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The mechanism of inhibitory action of secretin on gastric acid secretion in conscious rats

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1. Secretin has been recognized as an important enterogastrone. In order to investigate the mechanism of secretin-induced inhibition of gastric acid secretion, the effects of both anti-somatostatin antibody and indomethacin on acid secretion were examined in conscious rats with gastric cannulas.

2. Secretin given intravenously at 5·6 pmol kg^{-1} h^{-1} inhibited profoundly the acid secretion stimulated by pentagastrin at 0·3 μg kg^{-1} h^{-1}.

3. When a rabbit antisomatostatin serum was given intravenously, it not only abolished the secretin-induced inhibition on the pentagastrin-stimulated acid secretion, but also augmented both basal and pentagastrin-stimulated acid secretion.

4. Indomethacin also significantly augmented basal acid secretion, starting 45 min after the drug delivery began. It reversed the secretin-induced inhibition but it did not augment the pentagastrin-stimulated acid secretion.

5. Neither antisomatostatin serum influenced prostaglandin E_2-induced inhibition of the pentagastrin-stimulated acid secretion, nor did indomethacin affect the inhibition by somatostatin, suggesting strongly that the inhibition by somatostatin is not mediated by endogenous prostaglandins, nor is that by prostaglandins E_2 mediated by endogenous somatostatin.

6. It is concluded that the inhibitory action of secretin on pentagastrin-stimulated gastric acid secretion is mediated by both somatostatin and prostaglandins in conscious rats. The two inhibitors do not seem to interact endogenously for the inhibition of acid secretion. While endogenous somatostatin exerts a tonic inhibitory effect on both basal and pentagastrin-simulated acid secretion, prostaglandins augment basal acid secretion only.

Secretin is a well recognized enterogastrone (Kosaka & Lim, 1930) in rats (Chey, Sivasomboon & Hendricks, 1973; Rhee, Chang, Lee, Jo & Chey, 1991; Shiratori, Watanabe & Takeuchi, 1992), dogs (Chey, Kim, Lee & Chang, 1981; Jin, Lee, Chang, Chey & Dubois, 1994) and humans (You & Chey, 1987; Christiansen, Hansen, Hilstead & Schaffalitzky De Muckadell, 1988). Thus, physiological doses of secretin have been shown to inhibit postprandial gastric acid secretion (Chey *et al.* 1981; You & Chey, 1987; Christiansen *et al.* 1988; Shiratori *et al.* 1992; Jin *et al.* 1994). Recently, endogenous prostaglandins were shown to mediate the inhibitory action of secretin on gastric acid secretion in the isolated, perfused rat stomach (Chung, Li, Lee, Chang & Chey, 1994), the anaesthetized rat (Rhee *et al.* 1991; Shiratori, Watanabe & Takeuchi, 1993) and the conscious dog (Maclellan, Upp & Thompson, 1988). Secretin was also shown to stimulate the release of somatostatin from the isolated, perfused rat stomach (Chiba *et al.* 1980; Chung *et al.* 1994), cultured human antral cells (Buchan, Meloche, Kwok & Kofod, 1993) and D cells in the canine fundus (Chiba & Yamada, 1991), while a somatostatin antiserum has been shown to abolish the inhibitory action of secretin on carbachol-stimulated gastrin release in cultured rat antral mucosa (Wolfe, Reel & McGuigan, 1983). However, it has not been determined whether or not the inhibitory action of secretin on the release of gastrin and gastric acid secretion is mediated by somatostatin *in vivo*. Most of the previous studies (Seal, Meloche, Liu, Buchan & Brown, 1987; Seal, Liu, Buchan & Brown, 1988; Rhee *et al.* 1991; Shiratori *et al.* 1992) used the anaesthetized rat. It was shown by Yang, Wong, Wu, Walsh & Tache (1990) that urethane anaesthesia increases antral somatostatin synthesis in rats.

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The purpose of the present study is to investigate whether or not the inhibitory action of secretin on pentagastrin-stimulated gastric acid secretion is mediated through the release of somatostatin and/or prostaglandins under near-physiological conditions in conscious rats. In addition, the possible effect of interaction between somatostatin and prostaglandins was also investigated.

