ABSTRACT—The effects of KSG-504 ((S)-arginium (R)-4-[-N-(3-methoxypropyl)-N-pentylcarbamoyl]-5-(2-naphthylsulfonyl) pentanoate monohydrate), a new cholecystokinin (CCK)-receptor antagonist, on 125I-CCK-8 binding to rat pancreatic, canine gallbladder and guinea pig cerebrocortical membranes and the pancreatic amylase release from isolated rat acini stimulated by several kinds of secretagogues, including CCK, were investigated. The 125I-CCK-8 saturation experiment showed that pancreatic, gallbladder and cerebrocortical CCK receptors had a single high affinity binding component with dissociation constants (Kd) of 0.18, 0.31 and 0.88 nM, respectively. The maximum numbers of specific binding sites (Bmax) in these membranes were 1012, 52 and 20 fmol/mg protein, respectively. KSG-504 and CCK-8 displaced specific 125I-CCK-8 binding to CCK receptors in all membrane preparations in a competitive manner. The affinity of KSG-504 for pancreatic (Kd = 173 nM) and gallbladder (Kd = 283 nM) CCK receptors were > 3 orders of magnitude higher than its affinity for cerebrocortical CCK receptors. KSG-504 also inhibited 125I-gastrin-I binding to guinea pig gastric glands, but the IC50 value (18.2 μM) was apparently much higher. CCK-8-stimulated amylase release from isolated pancreatic acini of rats was antagonized by KSG-504 in a concentration-dependent manner. KSG-504 did not affect amylase release stimulated by secretagogues such as gastrin-releasing peptide, carbachol, vasoactive intestinal peptide and A23187. These results indicate that KSG-504 acts as a CCK-A-receptor-specific antagonist in the pancreas and gallbladder.

Keywords: KSG-504, Cholecystokinin receptor, Binding assay, Pancreatic acini, Amylase release

Cholecystokinin (CCK) was discovered in 1928 as an intestinal factor capable of stimulating gallbladder contraction (1). In the gastrointestinal system, CCK is released from I-cells of the duodenum into the blood circulation upon ingestion of food, and it plays a major role in the regulation of exocrine pancreatic enzyme secretion (2), gallbladder contraction and other smooth muscle activity at various levels of the gastrointestinal tract (3). In 1975, the presence of CCK-like immunoreactivity was also demonstrated in the brain (4). Brain CCK has been considered as a neurotransmitter or a neuromodulator and may regulate satiety, anxiety and pain (5–7).

In recent studies, two different types of CCK receptors have been described. One is termed the alimentary (CCK-A) type that has a high affinity for sulfated CCK-8 and a 1,000-fold lower affinity for gastrin (8); it is found in the pancreas, the gallbladder and the area postrema of the central nerve system. The other is the brain (CCK-B) type found in the central nerve system. It has high affinity for sulfated and desulfated CCK-8 (9). In addition to these two types of receptors, there is a gastrin type receptor in gastric glands, and its affinity for CCK-8 and gastrin is almost the same (10).

Several potent CCK receptor antagonists such as asperlicin (11), lorglumide (12), loxiglumide (13), L-364,718 (14), L-365,260 (15) and FK480 (16) have been described and extensively characterized. Recently, KSG-504 ((S)-arginium (R)-4-[-N-(3-methoxypropyl)-N-pentylcarbamoyl]-5-(2-naphthylsulfonyl) pentanoate monohydrate), a new non-peptide CCK-receptor antagonist, has been synthesized by Kissei Pharmaceutical Co., Ltd. We have clearly demonstrated that KSG-504 is highly specific for pancreatic CCK-A receptors and inhibits pancreatic exocrine secretion stimulated by CCK-8 (17). However, there have been no studies on the interaction of KSG-504 with gallbladder CCK or gastrin-type receptors. In addition, it should be clarified whether the inhibition of pancreatic enzyme secretion by KSG-504 is specific for CCK-8 or
not.

In the present study, we investigated the binding properties of KSG-504 to rat pancreatic, canine gallbladder, guinea pig cerebrocortical and guinea pig gastric membranes. The effects of KSG-504 on amylase release stimulated by several kinds of secretagogues from isolated rat pancreatic acini were also studied.

