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NEURAL CONTROL OF PERIODIC SECRETION OF THE PANCREAS AND THE STOMACH IN FASTING DOGS

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SUMMARY

1. The role of nerves in periodic secretion of the pancreas and the stomach in relation to the motility of the upper gastrointestinal tract was studied in conscious fasting dogs which had previously been provided with chronic gastric and pancreatic fistulae and a Heidenhain pouch.

2. Both atropine and pentolinium abolished the periodic increase in gastric and pancreatic secretion and motility of the gut.

3. Bilateral cervical vagal blockade with lidocaine reduced the motility of the stomach, the duodenum and the pouch preceding their peaks, but the motility at the peaks remained unchanged except in the case of the stomach.

4. Pancreatic secretion preceding its peak was also decreased by vagal blockade but that at the peak was not significantly different from the control peak.

5. Periodic pepsin secretion, from both the fistula and pouch, was decreased by vagal blockade.

6. It is concluded that the secretion and motility of the upper gut in fasting dogs is controlled by periodic activity of the vagus and intrinsic nerves.

INTRODUCTION

Periodic increases of basal pancreatic and gastric secretion associated with periodic contraction of the upper gastrointestinal tract in fasting dogs were reported by Boldyreff (1911). Periodic changes of secretion, once recognized, are unlikely to be confused with the effect of external stimuli (Thomas & Crider, 1946). However, more often they have been unrecognized and hence overlooked in many studies (Magee & Naruse, 1982; Becker, Singer, Eysselein & Goebell, 1982).

Babkin & Ishikawa (1912) found that both the periodic secretion and motility of the gut were abolished by atropine. Since then few studies of either phenomenon have been made and the mechanism of periodic secretion is obscure. We have, therefore, attempted to clarify the role of nerves in periodic pancreatic and gastric secretion in fasting conscious dogs.

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METHOD

Nine dogs (17–27 kg), each with a gastric fistula, a Heidenhain pouch and a Thomas duodenal fistula, were used. The installation of fistulae was performed in one stage under ether anaesthesia after thiopentone induction and 0·5 mg of atropine per animal. Standard methods were used for both the Heidenhain pouch and gastric fistulae (Emås, Swan & Jacobson, 1967). A one-piece Thomas cannula made of aluminium with a nylon internal flange was used rather than the original Thomas 1941 type, but the original dimensions were retained. All the experiments were carried out between 1 and 24 months after operation. The interval between tests was 1 week.