METHODS

Animal preparation

Male Sprague–Dawley rats weighing 200–300 g were used in this study. Before surgery, rats were fasted for at least 18 h with free access to water. After anaesthesia with intraperitoneal injection of sodium pentobarbitone (30 mg kg^{-1}), each rat was prepared with a chronic gastric fistula by inserting a stainless-steel cannula (6 mm i.d.) into the forestomach via a small incision in the anterior wall near the greater curvature. Both jugular veins were cannulated with polyethylene tube (PE-50, 0·58 mm i.d.) which was filled with heparin–saline (90 units heparin ml^{-1}) to prevent air embolus and blood coagulation. Seven days were allowed for recovery from the surgical procedures.

Before experiments, the rats were fasted for 24 h with free access to drinking water. The animals were placed into a Bollman's cage, and slow continuous intravenous infusion of 0·15 M NaCl solution was started with an infusion pump at a rate of 2·2 ml h^{-1}. The stomach was washed with a small volume of 0·15 M NaCl solution and a plastic tube was connected to the gastric cannula in order to collect gastric juice. The experiment was started 1·5 h after gastric washing.

Inhibitory effect of secretin on pentagastrin-stimulated acid secretion

Seventeen rats were used in this study. In the first group of ten rats, after 90 min basal period, pentagastrin (Peptavlon; Wyeth-Ayerest, Philadelphia, PA, USA) was infused intravenously for 1 h at a dose rate of 0·3 $\mu g\ kg^{-1}\ h^{-1}$. In the second group of seven rats, secretin (Coy, Coy, Lee & Chey, 1982) (a gift from Dr D. H. Coy, Tulane University) was infused at a physiological dose rate of 5·6 pmol $kg^{-1}\ h^{-1}$ starting 30 min before the infusion of pentagastrin was begun. This dose of secretin was chosen as a physiological dose that produces a plasma level of secretin comparable with that during intraduodenal infusion of oleic acid or ingestion of a liquid meal in rats (Lee, Zhou, Ren, Chang & Chey, 1990; Rhee *et al.* 1991). The gastric juice was collected continuously in 15 min samples. Both pentagastrin and secretin were dissolved in 0·15 M NaCl solution containing 0·5% bovine serum albumin (Sigma).

Effect of rabbit antisomatostatin serum and indomethacin on secretin-induced inhibition of gastric acid secretion

In another five rats as described above, 1 ml of a rabbit antisomatostatin serum was administered intravenously in a bolus 30 min before the infusion of secretin was initiated, which was followed by intravenous infusion of pentagastrin for 1 h. The rabbit antisomatostatin serum used was specific for somatostatin as described previously (Lee, Lee, Kim, Chang & Chey, 1994) and reacted only with somatostatin-14 and somatostatin-28 (78·7% as reactive as somatostatin-14). As a control, 1 ml of normal rabbit serum was tested in five rats.

In seven rats, indomethacin (Sigma) was infused at a dose rate of 0·5 mg $kg^{-1}\ h^{-1}$ for 2 h which immediately followed a bolus injection of 1 mg kg^{-1}, at 30 min before the infusion of secretin was initiated. Pentagastrin was started 30 min after secretin administration was begun.

Effect of indomethacin or antisomatostatin serum on basal and pentagastrin-stimulated gastric acid secretion

Thirty-one rats were studied. In each of five rats, after a 30 min basal period, 1 ml of the antisomatostatin serum was administered intravenously in a bolus. Then pentagastrin was infused for 1 h, starting 1 h after the injection of antisomatostatin serum. As a control study, 1 ml of normal rabbit serum per rat was tested in five rats. In seven rats, after a 30 min basal period, indomethacin was infused intravenously at a dose rate of 0·5 mg $kg^{-1}\ h^{-1}$ for 2 h immediately after a bolus injection of 1 mg kg^{-1}. In eight rats, indomethacin at the same dose rate as above was given for 2 h, starting 60 min before the infusion of pentagastrin was initiated. As a control study, 0·15 M NaCl solution was infused intravenously at a rate of 2·2 ml h^{-1} in six rats.

