Involvement of Cholinergic Motor Neurons in Pharmacological Regulation of Gastrointestinal Motility by Glucagon in Conscious Dogs

Tomohiko SHIMATANI
First Department of Internal Medicine, Hiroshima University School of Medicine

Abstract

To clarify the exact mechanisms of the pharmacological effects of glucagon on gastrointestinal motility, the following experiments were performed on the conscious and anesthetized dogs. 1) During phase I of interdigestive migrating contractions (IMC), glucagon (5 ~50 μg/kg, drip infusion for 5 minutes) induced phasic contractions in the duodenum, jejunum and ileum, but not in the antrum. These excitatory responses were also observed in the truncal vagotomized dogs. These contractions were abolished by atropine or hexamethonium in the conscious dogs, and also by tetrodotoxin in the anesthetized dogs. 2) Glucagon inhibited cisapride-induced contractions only in the antrum in the conscious dogs. After pre-treatment with hexamethonium, glucagon inhibited these contractions in the duodenum, jejunum and ileum as well as in the antrum. After pre-treatment with tetrodotoxin in the anesthetized dogs, glucagon did not affect acetylcholine-induced contractions in any region. 3) Glucagon inhibited spontaneous phase III contractions and erythromycin-induced phase III-like contractions in the antrum, but did not inhibit either contractions in the other regions in the conscious dogs. These paradoxical effects of glucagon between the antrum and intestine were similar to those involved in the blockade of 5-hydroxytryptamine 3 receptors. After pre-treatment with hexamethonium, glucagon inhibited these contractions in the duodenum, jejunum and ileum as well as in the antrum. In conclusion: 1) Glucagon latently inhibits cholinergic motor activities in the antrum and intestine not directly, by binding to either receptor on the smooth muscle cells, but through postganglionic cholinergic neurons and possibly through 5-hydroxytryptamine neurons. 2) On the other hand, in the intestine the reverse effects through preganglionic cholinergic neurons involving nicotinic and muscarinic receptors are more potent. 3) As a result, glucagon inhibits antral contractions and does not affect intestinal contractions in a conscious state.

Key words: glucagon, gastrointestinal motility, interdigestive migrating contractions, cholinergic neuron, conscious dogs
Introduction

Glucagon is one of the peptide hormones secreted from the A cells of the pancreatic islets. It antagonizes the effects of insulin and plays an important role in the regulation of the blood glucose. It has also a number of other actions, including a hypomotility and hypotonicity action on gastrointestinal motility (Stunkard et al., 1955; Sudsaneh et al., 1959; Detevall et al., 1963; Necheles et al., 1966). It is thus now commonly used as a pre-treatment drug for radiodiagnostics (Miller et al., 1974; Kreeel et al., 1975; Carsen et al., 1976; Ishii et al., 1978) or endoscopic examinations (Qvigstad et al., 1979) of gastrointestinal tract in patients with complications such as heart diseases (Giesen, 1978; Harada et al., 1997), glaucoma (Sissons et al., 1991; Fink et al., 1995) and hypertrophy of the prostate (Chernish et al., 1972). The enteric nervous system may be a target of glucagon (Takenaka et al., 1975; Lin et al., 1989), but the exact mechanisms of the inhibitory effects have not been elucidated.

On the other hand, the gene encoding proglucagon, the precursor of glucagon, is expressed not only in the pancreatic islets but also in the endocrine cells of the gastrointestinal mucosa. The proglucagon-derived peptides produced by the L cells in the jejunum, ileum and colon are called enteroglucagon and are partly composed of pancreatic glucagon. It is secreted into the blood in response to ingestion of carbohydrates and long-chain fatty acids, and may be one of the candidates of the "ileal-brake", which inhibits upper gastrointestinal functions elicited by the presence of unabsorbed nutrients in the ileum (Holst, 1997).

Glucagon and enteroglucagon interact with a common receptor in vitro (Gros, et al., 1993), but its physiological role in vivo is not yet clear.

