J. Pharm. Pharmacol. 1990, 42: 685–688
Received March 31, 1990

α_2-Adrenoceptor-mediated Inhibitory and Excitatory Effects of Detomidine on Rat Gastric Acid Secretion

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Abstract—The effects of the selective α_2-adrenoceptor agonist detomidine on gastric acid secretion from pylorus-ligated and stomach-perfused rats have been investigated. In pylorus-ligated rats i.p. injection of detomidine markedly inhibited acid secretion, this effect being prevented by yohimbine or idazoxan. Under the same conditions, idazoxan significantly increased secretion in a dose-independent fashion. In non-vagotomized and vagotomized stomach-perfused rats i.p. detomidine stimulated acid secretion: this excitatory effect was antagonized by idazoxan. The present results suggest that both inhibitory and excitatory gastric secretory effects of detomidine are mediated by α_2-adrenoceptors on cholinergic and adrenergic nerves, respectively. The stimulant activity of idazoxan on gastric secretion from pylorus-ligated rats may be interpreted in terms of increased excitatory vagal tone following the blockade of inhibitory α_2-adrenoceptors.

Several lines of evidence demonstrate that the activation of presynaptic α_2-adrenoceptors on the vagus nerve both at central and peripheral sites inhibits gastric acid secretion (Jennewein 1977; Cheng et al 1981; Del Tacca et al 1982; Nakadate et al 1982; Pascaud et al 1983). However, in those studies the most commonly used α_2-adrenoceptor agonists and antagonists were the imidazole derivatives clonidine, xylazine and tolazoline, which also possess a potent stimulant secretory effect on various pharmacological preparations, because of their histamine-like activity on peripheral H_2-receptors (Del Tacca et al 1982; Bernardini et al 1986). The lack of specificity of α_2-adrenoceptor agonists and antagonists has made it difficult to fully elucidate the mechanisms and pathways by which α_2-adrenoceptors could affect gastric acid secretion.

The present study set out to investigate the secretory effects of the imidazole derivatives detomidine and idazoxan which are respectively a selective α_2-adrenoceptor agonist and antagonist without affinity for H_2-receptors (Doxey et al 1983; Virtanen & MacDonald 1985; Virtanen & Nyman 1985).

Materials and Methods

Pylorus-ligated rats

Male Wistar rats, 220 g, fasted for 24 h, were prepared in accordance with the method of Shay et al (1954), the pylorus being tied under light ether anaesthesia and the animals allowed to recover. The rats received drugs intraperitoneally and were allowed to rest for 3 h after which they were killed, the cardias ligated and the whole stomach removed. The accumulated gastric juice was collected and centrifuged at 3000 rev min^{-1}. Samples with more than 0·5 mL of sediment were discarded. After the volume of supernatant had been measured, the acidity was determined by an automatic potentiometric titration to pH 7 with 0·01 M NaOH.

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Stomach-perfused rats

The stomachs of male Wistar rats, 220 g, fasted for 24 h, were continuously perfused in-situ according to Ghosh & Schild (1958). The rats were anaesthetized with urethane (1·2 g kg^{-1} i.p.), the trachea was cannulated, and a polyethylene catheter introduced into the oesophagus and advanced 5 mm beyond the gastro-oesophageal junction. A second catheter was introduced into the duodenum and pushed forward until its tip was about 5 mm beyond the pylorus. The stomach was then perfused continuously with 154 mM NaCl solution at 37°C, at a rate of 1 mL min^{-1} the effluent being collected for 3 h. Rectal temperature was monitored and body temperature maintained between 37 and 39°C with an infrared lamp.

Additional experiments were performed on rats in which the vagus nerves were separated from the carotid arteries and cut at the cervical portion (Yokotani et al 1988).

After stabilization for 30 min, the stomach-perfused rats were given the drugs intraperitoneally. Titration of gastric juice was as described above.

Drugs

The drugs used were: detomidine hydrochloride (Farmos Group Ltd, Turku, Finland); yohimbine hydrochloride (Lirca, Milan, Italy); idazoxan (Reckitt and Colman, Hull, UK), urethane ethyl carbamate (Sigma Chemicals Co., St Louis, MO).

Statistical analysis

Results are given as means ± s.e.m. The significance of differences was evaluated by Student's *t*-test for unpaired data and $P < 0.05$ values were considered significant; n indicates the number of animals.