Effect of indomethacin on somatostatin-induced inhibition of gastric acid secretion

To investigate whether somatostatin-induced inhibition of gastric acid secretion is mediated through endogenous prostaglandins, the following experiment was performed. After a basal period of 30 min, somatostatin (Bachem, Torrence, CA, USA) was infused at a dose rate of 300 pmol $kg^{-1}\ h^{-1}$ starting 30 min before the infusion of pentagastrin was begun in seven rats. In another group of seven rats, indomethacin was given at the same dose rate as described above, 30 min before the infusion of somatostatin was initiated.

Effect of antisomatostatin serum on prostaglandin E_2-induced inhibition of gastric acid secretion

In the same experimental design as described above, prostaglandin E_2 (PGE_2; Sigma) was administered intravenously at 40 $\mu g\ kg^{-1}\ h^{-1}$ starting 30 min before the pentagastrin infusion began in five rats. In another group of five rats, an antisomatostatin serum (1 ml) was administered 30 min before the infusion of PGE_2 was started.

Determinations

Gastric acid output was measured by titration with 0·01 N NaOH to an end-point of pH 7·4 using a computer-aided titrimeter (Fisher Scientific, Pittsburgh, PA, USA), and was expressed as microequivalents per fifteen minutes.

Analysis of data

All values were expressed graphically as means ± 1 S.E.M. The net increases of gastric acid output represented the cumulative (last 30 min) gastric acid output during the infusion of pentagastrin from which the cumulative (last 30 min) basal acid output was subtracted. Statistical significance was determined by using one-way analysis of variance followed by multiple comparison of the individual means using the method of Tukey (Kirk, 1982). All test statistics with $P < 0·05$ were regarded as significant.

RESULTS

Inhibitory effect of secretin on pentagastrin-stimulated gastric acid secretion

The basal gastric acid output for a 60 min period was 8·4 ± 1·4 μequiv $(15\ min)^{-1}$. After infusion of pentagastrin at a dose rate of 0·3 $\mu g\ kg^{-1}\ h^{-1}$, the acid output increased gradually to reach 29·8 ± 4·4 μequiv $(15\ min)^{-1}$ over a

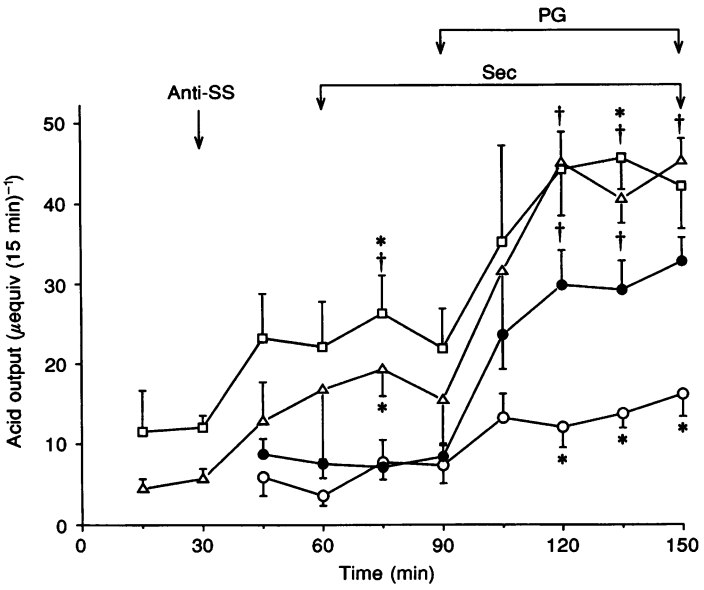

Figure 1. Effect of secretin on pentagastrin-stimulated gastric acid secretion in the absence or presence of antisomatostatin serum

Gastric acid secretion was studied with I.V. pentagastrin (PG) alone (●; 0·3 μg kg^{-1} h^{-1}; $n = 10$), PG with I.V. secretin (Sec; ○; at 5·6 pmol kg^{-1} h^{-1} given 30 min before PG infusion; $n = 7$), PG with I.V. antisomatostatin (Anti-SS) serum (△; $n = 5$), and PG with I.V. antisomatostatin (□; 30 min before secretin was administered; $n = 5$). Means ± S.E.M. * $P < 0·05$, compared with acid output in response to pentagastrin alone; † $P < 0·05$, compared with acid output in response to secretin and pentagastrin.

period of 30 min and then remained steady. Intravenous infusion of secretin at a dose rate of 5·6 pmol h^{-1} significantly inhibited the gastric acid output stimulated by pentagastrin ($P < 0·05$; Fig. 1).