The purpose of the present study was to investigate the pharmacological effects of glucagon and the exact mechanisms of its action on interdigestive contractions of the gastrointestinal tract in the conscious and anesthetized dogs.

Materials and methods

Preparation of animals

Eleven healthy adult mongrel dogs of either sex weighing 8.8–17.5 kg were used in these experiments. The procedures were approved by the Review Committee on Laboratory Animal Science of Hiroshima University, Japan. Under pentobarbital sodium anesthesia (25 mg/kg body weight, i.v.), the abdominal cavity was opened and strain gauge force transducers (Star Medical, Japan, F–12IS) were sutured onto the serosal side of various regions of the gastrointestinal tract (the gastric antrum 5 cm proximal to the pyloric ring, the duodenum at the level of the main pancreatic duct, the jejenum 15 cm distal to the ligament of Treitz, and the ileum 15 cm proximal to the ileo-cecal junction) so that the contractile activities of the circular muscle could be recorded. A truncal vagotomy was performed on two of the dogs at the level of the abdominal esophagus. The completeness of the truncal vagotomy was examined according to a previous report (Mukai, 1984). Transducer lead wires were taken out of the abdominal cavity through the subcutaneous tunnel and brought out through a skin incision at the middle
region of the superior end of the bilateral shoulder blade. After closure of the abdominal
cavity, Silastic tubes (Argyle, Japan, 1216-27-P) were inserted into the right and left femoral
vein for intravenous administration of agents or blood sampling. The tubes were brought out
through another skin incision on the back and their outer ends were fixed to the skin with nylon
sutures. After surgery, jacket-type protectors (Star Medical, Japan, FPJ-12) were put on the
dogs to protect the lead wires and the tubes from scratching and biting. The dogs were housed
in individual air-conditioned (26°C) cages and administered intravasously 200 ml of physiologi-
cal saline with 0.5g of cefminox sodium (CMNX) for 3 days after the operation. Pelleted dog
diet (150 g, Nihon Clea, Japan, CD-5) was mixed with bread gruel (bread 500 g boiled with 200
ml of water, and 25 g of powdered skim milk added), and given regularly at noon (approximately
600 kcal/day).

**Monitoring of gastrointestinal contractions**

The lead wires of the strain gauge force transducers were connected to an amplifier (Star
Medical, Japan, FS-02) and a recorder (Graphtec, Japan, WR-3701) during the experiments, and
the gastrointestinal contractile activities were recorded continuously in a conscious state
without restraint. Some experiments were under pentobarbital sodium anesthesia with a
respirator (New England Medical Instruments Inc., USA, 101A). Additionally, contractile
signals from the gastric antrum and duodenum were integrated (Nihon Koden, Japan, EI-601G)
and also recorded. The motility index was calculated as in a previous report (Okajima, 1988).

**Monitoring of blood glucose concentration**

Blood samples were drawn from the left femoral vein through the Silastic tube in a
conscious state. The blood glucose concentration was measured by a glucose oxidase method.

**Materials**

The following agents were used in these experiments: glucagon (Novo-Nordisk, Japan),
atropine sulfate (Tanabe Seiyaku, Japan), hexamethonium bromide (C₆) (Sigma Chemical,
USA), tetrodotoxin (TTX) (Sigma Chemical, USA), cisapride (Janssen Kyowa, Japan), acetyl-
choline chloride (Daiichi Seiyaku, Japan), erythromycin lactobionate (Abbott–Dainippon Seiyau-
ku, Japan), pentobarbital sodium (Abbott Laboratories, USA), cefminox sodium (CMNX) (Meiji
Bristol–Myers Squibb, Japan), physiological saline (Otsuka, Japan) and 20% glucose solution
(Otsuka, Japan).

