Effects of KSG-504, a New Cholecystokinin-A-Receptor Antagonist, on Pancreatic Exocrine and Endocrine Secretions in Rats

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ABSTRACT—The effects of KSG-504 ((S)-arginium (R)-4-[N-(3-methoxypropyl)-N-pentylcarbamoyl]-5-(2-naphthylsulfonyl) pentanoate monohydrate), a new cholecystokinin (CCK)-A-receptor antagonist, on pancreatic exocrine secretion in anesthetized rats and endocrine secretion in conscious rats were studied. Intravenous injection of KSG-504 inhibited the pancreatic amylase output stimulated by intravenous infusion of CCK-8 in a dose-dependent manner (ED₅₀: 18 ƒÊg/kg/min). Moreover, KSG-504 significantly reduced the CCK-8-stimulated increases in pancreatic juice volume and outputs of protein, trypsin and lipase. Intraduodenal infusion of casein increased the plasma CCK concentration and the pancreatic amylase output. KSG-504 significantly inhibited the pancreatic amylase output stimulated by casein. Pancreatic juice volume and bicarbonate output were significantly stimulated by intravenous infusion of secretin, but were not changed by KSG-504. When pancreatic exocrine secretion was stimulated by secretin plus CCK-8, KSG-504 suppressed the increases in juice volume and bicarbonate output to the level stimulated by secretin alone. Basal pancreatic amylase output was decreased by KSG-504. KSG-504 decreased the level of plasma immunoreactive insulin (IRI) stimulated by glucose plus CCK-8, but had no effect on IRI stimulated by glucose alone and the basal IRI. These in vivo studies suggest that KSG-504 has significant inhibitory effects both on the pancreatic exocrine and endocrine secretion stimulated by CCK, but has no effect on the exocrine secretion stimulated by secretin.

Keywords: KSG-504, Cholecystokinin, Rat pancreas, Exocrine secretion, Endocrine secretion

Cholecystokinin (CCK) is known as a gastrointestinal hormone and a potent regulator of the digestive process. After its release into the blood from duodenal L-cells (1), CCK stimulates pancreatic enzyme secretion (2), gallbladder contraction (3) and gut motility (4). In addition, the pancreatic endocrine secretion of insulin is regulated by CCK (5). CCK is also present in the central nervous system and may be associated with neuromodulation or neurotransmission (6). The signals of CCK are transduced through distinct classes of receptors, namely, CCK-A ( alimentary) and CCK-B (brain) receptors (7).

In recent studies, a number of CCK-A-receptor antagonists that are selective for pancreatic-type CCK receptors have been described; these include asperlicin (8), loxiglumide (9), L-364,718 (10) and FK480 (11). Clinical studies have been developed with loxiglumide, and the results obtained so far indicate the possible involvement of CCK in some pancreatic disorders (12). Moreover, CCK may be closely related to the etiology and development of pancreatitis, because CCK and its C-terminal analogue caerulein have been reported to produce acute pancreatitis (13, 14) or worsen it (15) in experimental animals and because pancreatitis patients frequently suffer from accompanying hypercholecystokinemia (16).

On the other hand, another secretagogue of pancreatic exocrine secretion, secretin, primarily stimulates the pancreatic bicarbonate output (17, 18), but, to our knowledge, there are no reports that secretin affects acute pancreatitis.

KSG-504 ((S)-arginium (R)-4-[N-(3-methoxypropyl)-N-pentylcarbamoyl]-5-(2-naphthylsulfonyl) pentanoate monohydrate) is one of the potent and selective CCK-A-receptor antagonists that was developed by Kissei Pharmaceutical Co., Ltd. We have previously reported that KSG-504 inhibited CCK-8-induced pancreatic exocrine secretion (19). Furthermore, protective effects of KSG-504 against experimental acute pancreatitis, induced by caerulein (20) or closed duodenal loop (21), have been demonstrated. These findings suggest that KSG-504 may have clinical utility in the treatment of acute pancreatitis.
In the present in vivo study, we investigated the effects of KSG-504 on pancreatic juice, bicarbonate and enzyme secretions stimulated by CCK or secretin in rats. The ability of KSG-504 to interact with pancreatic endocrine secretion in rats is also reported.

