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SK-896

Prokinetic
Motilin Agonist

H-L-Phe-L-Val-L-Pro-L-Ile-L-Phe-L-Thr-L-Tyr-Gly-L-Glu-L-Leu-L-Gln-L-Arg-L-Leu-L-Gln-L-Glu-L-Lys-L-Glu-L-Arg-L-Asn-L-Lys-Gly-L-Gln-L-homoserine-OH

[L-Leu_{13}]Human motilin-Hse

$C_{125}H_{197}N_{35}O_{37}$ Mol wt: 2782.1390

CAS: 131418-27-4

EN: 288845

Introduction

As early as 1915, a type of hormone to control gastrointestinal motility was thought to exist because duodenal and small intestinal acidification resulted in inhibition of gastric motility and gastric acid secretion (1). Brown et al. confirmed increasing pouch pressure with duodenal alkalinization using completely denervated Heidenhain pouch in the body of the dog stomach (2). They then clarified the existence of a hormone that controlled gastrointestinal motility. Moreover, they isolated and purified motilin, a polypeptide of 22 amino acids and a molecular weight of about 2700, and elucidated its amino acid sequence for the first time (3, 4). The amino acid sequence of motilin was subsequently identified in various species such as monkey, rabbit, cat and dog (5-8). Seino *et al.* produced a cDNA clone encoding the human motilin precursor isolated from an intestinal library using a synthetic oligonucleotide probe, and showed that the amino acid arrangement of human motilin was identical to that of porcine motilin (9). The amino acid sequence is the same in human and porcine motilin, whereas in the dog and cat (5) and rabbit (4), amino acids are different from humans (Fig. 1).

Since the discovery of motilin, many studies of its pharmacological profile have been done using both motilin and its analogs in *in vitro* and *in vivo* techniques. It has been confirmed that motilin exhibits species and regional specificity *in vitro*. It also induces a contractile response in gastrointestinal smooth muscle preparation isolated from humans and rabbits, but not in preparations isolated from rats and dogs (10). Moreover, motilin has direct and Ca^{2+}-dependent contractile effects on gastrointestinal smooth muscle preparations isolated from humans and rabbits, but not on those from guinea pigs (10-12). Motilin acts on gastrointestinal smooth muscle but not on other smooth muscle, such as gallbladder and aorta. On the other hand, *in vivo* studies have confirmed that exogenous administration of motilin in dogs causes interdigestive migrating contractions (IMC)-like motility (13).

With regard to the motilin receptor, autoradiography studies have confirmed that in humans and rabbits it is specifically recognized in the smooth muscle layer and is densely distributed in circular muscle tissue rather than in longitudinal muscle (14, 15). The motilin receptor is a heterotrimeric guanosine triphosphate-binding protein-coupled receptor, and it is thought that motilin increases in inositol triphosphate which is rapidly metabolized without affecting the metabolism of cyclic adenosine monophosphate, and which may release Ca^{2+} from intracellular stores (16). The existence of the motilin receptor in dogs has not yet been reported (17). A recent study determined the amino acid sequence of the motilin receptor identified in the human stomach (18). It is now clear that motilin plays an important role in the control of interdigestive gastrointestinal motility in humans. A study using various motilin analogs suggested that there is a difference between the motilin receptor on the gastrointestinal smooth muscle which is used for receptor binding *in vitro* and that which is concerned with IMC *in vivo* (19).

Structure-activity relationships

Since the discovery of motilin, many studies have been performed to clarify the pharmacological and biological profile of this peptide hormone. Either extracted or chemically synthesized motilin and several motilin analogs have been used in the studies. Early studies confirmed that chemically synthesized [Glu^{14}] or [Gln^{14}]-porcine motilin had the same biological activity as porcine motilin (20). It was also confirmed that the substitution of leucin or norleucin for methionin, the 13-position amino acid of porcine motilin, has no influence on biological activity (21). Results of studies of motilin fragments have