**Experimental procedures**

Experiments were started after regular occurrence of gastric phase III contractions.
After an overnight fasting, the first spontaneous phase III contractions of the day were recorded
and agents were administered 15 minutes after the end of phase III contractions or, in some
experiments, during phase III contractions. Glucagon was diluted with 20 ml of physiological
saline after being dissolved with 1 ml of pure water and administered from the right femoral
vein through the Silastic tube by drip infusion for 5 minutes. Administration of hexameth-
onium bromide was begun 5 minutes before the administration of glucagon. The other agents
were administered by bolus injection or drip infusion before or after the administration of glucagon.

Statistics

The results are expressed as the means ± S.D. of the values obtained from 3~5 dogs. The data for each group were compared using Student's t test. P values of <0.05 were considered statistically significant.

Results

1. *Excitatory effects of glucagon on intestinal motility during quiescent phase of IMC*

During the quiescent phase (phase I) of interdigestive migrating contractions (IMC), intravenous administration of glucagon (30 μg/kg body weight, drip infusion for 5 minutes) induced strong phasic contractions in the duodenum, jejunum and ileum, but did not induce any contractions in the antrum (Fig. 1-A).

These glucagon-induced excitatory responses were completely blocked by atropine sulfate (0.1 mg/kg body weight, i.v.) (Fig. 1-B) or hexamethonium bromide (10 mg/kg body weight, bolus injection and 10 mg/kg body weight, drip infusion for 30 minutes) (Fig. 1-C) in the conscious dogs. The excitatory responses of glucagon were observed at doses of 2, 5, 10, 20, 30 and 50 μg/kg body weight. When the dose was less than 5 μg/kg, the effects were inconstant. The maximal effects were observed at a dose of 20 μg/kg or more.

Similar contractions were also induced by glucagon in the truncal vagotomized dogs (Fig. 2).

After pre-treatment with tetrodotoxin (10 μg/kg body weight, i.v.) in the anesthetized dogs, glucagon did not induce contractions in any region (Fig. 3).

2. *Inhibitory effects of glucagon on gastric motility during quiescent phase of IMC*

Even if glucagon was administered intravenously during phase I of IMC, no contractions were induced in the antrum. However, it was not clear whether glucagon inhibited antral contractions or not. In order to clarify the effects of glucagon on antral phase I contractile activities, the following experiments were performed.

During phase I contractile activities, intravenous administration of cisapride (0.5 mg/kg body weight, drip infusion for 10 minutes) induced rhythmical phasic contractions in every region (Fig. 4-A). These contractions were completely inhibited only in the antrum by glucagon (Fig. 4-B). After pre-treatment with hexamethonium bromide, a nicotinic receptor antagonist, cisapride-induced contractions were partially inhibited and modified in every region (Fig. 4-C). Furthermore, after blocking the preganglionic excitatory responses of glucagon by hexamethonium bromide, glucagon completely inhibited cisapride-induced contractions in the duodenum, jejunum and ileum as well as in the antrum (Fig. 4-D). These results are shown in Fig. 5 by means of a motility index-30 (MI-30), an average of motility index for 30 minutes. In the antrum and duodenum, hexamethonium bromide partially inhibited cisapride-induced contractions (approximately 30 percent). In the antrum glucagon significantly inhibited cisa-
Fig. 1. Effects of glucagon on gastrointestinal motility during quiescent phase (phase I) of IMC in conscious dogs.

A: Intravenous administration of glucagon induced strong phasic contractions in the duodenum, jejunum and ileum during phase I contractile activities. However, it did not induce any contractions in the antrum.

B: Glucagon-induced contractions were completely inhibited by atropine sulfate.

C: Glucagon-induced contractions were also completely inhibited by hexamethonium bromide (C6).