Effect of antisomatostatin serum on basal and secretin-inhibited gastric acid secretion

In the five rats that received I.V. injection of a normal rabbit serum, the net increase of acid secretion stimulated by pentagastrin (99·0 ± 4·7 μequiv h^{-1}) was not significantly different from that in the ten rats which were given 0·15 M NaCl instead of normal rabbit serum (83·6 ± 9·6 μequiv h^{-1}). Similarly, net increase of acid secretion (27·8 ± 9·1 μequiv h^{-1}) in response to a combination of pentagastrin, secretin and a rabbit normal serum was not significantly different from that produced by pentagastrin and secretin with 0·15 M NaCl (24·4 ± 8·9 μequiv h^{-1}). As shown in Fig. 1, when antisomatostatin serum was administered, the basal secretion increased from 12·0 ± 1·5 to 26·3 ± 4·8 μequiv (15 min)$^{-1}$ over a 60 min period. Thus, the basal acid output in response to antisomatostatin serum was significantly higher than those in the other groups of rats without antisomatostatin serum treatment ($P < 0·05$). The inhibitory effect of secretin on the pentagastrin-stimulated acid secretion was reversed by antisomatostatin serum (Figs 1 and 2). Moreover, the pentagastrin-stimulated acid output in response to antisomatostatin serum was significantly

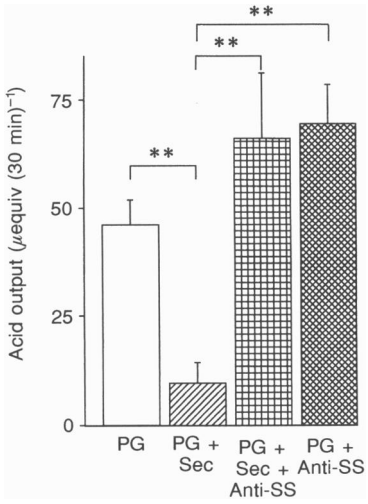

Figure 2. Net increase of gastric acid output in response to secretin with and without antisomatostatin serum

All data are expressed as mean ± S.E.M increase over basal value of four different experiments. PG, I.V. pentagastrin at 0·3 μg kg^{-1} h^{-1} alone ($n = 10$); PG + Sec, pentagastrin with secretin at a dose rate of 5·6 pmol kg^{-1} h^{-1}, starting 30 min before pentagastrin infusion was begun ($n = 7$); PG + Sec + Anti-SS, pretreatment with I.V. antisomatostatin serum 30 min before secretin infusion; pentagastrin was given 30 min after the infusion of secretin ($n = 5$); PG + Anti-SS, pretreatment with I.V. antisomatostatin serum; pentagastrin was given 60 min after I.V. antisomatostatin serum ($n = 5$). ** $P < 0·01$.

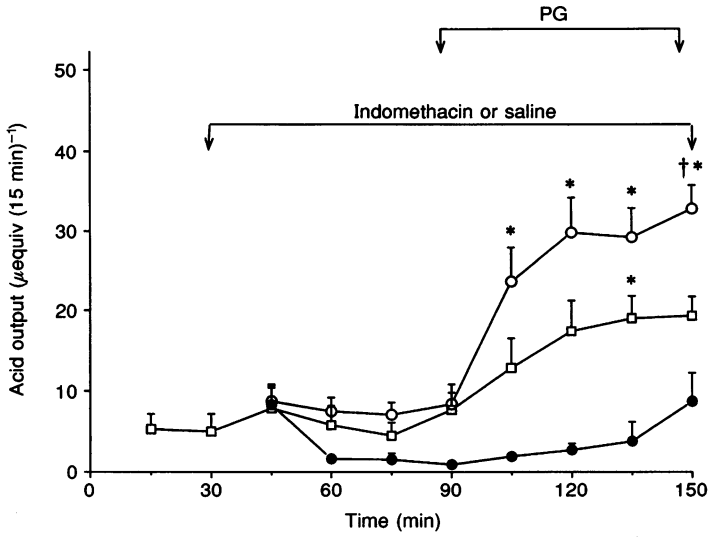

Figure 3. Gastric acid output in response to indomethacin

Gastric acid output in response to I.V. pentagastrin (PG; ○; 0·3 μg kg^{-1} h^{-1}; $n = 10$), I.V. indomethacin (□; 1 mg kg^{-1} + 0·5 mg kg^{-1} h^{-1}; $n = 7$), or I.V. saline alone (●; 1 ml h^{-1}; $n = 6$). * $P < 0·05$ compared with acid output in response to saline; † $P < 0·05$ compared with acid output in response to I.V. indomethacin.