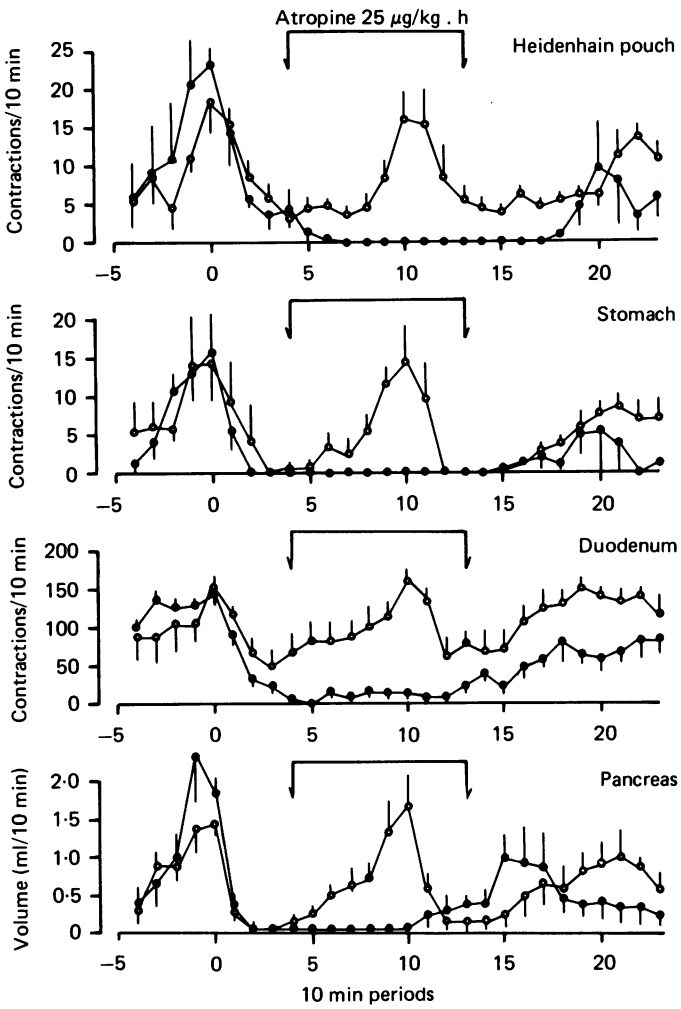

Fig. 1. The effect of atropine (25 μg/kg I.V., followed by 25 μg/kg . h) on periodic motility and secretion in five dogs. Motility and secretion were recorded simultaneously and the first duodenal peaks are designated as zero times. ○ and ● indicate control and atropine, respectively. Mean ± S.E. of mean ($n = 5$) are given.

The animals were fasted for 18 h and then restrained in Pavlov stands. An intravenous infusion of saline (150 mM-NaCl, 8 mM-KCl) was maintained at 2 ml/min throughout the study to replace the fluid loss. Collections of secretions were made at 10 min intervals. Pancreatic secretion was collected by cannulation of the duct, gastric secretion by drainage, and pouch secretion by the saline

washout method (Magee & Nakajima, 1968). The pancreatic duct was cannulated with a 10 cm length of a coeliac angiography catheter of suitable diameter (usually 2 mm o.d.). It was held in place by a thread tied around it level with the outside of the fistula. The loose ends of the thread were clamped to the outside rim of the Thomas cannula. The more usual glass cannula, because of its rigidity, was easily dislodged by duodenal activity. Simultaneous recording of gastric and duodenal motility was made using the balloon method. Small rubber balloons filled with 1 ml of water were placed about 3 cm distal to the edges of the cannulae and then were connected via pressure transducers to a polygraph (Narco Bioscience, Houston). For the pouch a transducer was connected to the collecting apparatus and the system was closed except for the short periods during which the secretion was collected.