Results

Pylorus-ligated rats

In conscious pylorus-ligated rats, detomidine (0·01, 0·03 and 0·1 mg kg^{-1} i.p.; n = 10 per dose) caused a marked dose-dependent inhibition of the secretory volume and acidity, the maximum effect being observed at 0·1 mg kg^{-1} (Fig. 1).

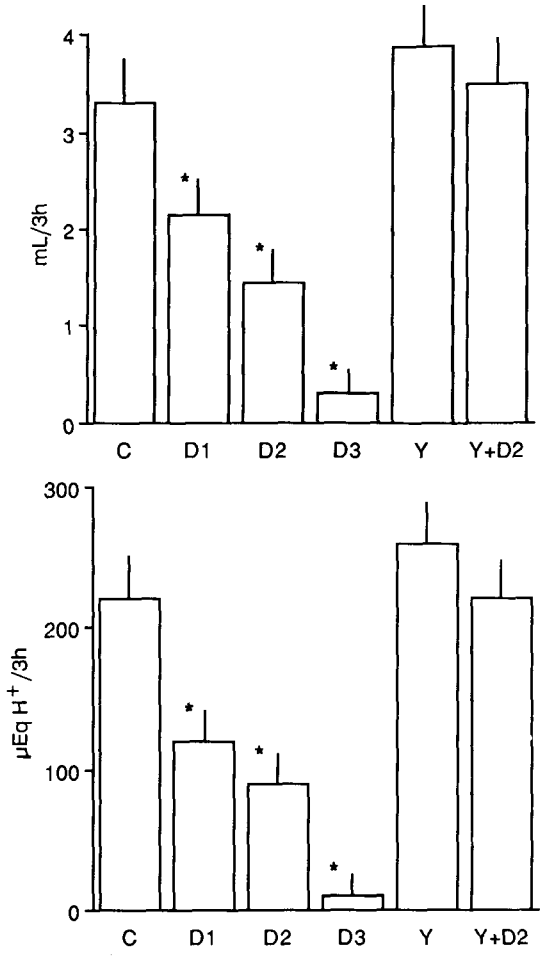

FIG. 1. Pylorus-ligated rats. Effects of i.p. administration of detomidine 0·01 (D1), 0·03 (D2), 0·1 (D3) mg kg^{-1}, yohimbine 5 mg kg^{-1} (Y), and yohimbine 5 mg kg^{-1} plus detomidine 0·03 mg kg^{-1} (Y + D2) on gastric secretion: total volume (mL/3h) and acid output (μequiv H^+/3 h). Columns indicate the mean values obtained from 6 to 10 animals ± s.e.m. (vertical lines). *$P < 0.05$, compared with control (C).