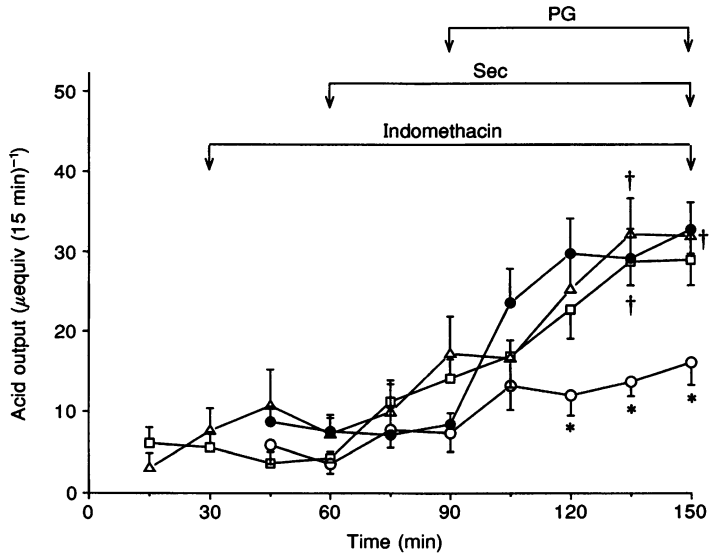

Figure 4. Effect of secretin on pentagastrin-stimulated gastric acid secretion with or without indomethacin administration

Gastric acid output in response to I.V. pentagastrin (PG) alone (●; 0·3 μg kg^{-1} h^{-1}; $n = 10$), PG with secretin (Sec) at a dose rate of 5·6 pmol kg^{-1} h^{-1}, starting 30 min before pentagastrin infusion was initiated (○; $n = 7$), PG with I.V. indomethacin at 0·5 mg kg^{-1} h^{-1} for 2 h following a 1 mg kg^{-1} bolus injection (△; $n = 8$), and PG with I.V. indomethacin at 0·5 mg kg^{-1} h^{-1} for 2 h following a 1 mg kg^{-1} bolus injection, starting 30 min before secretin administration (□; $n = 9$). Means ± S.E.M. * $P < 0·05$ comparing the acid output in response to PG alone with the results of 3 different experimental conditions. † $P < 0·05$ comparing with the acid output in response to the infusion of secretin and PG.

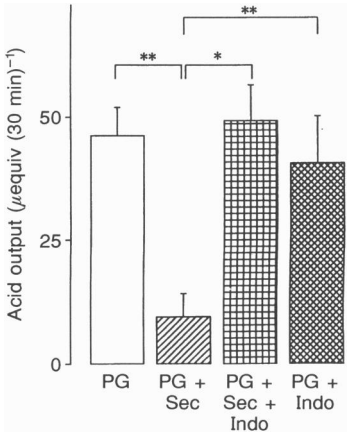

Figure 5. Net increase of gastric acid output in response to pentagastrin (PG) alone, and PG plus secretin in the absence or presence of indomethacin

Mean ± S.E.M. increase over basal value of four different experiments. □, PG, I.V. at 0·3 μg kg^{-1} h^{-1} alone ($n = 10$). ▨, PG + Sec, PG with secretin at 5·6 pmol kg^{-1} h^{-1}, starting 30 min before PG infusion ($n = 7$). ▦, PG + Sec + Indo, pretreatment with indomethacin at a dose rate of 0·5 mg kg^{-1} h^{-1} for 2 h following a 1 mg kg^{-1} bolus injection, starting 30 min before secretin infusion was initiated. PG was started 30 min after secretin infusion ($n = 9$). ▩, PG + Indo, pretreatment with indomethacin at 0·5 mg kg^{-1} h^{-1} for 2 h following a 1 mg kg^{-1} bolus injection, starting 60 min before PG infusion ($n = 8$). * $P < 0·05$, ** $P < 0·01$.

higher than that stimulated by pentagastrin alone ($P < 0·05$; Fig. 1). Also the percentage increase of acid output over basal values for the last 30 min during the infusion of pentagastrin in the presence of anti-somatostatin serum (755·4 ± 141·7%) was significantly higher than that with pentagastrin alone (372·0 ± 73·6%; $P < 0·05$).