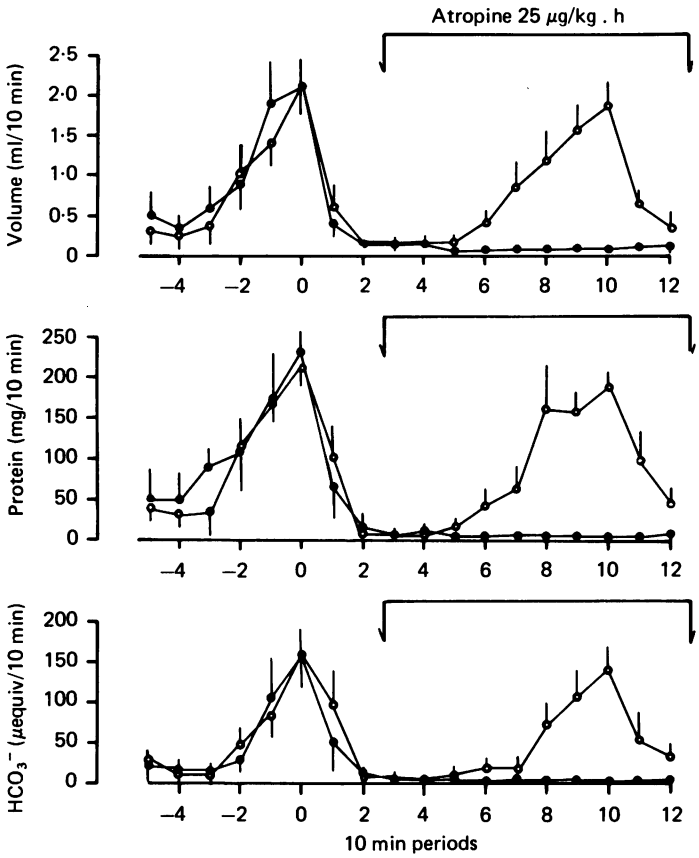

Fig. 2. The effect of atropine (25 μg/kg I.V., followed by 25 μg/kg.h) on pancreatic secretion (mean ± S.E. of mean, $n = 5$) in five dogs. ○ and ● indicate control and atropine, respectively.

After observing one control cycle, (from one nadir to the next) either blockade with atropine sulphate (Lilly, IN 25 μg/kg intravenously, followed by 25 μg/kg.h) or pentolinium tartrate (Wyeth, Philadelphia, 1 mg/kg subcutaneously) or bilateral cervical vagal blockade with a local anaesthetic (2% lidocaine HCl, Astra, Worcester, MA) was maintained for one more cycle. Criteria for lidocaine blockade were tachycardia and ocular signs of bilateral sympathetic blockade (Kondo & Magee, 1977*b*). Side effects, such as central excitation after atropine, collapse after ganglion blockade, and vomiting after lidocaine, were not observed with the doses used.

Acid was titrated to pH7 with an autotitrator (Radiometer, Copenhagen). Pepsin activity was estimated by the method of Anson (1938). Bicarbonate concentration was calculated from chloride concentration (Chloridemeter, Buchler Instruments, NJ; Bro-Rasmussen, Killman & Thaysen,

1956). Spectrophotometry at 280 nm (Hitachi-Perkin Elmer, Tokyo) was used to measure pancreatic juice protein concentration (Magee & Naruse, 1982).

Samples were renumbered to analyse the periodic change. For each dog one control sample which contained the peak pancreatic secretion was chosen as an origin. Means and standard errors were calculated for each of the newly numbered points; n represents the number of dogs. Secretion in one cycle was the sum for 100 min beginning from the nadir. Paired t tests were used for comparison unless otherwise stated. $P < 0.05$ was taken as the level of significance.

