Hypothalamic and Amygdaloid Influence on Gastric Motility in Dogs*

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THE source of neuronal control over gastric motility is a matter of great importance because of the relation of the latter to human emotional states.1-3,7-9,16 Change in motility has also been induced in anesthetized animals by stimulation of various areas of the brain.1-3,7-9,16 The present study extends these observations to stimulation through chronically implanted electrodes situated in basal diencephalic and amygdaloid areas. Dogs were studied under various conditions of food deprivation with the animals both awake and asleep.

Method

Nine beagles and 12 mongrel dogs were used. Under intraperitoneal nembutal anesthesia small gastric fistulae were prepared using plastic cannulae, 0.25 in. in diameter. Electrodes were stereotaxically implanted in either hypothalamus or amygdala. These electrodes consisted of 2-4 insulated stainless steel or silver wires, 0.01 in. in diameter, so cemented together that their bare tips were set 1-1.5 mm. apart. The electrodes and their outlet plugs were secured to the skull by stainless steel screws and acrylic cement. The dogs were allowed to recover for 1 week.

They were then placed in a modified Pavlov hammock, and an open-ended polyethylene tube, 3 mm. in diameter, was inserted into the stomach through the fistula. The other end of the tube was connected to a pressure transducer, and gastric pressure was recorded on a Grass polygraph. In 6 dogs simultaneous pressure recordings were also made from innervated Pavlov stomach pouches. After 2 to 3 days of adaptation, the dogs became quiet and relaxed, remaining in the stand for periods as long as 6 hours during which they often slept intermittently. Until the dogs had been trained to relax in the experimental situation, spontaneous stomach contractions remained minimal or non-existent. An empty stomach and relatively quiet surroundings were prerequisite to recording good spontaneous activity.

As soon as the dogs became accustomed to the situation, experiments were begun using a Grass S-4 rectangular wave generator with current wave form and amplitude monitored on a Tetronix oscilloscope. Parameters of stimulation ranged from 10-100 cycles per second, 0.03-2.0 mA current intensity, and 0.5-10 msec. pulse duration, given in 10 second trains. The most frequently used parameters were 0.2-1 mA, 1 msec. pulse duration, and 40 cps. frequency in 10-30 second trains.

The animals were fasted about 18 hours to insure an empty stomach and satisfactory gastric activity. Each recording session lasted 5 hours, the first hour being used to record spontaneous gastric activity. Thereafter, evoked activity was sought by beginning with very weak stimulation and gradually increasing the stimulus strength until either a behavioral response was evoked or a change in gastric motility was noted. Once thresholds were established, the reproducibility of the gastric response could be determined. Control of the experiment was maintained by random and planned mixing of stimuli applied to reactive and non-reactive electrodes. In 4 animals, experimental sessions were carried out before and after bilateral cervical vagotomy. Animals with vagotomy were studied for an average of 5 weeks; those without vagotomy for 4 weeks.

At the completion of the experiments the animals were killed and their brains perfused with saline followed by a mixture of potassium ferrocyanide and 10% formaldehyde. Prussian blue spots were deposited electrolytically at the electrode tips so that their sites could be identified histologically (Fig. 1).

Results

Gastric motility has been variously classified. For convenience of description we will follow the terminology of Hightower and Code6 where Type I waves have a contraction pressure of less than 10 cm. of water, Type II waves a contraction pressure greater than 10 cm. and Type III waves an elevation of the baseline with superimposed Type I and Type II waves. In the dog, the rate of Type I and II waves is 4-5 per minute in the stomach and 18 per minute in the duodenum.

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During periods of relative quiescence, Type II waves often occurred spontaneously at regular or irregular intervals. As shown in Fig. 2 B, they occurred at irregular intervals of 3–6 minutes when 15 of 19 stimulations of the anterior hypothalamus were followed after a 2-second latency by induced Type II waves closely resembling Type II waves that occurred spontaneously. This response was reproducible unless 2 courses of stimuli were given within 45 seconds of each other. In that case the second stimulus did not induce a response.

Fig. 2 C represents the gastric activity of an animal in which short courses of stimuli to the anterior hypothalamus, given during periods of quiescence, produced no alteration in activity. However, longer stimulus trains were followed consistently by increased amplitude and rate of contraction. The small, sharp waves which override the gastric contractions in this figure represent respiratory excursions.