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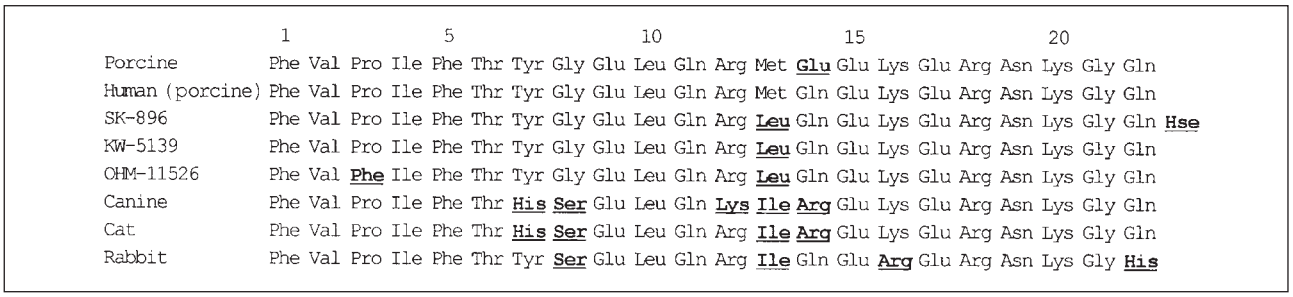

Fig. 1. Amino acid sequences of various types of motilin and motilin analogs. Bold-faced and underlined amino acids are different from those of human motilin.

suggested that the N-terminal of motilin is important for the preservation of biological activity. Moreover, it has been suggested that the C-terminal of motilin is also important for the preservation of biological activity because *N*-hexadeca porcine motilin has only 3% of biological activity as compared to porcine motilin (22).

Miller *et al.* tested the binding activity to rabbit antral smooth muscle motilin receptor and the contractile response to isolated rabbit duodenum using over 100 motilin fragments and analogs. They showed that three distinct regions are involved in the interaction of motilin with its receptor: the N-terminal region (amino acids 1-7) constitutes the minimal basic unit of binding and activity; the transition region (amino acids 8-9) links the N-terminal and C-terminal regions; and the C-terminal region (amino acids 10-22) forms an α-helix that stabilizes the interaction of the N-terminal residues at the active site (23). Moreover, Haramura *et al.* examined the binding profile of porcine motilin and its receptor using motilin analogs (24). Three points of interaction between motilin and its receptor (Phe^1, Ile^4 and Tyr^7) were found, as well as the presence of an open space beyond the N-terminus. The authors identified several agonists and antagonists for the motilin receptor in these studies. Depoortere *et al.* discovered that substitution of Phe for Pro, which is in the 3-position amino acid of porcine motilin, had an antagonistic effect on rabbit duodenum *in vitro*, which led to the discovery of [Phe^3, Leu^{13}]porcine motilin (OHM-11526), a potent motilin receptor antagonist (25). Interestingly, this analog is an antagonist for rabbit duodenal and human antral smooth muscle *in vitro*; however, it induces Phase 3 contractions in the conscious dog and rabbit and acts as an agonist (26). Moreover, OHM-11526 had the same effect as porcine motilin on human and dog jejunal circular smooth muscle preparation in a patch clamp study. Overall, OHM-11526 was shown to behave as a motilin agonist and antagonist.

We have also synthesized several porcine motilin analogs and investigated their biological activity in isolated rabbit duodenum *in vitro*. As a result, we found that [Val^{13}]porcine motilin, [Leu^{13}]porcine motilin and [Leu^{13}]-porcine motilin-Hse had contractile activity equal to porcine motilin on rabbit duodenum. Other studies focusing on the 13-position amino acid of motilin are in progress.

Production

Because motilin is associated with interdigestive gastrointestinal motility and causes IMC motility in the conscious dog *in vivo*, this peptide may be a potential treatment for gastrointestinal motility disorder. Ruppin *et al.* reported that intravenous administration of [Nle^{13}]porcine motilin in postoperative ileus patients increased the frequency of bowel sounds with no side effects, including circulatory ones, being observed (27). Janssen *et al.* reported that intravenous administration of porcine motilin in humans induced Phase 3 contractions in the stomach (28). The motilin analogs used in these clinical studies were obtained by either extraction or chemical synthesis. It is difficult to obtain these analogs in large quantities, in spite of their low cost, since they are polypeptides. Even though motilin is a potent gastroprokinetic drug, it has not been widely used in clinical treatment because of its low rate of production.