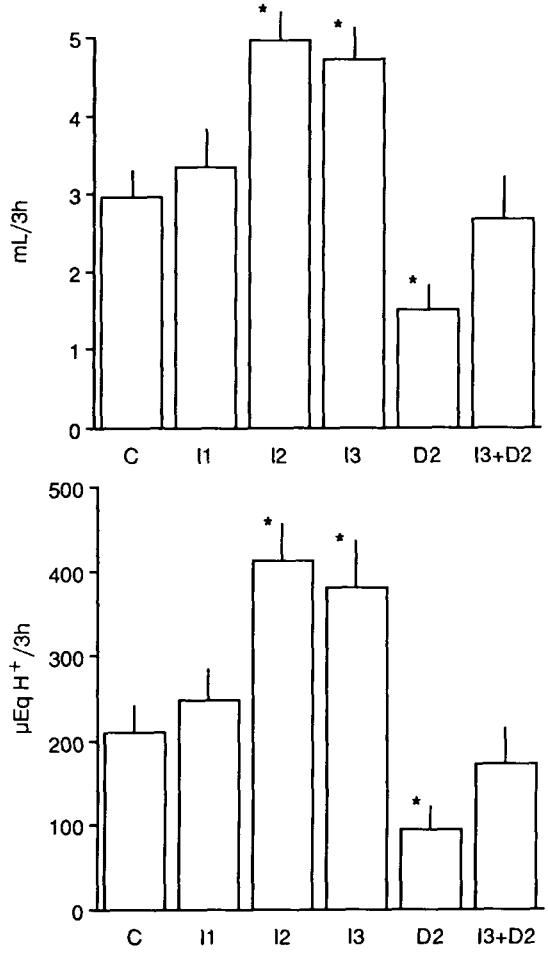

FIG. 2. Pylorus-ligated rats. Effects of i.p. administration of idazoxan 0·01 (I1), 0·03 (I2), 0·1 (I3) mg kg^{-1}, detomidine 0·03 mg kg^{-1} (D2), and idazoxan 0·1 mg kg^{-1} plus detomidine 0·03 mg kg^{-1} (I3 + D2) on gastric secretion: total volume (mL/3 h) and acid output (μequiv H^+/3 h). Columns indicate the mean values obtained from 6 to 10 animals ± s.e.m. (vertical lines). *$P < 0.05$, compared with control (C).

Yohimbine (0·1 to 5 mg kg^{-1} i.p.; n = 6 per dose) did not modify acid secretion, but at 5 mg kg^{-1} i.p. prevented the inhibitory effect of detomidine (n = 10; Fig. 1).

Idazoxan (0·1 mg kg^{-1} i.p.; n = 10) antagonized the inhibitory response of detomidine (Fig. 2). Furthermore, idazoxan at 0·01 mg kg^{-1} (i.p.; n = 6) was without effect, whereas 0·03 and 0·1 mg kg^{-1} i.p. (n = 8 per dose) significantly, but not dose-dependently, increased gastric secretory volume and acid output (Fig. 2).

Stomach-perfused rats

Detomidine 0·2, 1 and 5 mg kg^{-1} (i.p.; n = 10 per dose) produced a significant dose-dependent increase in gastric acid secretion in both non-vagotomized and vagotomized rats, the maximum effect occurring at 1 mg kg^{-1} (Fig. 3). Under the same conditions, idazoxan 3 mg kg^{-1} (i.p.; n = 6) did not affect acid secretion, but prevented the excitatory effect of detomidine (n = 10; Fig. 3).

Discussion

Evidence has been provided for the inhibitory action exerted on acid secretion by several α_2-agonists through the activation of presynaptic α_2-adrenoceptors on the vagus nerve both at central and peripheral sites (Del Tacca et al 1982; Pascaud et al 1983; Bernardini et al 1986; Savola et al 1989). In the present study, the selectivity of the α_2-adrenoceptor agonist detomidine indicated the existence of an additional α_2-mediated excitatory influence on gastric secretion, while confirming the α_2-mediated inhibitory influence on acid secretion.

In pylorus-ligated rats, detomidine induced a marked acid inhibitory response which was antagonized by yohimbine or idazoxan, both acting as antagonists at α_2-adrenoceptor sites (Ruffolo et al 1981; Doxey et al 1983). Although no data have been available on the effects of detomidine on acid secretion in rats, a similar inhibitory action was observed for detomidine in dogs (Soldani et al 1987). In the present experiments,