In Fig. 2 D, stimulation of the medial hypothalamus at threshold was associated with no behavioral change, but in 20 out of 27 stimulus courses it was followed by an increase in gastric activity. Here, stimulation during sleep had failed to arouse the dog. In Fig. 2 E, stimulation of the lateral hypothalamus produced minor arousal with sniffing and licking followed by increased duodenal activity. This was reproducible in 7 out of 9 trials. The 18 per minute contraction frequency is characteristic for the duodenum.

Four animals were studied after bilateral cervical vagotomy. In each case, the pre-vagotomy hypothalamic excitatory effect on the stomach was abolished by vagotomy, and in 3 animals inhibitory effects were obtained after vagotomy by stimulating through the same electrodes and at comparable parameters. Fig. 2 F illustrates the inhibitory effect obtained after vagotomy by stimulating the same anterior hypothalamic electrode which gave excitatory effect prior to vagotomy, as illustrated in Fig. 2 A. The behavioral response before and after vagotomy was the same.

During periods of gastric quiescence, stimulation by electrodes which produced inhibition was associated with minor fluctuations of the baseline that could not be interpreted. To demonstrate inhibitory effects, stimula-

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**Fig. 1.** Coronal section at the level of the mammillary bodies showing a posterior hypothalamic (inhibitory response) track with arrow indicating position of Prussian blue spot at tip. The more lateral electrode track at which stimulations were uniformly negative showed the electrode tip within the ventricle. Similar sections were used to identify all stimulus points referred to in these experiments. Nissl stain; × 3. Frozen section.

The empty stomach of the fasting dog shows alternate periods of relative quiescence and strong contraction. Strong contraction periods lasting for 25 to 45 minutes occur at intervals of 45 minutes to 2 hours, and are composed of Type II and Type III gastric activity. They correspond to the hunger contractions studied by Cannon in man. The frequency of gastric activity in the fasting dog recorded through an open-ended polyethylene tube is similar to that described by Carlson using the balloon-tambour method.

Stimulation of the anterior hypothalamus in 4 dogs, the lateral hypothalamus in 2 dogs, the medial hypothalamus in 1 dog, and the lateral amygdala in 1 dog produced an increase in gastric activity. In Figs. 2 and 3 the speed of the recording is maintained so that a single line represents 10 minutes of recorded gastric motility. The 3 lines of a set, such as set A (Fig. 2), represents 30 minutes of continuous gastric activity. In 21 out of 27 trials (Fig. 2 A), stimulation of the anterior hypothalamus during a period of almost complete quiescence was followed by increased activity. This induced gastric motility closely resembles spontaneous contractions. Using threshold stimuli to the anterior hypothalamus, the usual behavioral response consisted of minor alerting with searching movements of the eyes. Stronger stimuli caused withdrawal, voiding and defecation.
tion was carried out during periods of gastric contraction. Decreased gastric activity was induced in 3 dogs by stimulation of the posterior hypothalamus, in 3 dogs by stimulation of the anterior amygdala and in 1 dog by stimulation of the extreme lateral hypothalamus. Stimulation by one posterior hypothalamic electrode (Fig. 3 A) was associated with an abrupt decrease in activity in 14 of 18 tests. The other 4 of the 18 trials gave equivocal responses, but in no case was the response excitatory. A minor arousal was associated with each stimulus.

Short periods of quiescence spontaneously interrupted periods of strong gastric contraction. To differentiate these from induction of depressed activity is difficult. To make this differentiation, long stimu1us trains were applied to the posterior hypothalamus to produce sustained decrease in activity. This is illustrated in Fig. 3 B, and gave effects reproducible in 20 out of 24 stimulations. Fig. 3 C illustrates inhibition obtained 7 out of 8 times by stimulating the extreme lateral hypothalamic area of 1 animal. At threshold stimulation the behavioral response consisted of barely detectable alerting and licking movements.

Stimulation of the anterior amygdala inhibited gastric motility in 3 dogs. The upper line of Fig. 3 D shows 10 minutes of antral motility recording. The lower line illustrates simultaneously recorded Pavlov pouch motility. Gastric antral contractions occurred at regular 2½ minute intervals, pouch contractions at 4 minute intervals. Dissociation between gastric antral and body contractions has been described previously. 34 Stimulation of the anterior amygdala was followed 9 out of 10 times by decrease in both gastric and pouch activity. The behavioral response accompanying this stimulation was characteristic for stimulations of the anterior amygdala. It occurred after a 5-10 second latency and consisted of rhythmical chewing with protrusion of the tongue. However, this behavioral response was not necessary for the inhibitory gastric effect to develop. On occasion only mild behavioral changes such as minor alerting or rhythmical licking were seen at threshold. Retching followed 2 minutes after stimulation and occurred several times in other animals following anterior amygdaloid stimulation. It was not seen with stimulation at other sites. During 30 minutes of continuous gastric activity illustrated in Fig. 3 E, brief stimulation of the anterior amygdala was associated with moderately decreased amplitude of contraction, whereas a much longer stimulation (150 seconds) was associated initially with a moderate decrease followed by flattening of the record. The behavioral response following a 5-second latency consisted of a 20 second period of chewing which gradually gave way to quiet alertness during the final 2 minutes of stimulation.