Effect of indomethacin on basal and secretin-induced inhibition on gastric acid secretion

The infusion of indomethacin resulted in a gradual increase in the basal acid secretion starting 45 min after indomethacin infusion began (Fig. 3). The increase was statistically significant at 105 min. However, gastric acid output stimulated by indomethacin was significantly lower than that stimulated by pentagastrin ($P < 0·05$). When indomethacin was infused 30 min before the infusion of secretin was initiated, the pentagastrin-stimulated acid output gradually rose to 28·8 ± 3·0 μequiv (15 min)$^{-1}$ over a period of 30 min (Fig. 4). This value was significantly higher than the pentagastrin-stimulated acid output under the infusion of secretin (13·7 ± 1·8 μequiv (15 min)$^{-1}$; $P < 0·05$). However, it was not significantly different from that stimulated by pentagastrin alone (29·2 ± 3·7 μequiv (15 min)$^{-1}$). Figure 5 summarizes that net increase in the acid output stimulated by pentagastrin in the presence of secretin infusion (9·6 ± 8·9 μequiv h^{-1}) was significantly lower than that stimulated by pentagastrin alone (46·1 ± 5·8 μequiv (30 min)$^{-1}$; $P < 0·05$). However, when indomethacin was infused intravenously before secretin was given, the inhibition by secretin was completely reversed. The acid output (49·2 ± 7·2 μequiv (30 min)$^{-1}$) was not statistically different from that stimulated by both pentagastrin and indomethacin (40·5 ± 9·7 μequiv (30 min)$^{-1}$) or by pentagastrin alone (46·1 ± 5·8 μequiv (30 min)$^{-1}$; Fig. 5).

Effect of indomethacin and antisomatostatin serum on the inhibition by somatostatin or PGE_2 of gastric acid secretion

Intravenous infusion of PGE_2 significantly inhibited the pentagastrin-stimulated gastric acid secretion ($P < 0·01$) (Fig. 6). This inhibitory effect of PGE_2 on the acid secretion was not influenced by antisomatostatin serum. Likewise, indomethacin failed to influence the inhibition of acid secretion achieved by somatostatin (Fig. 6).

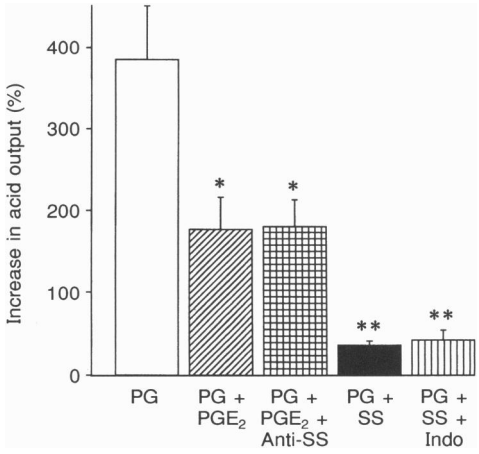

Figure 6. Effects of antisomatostatin serum and indomethacin on PGE_2- and somatostatin-induced inhibition of acid secretion stimulated by pentagastrin

Effects of antisomatostatin serum (Anti-SS) and indomethacin (Indo) on PGE_2 (40 μg kg^{-1} h^{-1})- and somatostatin (300 pmol kg^{-1} h^{-1})-induced inhibition of acid secretion stimulated by pentagastrin (PG). PG, I.V. at 0·3 μg kg^{-1} h^{-1} alone; $n = 10$. PG + PGE_2, I.V. PGE_2 at 40 μg kg^{-1} h^{-1} starting 30 min before PG infusion; $n = 5$. PG + PGE_2 + Anti-SS, I.V. Anti-SS (1 ml per rat bolus injection) followed by PGE_2 I.V., starting 30 min before PG infusion; $n = 5$. PG + SS, I.V. SS at 300 pmol kg^{-1} h^{-1}, starting 30 min before PG infusion; $n = 7$. PG + SS + Indo, I.V. indomethacin at 0·5 mg kg^{-1} h^{-1} for 2 h following a 1 mg kg^{-1} bolus injection, starting 30 min before SS infusion; $n = 7$. All data are expressed as percentage increase in acid output over basal value for last 30 min of each experiment. * $P < 0·05$, ** $P < 0·01$ compared with PG alone.