Many investigators have produced motilin or motilin analogs by applying recombinant DNA technology. Miyashita *et al.* (29) succeeded in producing a motilin analog in high yield, [Leu^{13}]human motilin (KW-5139) (Fig. 1); the peptide was expressed from a multicopied [Leu^{13}]motilin gene fused to a salmon growth hormone gene fragment. With this method, the monomeric KW-5139 was obtained by treating the fusion protein with cyanogen bromide, carboxypeptide A and B.

We have also discovered a method for producing a large quantity of a motilin analog by expressing a fused protein with motilin analog polypeptide and s-lectin in *Escherichia coli* (*E. coli*: HB101). However, production was inefficient because the greater part of the expressed fused protein became an s-lectin protein because the molecular weight of s-lectin is 8 times greater than that of motilin. On the other hand, Sung *et al.* reported that the quantity of expression varies with the oligopeptide that is added to the N-terminal in the human proinsulin expression system in *E. coli* (30). Applying those techniques, we solved the earlier problem and established a high-yield, low-cost production method for a new human motilin analog, [Leu^{13}]human motilin-Hse (SK-896) (Fig. 1). Namely, we constructed a plasmid which connected a leader peptide (Met-Thr-Met-Ile-Thr-Asn-Ser-Gln-Gln-Gln-Gln-Gln-Gln-Ile-Phe-Met) and four tandem linked [Leu^{13}]human

motilin-Met genes in *E. coli*. Each motilin gene was connected to a spacer region (Gly-Ile-Leu-Met). The monomeric motilin analog was obtained from cleavaged fused protein by cyanogen bromide. The treatment of cyanogen bromide converted methionine into homoserine, which was added at the end of the N-terminal of [Leu^{13}]human motilin in SK-896. Thus, we were able to obtain large quantities and high purity of SK-896 without using any protease, thereby establishing high-yield, low-cost production of human motilin. In a preliminary study, SK-896 had the same contractile activity as native human motilin *in vitro* in isolated rabbit duodenal preparations, and induced no signs of anaphylactic shock in mice and guinea pigs, and therefore was considered safe.

Pharmacological profile

The pharmacological effects of SK-896 were investigated in rabbits, dogs and rats *in vitro* (31). SK-896 induced contractions of smooth muscle preparations isolated from rabbit duodenum but not from the rat or dog. This response was not inhibited by pretreatment with tetrodotoxin (TTX) and atropine, but was inhibited by verapamil. These results indicated that the SK-896-induced contractions were Ca^{2+}-dependent and species-specific. Moreover, SK-896 induced contractions in other isolated gastrointestinal tract preparations, except gastric fundus, in a concentration-dependent manner, with an order of potency of duodenum > gastric pylorus = jejunum = descending colon > ascending colon more than or equal to ileum. On the other hand, SK-896 did not affect isolated gallbladder, uterine, aortic, bladder, vas deferens or tracheal smooth muscle preparations from rabbits. Thus, the effects of SK-896 were observed specifically in smooth muscle preparations isolated from the rabbit gastrointestinal tract and exhibited region specificity. SK-896 inhibited the binding of ^{125}I-human motilin to rabbit gastroduodenal motilin receptors with the same potency as unlabeled human motilin. The IC_{50} values of SK-896 and human motilin were 3.5 ± 1.5 nM and 3.1 ± 1.8 nM, respectively. The K_d of human motilin was 3.0 ± 1.5 nM and the K_i of SK-896 was 3.4 ± 1.5 nM.

In vitro, KW-5139 (0.1-1000 nM) concentration-dependently induced contractions in gastric antrum, duodenum, jejunum, ileum and ascending colon isolated from rabbits. Contractions were most potent in the duodenum and weakest in the ileum (32). Moreover, they were affected by verapamil and by pretreatment with high concentrations of motilin but not by TTX. KW-5139 (30-3000 nM) increased acetylcholine (ACh) release in isolated rabbit duodenal longitudinal muscle myenteric plexus preparation in a concentration-dependent manner (33). [Leu^{13}]porcine motilin, which has the same amino acid sequence as KW-5139, was reported to bind human and rabbit motilin receptors, with respective K_i values of 3.6 ± 1.6 nM and 1.1 ± 0.3 nM (17, 34). This analog was also reported to concentration-dependently induce contractions in isolated rabbit duodenal smooth muscle preparation, with an EC_{50} value of 7.4 ± 1.4 nM (35).

