decisive as regards inhibition of the afferent reactions of the stomach and duodenum in the initial stages of their acute injury. This stems from the fact that truncal vagotomy, while leading to intensification of afferent reactions of the intact GDC, did not change the tendency toward their inhibition in the early periods after injury.

The results of this investigation with drugs possessing opioid activity are striking, first, because it was found agonists and antagonists of opiate receptors act in the same direction. According to the experimental results, both completely prevented the development of the reaction of inhibition of visceral afferentation, which is characteristic of the initial period after infliction of injury (Fig. 1b, 2, 3, 4). The results are evidence that the main mechanism of "reversible deafferentation" of injured organs is linked with activation of the intramural opioid systems. Impairing the development of the partial deafferentation period on application of the test drugs is evidently linked with the onset of competitive relations between exogenous opioids (agonists – antagonists) and endogenous, involved in regulation of afferent reactions of injured organs of the GDC, for the opiate receptors. The doses of the drugs used in the experiments and their mode of administration emphasize the role of intramural mechanisms in the development of the reactions recorded.

It can thus be tentatively suggested that "autonomization" of visceral organs in the acute stage of a pathological process not only reflects ability to exert precentral modulation of afferent reactions, but also a tendency toward an increase in the resistance of organs and of the organism as a whole to injury.

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