Stimulation of the lateral amygdala (Fig. 3 F) caused alerting and rhythmical licking movements and was associated with a decreased amplitude of contraction during the stimulus period. After a 10 second latency a short burst of high amplitude contractions occurred. During periods of quiescence, stimulation through this electrode was followed consistently by short periods of high amplitude contractions. This facilitatory response was obtained at each of 9 stimulations.

Vagotony abolished the inhibitory effects of stimulation of the extreme lateral hypothalamic and anterior amygdaloid area.

Fig. 4 is a schematic representation of coronal sections; A is at the level of the optic chiasm, B the tuber cinereum and C the mammillary bodies. The closed rectangles represent electrode locations which induced decreased activity on stimulation, the closed circles those electrode locations which caused an increase in activity, and the open circles those electrode sites which had no influence on motility.

Inhibitory electrode sites are grouped in the posterior hypothalamus, extreme lateral hypothalamus and anterior amygdaloid region. Excitatory points are found in highest concentration in the anterior hypothalamus, a few being located in the lateral hypothalamus and basolateral nucleus of the amygdala.

Discussion

Increased gastric motility from stimulation of the anterior hypothalamic and tuberal regions has been reported in the past. 9,18,33,35 In Ranson's studies, 15 strong bladder contractions, decrease in rate and depth of respirations, and hypotension were produced by stimulation in this area. In later experiments, Wang et al. 35 reported increased motility of the small intestine and the colon. They de-
A. A single anterior hypothalamic stimulation, represented by a 10 sec. dash mark at beginning of middle line, followed by increased gastric motility.

B. Four anterior hypothalamic stimulations, middle line, evoked single gastric contractions.

C. Anterior hypothalamic stimulation in trains, middle and lower lines, producing increased gastric motility.

D. Middle hypothalamic stimulation in train, middle line. Increasing gastric motility.

E. Lateral hypothalamic stimulation inducing increased duodenal activity.

F. After bilateral cervical vagotomy, Anterior hypothalamic stimulation inducing decreased gastric motility.

Fig. 2. Continuous gastric motility recordings. Effect of stimulation at 40/sec. of the anterior, lateral and middle hypothalamus upon gastric (and E, duodenal) motility using pulses of 10 sec. duration. Each strip has a duration of 10 minutes. Single pulses are indicated by horizontal bars beneath a trace, multiple ones by broken lines. Effects of stimulation are indicated to the right of each set of traces.
A. Posterior hypothalamic stimulations inducing decreased gastric motility.

B. Posterior hypothalamic stimulation inducing decreased gastric motility.

C. Extreme lateral hypothalamic stimulation inducing decreased gastric motility.

D. Anterior amygdaloid stimulation. Inhibition of gastric antral motility, upper line and simultaneous Pavlov pouch motility, lower line. The heavy black marks represent 40–50/min. contractions of retching.

E. Anterior amygdaloid stimulation inducing decreased gastric motility.

F. Lateral amygdaloid stimulation inducing increased gastric motility.

Fig. 3. Gastric motility recordings. Effect of stimulation of posterior hypothalamus, and anterior and lateral amygdala upon gastric motility. $A$ and $B$ show posterior and $C$ lateral hypothalamic stimulation. $D$ and $E$ show anterior and $F$ lateral amygdaloid stimulation. The stimulus at $E$ was continuous at 40/sec; other single and multiple pulse stimuli indicated as in Fig. 2.
scribed 2 types of response. The most commonly found was of 40 to 60 second latency, followed by a period of increased motility lasting 2 to 7 minutes. Longer stimulus trains seemed to prolong the latency. With the onset of stimulation, pallor of the intestinal wall developed followed by hyperemia and gradually increasing motility. Less frequently observed was a short excitatory response which occurred after a 7 second latency. The latter response was abolished by vagotomy. Working with anesthetized cats, Eliasson obtained increased gastric motility from stimulation of electrode sites throughout the hypothalamus, the heaviest concentration being in the anterior hypothalamic region. The response was abolished by atropine and section of splanchnic nerves. Hesser and Perret, stimulating the anterior hypothalamus in cats following ablation of cephalad structures, obtained suppression of gastric motility with depression of pressure baseline; the effect was abolished by cord transection. Studying gastric secretions in monkeys, Porter et al. obtained increased hydrochloric acid secretion 30 to 60 minutes after stimulation of the anterior hypothalamus, an effect which was abolished by vagotomy. In dogs and cats with innervated gastric pouches and chronically implanted electrodes, Leonard et al. obtained similar secretory responses with simultaneous increase in gastric and mesenteric blood flow. Using higher frequencies of stimulation (over 60 cps.) acid secretion was markedly depressed. After vagotomy, stimulation of the anterior hypothalamus was associated with reduction in gastric blood flow.

