CNS blockade of acoustic stress-induced gastric motor inhibition by κ -opiate agonists in dogs

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GUE, M., C. HONDE, X. PASCAUD, J. L. JUNIEN, M. ALVINERIE, AND L. BUENO. *CNS blockade of acoustic stress-induced gastric motor inhibition by κ -opiate agonists in dogs*. *Am. J. Physiol.* 254 (Gastrointest. Liver Physiol. 17): G802–G807, 1988.—The influence of the κ -opioid substances dynorphin-(1–13), ethylketocyclazocine (EKC), and U 50488 and μ -opioid substance [D-Ala²-N-Me, p-nitro-Phe⁴-Gly⁵-ol]enkephalin (DAGO) on gastric motor inhibition induced by acoustic stress (AS) was investigated in fasted dogs with strain-gauge transducers chronically implanted on the antrum and proximal jejunum. AS induced by 1 h of music (80–90 dB) was delivered through earphones. Starting 40–50 min after the last migrating motor complex (MMC), AS delayed by 114% the occurrence of the next gastric MMC, whereas intestinal motility was unaffected. During AS plasma cortisol increased ($P < 0.05$) by 215%, 15 min after the beginning of noise and reached a peak at 30 min. When administered intracerebroventricularly at doses higher than 20 ng/kg, dynorphin abolished the AS-induced lengthening of the gastric MMC cycle. Similar blockade was observed for EKC and U 50488 at doses of 10 and/or 20 ng/kg, but DAGO was unable to affect the AS-induced gastric inhibition at any dosage tested (20–200 ng/kg icv). At doses effective against AS-induced hypomotility, both dynorphin-(1–13) and EKC reduced significantly ($P \leq 0.05$) the associated maximal increase in plasma cortisol level. Plasma cortisol was unmodified by intracerebroventricular administration of DAGO. None of the agonists affected basal plasma cortisol levels or the increase (0–90 min) in response to intravenous adrenocorticotrophic hormone (ACTH, 5 IU). Both EKC (50 ng/kg) and U 50488 (20 ng/kg) were unable to antagonize the inhibitory effect of ovine corticotropin-releasing factor (CRF, 100 ng/kg icv). We conclude that κ - but not μ -substances act centrally to block the inhibition of gastric motility and the plasma cortisol increase produced by AS. These effects are probably due to a blockade of CRF release rather than to an inactivation of CRF-induced pituitary ACTH release or to the direct inhibition of cortisol release at adrenal gland level.

opiates; κ -agonists; gastrointestinal motility

ENDOGENOUS OPIOIDS ARE INVOLVED in responses to many stressors, and exposure to stressful stimuli can produce opiate-like alterations that can be reversed by the opiate antagonist naloxone in both rats (27) and humans (39). Furthermore, some changes in gastrointestinal motility (36) or gastric emptying (38) associated with centrally acting stressful stimuli are reduced by the concomitant infusion of naloxone. Recently we have shown that the gastric motor inhibition induced by

acoustic stress (AS) in dogs is blocked by the previous administration of benzodiazepine and the γ -aminobutyric acid agonist muscimol but not by naloxone (18). In addition, both acoustic and cold-exposure stress in mice are accompanied by increased gastric emptying that is also reversed by diazepam and propranolol but not by naloxone (19). These recent findings support the idea that some effects of stressful stimuli on gastric motility may not be related to activation of opiate pathways at central nervous system (CNS) and/or peripheral levels.

In humans, opioid peptides have been shown to inhibit adrenocorticotrophic hormone (ACTH) and cortisol secretion (11, 17, 41). In contrast, the data obtained in rats are variable; while some groups have reported that opioid peptides stimulate the release of ACTH (12, 22) and corticotropin-releasing factor (CRF)-like bioactivity (4), others found that opioids inhibit ACTH secretion and that naloxone stimulates ACTH and corticosterone secretion (13, 31). More recently it was demonstrated that opioid peptides, particularly κ -agonists such as dynorphin, act through specific opioid receptors to inhibit CRF release from the rat hypothalamus (33, 40).