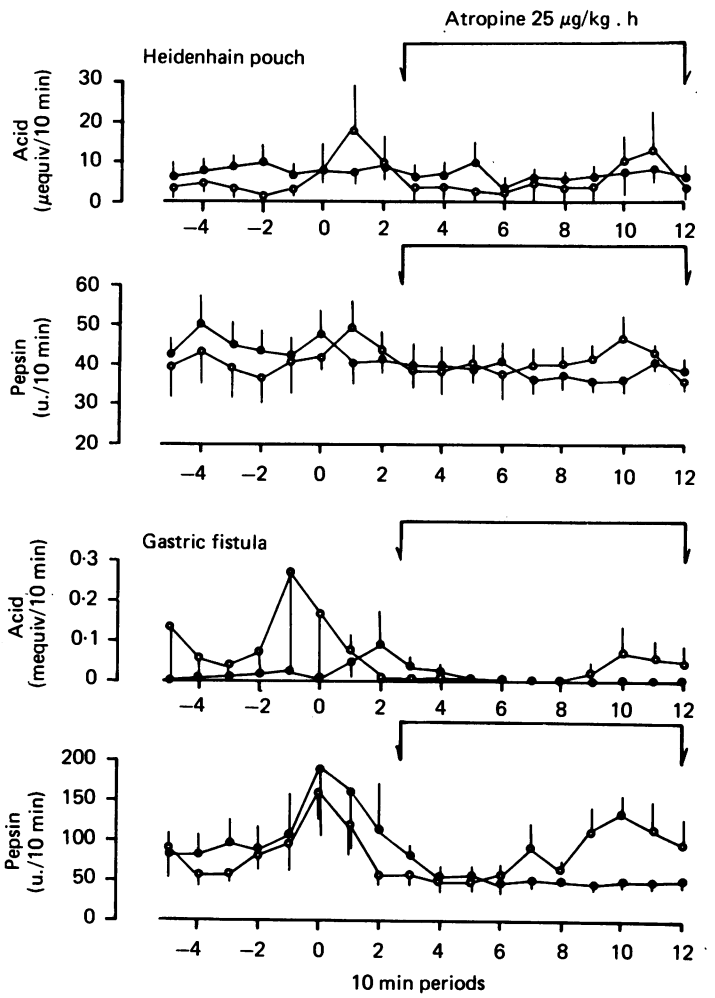

Fig. 3. The effect of atropine (25 μg/kg I.V., followed by 25 μg/kg.h) on gastric and Heidenhain pouch secretion (mean ± S.E. of mean, $n = 5$) in five dogs. Results are from the same experiments as Fig. 2.

RESULTS

Periodic secretion and motility. Secretion of the pancreas (water, bicarbonate and protein) and of the stomach (pepsin) showed a periodicity in phase with the motility of the gut (Figs. 1–3). Secretion and motility at the peak were significantly higher than those at the nadir.

Atropine and pentolinium. After either atropine or pentolinium the periodic surges

in stomach and duodenal motor activity were no longer seen. The pancreatic secretion of water bicarbonate and protein (Fig. 1) and the gastric secretion of pepsin from both pouch and main stomach remained constant at the normal nadir level throughout the succeeding cycle (Figs. 2 and 3).

Vagal blockade. Cervical vagal blockade by lidocaine increased the heart rate at the peak from 65±3/min to 174±15/min. The periodic motility of the duodenum and of the pouch was not abolished by vagal blockade and their activity peaks were as high as in the controls (Figs. 4 and 5). The motility preceding the peak, however, was significantly reduced. In the stomach the motility at the peak was also decreased and in one dog it disappeared completely.

