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Involvement of central K_{ATP} channels in the gastric antisecretory action of α_2-adrenoceptor agonists and β-endorphin in rats

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Abstract

The intracerebroventricularly (i.c.v.) injected presynaptic α_2-adrenoceptor agonists, clonidine and oxymetazoline, exerted a dose-dependent inhibition on the gastric acid secretion in pylorus-ligated rats; the ED_{50} values were 20 and 7.5 nmol/rat, respectively. Moreover, β-endorphin, given i.c.v., also decreased acid secretion ($ED_{50} = 0.25$ nmol/rat i.c.v.). The antisecretory effect of these compounds was highly reduced by glibenclamide (10 nmol/rat i.c.v.), a selective blocker of K_{ATP} channels. These results suggest that K_{ATP} channels in the central nervous system are likely to be involved in the centrally initiated antisecretory action of both α_2-adrenoceptor agonists and β-endorphin.

Keywords: Gastric acid secretion; Clonidine; Oxymetazoline; β-endorphin; Glibenclamide

1. Introduction

It is well documented that α_2-adrenoceptors that are presynaptically located at the cholinergic nerve terminals are involved in the regulation of gastric acid secretion as well as in mucosal defense mechanisms (Bhandare et al., 1991; Blandizzi et al., 1995; Brodie and Hooke, 1971; Del Soldato, 1986; Del Tacca et al., 1982; Gyires et al., 1996; Soldani et al., 1984; Jennewein, 1977; Kaess and von Mikuliez-Rodecki, 1971; Tazi-Saad et al., 1992). However, much less has been known on the precious role of central α_2-adrenoceptors in the regulation of gastric acid secretion. Nakadate et al. (1982) found that administration of different α_2-adrenoceptor agonists intracerebroventricularly (i.c.v.) exerted antisecretory action in pylorus-ligated rats. Recently, we demonstrated that activation of central α_2-adrenoceptors induced antisecretory (Müllner et al., 2001) as well as gastroprotective effects (Gyires et al., 2000a,b,c). Both actions could be antagonised by the opioid receptor antagonist naloxone, indicating the involvement of opioid components in the centrally initiated antisecretory and gastroprotective effects of α_2-adrenoceptor stimulants.

Opioids are also supposed to be involved in the regulation of acid secretion. However, data of the literature are rather contradictory. For example, morphine was demonstrated to have a dual effect on gastric acid secretion in various experimental models in rats, low doses have increased while higher doses have decreased gastric acid secretion (Del Tacca et al., 1989). Both stimulatory and inhibitory effects of opioids were also described in humans (Feldman et al., 1980). Other pharmacological studies showed that the δ-opioid receptor agonist [Met^5]-enkephalin has been reduced, while stimulation of μ-opioid receptors augmented the 2-deoxy-D-glucose-induced vagal stimulation of gastric acid secretion in conscious dogs with chronic gastric fistula (Anderson et al., 1982). In contrast, Improta and Broccardo (1994) reported that stimulation of the central μ-opioid receptors inhibited gastric acid secretion, but δ-opioid receptors have no influence on gastric secretion in pylorus-ligated rats. β-Endorphin, ligand of both μ- and δ-opioid receptors, inhibited the gastric acid secretion in conscious dogs and rats (Lenz et al., 1986; Roze et al., 1980).

Many studies have demonstrated a relationship between α_2-adrenoceptor and opioid receptor-mediated actions. Opioid receptor antagonists are known to antagonize, e.g. central antinociceptive (Bentley et al., 1983), antihypertensive (Van Giersbergen and De Jong, 1987; Farsang and Kunos, 1979), gastroprotective (Gyires et al., 2000b,c), and antisecretory actions (Müllner et al., 2001) of α_2-adrenoceptor stimulants.

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Table 1
The effect of i.c.v. injected clonidine, oxymetazoline and β-endorphin on the gastric acid secretion in pylorus-ligated rats ($n=7$)

Compound	Dose (nmol/rat i.c.v.)	Gastric volume (ml) (mean ± S.E.M.)	Total acid output (μEq/4 h) (mean ± S.E.M.)
Saline	–	6.23 ± 0.25	392.58 ± 38.43
Clonidine	11.25	4.48 ± 0.16[a]	292.83 ± 20.98
	23.5	2.58 ± 0.1[a]	95.54 ± 8.86[a]
	47.0	1.21 ± 0.09[a]	55.38 ± 7.91[a]
Saline	–	6.20 ± 0.13	450.78 ± 24.27
Oxymetazoline	8.4	3.16 ± 0.45[b]	193.69 ± 22.35[b]
	16.8	2.14 ± 0.22[a]	93.73 ± 25.14[a]
	67.5	1.54 ± 0.22[a]	62.86 ± 13.79[a]
	168.9	1.51 ± 0.11[a]	55.49 ± 10.04[a]
Saline	–	6.73 ± 0.12	488.79 ± 44.79
β-Endorphin	0.1	5.83 ± 0.24	464.02 ± 26.06
	0.2	5.62 ± 0.09	372.68 ± 16.87
	1.0	2.51 ± 0.13[a]	114.00 ± 14.95[a]
	2.0	2.97 ± 0.27[a]	272.64 ± 39.29[b]

[a] $P<0.01$.
[b] $P<0.05$.