MATERIALS AND METHODS

Drugs and chemicals

KSG-504 was synthesized by Kissei Pharmaceutical Co., Ltd. (Matsumoto). Other drugs and chemicals were obtained from the following commercial sources: cholecystokinin-octapeptide (CCK-8), gastrin-I, gastrin-releasing peptide (GRP), secretin and vasoactive intestinal peptide (VIP) (Peptide Institute, Inc., Minoh); 125I-CCK-8 (New England Nuclear, Boston, MA, USA); 125I-gastrin-I (Ammersham, Buckinghamshire, England); collagenase type I, soybean trypsin inhibitor, bacitracin and Ca\(^{2+}\) ionophore A23187 (Sigma, St. Louis, MO, USA); carbachol (Aldrich, Milwaukee, WI, USA); BayK 8644 (Calbiochem, San Diego, CA, USA); and bovine serum albumin F-V (Nacalai Tesque, Kyoto). Other chemicals used were of analytical grade.

KSG-504 was dissolved in distilled water.

Animals

Male Wistar rats (200–250 g; SLC, Hamamatsu), male Hartley guinea pigs (350–530 g, SLC) and mongrel dogs of either sex (5–18 kg; Nakajima Animal Labo., Nagoya) were used.

Radioligand binding assay

Rat pancreatic and guinea pig cerebral cortex homogenates were prepared according to the method of Chang et al. (18). The pancreas isolated from the rat and the cerebral cortex isolated from the guinea pig were homogenized in 50 volumes of 50 mM Tris-HCl buffer (pH 7.7 at 25°C) for 10 sec using an Ultradisperser (Junke and Kunkel GmbH, Staufen, Germany) and centrifuged at 50,000 \( \times \) g for 10 min. The pellet was resuspended in the original volume of fresh Tris-HCl buffer and centrifuged at 50,000 \( \times \) g for 10 min. The pellet was resuspended in binding assay buffer containing 10 mM Hepes (pH 6.5), 1 mM EGTA, 5 mM MgCl\(_2\), 130 mM NaCl, 0.25 mg/ml of bacitracin and 0.2 mg/ml of soybean trypsin inhibitor. The membrane preparation (1.5 mg protein/ml) was incubated with 30 pM 125I-CCK-8 in binding assay buffer for 2 hr at 25°C. The incubation was terminated by filtration, and radioactivity was counted as described above.

Specific 125I-CCK-8 binding was determined by the difference between the counts in the absence and the presence of 10\(^{-6}\) M CCK-8. All assays were conducted in duplicate. The apparent dissociation constant (K\(_d\)) and maximum binding site density (B\(_{\text{max}}\)) for 125I-CCK-8 were estimated by Scatchard analysis of the saturation data (19). The value of the inhibition constant (K\(_i\)) was calculated from the equation K\(_i\) = IC\(_{\text{50}}\)/(1 + L/K\(_d\)) (20), where L represents concentration of 125I-CCK-8 used. The protein concentration was determined by the method of Lowry et al. (21).

To obtain the guinea pig gastric gland preparation, the gastric mucosa was removed and digested as previously described by Chang et al. (22). The glands (3 \( \times \) 10\(^5\) cells/ml) were incubated with 500 pM 125I-gastrin-I in binding assay buffer [5 mM Hepes (pH 7.4), 130 mM NaCl, 2 mM MgSO\(_4\), 1 mM CaCl\(_2\) and 12 mM NaHCO\(_3\)] for 30 min at 20°C. The reaction was terminated by filtration through a filter (GC-50; Toyo Roshi, Tokyo), and the filter was washed six times with 2 ml of ice-cold assay buffer, each time. Nonspecific binding was defined as the radioactivity bound in the presence of 10\(^{-5}\) M of gastrin-I.

Release of amylase from pancreatic acini

Amylase release from rat pancreatic acini was estimated according to the method of Otsuki and Williams (23). Rats were fasted overnight and exsanguinated before removing the pancreas. After removal of adherent fat and connective tissue, 5 ml of Krebs-Henseleit buffer (pH 7.35 at 25°C) containing 120 unit/ml of collagenase was injected into the tissue. The tissue was incubated at 37°C for 50 min. Acini were then mechanically dissociated by forceful pipetting, purified by filtration through a nylon mesh (150 \( \mu \)m), and centrifuged at 50 \( \times \) g for 4 min through Krebs-Henseleit buffer containing 4% bovine serum albumin.
The isolated acini were preincubated at 37°C for 30 min with 10 mM Hepes-Ringer buffer (pH 7.35 at 25°C) containing cycloheximide (final concentration: 300 μg/ml). Then the acini suspension (1 ml total) gassed with 100% O2 was incubated at 37°C for 30 min with drugs, and the amylase activity in the medium was measured by the CM-amylose DEX method (Amylase-B Test Wako; Wako Pure Chemical, Osaka). Amylase output was expressed as a percentage of the amylase originally present in the acini. Pancreatic acinar cell damage was evaluated by the trypan blue exclusion test during a 30-min incubation of the acini with the drug.