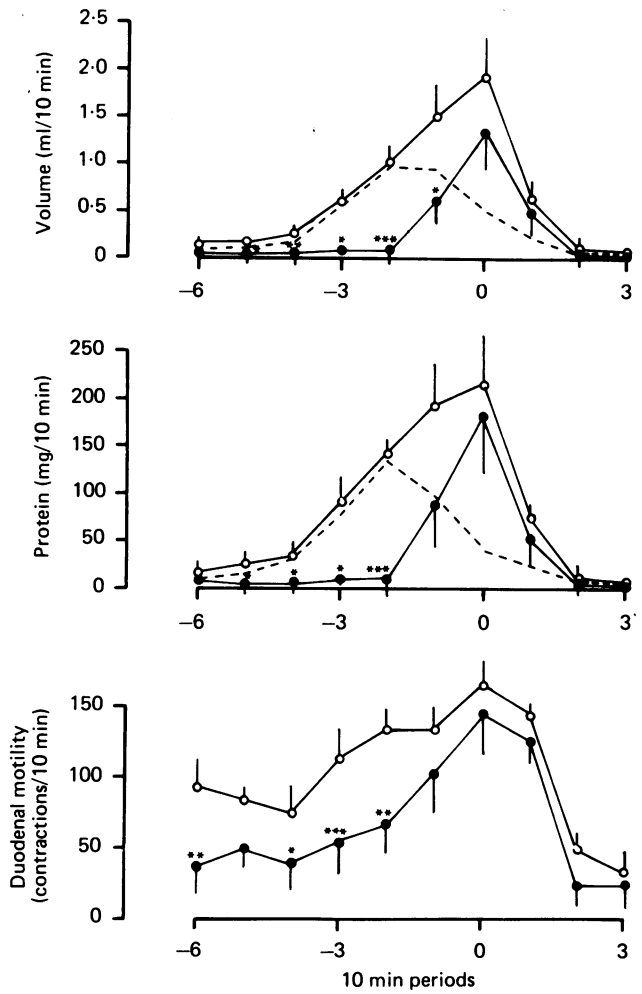

Fig. 4. The effect of bilateral vagal blockade on pancreatic secretion and duodenal motility (mean±S.E. of mean, $n = 5$) in five dogs. The time of pancreatic peak in both control (○) and vagal blockage (●) is designated zero and both results are lined up to the same time scale. Dotted lines indicate the difference between control and vagal blockade in each of the periods. Asterisks indicate significant differences (* $P < 0{\cdot}05$, ** $P < 0{\cdot}01$, *** $P < 0{\cdot}001$) from control.

Secretion by the pancreas (water, bicarbonate and protein) was periodic after vagal blockade, but that preceding the peak was reduced to the level of the nadir (Fig. 4). Periodic pepsin secretion from the pouch and the fistula, either at the peak or during the phase preceding it, was decreased significantly by vagal blockade (Fig. 5).

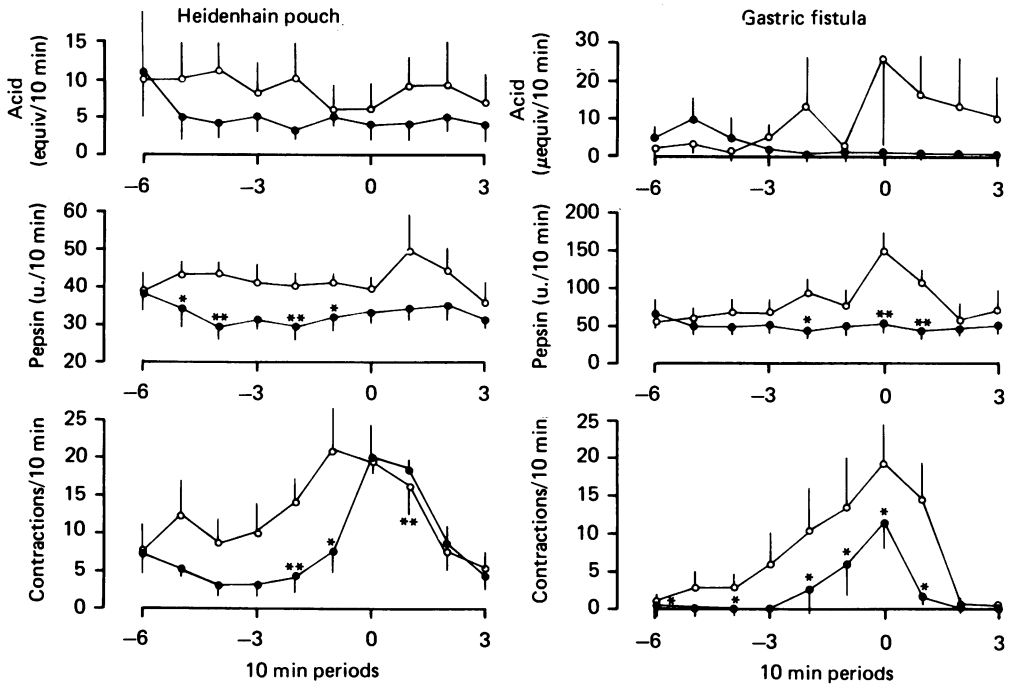

Fig. 5. The effect of bilateral vagal blockade on the secretion and motility of the stomach and Heidenhain pouch (mean ± S.E. of mean, $n = 5$) in five dogs. Results are from the same experiments as Fig. 4. See Fig. 4 for explanation.

The over-all effect. Vagal blockade reduced the pancreatic secretion in one cycle by about 50%. The effect of atropine and pentolinium was much more profound (about 90% reduction). The decrease of fistula pepsin secretion was largest following vagal blockade (−43%) and least following ganglion blockade (−18%). The effect of ganglion blockade on the main stomach pepsin secretion was significantly less ($P < 0{\cdot}05$) than that of either vagal blockade or atropine. Pouch pepsin secretion was also decreased from control by vagal blockade, atropine and pentolinium, but the differences between treatments were not significant. Acid secretion was highly variable between individual dogs (range 3–409 μequiv/100 min for pouch, 0–1067 μequiv/100 min for fistula). When present, it was invariably suppressed by all three treatments.