DISCUSSION

In the present study using conscious rats, a physiological dose of secretin (Lee *et al.* 1990; Rhee *et al.* 1991) significantly inhibited the gastric acid secretion stimulated by pentagastrin. This inhibition of the acid secretion was completely blocked by immunoneutralization of somatostatin with a rabbit antisomatostatin serum. This confirms the recent observation by Chung *et al.* (1994) in a totally isolated, perfused rat stomach. Moreover, I.V. injection of the antisomatostatin serum resulted in a significantly increased basal acid secretion, indicating that endogenous somatostatin exerts a tonic inhibitory effect on basal acid secretion. This tonic action of somatostatin appears to be operative also in the pentagastrin-stimulated state, since pentagastrin-stimulated acid secretion preceded by the antisomatostatin serum injection was significantly greater than the acid secretion stimulated by pentagastrin alone. The observation supports a previous study by Schubert, Edwards, Arimura & Makhlouf (1987) in an isolated, luminally perfused mouse stomach model. However, this phenomenon could not be observed in an isolated and vascularly perfused rat stomach model (Short, Doyle & Wolfe, 1985; Chung *et al.* 1994). Indomethacin also significantly increased basal acid secretion, although it took more than 1 h after indomethacin infusion began to exhibit the increase in the acid secretion. This delayed effect of indomethacin could be due to one of two reasons or a combination of both. First, it probably took at least 45 min or longer for the circulating indomethacin to reach its plateau level. We gave indomethacin in both bolus injection (1 mg kg^{-1}) and continuous I.V. (0·5 mg kg^{-1} h^{-1}). Second, since indomethacin inhibits synthesis of prostaglandin and does not influence storage and release of prostaglandins, the timing of its inhibitory effect was delayed. The inhibitory effect of secretin on the pentagastrin-stimulated acid secretion was completely reversed by indomethacin. Thus, the present study indicates that the inhibition by secretin of the pentagastrin-stimulated gastric acid secretion is mediated by both somatostatin and prostaglandins in conscious rats. Thus, the inhibitory action of secretin is mediated by local actions of two well-known chemical messengers, namely somatostatin and prostaglandins.

This inhibitory action by somatostatin on gastric acid secretion has been shown to involve three recognized mechanisms that include its direct suppression of acid secretion from gastric parietal cells (Park, Chiba & Yamada, 1987) and its direct action via its inhibitory effect on gastrin release from G-cells in antral mucosa (Bloom, Mortimer & Thorner, 1973; Hayes, Johnson, Koeker & Williams, 1975; Larsson, Goltermann, Demagistris, Rehfeld & Schwartz, 1979; Harty, Maico & McGuigan, 1981; Wolfe, Jain, Reel & McGuigan, 1984; Sugano, Park, Soll & Yamada, 1987). Wolfe *et al.* (1983) were the first to report that secretin inhibited carbachol-stimulated gastrin release in cultured rat antral mucosa, which was accompanied by elevation of somatostatin in the medium. Inclusion of somatostatin antibody in the culture medium abolished the capacity of secretin to inhibit carbachol-stimulated gastrin release. Furthermore, secretin was recently shown to stimulate the release of somatostatin from cultured human antral epithelial cells enriched for D cells (Buchan *et al.* 1993), and releases somatostatin from canine fundic D cell preparation (Chiba & Yamada, 1991). These *in vitro* studies suggest that the action of secretin to inhibit gastrin release is mediated, at least in part, locally through the release of antral somatostatin. Moreover, the inhibition by secretin of acid secretion is mediated by somatostatin released from D cells in gastric fundic mucosa. In the present study, peripheral venous plasma somatostatin-like immunoreactivity did not increase when secretin was given intravenously (data was not shown). The fact that a rabbit antisomatostatin serum abolished the inhibitory action of secretin on the pentagastrin-stimulated gastric acid secretion suggests that local somatostatin in the gastric mucosa is neutralized by the antiserum. It suggests that a physiological dose of secretin stimulates local release of somatostatin *in vivo*. Indeed, it has been reported recently that in a totally isolated, perfused rat stomach system, intra-arterial infusion of secretin significantly increased concentration of somatostatin in the portal venous effluent (Chung *et al.* 1994), which supports the concept that somatostatin is indeed released by secretin from the stomach.