Data analyses
The results obtained were expressed as means±S.E. Statistical significance was determined by the Dunnett's multiple comparison test.

RESULTS

Radioligand binding assay
Nonspecific binding of [125I]-CCK-8 to these membranes increased linearly with increasing radioligand concentrations. Specific binding of the radioligand to pancreatic, gallbladder and cerebrocortical membrane preparations were saturable. Scatchard analysis of the data where the plots were linear in all tissue membranes suggested a single population of binding sites. The apparent dissociation constant (Kd) and the maximum binding site (Bmax) are shown in Table 1. The Kd value of the radioligand in rat pancreas was the lowest among the membranes tested, and guinea pig cerebral cortex had the highest Kd value.

The Kd value for canine gallbladder was intermediate. The ranking order of the Bmax was: rat pancreas > canine gallbladder ≥ guinea pig cerebral cortex.

The binding of [125I]-CCK-8 to rat pancreas membranes was effectively displaced in a concentration-dependent manner by KSG-504 (Fig. 1) and CCK-8 (data not shown). The Ki values of KSG-504 and CCK-8 were 173 and 0.242 nM, respectively (Table 2). KSG-504 and CCK-8 also inhibited [125I]-CCK-8 binding to canine gallbladder membranes with Ki values of 283 and 0.528 nM, respectively. KSG-504 and CCK-8 inhibited [125I]-CCK-8 specific binding to guinea pig cerebrocortical membranes in a concentration-dependent manner, and the Ki values were 413 μM and 5.82 nM, respectively.

The lower Ki values for KSG-504 were found in rat pancreatic and canine gallbladder membranes. The Ki value of KSG-504 for guinea pig cerebrocortical membranes was 1500–2400 times higher than those for rat pancreas and canine gallbladder. These three membranes showed small differences in the Ki values for CCK-8, with an overall variation of 24-fold.

![Fig. 1. Displacement of [125I]-CCK-8 binding by KSG-504 in rat pancreatic (○), canine gallbladder (●) and guinea pig cerebrocortical (□) membrane preparations. Specific binding of [125I]-CCK-8 is expressed as a percentage of the control binding. Each value indicates the mean ± S.E. of 5–8 experiments.](image-url)
KSG-504 also inhibited $^{125}$I-gastrin-I binding to guinea pig gastric glands in a concentration-dependent manner (Fig. 2), with an IC$_{50}$ value of 18.2 nM.

**Table 2. Effects of KSG-504 and CCK-8 on the [125I]-CCK-8 binding**

| Drug      | Tissue         | n  | IC$_{50}$ (M)        | K$_i$ (M)        |
|-----------|----------------|----|----------------------|------------------|
| KSG-504   | Pancreas       | 8  | $(2.02 \pm 0.11) \times 10^{-7}$ | $(1.73 \pm 0.09) \times 10^{-7}$ |
|           | Gallbladder    | 5  | $(3.01 \pm 0.63) \times 10^{-7}$ | $(2.83 \pm 0.57) \times 10^{-7}$ |
|           | Cerebral cortex | 7  | $(4.60 \pm 2.15) \times 10^{-4}$ | $(4.13 \pm 1.93) \times 10^{-4}$ |
| CCK-8     | Pancreas       | 8  | $(2.82 \pm 0.09) \times 10^{-10}$ | $(2.42 \pm 0.08) \times 10^{-10}$ |
|           | Gallbladder    | 5  | $(5.79 \pm 0.78) \times 10^{-10}$ | $(5.28 \pm 0.71) \times 10^{-10}$ |
|           | Cerebral cortex | 7  | $(6.48 \pm 0.81) \times 10^{-9}$ | $(5.82 \pm 0.72) \times 10^{-9}$ |

n: number of experiments, IC$_{50}$: molar concentration of the drug producing 50% displacement of the specific binding, K$_i$: calculated from the IC$_{50}$ values according to the equation of Cheng and Prusoff. Each of the values represents the mean ± S.E.

**Release of amylase from pancreatic acini**

KSG-504 (10$^{-7}$–10$^{-4}$ M) itself did not release amylase from isolated pancreatic acini (Fig. 3).