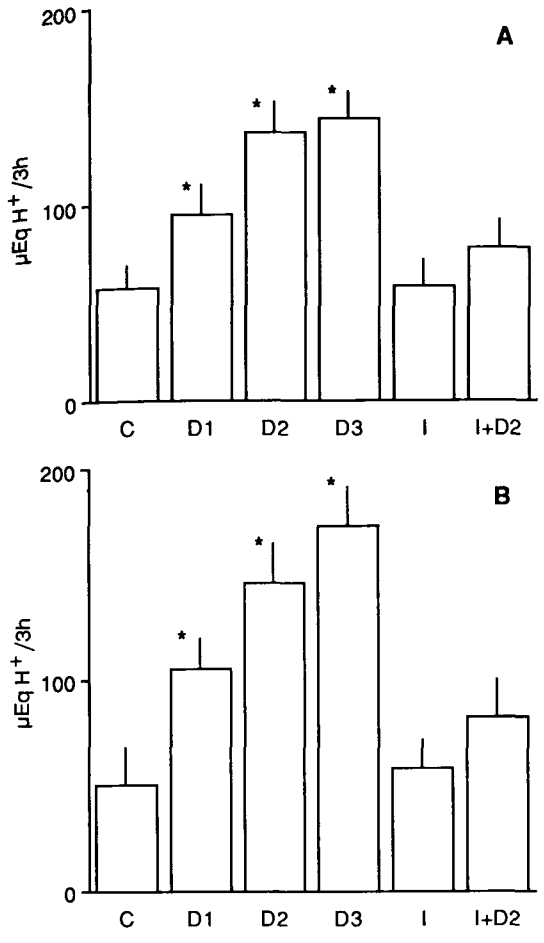

FIG. 3. Non-vagotomized (A) and vagotomized (B) stomach perfused rats. Effects of i.p. administration of detomidine 0·2 (D1), 1 (D2), 5 (D3) mg kg^{-1}, idazoxan 3 mg kg^{-1} (I), and idazoxan 3 mg kg^{-1} plus detomidine 1 mg kg^{-1} (I+D2) on gastric acid secretion (μequiv H^+/3 h). Columns indicate the mean values obtained from 6 to 10 animals ± s.e.m. (vertical lines). *$P < 0.05$, compared with control (C).

the dose of detomidine that induced the maximal inhibitory effect on gastric secretion was about one fifth on a molar basis of that found for clonidine by Bernardini et al (1986), thereby providing further evidence for the high potency of detomidine at α_2-adrenoceptor sites.

The stimulant activity of idazoxan in pylorus-ligated rats, in which gastric hypersecretion is evoked by central excitatory cholinergic mechanisms (Sharma et al 1963), may be interpreted as an increased excitatory vagal tone caused by the blockade of α_2-adrenoceptors. This effect confirms a tonic inhibitory influence on vagally stimulated acid secretion via adrenergic pathways (Yokotani et al 1984). The lack of acid stimulant effects of idazoxan in stomach-perfused rats, in which vagal tone is markedly depressed by anaesthesia (Maggi & Meli 1986; Del Tacca et al 1990), further supports this view. On the other hand, despite its imidazoline-based structure, idazoxan, unlike tolazoline (Bernardini et al 1986), does not stimulate acid secretion through the activation of H_2-receptors. In support of this view, idazoxan displayed low affinity towards H_2-receptors in both in-vivo and in-vitro experiments (Doxey et al 1983). Finally, the present data show that the hypersecretory effect of idazoxan was not dose-dependent, suggesting that additional mechanisms other than α_2-adrenoceptor blockade may be involved. The failure of yohimbine to increase gastric secretion under the same experimental conditions might result from the simultaneous α_2-antagonist and atropine-like effects of the drug (Andrejak et al 1980; Del Tacca et al 1988).

The gastric stimulant effect of detomidine in stomach perfused rats provides new evidence for the involvement of α_2-adrenoceptors on adrenergic nerve pathways in the regulation of gastric secretion.

A sympathetic α_2-adrenoceptor-mediated pathway has been postulated to participate in the control of gastric secretion (Yokotani et al 1984). Spriggs (1965) showed that urethane anaesthesia induces activation of the rat sympathetic nervous system, an effect which might exert an inhibitory action on acid secretion. Under urethane anaesthesia, detomidine caused a dose-dependent increase in basal acid secretion in both non-vagotomized and vagotomized rats. This excitatory effect was prevented by idazoxan, suggesting that the stimulant action of detomidine is mediated through α_2-adrenoceptors. In a previous study yohimbine was shown to directly increase acid secretion in stomach-perfused rats, an effect associated with its central cholinergic stimulant action (Bernardini et al 1986); therefore yohimbine was not used to investigate the possible involvement of α_2-adrenoceptors in the present acid secretory effect of detomidine.

In summary, it may be concluded that the dual action of detomidine on acid secretion might be mediated by regulation of cholinergic and adrenergic neurotransmission by α_2-adrenoceptors. The new data on excitatory responses by detomidine support the notion of an inhibitory influence of catecholamines on basal acid secretion.

Acknowledgements

The experiments were performed with the technical assistance and collaboration of Mr Bruno Stacchini. Grants from Italian Ministry of University and Scientific Research (40 + 60% funds).

References

Andrejak, M., Pommier, Y., Mouillé, P., Schmitt, H. (1980) Effects of some alpha-adrenoceptor agonists and antagonists on the guinea-pig ileum. Naunyn-Schmiedeberg's Arch. Pharmacol. 314: 83–87

Bernardini, C., Del Tacca, M., Soldani, G., Martinotti, E. (1986) The effects of alpha-2 agonists and antagonists on gastric acid secretion. Arch. Int. Pharmacodyn. 281: 134–144

Cheng, H. C., Gleason, E. M., Nathan, B. A., Lachmann, P. J., Woodward, J. K. (1981) Effects of clonidine on gastric acid secretion in the rat. J. Pharmacol. Exp. Ther. 217: 121–126