On the other hand, in the anesthetized dogs after pre-treatment with tetrodotoxin, glucagon did not affect exogenous acetylcholine, acetylcholine chloride (0.5 mg/kg body weight, drip infusion for 10 minutes)-induced contractions in any region (Fig. 6).
3. *Inhibitory effects of glucagon on spontaneous phase III gastrointestinal contractions and erythromycin lactobionate-induced phase III-like contractions*

Intravenous administration of glucagon inhibited spontaneous phase III contractions only in the antrum (Fig. 7-A and B). Erythromycin lactobionate (0.15 mg/kg body weight, drip infusion for 10 minutes), a nonpeptide motilin agonist, induced phase III-like contractions in the conscious dogs (Fig. 8-A). As shown in Fig. 8-B, glucagon inhibited these contractions only in the antrum. These glucagon-induced inhibitory responses were observed at doses of 5, 10, 20, 30 and 50 μg/kg body weight and seemed to be dose-dependent. When the dose was less than 10 μg/kg, the effects were inconstant. The maximal effects were observed at a dose of 30 μg/kg or more. Furthermore, pre-treatment with hexamethonium bromide partially inhibited and modified erythromycin lactobionate-induced contractions (Fig. 8-C). After blocking the preganglionic excitatory responses of glucagon with hexamethonium bromide, glucagon completely inhibited these contractions in the duodenum, jejunum and ileum as well as in the antrum (Fig. 8-D). These results are shown in Fig. 9 by means of a motility index—15 (MI–15). In the antrum and duodenum, hexamethonium bromide partially inhibited erythromycin lactobionate-induced contractions (approximately 30 percent). In the antrum, glucagon significantly inhibited erythromycin lactobionate-induced contractions with or without pre-treatment with
Fig. 4. Effects of glucagon on cisapride-induced gastrointestinal contractions with or without pre-treatment with hexamethonium bromide (C₆).
A: When cisapride was administered during phase I contractile activities of IMC, rhythmical phasic contractions occurred in every region.
B: Glucagon completely inhibited cisapride-induced contractions only in the antrum, but scarcely had any influence in the duodenum, jejunum and ileum.
C: With pre-treatment with hexamethonium bromide, cisapride-induced contractions were partially inhibited.
D: With pre-treatment with hexamethonium bromide, glucagon completely inhibited cisapride-induced contractions in the duodenum, jejunum and ileum as well as in the antrum.
Fig. 5. Effects of glucagon on cisapride-induced antroduodenal contractions in conscious dogs by means of motility index-30 (MI-30).

**A:** In the antrum glucagon significantly inhibited cisapride-induced contractions with or without pre-treatment with hexamethonium bromide (C$_6$) ($p<0.001$ and $p<0.01$, respectively).

**B:** In the duodenum glucagon inhibited these contractions only with pre-treatment with hexamethonium bromide ($p<0.01$).

Values are means±S.D. for six experiments.

(Cisa: cisapride, C$_6$: hexamethonium bromide)

Fig. 6. Effects of glucagon on acetylcholine chloride (ACh)-induced gastrointestinal contractions pre-treated with tetrodotoxin (TTX) in anesthetized dogs.

Glucagon did not inhibit these contractions in any region.

hexamethonium bromide ($p<0.001$ and $p<0.01$, respectively), whereas in the duodenum, glucagon inhibited these contractions only after pre-treatment with hexamethonium bromide ($p<0.05$).
4. Influences of glucagon on gastrointestinal motility through hyperglycemia or hyperinsulinemia

After intravenous administration of glucagon (30 μg/kg body weight, drip infusion for 5 minutes), the blood glucose concentration was measured. The maximal glucose concentration, approximately 180 mg/dl, was observed 5 minutes after the administration of glucagon. The maximal glucose concentration was compatible with that of an administration of glucose at a dose of 0.3 g/kg (Fig. 10). In order to examine the indirect effects of glucagon on gastrointestinal motility through hyperglycemia, glucose was used in place of glucagon. On phase I contractile activities administration of glucose (0.3 g/kg body weight, i.v.) did not induce contractions in any region (Fig. 11-A). Moreover, glucose did not affect either the cisapride–induced contractions (Fig. 11-B) or erythromycin lactobionate–induced contractions (Fig. 11-C) in any region. On the other hand, insulin was released in response to glucagon–induced hyperglycemia. As insulin–induced contractions were via the central nervous system, in the truncal vagotomized dogs insulin–induced contractions could not be observed in any region, but glucagon–induced excitatory responses were induced even in the truncal vagotomized dogs in my experiments (Fig. 2).
Erythromycin 0.15mg/kg, i.v.