When isolated rat pancreatic acini were incubated with increasing concentrations of CCK-8, a minimal stimulation of amylase release was observed with 3 × 10$^{-12}$ M CCK-8, reaching a maximum at 3 × 10$^{-10}$ M. GRP stimulated amylase release with a maximal efficacy similar to that of CCK-8 at a concentration of 3 × 10$^{-9}$ M. Carbachol induced the release of amylase in a concentration-dependent manner, and the maximal increase of amylase release was obtained with 3 × 10$^{-6}$ M of carbachol. A23187 and secretin also stimulated amylase release, and

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**Fig. 2.** Displacement of $^{125}$I-gastrin-I binding by KSG-504 in guinea pig gastric glands. Specific binding of $^{125}$I-gastrin-I is expressed as a percentage of the control binding. Each value indicates the mean ± S.E. of 5 experiments.

**Fig. 3.** Effects of KSG-504 (●), CCK-8 (○), GRP (●●), carbachol (●●), A23187 (■), secretin (△), VIP (▲) or BayK 8644 (▼) on amylase release from isolated rat pancreatic acini. Amylase release was expressed as a percentage of the initial content in acinar cells. Each point indicates the mean ± S.E. of 6–7 experiments.
maximal responses were observed with $3 \times 10^{-5}$ M and $10^{-7}$ M, respectively. VIP caused only a weak release, and the maximal response was observed with $3 \times 10^{-9}$ M. BayK 8644 ($10^{-5}$-$10^{-4}$ M) did not induce the release of the enzyme from pancreatic acini.

KSG-504 inhibited CCK-8 ($10^{-10}$ M)-stimulated amylase release in a concentration-dependent manner, with an IC$_{50}$ value of $1.9 \times 10^{-6}$ M (Fig. 4). Neither carbachol ($3 \times 10^{-6}$ M)-, GRP ($3 \times 10^{-9}$ M)-, A23817 ($10^{-5}$ M)-, secretin ($10^{-7}$ M)- nor VIP ($3 \times 10^{-9}$ M)-stimulated amylase release was inhibited by KSG-504 ($10^{-7}$-$10^{-4}$ M) (Fig. 5).

Judging from the results of the trypan blue exclusion test, KSG-504 did not damage acinar cells at concentrations between $10^{-4}$ M and $5 \times 10^{-3}$ M, but the treatment with $10^{-2}$ M caused significant damage (Table 3).

**DISCUSSION**

In the present study, we clearly demonstrated the CCK-A-specific interaction of KSG-504 by receptor level and pancreatic secretion studies. 125I-CCK-8 bound specifically to the pancreatic, gallbladder and cerebrocortical membranes, and Scatchard analysis of the data indicated a linearity of the plots that demonstrated the presence of a single class of recep-

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**Table 3. Effect of KSG-504 on trypan blue exclusion in rat pancreatic acinar cells**

| Drug      | Concentration (M) | Stained (%) |
|-----------|-------------------|-------------|
| Control   |                   | 6.8±1.0     |
| KSG-504   | $10^{-4}$         | 6.2±0.8     |
|           | $2 \times 10^{-4}$| 7.5±0.9     |
|           | $5 \times 10^{-4}$| 6.5±1.0     |
|           | $10^{-3}$         | 7.1±0.6     |
|           | $2 \times 10^{-3}$| 7.8±0.7     |
|           | $5 \times 10^{-3}$| 10.0±1.4    |
|           | $10^{-2}$         | 69.1±8.0**  |

Each of the values represents the mean±S.E. of 6 experiments. **Significantly different from the control at P<0.01.
tor in each membrane. The $K_d$ value of the radioligand binding to the pancreatic membrane was 0.19 nM, which is comparable to the value reported by Chang et al. (about 0.10 nM) (18). There is little information regarding $^{125}$I-CCK-8 binding to canine gallbladder CCK receptors. In this study, we obtained a $K_d$ value of 0.31 nM, which is almost the same value reported in guinea pigs (0.3 nM), cattle (0.6 nM) and pigs (0.5 nM) (24–26). As for the cerebrocortical membrane of guinea pigs, the $K_d$ value for $^{125}$I-CCK-8 binding was somewhat higher than the value reported by Innis and Snyder (about 0.3 nM) (9).

The order of the $B_{max}$ in this study was: rat pancreas $>$ canine gallbladder $>$ guinea pig cerebral cortex. The number of CCK receptors in the pancreas was 50 times more than that in the cerebral cortex. Innis and Snyder reported that the rat pancreas had about 300 times more binding sites than the brain of guinea pigs (9). The $B_{max}$ of CCK receptors in the canine gallbladder membrane was between the estimates for guinea pig gallbladder (12 fmol/mg protein) (24) and for bovine gallbladder (101 fmol/mg protein) (25). With regard to the 20-fold difference of the $B_{max}$ of CCK receptors in the pancreas and gallbladder, more than 2 binding sites were reported in a single smooth muscle cell of the hamster gallbladder (27), whereas rat pancreatic acinar cells possessed at least 5,000–10,000 binding sites on each of its basolateral plasma lemma (28).

