Effect of Somatostatin on Blood Levels of Motilin and the Interdigestive Myoelectric Complex in Dogs

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Motilin has been called an interdigestive hormone, suspected to induce the interdigestive myoelectric complex (IDMC) in dog (Itoh *et al.*, 1978). Somatostatin (GH-RIH) has been shown to inhibit motilin release in man (Mitznegg *et al.*, 1977). The following study was designed to look at the effect of GH-RIH on blood levels of motilin and on the IDMC in dog.

Methods

A) Radioimmunoassay for motilin

Synthetic porcine motilin (gift from Dr. H. C. Beyerman, Guelph, Netherlands) was iodinated by Hunter and Greenwood's technique (1963). Motilin labeled with ^{125}I was purified on G-10 Sephadex and CM Sephadex G-25 columns. Motilin antibody (obtained from Dr. Yanaihara, Shizuoka, Japan) was used in a final dilution of 1/200,000. This antibody did not cross react with 10 pmol of gastrin 17, secretin, pancreatic polypeptide, bombesin, VIP, GIP or somatostatin. The antibody was specific for the central portion of motilin. At a final dilution of 1:10, the assay was sensitive to 50 pg/ml in plasma and the ID_{50} was 300 pg/ml of synthetic motilin added to plasma. The intra-assay variation was between 4.5 and 6.6% and the inter-assay variation was 8.6% when tested with plasma motilin concentrations between 100 and 1000 pg/ml.

B) Dog experiments

Under general anesthesia, monopolar silver-silver chloride electrodes were implanted to the serosal surface of the antrum and small intestine of mongrel female dogs (Carlson *et al.*, 1975). Recording sessions on conscious animals were begun 2 weeks post-operatively. The dogs were fasted for 15 hr before each experiment. Recordings were made with an 8 channel Brush Mark 200 recorder with the cannula used as an indifferent electrode. The four phases of the interdigestive complex were identified by visual inspection of the electromyograph (Code and Marlett, 1975).

Part 1: Normal cycles of motilin and interdigestive activity. Three dogs were observed in a basal state for 3 consecutive cycles of interdigestive myoelectric complexes. Through an indwelling intravenous catheter, 3 ml samples of blood were collected in EDTA tubes at 10 min intervals during the whole experiment.

Part 2: Effects of exogenous GH-RIH (somatostatin) on normal cycles. Each experiment was performed once on each of 4 dogs. Thirty min after the end of a recorded activity front (phase III) in the duodenum, GH-RIH (Boehringer Mannheim Biochemicals) was infused at 2.5 $\mu\text{g/kg/h}$ or 0.625 $\mu\text{g/kg/h}$ for 3 hr by a Harvard pump. Each dose was administered on a separate day. In an additional experiment, 2 animals received 5 $\mu\text{g/kg/h}$.

Part 3: Effect of exogenous GH-RIH on activity induced by exogenous motilin. Each experiment was performed once on 3 dogs. Motilin was administered twice to each dog, once during saline infusion and once during GH-RIH infusion. Synthetic motilin (0.5 $\mu\text{g/kg/h}$ for 30 min; gift from Dr. Yajima) was started 30 min after the end of a spontaneous activity front in the duodenum or 60 min after the start of GH-RIH. A 2 hr infusion of GH-RIH was administered at 2.5 $\mu\text{g/kg/h}$ in 2 dogs and 0.625 $\mu\text{g/kg/h}$ in one dog. The activity induced by infusion of exogenous motilin on a background of GH-RIH was compared to the activity induced by the same dose

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Fig. 1. Spontaneous increase in motilin blood levels concomitant with induction of activity fronts in the duodenum. Blood levels of motilin are shown in the upper part of the graph and are expressed in pg/ml. The lower two-thirds of the graph represents intestinal electrical activity. The 4 phases are represented graphically as follows: phase I: -; phase II: *; phase III: #; phase IV: @. Letters on the left margin indicate electrode position. S—stomach, D—duodenum, J—jejunum, I—ileum.

of exogenous motilin on a background of saline in the same dog on the same day.

Results

Part 1: Normal cycles of motilin and interdigestive activity. In each dog, 3 activity fronts (phase III) started regularly each 90 to 120 min in the duodenum and propagated to the caecum. The initiation of each of these fronts in the upper intestine was concomitant with a cyclical increase in blood levels of motilin. One representative experiment is shown in Figure 1.

Part 2: Effect of exogenous GH-RIH on normal cycle. A GH-RIH infusion was started 30 min after the end of an activity

front in the duodenum. In all dogs the expected cyclical duodenal activity front was abolished during the 3 hr infusion of GH-RIH $2.5 \mu\text{g}/\text{kg}^{-1}/\text{h}^{-1}$. In 2 dogs the activity of the whole small intestine remained fixed in phase 1 or 2 during this infusion (Figure 2). In 2 dogs, a propagating activity front started in the jejunum despite the infusion. When GH-RIH was increased to $5 \mu\text{g}/\text{kg}^{-1}/\text{h}^{-1}$, a jejunal front failed to occur in one of these dogs but was still observed in the other. In all dogs, the expected cyclic increase of motilin did not occur during infusion of GH-RIH and the blood concentrations of motilin were less than the lowest concentrations measured in a normal cycle. After the cessation of GH-RIH, motilin concentration increased immediately.

Fig. 2. During GH-RIH infusion motilin release was blocked and no activity front occurred in the duodenum or lower intestine.

When a smaller dose of GH-RIH was infused ($0.625 \mu\text{g/kg}^{-1}/\text{h}^{-1}$), in 3 dogs, the expected cyclical increase of motilin did not occur, nor did the expected cyclical phase III in duodenum, but in each dog, activity fronts started in jejunum or ileum and propagated to the ileocecal valve.

All duodenal fronts initiated before the GH-RIH infusion was begun were propagated normally to the caecum as were the fronts initiated in the distal intestine during the infusion of GH-RIH.

Part 3: Effect of exogenous GH-RIH on the activity induced by exogenous motilin. In all dogs, the administration of motilin ($0.5 \mu\text{g/kg}^{-1}/\text{h}^{-1}$ for 30 min) during an infusion of saline induced an activity front which started in the duodenum and propagated normally over the entire small bowel. However when GH-RIH was given,

the same dose of motilin failed to induce a front despite an increase in motilin blood concentrations. In each dog the myoelectrical activity increased with motilin infusion but never reached the level of a phase 3 (50 or more consecutive pacesetter with multiple action potentials on each pacesetter).

Discussion

Inhibitory effects of GH-RIH on the IDMC of the dog have been reported previously by Lee and Chey (1976) and Ormsbee *et al.* (1978). Our study indicates that such an action may be mediated by an inhibitory effect on motilin release or by a direct action on the intestinal smooth muscle. Dual and complementary actions of

Fig. 3. Administration of motilin (mot.) during somatostatin infusion failed to induce an activity front.

GH-RIH have been described before when GH-RIH inhibited the release of gastrin and secretin and their respective stimulatory actions on gastric and pancreatic secretions (Konturek *et al.*, 1976a, b, Raptis *et al.*, 1975, 1978).

Our study supports the theory that motilin is the physiological inducer of activity fronts of the IDMC in the canine duodenum. Our results also suggest that the propagation of an activity front along the small intestine and the induction of activity fronts in jejunum or lower in the ileum are motilin independent.

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