The present study was performed in dogs 1) to compare the effects of centrally administered μ - and κ -agonist peptides on the inhibition of gastric motility and the associated cortisol release induced by acoustic stress and 2) to determine the action of these opioid peptides by testing their ability to influence the ACTH-induced cortisol release and the effects of centrally administered CRF on gastric motility.

METHODS

Animal Preparation

Six adult mongrel dogs weighing 15–18 kg were used for the experiments. Under halothane (Fluothane ND) anesthesia, three strain-gauge transducers prepared according to a method previously described (32) were sewn on the stomach 15 and 7 cm from the pylorus and on the proximal jejunum, 60 cm from the ligament of Treitz. In addition, a stainless steel cannula, 19 mm long, was implanted into the right lateral ventricle of the brain through a hole made on the frontal bone 2 mm posterior to the bregma and 5 mm lateral to the sagittal suture; in four animals, a silicone catheter was also inserted into the right jugular vein. At the end of surgery, the free

ends of the strain-gauge wires and the catheter were brought subcutaneously to the back of the neck, and the animals were allowed to recover 10–15 days before beginning the experiments. Each day at 1700, the dogs received a standard meal of 600 g of canned food (Fido-Quaker, France), containing 21.7% dry matter, 7.7% protein, 4.5% fat, 6.9% carbohydrates, and 2.6% minerals. Water was available ad libitum.

Motility Recordings

Gastrointestinal mechanical activity was recorded continuously 23 h/day by connecting the strain gauges to a four-channel wheatstone-bridge amplifier (Vishay, France) and a potentiometric recorder. Each strain gauge was calibrated before implantation. The transducer was clamped firmly in an horizontal position at the level of the strain gauge, and weights (1–5 g) were attached 1 mm lateral from the soldering point. The amplitude (mV) was noted, and an average calibration curve was calculated. Before the first recording session, corresponding direct current voltages were applied to calibrate the potentiometric recorder (Rikadenki, Japan).

Experimental Procedure

The experiments were performed at 2-day intervals and 15 h after the last meal. In a first series of experiments, 40–50 min after the occurrence of a gastric migrating motor complex (MMC) the animals were subjected to music by earphones (80–90 dB broad frequency noise) for 1 h according to a procedure previously described (18). In the four animals with jugular catheters, blood samples for plasma cortisol measurements were taken 5 min before and after the beginning of AS and at 15-min intervals during the next 90 min. AS was preceded (10 min) by intracerebroventricular administration of sterilized saline (vehicle) or saline containing various concentrations of dynorphin-(1–13) (Sigma, Laverpilliere, France) ethylketocyclazocine (EKC; Sterling-Winthrop, Guilford, UK), U 50488 (Upjohn, Kalamazoo, MI), and [D-Ala², N-Me, p-nitro-Phe⁴-Gly⁵-ol]enkephalin (DAGO; Sigma, France). These substances were administered at the following dosages (in ng/kg): dynorphin-(1–13), 10–200; EKC, 10–50; U 50488, 20; and DAGO, 20–200. Each treatment was applied twice in each animal and in a randomized order. Dynorphin-(1–13), EKC, U 50488, and DAGO were also administered alone at the same doses with blood sampling but without AS (control).

In a second series of experiments the same animals also received 5 IU of ACTH (Choay, Paris, France) administered 10 min after intracerebroventricular injection of dynorphin-(1–13) (100 ng/kg), EKC (20 ng/kg), or vehicle. In a last series of trials, ovine CRF (Sigma, France) was injected intracerebroventricularly at a dose of 100 ng/kg, 10 min after previous administration of EKC (50 ng/kg icv), U 50488 (20 ng/kg icv), or vehicle.

Motor effects were assessed by measuring the duration of gastric and/or jejunal disruption of the MMC pattern. The values are expressed as means $\pm$ SE and were compared by analysis of variance and Student's *t* test.