We have also found that indomethacin, an inhibitor of prostaglandin synthesis, completely abolished the inhibitory effect of secretin on the pentagastrin-stimulated gastric acid secretion. The observation supports the report by Shiratori *et al.* (1993) that secretin in a physiological dose increased prostaglandin E_2 content of the gastric mucosa and indomethacin completely suppressed the inhibitory effect of secretin on gastric acid secretion in anaesthetized rats, which was accompanied by marked suppression of the increase in gastric mucosal prostaglandin content induced by secretin. It further supports our previous observation in rats (Rhee *et al.* 1991) that the effect of indomethacin on the inhibitory action of secretin was completely reversed by exogenous prostaglandin E_2. Recently, we have shown that secretin increased the concentration of prostaglandin E_2 in portal venous effluent which was markedly suppressed by indomethacin in a totally isolated, perfused rat stomach model (Chung *et al.* 1994). Furthermore, indomethacin and meclofenamate, another prostaglandin inhibitor, blocked the inhibitory effect of secretin on the gastric acid secretion stimulated by pentagastrin in dogs (Maclellan *et al.* 1988). These observations indicate that the inhibitory action of secretin is mediated by local releases of both somatostatin and prostaglandins.

The present study was extended further to determine a possible relationship between endogenous somatostatin and prostaglandins in the inhibitory mechanism by secretin of the acid secretion. Neither antisomatostatin serum nor indomethacin at the dose employed influenced prostaglandin E_2- or somatostatin-induced inhibition of acid secretion. This observation in our conscious rats is also in accord with our recent study using an isolated and perfused rat stomach model (Chung *et al.* 1994). However, it is at variance with the report by Ligumsky *et al.* (Ligumsky, Goto, Debas & Yamada, 1983) that in isolated perfused rat stomach, somatostatin enhanced prostaglandin synthesis and release in the presence of carbamylcholine, and the effect of somatostatin in inhibiting bethanechol-stimulated acid secretion was blocked by indomethacin. They suggested that the inhibitory action of somatostatin is mediated by prostaglandins. However, their observation was in contrast to the report that prostaglandin synthesis inhibition by indomethacin did not influence somatostatin-induced inhibition of either bethanechol-stimulated acid secretion in both conscious and anaesthetized rats (Mogard, Kauffman, Pehlevanian, Golanska, Elashoff & Walsh, 1985), or pentagastrin-stimulated gastric acid and pepsin secretion in conscious cats (Albinus, Gomez-Pan, Hirst & Shaw, 1985). Also, immunoneutralization of somatostatin did not suppress the inhibitory effect of prostaglandin E_2 on forskolin-stimulated gastrin release in canine antral mucosal cell culture (Schepp *et al.* 1994), indicating that inhibition by prostaglandin E_2 was not mediated by somatostatin.

From the present study in conscious rats, it is apparent that both antisomatostatin serum and indomethacin reverse the inhibition by secretin of pentagastrin-stimulated acid secretion and both augment basal acid secretion, whereas antisomatostatin serum also augments the pentagastrin-stimulated acid secretion. Somatostatin-induced inhibition of acid secretion is not mediated by local release of prostaglandins and prostaglandin E_2-induced inhibition is not mediated by endogenous somatostatin. The augmentation by antisomatostatin serum of basal acid secretion, as well as pentagastrin-stimulated acid secretion, suggests that somatostatin is an important tonic inhibitory hormone of gastric acid secretion in rats. The mechanism involved in this interesting phenomenon requires future studies.

It is concluded that in conscious rats, the inhibitory mechanism of secretin on gastric acid secretion is mediated independently by the release of both somatostatin and prostaglandins. Furthermore, endogenous somatostatin exerts a significant tonic inhibitory effect on both basal and pentagastrin-stimulated gastric acid secretion, while prostaglandins appear to be a tonic inhibitor in the basal acid secretory state.

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