DISCUSSION

Our study has confirmed the observation by Babkin & Ishikawa (1912) that the periodic secretion and motility of the gut is abolished by atropine. Similarly pentolinium, a ganglion blocker, inhibited the periodic increase and kept the secretion

at the level of the nadir. It seems that the periodic activities of the gut are dependent on cholinergic and ganglionic mechanisms.

The role of the vagus in this phenomenon is not clearly understood. The periodic motility of the gut is not abolished by vagotomy (Carlson, 1913; Marik & Code, 1975; Weisbrodt, Copeland, Moore, Kearley & Johnson, 1975). Periodic activities of Heidenhain pouches (Robins & Boyd, 1923) and of transplanted gastric pouches (Farrall & Ivy, 1926) support the view that the extrinsic innervation is not a *sine qua non* for periodic contraction. Ruckebush & Bueno (1977), however, found that the intestinal myoelectric activity preceding the peak ('irregular spike activity') was decreased in vagotomized dogs and sheep. The findings of Hall, El-Sharkawy & Diamant (1982) on intestinal motility were similar except that they claimed complete cessation of gastric and esophageal periodic motility after vagal blockade. Our observation on duodenal motility was in agreement with Hall *et al.* (1982) but, unlike theirs, the gastric motility in phase with the peak of the duodenum and the pouch was not completely abolished.

Conflicting findings have been reported on the effect of vagotomy on basal pancreatic secretion: no effect (Tankel & Hollander, 1958; Henriksen, 1969), decrease in juice volume (Routley, Mann, Bollman & Grindlay, 1952), decrease in protein secretion (Moreland & Johnson, 1971), and decrease in both (Debas, Konturek & Grossman, 1975). In most studies the collection was made for only a short period and the periodic nature of the secretion therefore seems to have been overlooked. Those who observed for long enough found decreased secretion (Hayama, Magee & White, 1963; Lenninger, Magee & White, 1965). Our study showed that vagal blockade reduced the secretion preceding its peak, which resulted in about a 50 % reduction in the water, bicarbonate and protein secretion in one cycle. Secretion at the peak, however, seemed to be independent of the vagi. The abolition of this phase by either atropine or ganglion blockade suggests that it is dependent on intrinsic nervous mechanisms.

Periodic pepsin secretion from the gastric fistula seemed to be more dependent on a vagal mechanism than pancreatic secretion. Pentolinium, a potent inhibitor of pancreatic secretion, was less effective than atropine or vagal blockade on the secretion of pepsin from the fistula. Though the involvement of sympathetic mechanisms in this phenomenon is not known, the difference may be due to inhibitory mechanisms mediated by the sympathetic innervation (Magee, 1976; Kondo & Magee, 1977*a*, *b*). According to this hypothesis a vagal stimulatory mechanism predominates over a sympathetic inhibitory one under ordinary conditions. The effect of vagotomy or atropine is, therefore, not only to remove a stimulatory effect but also to unmask an inhibitory one. Since pentolinium can inhibit both effects by its action on ganglia, the final effect would be removal of vagal influence alone.

Periodic contraction of the stomach and the pouch is not always accompanied by acid secretion (Boldyreff, 1911; Schofield, 1959). This results in a dissociation between acid and pepsin secretion. When spontaneous acid secretion occurred it was suppressed by vagal blockade, atropine, or pentolinium. In earlier experiments (Odori & Magee, 1969) ganglion blocking agents augmented acid secretion. Nevertheless, there is no contradiction as the secretion studied formerly was stimulated by pentagastrin in dogs with innervated antral pouches.

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