The binding ability of [Nle^{13}]porcine motilin to the motilin receptor was the same as that of intact porcine motilin. [Nle^{13}]porcine motilin also induced contractions in isolated rabbit duodenal smooth muscle preparation in a concentration-dependent manner, with an EC_{50} value of 1.3 ± 0.2 nM (36), but did not induce contractions in isolated gallbladder smooth muscle preparations from humans and rabbits (10, 37). In addition, it had no effect on isolated uterine and aortic smooth muscle preparations from rabbits at a concentration of 3.7 μM (10).

OHM-11526 was reported to displace ^{125}I[Nle^{13}]-porcine motilin bound to rabbit gastric antral smooth muscle motilin receptor with a pK_d value of 9.26 ± 0.04 (25). However, the biological activity of OHM-11526 was very different from that of SK-896 and KW-5139. It did not induce contractions in segments of isolated rabbit duodenum but did inhibit motilin- and motilide-induced contractions. It did not affect ACh-, substance P- or 5-HT-induced contractions in the same preparations. Furthermore, OHM-11526 did not induce contractions in gastric antrum isolated from humans *in vitro*, suggesting that it is a motilin antagonist. Interestingly, the compound induced contractions in chicken small intestine preparations similar to motilin, a full motilin agonist (pD_2 = 6.84) (25). Moreover, OHM-11526 and motilin increased inward current through L-type Ca^{2+} channels in isolated canine and human jejunal circular smooth muscle cells using whole cell patch-clamp techniques with Ba^{2+} as the charge carrier (19).

Taken together, these results demonstrate that the motilin analogs SK-896 and KW-5139 have the same in vitro pharmacological profile as human motilin.

Mechanism of action in gastrointestinal motility and transit

The recovery effect of SK-896 on gastrointestinal motility and transit in dogs with postoperative ileus was compared to that of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), a well-known gastroprokinetic agent, using chronically implanted force transducers to measure motility and radiography of radio-opaque markers to measure transit (38). Infusion of SK-896 at 1 μg/kg/h for 20 min twice a day starting 18 h after laparotomy induced IMC-like motility beginning 30 h after laparotomy. Infusion of $PGF_{2\alpha}$ at 20 μg/kg/h for 1 h twice a day induced continuous contractions in the distal part of the small intestine. The time of first appearance of IMC in the stomach (gastric IMC) and gastric emptying time, small intestinal transit time and whole intestinal transit time of solid marker were significantly less with SK-896 than with $PGF_{2\alpha}$.

Yokoyama *et al.* investigated the recovery effect of KW-5139 on postoperative ileus dogs and compared it with that of $PGF_{2\alpha}$. Their results showed that the appearance time of Phase 3 contractions in the stomach was shorter with KW-5139 and KW-5139 significantly increased motility in the stomach as compared to $PGF_{2\alpha}$ (39). In another study, KW-5139 was reported to signifi-

Table I: The pharmacological profile of motilin analogs in vitro.