Plasma cortisol was determined by high-performance

liquid chromatography after extraction with methylene chloride using a microparticulate silica gel column with ultraviolet detection at 254 nm and a 2 ng/ml sensitivity (1).

RESULTS

Motility Studies

Effects of acoustic stress. The control antral mechanical activity was characterized by cyclic phases of gastric contractions lasting 28 ± 9 min ($n = 12$) and occurring at 1.5- to 2-h intervals (Fig. 1). These antral activity fronts or MMC were associated with the occurrence of jejunal motor activity, migrating aborally. The jejunal MMC presented two phases of irregular (phase II) and regular (phase III) activities lasting 39 ± 11 and 6.4 ± 0.6 min, respectively. The AS that began 40 min after the beginning of the last gastric MMC delayed by 114% the occurrence of the next gastric MMC. However, jejunal MMC continued at a normal frequency (Fig. 1 and Table 1). The time interval between the first and second gastric MMCs after AS was not significantly different ($P > 0.05$) from the control interval. No difference in gastric response was observed between naive and previously tested animals.

Influence of κ - vs. μ -agonists. When administered intracerebroventricularly at doses of 10 and 20 ng/kg in 15-h fasted dogs, dynorphin-(1–13) did not affect significantly ($P > 0.05$) the duration of the gastric MMC cycle. However, a lengthening of the gastric MMC cycle with no change in intestinal motility was observed with a higher dose (Table 1). Similarly, EKC administered intracerebroventricularly at doses higher than 20 ng/kg also delayed the occurrence of the next gastric MMC. These substances were therefore tested on stress-induced gastric motor changes only at doses inactive per se on the pattern of gastric contractions.

Intracerebroventricular administration of dynorphin-(1–13) at a dose of 20 ng/kg 10 min before AS completely abolished the AS-induced lengthening of the gastric MMC cycle (Fig. 1 and Table 1), whereas a significant reduction ($P < 0.05$) was obtained at the lower dose (10 ng/kg). Similarly EKC injected intracerebroventricularly (10 and 20 ng/kg) and U 50488 (20 ng/kg) also suppressed the inhibition of gastric contractions induced by AS (Table 1); in contrast, DAGO injected centrally at doses inactive per se (< 200 ng/kg) was unable to modify the AS-induced gastric motor changes (Fig. 1). Given alone at a dose of 200 ng/kg, DAGO delayed the occurrence of gastric MMC and increased the duration of phase II in the jejunum.

Plasma cortisol level and ACTH responsiveness. In the four dogs with jugular vein catheters, the plasma cortisol level, which was 9.6 ± 2.7 ng/ml ($\pm$ SE, $n = 8$) during the control period corresponding to phase I of the gastric MMC, was significantly increased by AS as early as 5 min after the beginning of AS ($P < 0.01$). It reached a maximal value of 51.8 ± 8.2 ng/ml 25 min later, and this increase was significant ($P < 0.05$) during at least 45 min (Fig. 2).

Dynorphin-(1–13) injected intracerebroventricularly at doses of 100 ng/kg significantly ($P < 0.01$) reduced by

FIG. 1. Influence of acoustic stress (AS) and previous intracerebroventricular (icv) administration of dynorphin (1—13) on gastrointestinal motility in a fasted dog.

TABLE 1. Comparative influence of dynorphin, EKC, U 50488, and DAGO centrally administered on acoustic stress-induced lengthening of duration of gastric MMC cycle in fasted dogs

	Dose, ng/kg	Duration of Gastric MMC Cycle, min	
		Control	Acoustic stress
Vehicle		76±36	189±46*
Dynorphin-(1—13)	10	89±10	146±31*
	20	111±24†	88±27†
	50	84±21	92±29
	100	106±13	101±16
	200	207±37*	
EKC	10	86±17	91±13†
	20	110±31	108±12†
	50	244±49†	
U 50488	20	104±16	105±16†
DAGO	20	108±17	199±44*
	100	111±18	176±29*
	200	269±34†	

Values are means ± SE for 6 dogs. Administrations were done intracerebroventricularly. See text for definition of abbreviations. *,† Significantly ($P < 0.05$) different from corresponding control or vehicle values, respectively.