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: CCK-8 and secretin (Peptide Institute, Inc., Minoh); entero-kinase and benzoyl-arginine p-nitroanilide (BAPNA) (Sigma, St. Louis, MO, USA); casein, glucose and bovine serum albumin F-V (BSA) (Nacalai Tesque, Kyoto); triethylamine and acetonitrile (Wako Pure Chemical, Osaka); 125I-CCK-39 and CCK-8-specific antiserum (Otsuka Assay, Inc., Tokushima); and urethane (Kantoh Chemical, Tokyo).

The drugs were dissolved as follows: CCK-8 and secretin, in physiological saline containing 1% BSA; KSG-504 and casein, in physiological saline; the other chemicals, in distilled water.

Pancreatic exocrine secretion in anesthetized rats
Rat pancreatic exocrine secretion was measured by the method of Shiratori et al. (22). Male Wistar rats weighing 200 to 350 g (SLC, Hamamatsu) were used after an overnight fast with free access to water. The animals were anesthetized with urethane (1.5 g/kg, s.c.), and the abdomen was incised. The common bile duct was ligated proximal to the pancreas below the hilum of the liver, and a polyethylene tube (PE-10; Becton Dickinson, Parsippany, NJ, USA) was inserted into the bile duct above the ligature. Another polyethylene tube (PE-10) was also inserted into the pancreatic duct at its entrance to the duodenum. Pancreatic juice was collected and the effects of KSG-504 on pancreatic exocrine secretion were tested under 4 different experimental conditions:

**CCK-8-stimulated pancreatic exocrine secretion:** In the former experiment, CCK-8 was infused intravenously for 30 min at a dose of 1 ng/kg/min. The intravenous infusion of KSG-504 was initiated 30 min before the start of the CCK-8 infusion. The pancreatic juice was collected every 30 min; and its amylase concentration was measured. In the latter experiment, CCK-8 was injected at a dose of 0.5 µg/kg intravenously. KSG-504 was administered intravenously 1 min before the CCK-8 injection. Pancreatic juice was collected every 30 min; and its volume, protein, amylase, trypsin and lipase concentrations were measured. In normal rats, physiological saline containing 1% BSA was infused or injected intravenously, instead of CCK-8.

**Casein-stimulated pancreatic exocrine secretion:** A fresh 10% casein suspension (pH 7.0) was infused intraduodenally for 30 min at a rate of 2.3 ml/30 min. Intravenous infusion of KSG-504 was initiated 30 min before the start of casein infusion. Pancreatic juice was collected every 30 min, and its amylase concentration was measured. In normal rats, physiological saline was infused intraduodenally, instead of casein. At the end of the experiments, blood samples of normal and control rats were obtained. The plasma samples were separated from the blood samples by centrifugation (3,000 rpm for 10 min) in a refrigerated centrifuge (KR-600P; Kubota, Tokyo) and stock for future radioimmunoassay of CCK, frozen at a temperature below -20°C.

**Secretin plus CCK-8-stimulated pancreatic exocrine secretion:** Secretin (0.3 ng/kg/min) alone, CCK-8 (1 ng/kg/min) alone or both secretin plus CCK-8 was infused for 1 hr intravenously. The infusion of KSG-504 was initiated 30 min before the start of the secretagogues infusion. Pancreatic juice was collected every hour and its volume, bicarbonate and amylase concentrations were measured. In normal rats, physiological saline containing 1% BSA was infused intravenously, instead of secretin or CCK-8.

**Basal pancreatic exocrine secretion:** Pancreatic juice was collected every 30 min after the intravenous injection of saline or KSG-504, and its volume and amylase concentration was measured.

**Pancreatic endocrine secretion of insulin in conscious rats**
Male Wistar rats (200–300 g) were used after an overnight fast with free access to water. Under ether anesthesia, 0.5 ml of blood was collected from the orbital artery 30 min before and 15 and 60 min after the KSG-504 injection. Plasma was separated from the blood samples by centrifugation (3,000 rpm for 10 min, KR-600P; Kubota) and the concentration of IRI was measured. The effects of KSG-504 on insulin secretion were tested under 3 different experimental conditions:

**Glucose-stimulated insulin secretion:** Glucose was administered orally at a dose of 1 g/kg. KSG-504 was administered intravenously 1 min before the glucose administration.