Motilin/Motilin Analog	Binding Assay Parameter		Bioassay Parameter		Ref.
Human (porcine)	IC_{50}	1.2 nM[a]	–		36
	IC_{50}	0.76 nM	EC_{50}	6.4 nM	35
	K_d	nM[b]	–		31
	100% inhibition at 10^{-6} M		EC_{50}	1 nM	23
	IC_{50}	1 nM[c]	EC_{50}	5 nM	24
SK-896	K_i	3.4 nM[b]	Same potency as human motilin		31
[Nel[13]]porcine	IC_{50}	0.8 nM[a]	EC_{50}	1.3 nM	36
[Leu[13]]porcine	IC_{50}	0.8 nM[a]	–		36
	IC_{50}	0.66 nM	EC_{50}	7.4 nM	35
	K_d	1.1 nM	–		34
OHM-11526	pK_d	9.26 nM	pA_2	7.79	25
	–		pD_2	6.84[d]	25
ANQ-11125	pK_d	8.24	–		25
	pK_d	8.16	pA_2	7.03	77
[Tyr[1]]porcine	125% inhibition at 10^{-6} M		EC_{50}	2 nM	23
[His[1]]porcine	103% inhibition at 10^{-6} M		EC_{50}	250 nM	23
[Tyr[5],Phe[7]]porcine	102% inhibition at 10^{-6} M		EC_{50}	3 nM	23
[Phe[7]]porcine	109% inhibition at 10^{-6} M		EC_{50}	7 nM	23
[Ala[7]]porcine	106% inhibition at 10^{-6} M		EC_{50}	146 nM	23
[Ala[14]]porcine	107% inhibition at 10^{-6} M		EC_{50}	16 nM	23
[Lys[14]]porcine	106% inhibition at 10^{-6} M		EC_{50}	27 nM	23
Canine	IC_{50}	0.6 nM[a]	EC_{50}	1 nM	36

Binding assay was performed as displacement of ^{125}I-porcine motilin or ^{125}I-[Nle[13]]porcine motilin to rabbit antral smooth muscle homogenate. Bioassay was performed as contractile response to duodenum isolated from rabbit. [a]Rabbit duodenal smooth muscle homogenate, [b]rabbit gastroduodenum homogenate, [c]rabbit upper intestine homogenate, [d]chicken duodenum preparation.

cantly decrease gastric juice output after pylorus-preserving pancreatoduodenectomy (40).

In dogs with postoperative ileus, plasma levels of motilin increased slightly and transiently with the onset of postoperative ileus, but the cyclical peaks in motilin usually found under healthy conditions during fasting were completely abolished during the first 3 postoperative days (41). Thus, it is thought that the absence of cyclical peaks in motilin levels results in ileus and that production of cyclical peaks in motilin levels induces recovery from ileus. In another study, we confirmed that treatment with SK-896 (0.33 μg/kg i.v., b.i.d.) in dogs with postoperative ileus induced 200-800 pg/ml of endogenous motilin 13 h after laparotomy. The results regarding SK-896 and KW-5139 thus suggest that periodic exogenous administration of motilin analogs might normalize the cyclical changes in motilin concentrations that are disturbed by laparotomy. It appears that gastric IMC plays an important role in the gastrointestinal transit of substances, especially solid substances, and that motilin analogs, which induce gastric IMC motility, are effective in inducing early recovery from postoperative ileus.

It is known that both SK-896 and KW-5139 administered intravenously induce Phase 3 contractions in the stomach and duodenum of dogs during the interdigestive period (42, 43). SK-896-induced Phase 3 activity was inhibited by treatment with atropine, hexamethonium, dopamine, granisetron and yohimbine but was not affected by treatment with ketanserin, phentolamine, timolol or naloxone (Table II) (42). These results indicate that the final neurotransmitter in SK-896-induced Phase 3 activity which acted on the motilin receptors was ACh, and that the cholinergic nerve participates in the downstream stimulation of SK-896. In addition, because the inhibition of signal transmission from the cholinergic preganglionic nerve terminal to the myenteric plexus suppressed SK-896-induced Phase 3 activity, it is thought that SK-896 acts more on the upper streams than on the parasympathetic nerve terminal.

Some authors have reported that adrenergic receptors have effects on motilin-induced stomach motility and others have reported that they do not (44, 45). In our study, SK-896-induced Phase 3 activity was not affected by a β-receptor antagonist and a nonselective α-receptor antagonist but was inhibited by an α_2-receptor antagonist, yohimbine, which is thought to enhance gastric antrum motility. In general, it is thought that the main role of the postganglionic sympathetic adrenergic nerve in gastrointestinal motility is to inhibit the cholinergic nerve. In another study, it was reported that yohimbine had an antagonistic effect on 5-HT receptors in the periphery (46). Therefore, it is thought that adrenergic receptors have a weak effect on SK-896-induced Phase 3 activity, and that the inhibitory effect of yohimbine on gastric antrum motil-

Table II: Effects of treatment with various drugs on SK-896 induced Phase 3 activity in conscious dogs in the interdigestive period.