In the displacement experiments, CCK-8 inhibited $^{125}$I-CCK-8 binding to the membranes in a concentration-dependent manner. The $K_i$ values (Table 2) of CCK-8 for pancreatic and gallbladder CCK receptors nearly agreed with their $K_d$ values (Table 1). However, there was a six-fold difference between the $K_i$ and $K_d$ values of CCK-8 for cerebrocortical CCK receptors. Similar findings were reported by Kuwahara et al. (29) and others (12–15, 26). The differences in $K_i$ and $K_d$ values of CCK-8 for the cerebral cortex may occur when there is a co-existence of CCK-A and -B receptors in the brain region.

KSG-504 inhibited $^{125}$I-CCK-8 binding to the pancreatic, gallbladder and cerebrocortical membranes at $IC_{50}$ values of 202 nM, 310 nM and 460 $\mu$M, respectively. The selectivity of KSG-504 for CCK-A receptors was 1,500–2,300 times higher than that for CCK-B receptors. The $IC_{50}$ values of other CCK-antagonists in the case of rat pancreas and guinea pig or mouse brain were as follows: asperlicin (1.4 $\mu$M and $>$ 100 $\mu$M) (11), lorglumide (130 nM and 300 $\mu$M) (12), loxiglumide (330 nM and 9.1 $\mu$M) (13), L-364,718 (0.08 nM and 245 nM) (14), L-365,260 (280 nM and 2.0 nM) (15) and FK480 (0.4 nM and 72 nM) (16). Thus, the selectivity of KSG-504 for CCK-A receptors is comparable to that of L-364,718 or lorglumide.

Recently, a gastrin type CCK receptor identified in gastric glands was found to have high affinity for both CCK-8 and gastrin (10). L-365,260, a selective CCK-B-receptor antagonist, has been reported to inhibit $^{125}$I-CCK-8 binding to the cerebrocortical membrane and $^{125}$I-gastrin-I binding to gastrin receptors in the gastric glands of guinea pigs more effectively (15). KSG-504 also inhibited $^{125}$I-gastrin-I binding to gastric glands of the guinea pig, but the $IC_{50}$ value was 18.2 $\mu$M, which is about 90 times higher than the $IC_{50}$ value for the pancreas.

Pancreatic exocrine secretion is regulated physiologically by the gut hormone CCK, GRP, secretin or VIP, and by the neurotransmitter acetylcholine. All these agents interact initially with receptors on the plasma membrane of acinar cells. The effects of CCK-8, GRP and carbachol on pancreatic secretion are mediated through increases in intracellular Ca$^{2+}$ (30, 31). Thus, the Ca$^{2+}$ ionophore A23187 stimulates the secretion. On the other hand, BayK 8644, a voltage-dependent Ca$^{2+}$ channel agonist does not affect pancreatic amylase secretion. This result indicates that the pancreatic acinar cells lack this Ca$^{2+}$ influx mechanism. The effects of secretin and VIP on pancreatic secretion are mediated through increases in intracellular cAMP (32).

KSG-504 (10$^{-7}$–10$^{-4}$ M) itself did not stimulate amylase release from pancreatic acinar cells, indicating that KSG-504 has no CCK-agonistic activity on pancreatic secretion. Only the CCK-8-stimulated amylase release was completely abolished by KSG-504. KSG-504 had no inhibitory effects on the amylase release stimulated by other secretagogues that interact with different receptors or by a secretagogue that acts on a post-receptor mechanism. We have previously reported that the antagonism of KSG-504 against the pancreatic CCK-A receptors is competitive (17). Thus, the results of the current study clearly demonstrated that the antagonistic action of KSG-504 on the amylase release from the pancreatic acini was selective for CCK-A receptors.

In addition, KSG-504 at concentrations up to 5 x 10$^{-3}$ M did not damage acinar cells, as shown by the trypan blue exclusion test. This may indicate that the cytotoxicity of KSG-504 is extremely low.

Thus, based on the results presented here, we conclude that KSG-504 distinguishes pancreatic and gallbladder CCK-A receptors from cerebrocortical CCK-B and gastrin receptors. Furthermore, the inhibitory effect of KSG-504 on pancreatic secretion is the results of specific binding to CCK-A receptors. KSG-504 may serve as a tool for examining the physiological role of CCK-A receptors and a potential therapeutic agent for pancreatic disorders.
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