In our experiments increased gastric motility resulted from stimulation of the anterior hypothalamic area and the medial hypothalamus. Using trains of threshold intensity, prolonged periods of strong gastric contractions were elicited, with minimal or no detectable behavioral accompaniments. In one dog short latency responses consisting of single Type II waves occurred after stimulation of the most medial portion of the anterior hypothalamus. After vagotomy, repeated stimulations of several anterior hypothalamic sites produced reversed effects, excitatory responses being replaced by a highly reproducible inhibitory effect. This suggests the presence of both mechanisms at this level in the intact animal, inhibitory effects becoming apparent only after removal of the predominant, vagally mediated, excitatory responses.

Decreased gastric motility from stimulation of the posterior hypothalamus was re-
ported by Beattie and Sheehan, Ranson suggested the presence of a thoracolumbar sympathetic center in the extreme lateral hypothalamus which extended caudally in a concentrated, narrow zone dorso-lateral to the mammillary bodies and supramammillary decussation. In Kabat’s experiment conducted in cats studied fluoroscopically a few hours after anesthesia, gastric motility responses were of high threshold and always were accompanied by a marked thoracolumbar autonomic discharge. In Eliasson’s study decreased gastric motility followed stimulation of the lateral hypothalamus. The response remained after vagotomy and atropine injection. In our experiments, stimulation of extreme lateral hypothalamic and posterior hypothalamic areas induced a short-latency, inhibitory effect on gastric motility using threshold stimuli; only minor alerting responses were obtained. Vagotomy abolished this inhibitory effect in 1 dog with electrodes placed in the extreme lateral hypothalamus. No change was noted after vagotomy in 2 animals with electrodes placed in the posterior hypothalamus.

Autonomic responses evoked by stimulation in the amygdaloid nucleus have been reported by several authors, and a possible role in regulation of food intake has, in fact, been suggested by both stimulation and lesions of the amygdaloid nucleus. Eliasson reported vagally mediated increased gastric motility. Koikegami found that inhibitory effects on gastric and small intestine motility, obtained from stimulation of the medial amygdaloid nucleus, were abolished by lesions of the ipsilateral hypothalamus. Shenly and Peele obtained decreased gastric motility from stimulation of the basal and lateral amygdaloid nuclei and increased gastric motility from stimulation of central and medial nuclei in anesthetized cats. In our experiments, a strong inhibitory response of short latency was obtained from stimulation of the anterior amygdaloid area. In 1 dog, with electrodes situated in the lateral amygdaloid nucleus, stimulation was followed by a brief excitatory response. Both excitatory and inhibitory responses were highly reproducible. No reversed effects were noted on repeated stimulations or by varying frequency and pulse duration. Both responses were invariably abolished by bilateral, cervical vagotomy. Vagally mediated, inhibitory effects on gastric motility have previously been reported from stimulation of the medulla oblongata, the peripheral vagus, and in isolated stomach preparations.

Summary
1. Changes in gastric motility induced by electrical stimulation of hypothalamic and amygdaloid areas have been studied in healthy unanesthetized dogs with chronically implanted electrodes.
2. Stimulations of the anterior hypothalamus, medial hypothalamus, lateral hypothalamus and lateral amygdala produced increase in gastric motility. This response was either abolished or reversed after bilateral cervical vagotomy.
3. Stimulation of the anterior amygdaloid area, and the lateral and posterior hypothalamus inhibited gastric motility. Inhibitory effects from the anterior amygdaloid area and extreme lateral hypothalamus were abolished by bilateral cervical vagotomy. Those from the posterior hypothalamus were not.
4. Among various animals there was no consistent correlation between the type of behavioral response and the induced change in gastric motility.

References