74.8% the maximal increase in plasma cortisol level induced by AS (Fig. 2). A significant reduction of the plasma cortisol response to AS was also observed at a lower dose (50 ng/kg) of dynorphin-(1—13) injected in-

tracerebroventricularly ($P < 0.01$). At these two doses (50 and 100 ng/kg) dynorphin had no effect per se on basal plasma cortisol level.

Similarly, EKC injected intracerebroventricularly at doses of 10 and 20 ng/kg had no effect on basal plasma cortisol levels during at least 60 min but significantly ($P < 0.05$) reduced by 72.1 and 45.2% the maximum increase of plasma cortisol induced by AS (Fig. 2). In contrast, DAGO centrally administered at a dose of 100 ng/kg intracerebroventricularly was unable to reduce significantly ($P > 0.05$) the plasma cortisol increase induced by AS (41.1 ± 5.4 vs. 36.9 ± 8.1 ng/ml).

ACTH (5 IU/kg) injected intravenously 10 min after previous intracerebroventricular vehicle (control) administration produced an increase in plasma cortisol that reached 80.7 ± 4.1 ng/ml ($n = 8$) at $t = 90$ min, the basal value being 13.1 ± 2.1 ng/ml. These values were not significantly affected when ACTH injection was preceded (10 min) by intracerebroventricular administration of dynorphin (50 ng/kg) and EKC (20 ng/kg) in place of vehicle (Table 2).

Influence of EKC and U 50488 on CRF-induced gastric motor inhibition. As previously described (5) and similar to AS, ovine CRF administered intracerebroventricularly at a dose of 100 ng/kg in 17-h fasted dogs immediately abolished the cyclic MMC of the stomach during 213 ± 46 min, replacing the cyclic MMC with irregular contractions of very small amplitude, whereas the jejunal

FIG. 2. Comparative effects of intracerebroventricular (icv) administration of dynorphin and ethylketocyclazocine (EKC) on plasma cortisol changes associated with acoustic stress in dogs (mean $\pm$ SE, $n = 6$ dogs). * Significantly different from control values at $P \leq 0.05$, t test.

TABLE 2. Influence of central administration of dynorphin-(1–13) and EKC on time-related plasma cortisol increase following intravenous administration of ACTH in dogs

	Time After 5 IU/kg ACTH, min			
	0	10	30	90
	Plasma cortisol, ng/ml			
Vehicle (0.2 ml icv)	13.1 $\pm$ 2.1	63.2 $\pm$ 1.2	82.4 $\pm$ 2.7	80.7 $\pm$ 4.1
Dynorphin (100 ng/kg icv)	15.8 $\pm$ 4.8	51.3 $\pm$ 3.1*	79.0 $\pm$ 3.3	81.7 $\pm$ 2.7
EKC (20 ng/kg icv)	12.5 $\pm$ 5.3	63.6 $\pm$ 1.7	85.8 $\pm$ 5.2	77.1 $\pm$ 5.1

Values are means $\pm$ SE for 8 dogs. See text for definition of abbreviations. * Significantly different ($P \leq 0.05$) from corresponding control values.

MMCs were unaffected. Both EKC (50 ng/kg) and U 50488 (20 ng/kg) administered 10 min before ovine CRF were unable to affect the duration of its inhibitory effect on gastric MMC (Table 3).

DISCUSSION

These results confirm previous data showing that AS selectively inhibits gastric motility and increases plasma cortisol levels in the fasted dog (18). They also indicate that effects of AS on gastric motility and cortisol levels are blocked by central administration of κ - but not μ -opioid agonists.

These results contrast with previous studies in humans showing that the inhibition of antral postprandial activity induced by stressful stimuli is prevented by a concomitant infusion of the opiate antagonist naloxone (36). However, naloxone is unable to reduce or suppress the AS-induced gastric hypomotility in dogs (20).