Drugs	Dose Bolus (mg/kg)	Dose Infusion (mg/kg)	Inhibition (%)
Saline			10.7 ± 6.6
Atropine	0.01	0.01	35.7 ± 0.8
	0.02	0.02	74.7 ± 6.7**
	0.05	0.05	89.4 ± 3.4***
Saline			6.4 ± 3.9
Hexamethonium	1.0	1.0	32.9 ± 11.5*
	5.0	5.0	49.9 ± 13.6**
Saline			4.6 ± 6.0
Ketanserin		2.0	–8.9 ± 8.7
Saline			1.8 ± 4.9
Granisetron		0.01	86.6 ± 4.4***
		0.05	90.4 ± 3.9***
Saline			10.2 ± 0.8
Phentolamine		2.0	17.5 ± 9.2
Saline			4.6 ± 6.0
Yohimbine		0.5	39.7 ± 2.2
		1.0	60.2 ± 5.3**
		2.0	67.4 ± 18.5*
Saline			5.3 ± 5.3
Timolol		1.0	–6.3 ± 4.8
Saline			10.7 ± 6.6
Naloxone		1.0	7.1 ± 14.4
Saline			10.2 ± 0.8
Dopamine		0.2	41.8 ± 10.9
		0.5	71.3 ± 9.0**
		1.0	73.9 ± 11.6**

Results are expressed as mean ± SEM of 3-4 experiments. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$ for comparison with control (saline) of each group analyzed by Dunnett's multiple test. (From Tsukamoto, K. *et al.* The gastroprokinetic effect and mechanism of SK-896, a new motilin analogue, in the interdigestive period in conscious dogs. Pharmacology 2001, in press. Reproduced with permission of S. Karger AG, Basel, Switzerland.)

ity is an antagonistic effect predominantly on 5-HT receptors in the periphery rather than on α_2 receptors.

5-HT_2 and 5-HT_3 receptors exist on the smooth muscle and on the cholinergic postganglionic nerve, respectively, and regulate smooth muscle contractions and the release of ACh from the cholinergic nerve terminal, respectively. SK-896-induced Phase 3 activity was inhibited by a 5-HT_3 receptor antagonist but not by a 5-HT_2 receptor antagonist. Itoh *et al.* reported that the 5-HT_3 receptor was closely related to the regulation of Phase 3 activity by motilin and suggested the possible involvement of 5-HT_3 receptors in vagal afferents, especially in terms of endogenous release of ACh in the control of interdigestive Phase 3 activity in the stomach by motilin (47). Therefore, it is thought that SK-896 has some effects on signal transmission from the 5-HT neuron in the myenteric plexus to the cholinergic postganglionic nerve.

Mochiki *et al.* reported that exogenously administered motilin stimulated endogenous motilin release through muscarinic receptors on motilin-producing cells via preganglionic pathways involving 5-HT_3 receptors (48). Poitras *et al*. reported that exogenously administered opioid receptor agonists stimulated small intestinal motility and increased plasma motilin levels in dogs, and that opioid receptor antagonists significantly delayed the cyclic recurrence of plasma motilin peak increases and IMC (49). In human studies, a 5-HT_3 antagonist suppressed Phase 3 contractions in the stomach and simultaneously inhibited plasma motilin peaks (50). In another study, we confirmed that SK-896 administered to dogs with postoperative ileus induced endogenous dog motilin (200-800 pg/ml) 13 h after laparotomy. However, SK-896-induced Phase 3 activity was inhibited by a 5-HT_3 antagonist but not by an opioid receptor antagonist. Therefore, the kind of influence endogenous motilin has on SK-896-induced Phase 3 activity is unknown.