A

Antrum 150g
Duodenum 150g
Jejunum 150g
Ileum 150g

Glucagon 30µg/kg, i.v.
Erythromycin 0.15mg/kg, i.v.

B

Antrum 150g
Duodenum 150g
Jejunum 150g
Ileum 150g

Cs 20mg/kg, i.v.
Erythromycin 0.15mg/kg, i.v.

C

Antrum 150g
Duodenum 150g
Jejunum 150g
Ileum 150g

Cs 20mg/kg, i.v.
Glucagon 30µg/kg, i.v.
Erythromycin 0.15mg/kg, i.v.

D

Antrum 150g
Duodenum 150g
Jejunum 150g
Ileum 150g

10min
Effect of glucagon on GI motility in dogs

Fig. 9. Effects of glucagon on erythromycin lactobionate-induced antroduodenal contractions in conscious dogs by means of motility index-15 (MI-15).
A: In the antrum glucagon significantly inhibited erythromycin lactobionate-induced contractions with or without pre-treatment with hexamethonium bromide (C₆) (p<0.001 and p<0.01, respectively).
B: In the duodenum glucagon inhibited these contractions only with pre-treatment with hexamethonium bromide (p<0.05).
Values are means±S.D. for six to eight experiments.
(EM: erythromycin lactobionate, C₆: hexamethonium bromide)

Discussion

One of the important actions of glucagon is a hypomotility and hypotonicity action on gastrointestinal motility (Necheles et al., 1966). Zollinger and Ellison (1955) were the first to recognize the effects of glucagon on the gastrointestinal tract. It reduced gastric hunger contractions in 7 healthy volunteers (Stunkard et al., 1955) and promptly inhibited motor activities of the stomach and duodenum (1mg/body, i.m.) for 25 minutes in humans (Nishioka et al., 1984). On the other hand, it (0.05 μg/kg body weight, i.v.) induced strong contractions in the duodenum in dogs (Furukawa, 1987), and a low dose continuous administration activated
Glucagon/Glucose, i.v.

Fig. 10. Effects of glucagon and glucose on blood glucose concentration in conscious dogs. When glucagon (30 µg/kg) was administered intravenously, the blood glucose concentration rose immediately to approximately 180 mg/dl. The maximal concentration was nearly the same as that of glucose (0.3 g/kg). Values are means±S.D. for six to seven experiments.

duodenal motility while a high dose bolus injection inhibited it in dogs (Wingate et al., 1979). As seen above, in previous papers the effects of glucagon on gastrointestinal motility were inconsistent in various regions and various species. The mechanisms of its inhibitory effects were focused on in some previous experiments. They were not concerned with direct effects on the receptors on smooth muscle, but on the myenteric nervous system in rabbits (Takenaka et al., 1975), or the interference of intramural cholinergic neuronal transmission in rat esophagus (Lin et al., 1989). Until now it has been thought that the enteric nervous system might be a target of glucagon. On the other hand, some papers have indicated that glucagon acts directly on gastric smooth muscle cells in humans (Wingate et al., 1979; VandeCreek et al., 1986). In my experiments the exact mechanisms of glucagon on upper gastrointestinal motility were examined in the conscious or anesthetized dogs.