Blockade of the AS induced hypomotility and associated cortisol release by diazepam and muscimol (18), and the similarity with the effects of centrally administered CRF (5) have led us to speculate that CRF release is involved in the central mediation of AS-induced inhibition of gastric motility. Consequently it may be postulated that κ -opioid agonists affect the release of CRF or the pathways involved in the effect of stress.

Numerous studies have demonstrated that endogenous peptides are implicated in CNS control of the release of

pituitary hormones (15, 29, 35). Dynorphin is widely distributed throughout the brain (21, 26) with high concentrations found in the hypothalamus and the pituitary (30, 32). Recently it has been demonstrated that dynorphin, an endogenous ligand for κ -receptors (7), has selective opioid effects on the secretion of anterior pituitary hormones (17) and on feeding behavior (2, 23). By use of a hypothalamic perfusion system it has been shown in vitro that dynorphin-(1–13) reduces the release of CRF from rat hypothalamus, an effect only partly blocked by naloxone (42). The similarity between the antagonistic action of dynorphin-(1–13) and EKC on AS-induced gastric motor inhibition and cortisol release suggests the selective involvement of κ -receptors.

Acute stress induces an activation of central muscarinic systems with an ability to activate adrenergic networks responsible for most of the behavioral and neuroendocrine responses to stress (24, 25). Consequently κ -agonists may antagonize the effects of AS by reducing the stress-induced increases in central cholinergic activity. In agreement with this hypothesis, it has been shown that opioid drugs, particularly κ -agonists, are able to reduce central cholinergic activity (8, 9). However, this involvement of κ -opioids could occur at least at three levels: 1) an action of the CNS on the adrenal gland through extra hypothalamopituitary pathways, 2) a negative influence on CRF-induced neuronal firing responsible for gastric motor inhibition, or 3) at higher levels by inhibiting stress-induced CRF release.

The gastric motor effects of centrally administered

TABLE 3. Comparative influence of EKC and U 50488 centrally administered on ovine CRF-induced inhibition of gastric MMC cycle in dogs

	Duration of Gastric MMC Cycle, min	
	Control	Ovine CRF (100 ng/kg icv)
Vehicle	76 $\pm$ 36	213 $\pm$ 46*
EKC (50 ng/kg icv)	86 $\pm$ 17	192 $\pm$ 45*
U 50488 (20 ng/kg icv)	104 $\pm$ 16	220 $\pm$ 38*

Values are means $\pm$ SE for 6 dogs. See text for definition of abbreviations. * Significantly ($P \leq 0.05$) different from corresponding control values.

CRF as well as those of AS are abolished after bilateral vagotomy (20) as are other digestive effects of centrally administered CRF (37).

The lack of effects of intracerebroventricular dynorphin-(1-13) and EKC on ACTH-induced cortisol release and the lack of involvement of ACTH and cortisol in the mediation of the gastric motor effects induced by central administration of CRF (5) are consistent with the hypothesis that κ -agonists act either on CRF-induced ACTH release and central muscarinic activation or on CRF release. An inhibition of CRF release is more likely in the light of the lack of antagonistic effects of centrally administered κ -agonist on CRF-induced gastric motor inhibition.

In rats, only the μ -subtype of receptors has been postulated to be involved in the central control of gut motility (34). In agreement with such a hypothesis, DAL-AMIDE and DAGO, but not DADLE, are known to affect both gastric and intestinal motility when centrally administered in dogs (6). In the present experiment dynorphin and EKC, at least in dogs, were able to affect gastric motility selectively when centrally administered, whereas they were inactive by the systemic route (14). Our findings have also shown that κ -agonists may exert selective centrally mediated effects on other physiological functions (3), for example by blocking the rat bombesin scratch test while μ - and δ -selective agonists are inactive (10).

In summary, the present work indicates that κ -agonists may exert centrally mediated inhibitory effects on AS-induced gastric motor alterations and cortisol release by inhibiting the CNS release of CRF, but the mechanism involved remains partly unknown and requires further investigations.

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