ACTION OF MORPHINE ON PERIODIC GASTRIC MOTOR ACTIVITY IN DOGS AFTER SELECTIVE DISTAL VAGOTOMY

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A particularly interesting stage in the study of the role of opioid peptides in the regulation of functions of organs of the gastrointestinal tract [6, 8] is the further study of the mechanisms of action of morphine on periodic motor activity of the stomach. Its action on the evacuatory movements of the gastrointestinal tract depends on dose, mode of adminstration, species differences in regulatory mechanisms producing the act of vomiting, and also the initial functional state of organs of the gastrointestinal tract (hunger, satiation) [4]. Without discussing disorders of theabove-mentioned activity arising as side

TABLE 1. Representation of Stages in Responses of Gastric PA to Morphine depending on Dose and Sensitivity in Dogs with Intact (group 1) and Disturbed (group 2) Gastric Innervation

Group	Sensitivity to morphine	Dog's name	Minimal TVD, μg/ml	Stage	Representation of stage	Maximal VSTD μg/kg	Stage	Representation of stage
1	High	Rex	27	I	+*	20	I	+
				II	+		II	+
				III	+		III	−
		Nord	60	I	+*	50	I	+
				II	+		II	+
				III	+		III	−
	Low	Kashtan	95	I	+*	84	I	+
				II	+		II	−
				III	−		III	+
		Baikal	125	I	+*	90	I	+
				II	+		II	−
				III	−		III	+
2	High	Blek	36	I	+*	29	I	±
				II	−		II	−
				III	+		III	+
		Tsygan	61	I	+*	56	I	±
				II	−		II	−
				III	+		III	+
	Low	Etalon	80	I	+*	66	I	±
				II	−		II	−
				III	+		III	+
		Druzhok	94	I	+*	74	I	±
				II	−		II	−
				III	+		III	+
		Barbos	93	I	+*	85	I	±
				II	−		II	−
				III	+		III	+

Legend. +) Stage well defined, −) stage absent, ±) stage ill defined, *) accompanied by one attack of vomiting.

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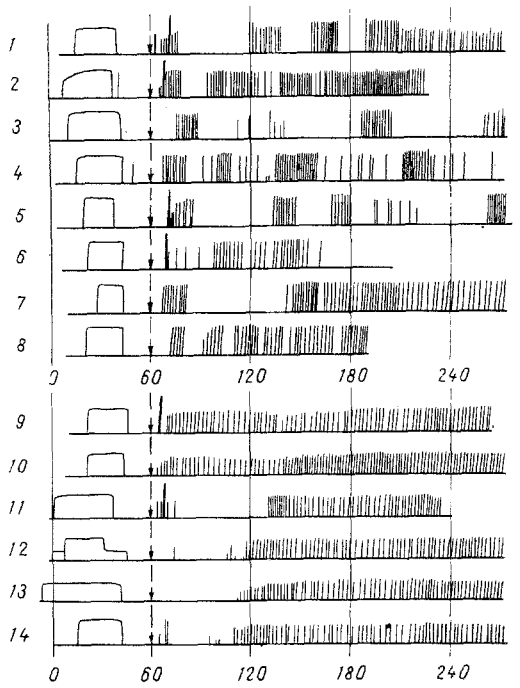

Fig. 1. Effect of morphine on gastric PA of dogs with intact (1-8) and previously disturbed (9-14) gastric innervation. Each horizontal line with vertical lines above it is the scheme of a separate experiment. Arrows indicate time of injection of morphine (doses shown in Table 1). Periods of contractions before injection of morphone shown on left of arrows on time scale; actual gastric movements shown on right. Each vertical line corresponds to a separate gastric contraction, thicker high vertical lines indicate attacks of vomiting. Abscissa shows time scale (in min). Thin vertical lines running through all schemes are boundaries of intervals of 1 h. 1-4, 9, 10) Dogs highly sensitive to morphine; 5-8, 11-14) dogs with low sensitivity. 1 and 3) Dog Nord, TVD, and VSTD, respectively; 2 and 4) dog Rex, the same; 5 and 7) dog Baikal, the same; 6 and 8) dog Kashtan, the same; 9 and 10) dog Blek, the same; 11 and 13) dog Tsygan, the same; 12 and 14) dog Druzhok, VSTD.

effects of analgesic doses of morphine, it must be pointed out that morphine, in low doses, has been used for pharmacologic analysis of the mechanisms of gastric periodic activity (PA) in dogs [3, 4]. After injection of morphine in doses not giving rise to vomiting (30-100 μg/kg body weight, subcutaneously) during periods of rest, extra periods of contractions of the stomach and various parts of the small intestine, indistinguishable graphically from natural contractions, regularly arise. These facts provided a basis for the hypothesis of the existence of an autonomous "gastric motor center," independent of the vomiting center [4], but this was not later confirmed, although it stimulated further and more detailed studies of the central and peripheral neurohumoral mechanisms of gastric PA [3].

Considering the contradictory data on the role of vagus innervation in the mechanism of the effects of morphine on gastric PA, in the investigation described below these effects were studied after preliminary disturbance of this activity.