**Glucose plus CCK-8-stimulated insulin secretion:** Glucose (1 g/kg, p.o.) and CCK-8 (0.5 µg/kg, i.v.) were administered simultaneously 1 min after the intravenous injection of KSG-504.

**Basal insulin secretion:** After the intravenous injection of KSG-504, its effect on basal plasma IRI was measured.

Analytical methods
The pancreatic amylase level was determined by the
CM-amylose DEX method (Amylase-B Test Wako, Wako Pure Chemical). The lipase concentration was assayed by the BALB-DTNB method (Lipase kit A "Marupi"; Dainippon Pharm., Osaka). The trypsin activity was determined by the BAPNA method (23) after activation of trypsinogen with enterokinase (24). The pancreatic juice protein concentration was determined by the method of Lowry et al. (25). The bicarbonate concentration was measured with an automatic blood-gas system (Sysmex AVL995; Toa, Tokyo).

Plasma CCK was eluted by the previously described method (26). Two milliliters of plasma was mixed with 2 ml of 0.5 M triethylamine and applied to octadecylsilica (Sep-Pak) cartridges (Waters, Milford, MA, USA) previously washed with 5 ml of acetonitrile and 10 ml of ethanol. After a wash with 20 ml of water, CCK was eluted with 2 ml of acetonitrile/water (50:50, v/v) and dried under nitrogen. The dried sample was dissolved in 0.2 ml of 0.03 M phosphate buffer (pH 7.6), and CCK concentrations were measured by using $^{125}$I-CCK-39 and CCK-8-specific antiserum modulated for the CCK radioimmunoassay (27). The sample or standard CCK-8 (0.2 ml), $^{125}$I-CCK-39 (0.2 ml) and phosphate buffer (0.4 ml) was pre-incubated at 4°C for 48 hr and then added with 0.2 ml of CCK-8 specific antiserum. After incubation at 4°C for 24 hr, the reaction was terminated by centrifugation (3,000 rpm for 30 min, KR-600P; Kubota) and the radioactivity of the pellet was counted in a gamma-counter (Auto-Gamma 5650; Packard, Downers Grove, IL, USA).

The plasma immunoreactive insulin (IRI) was measured by a two-antibody method (Insulin 'Eiken' Radioimmunoassay Kit; Eiken, Tokyo).

Data analyses

The results obtained are expressed as means±S.E. Statistical significance of differences between multiple groups was determined by the Dunnett multiple comparison test, and statistical significance of difference between two groups was determined by Student's t-test. Differences with a probability of less than 0.05 were considered to be significant.

RESULTS

**CCK-8-stimulated pancreatic exocrine secretion in anesthetized rats**

The output of amylase increased from the basal level of 473±114 IU/30 min to 973±159 IU/30 min after the intravenous injection of CCK-8 (1 ng/kg/min) (n=16). Intravenous administration of KSG-504 inhibited the amylase output stimulated by intravenous infusion of CCK-8 in a dose-dependent manner. The ED$_{50}$ value of KSG-504 was 18 μg/kg/min (Fig. 1).

CCK-8 (0.5 μg/kg, i.v.) increased the pancreatic juice volume by 2.4 times and the outputs of protein, amylase, trypsin and lipase by 6.3, 10.4, 8.4 and 16.2 times, respectively. KSG-504 inhibited the increase in the vol-

![Graph](attachment:image)

**Fig. 1.** Effects of KSG-504 on pancreatic amylase secretion stimulated by intravenous infusion of CCK-8 at a dose of 1 ng/kg/min in anesthetized rats. Intravenous infusion of KSG-504 was started 30 min before CCK-8 infusion. Each column indicates the mean±S.E. of 12-16 rats. *Significantly different from the control at P<0.05.