Intravenous administration of glucagon during the quiescent phase of IMC induced a series of strong contractions in the duodenum, jejunum and ileum in the conscious dogs. However, no contractions were induced in the antrum (Fig. 1-A). These contractions were also induced in the truncal vagotomized dogs in a fasted state (Fig. 2). The glucagon-induced contractions were inhibited by atropine sulfate or hexamethonium bromide (Fig. 1-B and C). Moreover, after pre-treatment with tetrodotoxin in the anesthetized dogs, glucagon did not induce contractions in any region (Fig. 3). These facts indicate that glucagon-induced excitatory responses in the duodenum, jejunum and ileum may be mediated by preganglionic cholinergic neurons involving nicotinic and muscarinic receptors in the myenteric plexus.

In previous reports it was not clear how glucagon affected antral motility during the quiescent phase of IMC. To clarify whether glucagon inhibited antral motility or not, I investigated the effects of glucagon on contractions induced by cisapride, which is known to be an agonist at neural 5-hydroxytryptamine (5-HT) 4 receptors in the cholinergic motor path-
ways and accelerates endogenous acetylcholine release from cholinergic nerve endings in the myenteric plexus (Hardcastle et al., 1984; Suzuki et al., 1985; Fujii et al., 1988; Taniyama et al., 1991). Cisapride induced strong rhythmical contractions in every region (Fig. 4-A), and glucagon inhibited cisapride–induced contractions only in the antrum (Fig. 4-B). Furthermore, after administration of hexamethonium bromide to prevent the preganglionic excitatory responses of glucagon, glucagon completely inhibited cisapride–induced contractions in the duodenum, jejunum and ileum as well as in the antrum (Fig. 4-D). On the other hand, glucagon did not inhibit exogenous acetylcholine–induced contractions in any region after pre–treatment with tetrodotoxin in the anesthetized dogs (Fig. 6). These facts indicate that glucagon latently
inhibits cholinergic motor activities not directly via either receptor on the smooth muscle cells but through postganglionic neurons in the duodenum, jejunum and ileum as well as in the antrum, whereas glucagon also preganglionically activates cholinergic activity in the duodenum, jejunum and ileum. As a result, cisapride-induced contractions were inhibited by glucagon only in the antrum, and were not inhibited in the duodenum, jejunum and ileum in a conscious state (Fig. 4-B).

How glucagon affects phase III contractions is not yet clear. In my experiments glucagon instantly eliminated phase III contractions in the antrum and somewhat altered the patterns of phase III contractions in the duodenum, jejunum and ileum (Fig. 7-A and B). These findings in the antrum and duodenum are consistent with previous reports in dogs (Wingate et al., 1979; Furukawa, 1987). To clarify these mechanisms, erythromycin lactobionate was used to induce phase III-like contractions (Itoh et al., 1984; Satoh et al., 1994). Administration of erythromycin lactobionate during phase I of IMC immediately induced strong rhythmical contractions similar to spontaneous phase III contractions (Fig. 8-A). It has been commonly accepted that the cholinergic pathways and 5-HT3 neurons are involved in these contractions. (Itoh et al., 1977; Itoh et al., 1978; Itoh et al., 1991; Mizumoto et al., 1993; Haga et al., 1996). In fact, these contractions were completely inhibited by atropine sulfate and partially inhibited by hexamethonium bromide (Qin et al., 1993; Shiba et al., 1995). Glucagon inhibited erythromycin lactobionate-induced contractions only in the antrum (Fig. 8-B), whereas in the duodenum, jejunum and ileum they were strongly inhibited by glucagon only after pre-treatment with hexamethonium bromide (Fig. 8-C and D).

As stated above, it is suspected that glucagon latently postganglionically inhibits phase III contractions or erythromycin lactobionate-induced phase III-like contractions in any region, but in the duodenum, jejunum and ileum reverse effects through preganglionic cholinergic neurons are so strong that intestinal motility is not quite affected in a conscious state (Fig. 7-B and 8-B). These paradoxical effects of glucagon between antral and intestinal phase III contractions are similar to the antagonism of neural 5-HT3 receptors (Itoh et al., 1991). These facts indicate the involvement of cholinergic neurons and possibly 5-HT3 receptors or neurons in terms of the inhibitory effects of glucagon.