Motilin induced Phase 3 contractions in the vagally denervated fundic pouch (Heidenhain pouch) in dogs (47) and in isolated perfused canine stomach (44). It has been hypothesized that motilin receptors exist in canine stomach as in human stomach, although there are no published reports, and consequently the mechanism of action of motilin is unknown. Our findings suggest that SK-896 induces gastrointestinal motility in interdigestive dogs with regulation of ACh release from the cholinergic nerve terminal via the parasympathetic nervous system, including 5-HT neurons, in the same fashion as human motilin. On the other hand, motilin receptor has been shown to exist on stomach smooth muscle in humans and its amino acid sequence has been ascertained (18). Therefore, it is possible that motilin analogs have a direct effect on smooth muscle in humans and that they induce IMC-like motility in humans via the same signaling from the motilin receptor as in dogs.

Clinical Application

Clinically, gastrointestinal motility disorders are generally present after laparotomy, with several days required for recovery (51). Ileus after laparotomy is a major impediment to patient recovery, since it necessitates the use of a nasal tube for drainage of retained intragastric fluid and parenteral alimentation, induces abdominal distention, pain and vomiting and often results in pulmonary complications (52). Therefore, attempts have been made to reduce the duration of postoperative ileus, to permit removal of the nasal gastric tube as early as possible and to enable oral nutritional intake. Types of gastroprokinetic agents investigated for clinical use include cholinergic agents such as bethanachol (53, 54), benzamide derivatives such as metoclopramide or cisapride (55-57), somatostatin analogs (58) and $PGF_{2\alpha}$ (59-61). Other gas-

troprokinetic agents, dopamine receptor antagonists, gastrointestinal peptides, macrolide antibiotics and opioid receptor antagonists have also been studie (62). However, it is hard to say that any gastroprokinetic agents provide satisfactory treatment effects.

IMC is thought to play the role of housekeeper in the gastrointestinal tract, and that food residuals and secretions remaining in the gastrointestinal tract cause abdominal distention and disorders when this motility is lost, as it is in postoperative ileus. It is also thought that the cyclical enhancement of gastroprokinetic activity in the gastrointestinal tract during the interdigestive period is a preparative state for subsequent food intake rather than a performance of housekeeping functions (63, 64). Therefore, the induction of gastrointestinal motility for transit of substances from the upper to the lower gastrointestinal tract may be important for early recovery from postoperative ileus, since abdominal surgery is performed under fasting conditions. In a previous study, we suggested that occurrence of Phase 3 contractions in the stomach and IMC in the gastrointestinal tract play important roles in transporting liquid and/or solid substances from the upper to the lower gastrointestinal tract in dogs with postoperative ileus, and that this motility was principally responsible for recovery from ileus (65). Therefore, a motilin analog capable of inducing IMC-like motility could be effective for the treatment of postoperative ileus.

During the period of postoperative ileus after laparotomy, patients are administered nutrients and body fluids via an intravenous drip injection because they cannot be fed orally. For the same reason, some drugs are also administered intravenously. When administered intravenously, peptides such as motilin analogs, which normally have a short half-life in blood, have increased concentrations, thus improving their efficacy. In earlier studies, SK-896 and KW-5139 were shown to be more effective than $PGF_{2\alpha}$ on postoperative ileus in dogs. Therefore, it is believed that motilin analogs could improve the quality of life in patients with postoperative ileus. However, the current standards for determining the clinical end point of postoperative ileus are insufficient, and better diagnosis and evaluation criteria as an index of recovered gastrointestinal motility from ileus are needed.

Low motilin levels have been found in patients with idiopathic gastroparesis and constipation, and also during pregnancy, a condition associated with constipation (66-68). Motilin analogs may be useful for treating these conditions which result from low motilin levels. In addition to its effects on gastrointestinal motility, motilin also stimulates pepsin secretion in the stomach (69-71), gallbladder contractions (72) and the secretion of enzymes in the pancreas such as amylase, pancreatic polypeptide and insulin (73-75). Therefore, motilin analogs may be a possible treatment for digestive diseases, in general, and for diabetes. Because they are polypeptides and have a short half-life in blood, motilin analogs are difficult to use for these diseases. Therefore, motilides, which can be administered orally, may be more efficient (76).

To date, there are still many questions regarding motilin and its receptor and further studies are needed to determine the possible application of motilin analogs to clinical disease in the future.

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Manufacturer

Sanwa Kagaku Kenkyusho Co., Ltd. (JP).

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