| Group       | Dose (mg/kg, i.v.) | n  | Volume (μl/30 min) | Protein (mg/30 min) | Amylase (IU/30 min) | Trypsin (ng/30 min) | Lipase (IU/30 min) |
|-------------|--------------------|----|--------------------|---------------------|---------------------|---------------------|-------------------|
| Normal      |                    | 7  | 24.1±2.7           | 0.93±0.25           | 177±44              | 42±16               | 7.8±2.4           |
| Control (CCK-8) |               | 8  | 59.6±3.3**        | 5.85±0.25**        | 1832±187**          | 352±42**           | 126.5±11.5**     |
| KSG-504     | 0.3                | 8  | 48.6±4.0          | 4.09±0.42**        | 1048±135            | 235±36*            | 68.9±14.4        |
|             | 1                  | 8  | 44.5±3.1**       | 3.67±0.32**        | 886±87*             | 200±29**           | 43.8±11.5*       |
|             | 3                  | 7  | 28.8±2.9**      | 2.10±0.25**        | 457±67**            | 119±20**           | 33.6±8.3**       |

Each value represents the mean±S.E. of 7-8 rats. **P<0.01, vs normal group. *P<0.05, **P<0.01, vs control group.
ume of pancreatic juice in a dose-dependent manner with an \( \text{ED}_{50} \) value of 0.86 mg/kg. CCK-8-stimulated pancreatic protein and enzyme secretions were also inhibited by KSG-504. The \( \text{ED}_{50} \) values of KSG-504 for the inhibition of protein, amylase, trypsin and lipase outputs were 0.43, 0.76, 0.29 and 0.84 mg/kg, respectively (Table 1).

After the intraduodenal infusion of casein, the plasma concentration of CCK increased to 3.44±0.52 pM,
whereas the plasma CCK concentration of normal rats was $0.91 \pm 0.25$ pM (Fig. 2). The output of amylase increased from the basal level of $226 \pm 28$ IU/30 min to $573 \pm 96$ IU/30 min ($n=18$) (Fig. 3). On the other hand, the intraduodenal infusion of physiological saline had no effects on amylase secretion ($218 \pm 48$ IU/30 min vs $228 \pm 61$ IU/30 min) ($n=12$). KSG-504 significantly inhibited the casein-stimulated pancreatic amylase secretion in a dose-dependent manner. The increase of amylase secretion after casein administration was completely blocked by 50 pg/kg/min of KSG-504.

**Secretin plus CCK-8-stimulated pancreatic exocrine secretion in anesthetized rats**

In this experiment, pancreatic exocrine secretion was stimulated by secretin alone, CCK-8 alone or secretin plus CCK-8. Pancreatic bicarbonate output was significantly stimulated by intravenous infusion of secretin (0.3 ng/kg/min), whereas pancreatic amylase output was stimulated by CCK-8 (1 ng/kg/min) (Fig. 4). Pancreatic juice volume was significantly stimulated by both secretin and CCK-8. KSG-504 (100 pg/kg/min) did not affect the pancreatic juice volume and bicarbonate output stimulated by secretin, but suppressed the amylase output to half (Fig. 5). When CCK-8 was administered in combination with secretin, a further increase in pancreatic secretion was observed (Table 2). The increase of amylase output was statistically significant. KSG-504 suppressed the pancreatic juice volume and bicarbonate output stimulated by secretin plus CCK-8 to the level observed with secretin alone and reduced the amylase output to a level less than that stimulated by secretin alone.

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**Table 2.** Effect of KSG-504 on secretin plus CCK-8 stimulated pancreatic exocrine secretion in anesthetized rats

| Group                     | Dose (pg/kg/min, i.v.) | n  | Volume (μl/hr) | HCO₃⁻ (μEq/hr) | Amylase (IU/hr) |
|---------------------------|------------------------|----|----------------|----------------|----------------|
| Secretin                  | 9                      | 62.8 ± 4.5 | 5.07 ± 0.35 | 452 ± 118 |
| Control (Secretin + CCK-8)| 8                      | 97.8 ± 17.3 | 6.57 ± 0.73 | 1480 ± 400* |
| KSG-504                   | 10                     | 7 | 75.7 ± 10.5 | 5.37 ± 0.65 | 961 ± 243      |
|                           | 30                     | 8 | 71.7 ± 7.1   | 4.81 ± 0.31 | 990 ± 339      |
|                           | 100                    | 8 | 67.1 ± 4.0   | 4.93 ± 0.58 | 344 ± 70*      |