Finally, to confirm that these excitatory or inhibitory effects were not an indirect action of glucagon through hyperglycemia or hyperinsulinemia, some additional experiments were performed. It is well known that continuous hyperglycemia inhibits gastrointestinal motility in a conscious state. Gastric contractions were nearly absent at a serum glucose level of 250 mg/kg for 3 hours and markedly reduced at 175 and 140 mg/dl, but duodenal phase III activities were unchanged at all levels of glucose infusion in healthy volunteers (Barnett et al., 1988). However, in my experiments hyperglycemia followed by glucagon administration continued for a short period (Fig. 10), so even when glucose was administered in place of glucagon, no excitatory or inhibitory responses were observed in any region (Fig. 11-A, B and C). On the other hand, it was also reported that hyperinsulinemia enhanced cholinergic motor activities via the central nervous system (Rayner et al., 1981) and increased antral motility in the vagal innervated dogs but did not increase it in the truncal vagotomized dogs (Yokomichi et al., 1976). In my experiments, glucagon-induced excitatory responses were induced even in the truncal...
vagotomized dogs (Fig. 2). These facts indicate that these excitatory and inhibitory effects are not an indirect action through secondary hyperglycemia or hyperinsulinemia, but a direct pharmacological action of glucagon itself in the myenteric plexus.

In my experiments it was evident that glucagon inhibited cholinergic motor activities not via either receptor, including muscarinic receptor, on the smooth muscle cells, but through postganglionic cholinergic neurons in the myenteric plexus. Consequently, glucagon is safe and useful as a pre-treatment drug for X-ray studies and endoscopic examinations of the upper gastrointestinal tract even in patients with various complications which are incompatible with anticholinergic drugs.

In previous studies it was not clear whether glucagon acted directly on glucagon receptors or other receptors located on the neurons, or acted indirectly through other chemical mediators. Many hormones, including enteroglucagon, might act through paracrine release of somatostatin (Lloyd, 1994). In fact, glucagon receptors were detected in a somatostatin-secreting cell line RIN T3 (Gros et al., 1993). Furthermore, glucagon receptor mRNA transcripts were detected in the central nervous system, jejunum and ileum in both fetal and adult mice (Campos et al., 1994), but what kind of neurons glucagon receptors were located on was not ascertained. Further examination will clarify the location of glucagon receptors.

In conclusion, glucagon inhibits cholinergic motor activities not directly by binding to either receptor on the smooth muscle cells but through postganglionic cholinergic neurons, and possibly 5-HT neurons, in the duodenum, jejunum and ileum as well as in the antrum. On the other hand, glucagon activates cholinergic motor activities through preganglionic cholinergic neurons involving nicotinic and muscarinic receptors in the duodenum, jejunum and ileum. Eventually, in a conscious state, glucagon inhibits only antral contractions.

Acknowledgements

I express my thanks to Prof. Goro KAJIYAMA, First Department of Internal Medicine, Assoc. Prof. Masaki INOUE, Department of General Medicine, Dr. Masazumi OKAJIMA, Second Department of Surgery, Hiroshima University School of Medicine, and to Prof. Kazumoto FUJII, Department of Physiology, Faculty for Human Development, Hiroshima Jogakuin University for valuable discussions and for kindly reviewing the manuscript.

I also appreciate the helpful suggestions, operational guidance and animal care provided by Dr. Hiroshi MIENO, Dr. Kazuhiro TOYOTA, Dr. Yasutomo OJIMA, Dr. Michinori ARITA, Dr. Riichiro KOBAYASHI, and Dr. Masafumi KIKKAWA, members of the GI Motility Research Group of Hiroshima University.

Some parts of these experiments were presented at the 38th and 39th annual meetings of the Japanese Society of Smooth Muscle Research.

References


Effect of glucagon on GI motility in dogs

136.


(Received October 23, 1997: Accepted November 17, 1997)