Del Tacca, M., Soldani, G., Bernardini, C., Martinotti, E., Impicciatore, M. (1982) Pharmacological studies on the mechanisms underlying the inhibitory and excitatory effects of clonidine on gastric acid secretion. Eur. J. Pharmacol. 81: 255–261

Del Tacca, M., Tadini, P., Blandizzi, C., Bernardini, M. C. (1988) Excitatory and inhibitory effects of yohimbine on isolated guinea-pig small intestine. Pharmacol. Res. Commun. 20: 673–684

Del Tacca, M., Blandizzi, C., Bernardini, M. C. (1990) Central GABA-A excitatory and GABA-B inhibitory receptors regulate gastric acid secretion in rats. Eur. J. Pharmacol. 177: 189–194

Doxey, J. C., Roach, A. G., Smith, C. F. C. (1983) Studies on RX 781094: a selective, potent and specific antagonist of alpha-2 adrenoceptors. Br. J. Pharmacol. 78: 489–505

Ghosh, M. N., Schild, H. O. (1958) Continuous recording of acid gastric secretion in the rat. Ibid. 13: 54–61

Jennewein, H. M. (1977) The effect of clonidine on gastric acid secretion in rats and dogs. Naunyn-Schmiedeberg's Arch. Pharmacol. 297: 85–90

Maggi, C. A., Meli, A. (1986) Suitability of urethane anaesthesia for physiopharmacological investigation in various systems. Part 3: Other systems and conclusions. Experientia 42: 531–537

Nakadate, T., Nakaki, T., Muraki, T., Kato, R. (1982) Inhibitory alpha-2 adrenergic mechanisms regulating gastric secretion in pylorus-ligated rats. Naunyn-Schmiedeberg's Arch. Pharmacol. 320: 170–174

Pascaud, X., Roger, A., Genton, M., Roze, C. (1983) Further support for the central origin of the gastric antisecretory properties of clonidine in conscious rats. Eur. J. Pharmacol. 86: 247–257

Ruffolo, R. R., Waddell, J. E., Yaden, E. L. (1981) Postsynaptic alpha-adrenergic receptor subtypes differentiated by yohimbine in tissues from rat. Existence of alpha-2 adrenergic receptors in rat aorta. J. Pharmacol. Exp. Ther. 217: 235–240

Savola, M., Savola, J. M., Puurunen, J. (1989) Alpha-2 adrenoceptor-mediated inhibition of gastric acid secretion by medetomidine is efficiently antagonized by atipamezole in rats. Arch. Int. Pharmacodyn. 301: 267–276

Sharma, K. H., Dua, S., Anand, B. K. (1963) Effects of hypothalamic lesions on experimental gastric ulceration in rats. Ind. J. Med. Res. 51: 705–715

Shay, Y., Sun, D., Gruenstein, M. (1954) A quantitative method for measuring spontaneous gastric secretion in the rat. Gastroenterology 26: 906–913

Soldani, G., Mengozzi, G., Intorre, L. (1987) Inhibition of gastric acid secretion in dogs by detomidine. J. Vet. Pharmacol. Ther. 10: 266–268

Spriggs, T. L. B. (1965) The effect of anaesthesia induced by urethane or phenobarbitone upon the distribution of peripheral catecholamines in rats. Br. J. Pharmacol. 24: 752–758

Virtanen, R., MacDonald, E. (1985) Comparison of the effects of detomidine and xylazine on some alpha-2 adrenoceptor-mediated responses in the central and peripheral nervous systems. Eur. J. Pharmacol. 115: 277–284

Virtanen, R., Nyman, L. (1985) Evaluation of the alpha-1 and alpha-2 adrenoceptor effects of detomidine, a novel veterinary sedative analgesic. Ibid. 108: 163–169

Yokotani, K., Muramatsu, I., Fujiwara, M. (1984) Alpha-1 and alpha-2 type adrenoceptors involved in the inhibitory effect of splanchnic nerves on parasympathetically stimulated gastric acid secretion in rats. J. Pharmacol. Exp. Ther. 229: 305–310

Yokotani, K., Okuma, Y., Osumi, Y. (1988) Alpha-2 adrenoceptor-mediated inhibition of vagally induced gastric acid secretion with the anti-ulcer agent DQ-2511. Jpn. J. Pharmacol. 48: 299–302