Each value represents the mean ± S.E. of 7–9 rats. *P < 0.05, vs secretin-treated group. *P < 0.05, vs control group.
Table 3. Effect of KSG-504 on basal pancreatic exocrine secretion in anesthetized rats

| Group   | Dose (mg/kg, i.v.) | n  | Volume (μl/30 min) | Amylase (IU/30 min) |
|---------|-------------------|----|--------------------|---------------------|
| Normal  |                   | 10 | 21.5 ± 1.8         | 380 ± 71            |
| KSG-504 | 1                 | 9  | 19.7 ± 2.2         | 267 ± 79            |
|         | 3                 | 10 | 18.1 ± 1.2         | 176 ± 31            |

Each value represents the mean ± S.E. of 8–10 rats. *P < 0.05, vs normal group.

Basal pancreatic exocrine secretion in anesthetized rats

As shown in Table 3, the basal volume of pancreatic juice and the amylase output were 21.5 ± 1.8 μl/30 min and 380 ± 71 IU/30 min, respectively. KSG-504 at a dose of 3 mg/kg significantly inhibited the basal amylase output, whereas the volume of pancreatic juice was not affected.

Glucose-stimulated insulin secretion in conscious rats

The level of plasma IRI increased from 14.7 ± 3.2 μU/ml to 67.5 ± 9.2 μU/ml 15 min after an oral administration of glucose (1 g/kg) and then decreased to the basal levels after 60 min of administration. KSG-504 at a dose of 10 mg/kg did not affect the glucose-stimulated increase of plasma IRI (Table 4).

Glucose plus CCK-8-stimulated insulin secretion in conscious rats

After simultaneous intravenous injection of CCK-8 (0.5 μg/kg) with oral administration of glucose, an approximately 2-fold increase in plasma IRI in comparison with glucose alone was observed during the experiment. KSG-504 suppressed the increase of IRI stimulated by CCK-8 plus glucose to the level observed after glucose alone (Table 4).

Table 4. Effect of KSG-504 on the level of plasma IRI in conscious rats

| Treatment | Group               | Dose (mg/kg, i.v.) | n  | IRI (μU/ml) |
|-----------|---------------------|-------------------|----|-------------|
| Glucose   | Control (Glucose)   | 7                 | 14.7 ± 3.2 | 67.5 ± 9.2  | 15.7 ± 2.0  |
|           | KSG-504             | 3                 | 9.2 ± 1.6  | 49.8 ± 5.8  | 13.1 ± 2.4  |
|           |                     | 10                | 10.9 ± 2.8 | 66.6 ± 6.1  | 18.0 ± 3.0  |
| Glucose   | Control (Glucose+CCK-8) | 8                | 11.9 ± 2.1 | 84.5 ± 10.8 | 47.6 ± 9.9  |
|           | KSG-504             | 1                 | 12.8 ± 1.9 | 51.4 ± 10.1 | 43.8 ± 6.6  |
|           |                     | 3                 | 19.8 ± 4.6 | 43.4 ± 5.7**| 34.4 ± 9.9  |
| Basal     | Normal              | 9                 | 11.8 ± 2.2 | 18.3 ± 2.7  | 9.4 ± 0.8   |
|           | KSG-504             | 3                 | 14.8 ± 2.7 | 18.8 ± 4.1  | 22.5 ± 9.9  |
|           |                     | 10                | 11.7 ± 2.3 | 19.0 ± 4.5  | 12.7 ± 2.2  |

Each value represents the mean ± S.E. of 7–9 rats. *P < 0.05, vs glucose-treated group. **P < 0.05, ***P < 0.01, vs control group.

DISCUSSION

In the present study, we investigated the effects of KSG-504 on pancreatic exocrine and endocrine secretions in rats. We previously reported that the ED50 value of KSG-504 for rat pancreatic amylase secretion was about 52 μg/kg/min (19), when amylase secretion was stimulated by a pharmacological experimental dose of CCK-8 (5 ng/kg/min) that produced submaximal pancreatic secretion. However, as for the physiological concentration of plasma CCK, it was considered that after the intravenous infusion of 0.5–2 ng/kg/min of CCK-8, the concentration of plasma CCK reaches the meal-stimulated concentration of plasma CCK (28). The intravenous infusion of exogenous CCK-8 (1 ng/kg/min) increased the output of pancreatic amylase to levels of twice the basal level. KSG-504 inhibited the pancreatic exocrine secretion stimulated by this physiological dose of CCK-8 with an ED50 value of 18 μg/kg/min.