EXPERIMENTAL METHODS

Experiments were carried out on nine mongrel dogs with fistulas into the fundal part of the stomach. Gastric PA was recorded graphically by means of an intragastric balloon. Morphine was injected subcutaneously 20 min after the end of a regular period of contractions in doses of 20-125 μg/kg in 0.1% solution. Doses were chosen individually for each dog. The minimal dose which, on repeated injections, caused a single attack of vomiting accompanied by a group of strong contractions, was called the threshold vomiting dose (TVD). The maximal dose of morphine which induced only a period of contractions without an attack of vomiting (usually 7-15 μg/kg below the TVD) was called the vomiting subthreshold dose (VSTD). To study the role of vagal innervation, selective distal vagotomy was performed [1] without pyloroplasty on five of the nine dogs 2-4 months before the experiment began. The operation consisted of high total transverse gastrotomy in the upper third of the fundal region, with immediate reanastomosis. In this way sufficiently complete vagal and partial sympathetic denervation of the distal parts of the stomach and the duodenum was achieved. The experiments began when the reaction of the gastric mucosa was alkaline, 18-20 h after feeding, and they were repeated not more often than once a week.

EXPERIMENTAL RESULTS

Considerable individual differences were found when the TVD of morphine was chosen, and accordingly the dogs were divided into groups with high and low sensitivity to morphine. TVD for these groups differed significantly, and averaged 44 and 110 μg/kg, respectively (Table 1). The number of dogs with high and low sensitivity in these experiments was almost equal. Sensitivity to morphine did not change in the course of long periods of observation (up to 6 months) or after preliminary vagal denervation of the stomach.

In dogs with an intact gastric innervation the typical fully developed response of the gastric PA to injection of morphine consisted (in the course of experiments of the usual duration, namely 6-8 h) of three successive stages. During a period of rest 7-9 min after injection of the TVD of morphine a group of strong contractions appeared, accompanied by a single attack of vomiting, which was followed by a pause of 11-45 min, namely stage I of the reaction. In highly sensitive dogs, i.e., receiving relatively lower doses of morphine, stage II appeared — a series of groups of contractions alternating with pauses, resembling shortened cycles of PA, folllowed by transition into stage III — continuous contractions. The latter could last for hours (Fig. 1: 1, 2). In dogs with low sensitivity, i.e., with relatively higher doses of morphine, during the same periods of observation no continuous contractions arose (Table 1; Fig. 1: 5, 6).

After injections of morphine into the same dogs in VSTD, not causing an attack of vomiting, the group of contractions and a short pause (stage I) in dogs with high sensitivity was followed by stage II (more frequent cycles), which did not change into continuous contractions (Fig. 1: 3, 4). In dogs with low sensitivity continuous contractions arose without any marked intermediate stage of alternating short cycles (Table 1; Fig. 1: 7, 8).

In the lowest doses morphine (the maximal VSTD for dogs with high sensitivity averaged 35 μg/kg) only the first two of the possible three stages of the response to morphine were thus represented. With an increase in dose to the minimal TVD (mean 44 μg/kg) the response of these same dogs was fully developed and all three stages were represented. With a further increase in the dose of morphine (VSTD for dogs with low sensitivity averaged 87 μg/kg) stage II of the response to morphine was omitted (Table 1), but with the highest doses used (the minimal TVD for dogs with low sensitivity averaged 110 μg/kg) stage III of the response of these dogs to morphine was omitted. In cases when stage III of the response to morphine was omitted, the possibility of its appearance at times other than those chosen for observation of the animals could not be completely ruled out.

After denervation gastric PA were preserved, and the rhythm did not differ quantitatively from that in dogs with an intact innervation. However, the periods of rest were shortened, periods of contractions were lengthened, and the amplitude of the contractions was reduced, evidence on the whole of some degree of weakening of central inhibitory influences on periodic motor activity.

The latent period of appearance of the primary response (stage I) in most experiments did not change appreciably, but the intensity of the response weakened, especially to VSTD (only one to three contractions). The pause after reduced contractions of this sort was

also shortened or (in most experiments) lengthened (to 50 min). The main distinguishing feature of gastric motor response to morphine in these dogs was the complete omission of stage II irrespective of the dose of morphine and the sensitivity of the dogs to it (Table 1; Fig. 1: 9, 14). Depending on the value of TVD they were divided, like the dogs with intact gastric innervation, into animals with high and low sensitivity (Table 1).

Differences in the sensitivity of dogs to morphine were thus manifested as a significant difference in the minimal TVD values and the representation of the stages subsequently in the response. The fact that differences in TVD remained after vagal denervation of the stomach is evidence that individual reactivity to morphine is formed without the participation of central parasympathetic mechanisms of regulation of gastric motor activity, in agreement with data in the literature [5]. Since an essential component of the central vomiting act is an intestinal phase [2, 3], which is not blocked by trunk vagotomy, or by injections of atropine, adrenalin, certain derivatives of the phenothiazine series, and naloxone [3], it can be tentatively suggested that it is this phase, in conjunction with depression of central inhibitory influences on gastric motor activity under the influence of morphine, that is the principal triggering mechanism for stage I of the response in dogs with a denervated stomach. However, whereas in dogs with an intact gastric innervation, intestinal contractions arising simultaneously with those of the stomach evoke inhibition of gastric motor activity through the mechanism of the enterograstric reflex, followed by a fresh group of contractions on account of the altered functional state of the regulatory mechanisms, and so on, i.e., a marked stage II of more rapidly alternating cycles arises, this mechanism does not operate in dogs with a denervated stomach and gastric contractions, after stage I, change into continuous contractions.

Morphine thus stimulates gastric PA by abolishing the central inhibitory mechanisms responsible for the onset of rest periods. Local enterogastric reflexes, against the background of gastric denervation, are unable to maintain alternation of the cycles that is essential for performance of the evacuatory function of PA. As a result of the considerable "desynchronization" of the components of PA in different sections of the gastrointestinal tract, the evacuatory function of PA 90-100 min after injections of morphine is severely disturbed [3]. Some drugs which effectively block morphine vomiting, including nalorphine, incidentally, also inhibit gastric periodic motor activity to a varied degree.

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