The inhibitory effects of KSG-504 on pancreatic juice
volume and enzyme secretion induced by exogenous CCK injection were examined. The volume of rat pancreatic juice, as well as the outputs of protein, amylase, trypsin and lipase were increased 2.4, 6.3, 10.4, 8.4 and 16.2 times, respectively, in comparison to their values in pancreatic juice under normal conditions. Moriyoshi also reported that the intravenous infusion of CCK-8 (1 ng/kg/min) produced a 3- to 6-fold increase of the pancreatic juice volume as well as amylase and trypsin secretion (28). All these pancreatic exocrine secretions were equally inhibited by KSG-504, in a dose-dependent manner.

It was reported that casein (protein) but not amino acids, carbohydrate and fats infused into the duodenum increased the plasma concentration of CCK (29). On the other hand, another secretagogue of pancreatic exocrine secretion, secretin, was mainly stimulated by fats (26). We also confirmed that intraduodenal infusion of 10% casein at a volume of 2.3 ml/30 min significantly increased the plasma CCK and pancreatic amylase output. These results suggest that the increase of pancreatic exocrine secretion stimulated by the intraduodenal infusion of casein is attributable to the release of endogenous CCK. KSG-504 inhibited the casein-induced pancreatic amylase output in a dose-dependent manner. Therefore, it is likely that KSG-504 affects the endogenous CCK-induced pancreatic exocrine secretion.

It has been reported that bicarbonate output is stimulated primarily by secretin in humans (17) and dogs (18). In fact, pancreatic juice volume and bicarbonate output were significantly stimulated by intravenous infusion of secretin. However, the ability of secretin to stimulate the amylase output was weak in contrast to that of CCK. We examined the effects of a high dose KSG-504 (100 μg/kg/min), which abolished the CCK-8 stimulated pancreatic amylase output, on the volume of pancreatic juice, and bicarbonate and amylase outputs stimulated by secretin. KSG-504 did not affect the pancreatic juice volume and bicarbonate output, but decreased the amylase output to half. The combined administration of secretin plus CCK-8 significantly stimulated amylase secretion, when compared with secretin alone. KSG-504 abolished the pancreatic juice volume and bicarbonate output stimulated by secretin plus CCK-8 to the level observed with secretin alone. The secretin plus CCK-8 stimulated amylase output was decreased by KSG-504 to the level below that stimulated by secretin alone. In addition, basal pancreatic amylase secretion was significantly inhibited by 3 mg/kg of KSG-504. This data indicates that endogenous CCK takes part in the continual basal amylase secretion. We also reported that the amylase release stimulated by secretin in isolated rat pancreatic acini was not affected by 10^{-4} M of KSG-504 (30). Thus, it seems that the decrease of secretin stimulated pancreatic amylase output by KSG-504 may result from the inhibition of CCK-related basal amylase output by KSG-504.

As for pancreatic endocrine secretion, CCK-8 is known to stimulate insulin secretion (5). Moreover, it has been demonstrated that specific CCK receptors exist within the islets of Langerhans (31). The insulin secretion induced by CCK is mediated by activation of CCK-A receptors, and this secretion is inhibited by L-364,718, a CCK-A receptor-specific antagonist in mice (32). However, it has been reported, that CCK is not one of the major secretagogues of insulin endocrine secretion in humans (33). KSG-504 inhibited the level of IRI induced by exogenous CCK, but did not affect the glucose-induced or basal IRI. Karlsson and Ahren reported that L-364,718 and lorglumide inhibited the CCK-induced insulin secretion in mice (32). However, L-364,718 did not affect the glucose-induced or basal insulin secretion (33, 34). Our data indicate that the inhibition of pancreatic endocrine secretion by KSG-504 is confined to CCK-related endocrine secretion.

In conclusion, our in vivo results suggest that KSG-504 inhibits the pancreatic exocrine secretion induced by exogenous and endogenous CCK, as well as the pancreatic endocrine secretion induced by exogenous CCK, but has no effect on the exocrine secretion stimulated by secretin.

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