The purpose of the present experiments was to analyse the role of the α_2-adrenoceptor and opioid receptor agonists in the regulation of gastric acid secretion. Moreover, since K_{ATP} channels were involved in different actions of opioid receptor and α_2-adrenoceptor stimulants by hyperpolarizing the neurons (North and Surprenant, 1985; North et al., 1987), we aimed to investigate whether K_{ATP} channels in the central nervous system would participate in the centrally initiated antisecretory effects of α_2-adrenoceptor agonists and β-endorphin.

2. Materials and methods

2.1. Animals

The experiments were carried out on male, outbreed Wistar rats (weight range: 160–180 g), each group containing seven animals. They were kept on a 12-h light–dark cycle and under condition of controlled temperature (22 ± 1 °C). The animals were deprived of food for 24 h (to avoid the effect of feeding on gastric acid secretion), but free access to water was allowed up to 2 h before the experiment. During fasting, the animals were placed in raised, mesh-bottom cages to prevent coprophagy.

2.2. Methods

The pylorus ligation was carried out under light ether anaesthesia (Shay et al., 1954). The different test com-

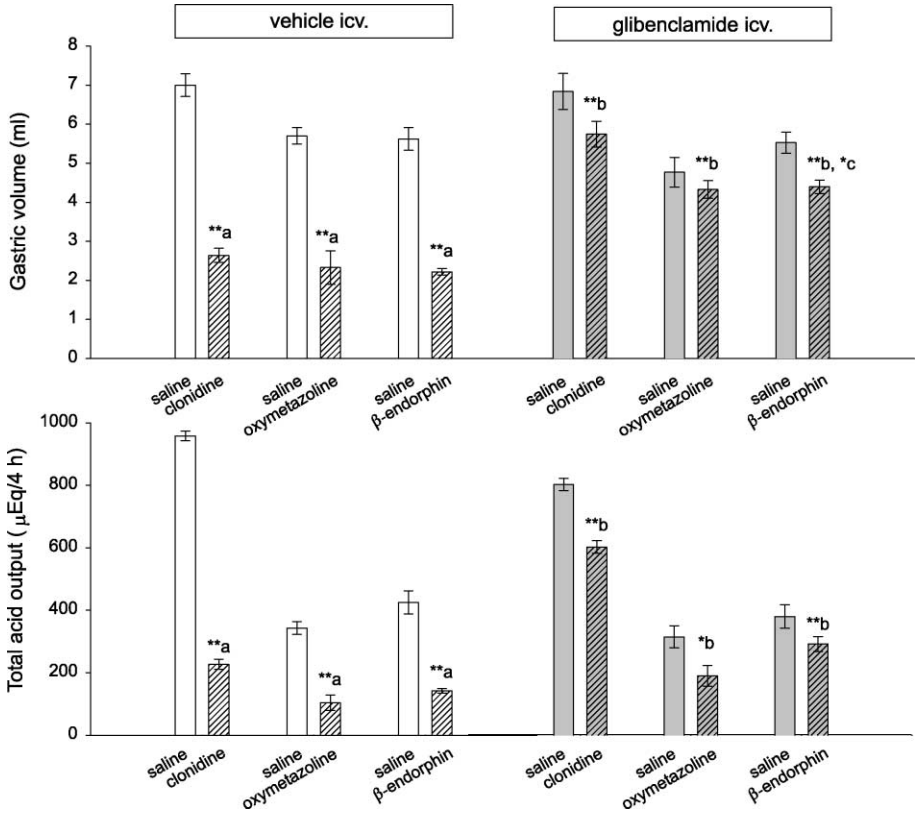

Fig. 1. The effect of glibenclamide (10 nmol/rat i.c.v.) on the antisecretory action of clonidine (47 nmol/rat i.c.v.), oxymetazoline (16.8 nmol/rat i.c.v.), and β-endorphin (1 nmol/rat i.c.v.) ($n=7$). Upper panel: the effect of the substances on the volume of gastric juice; lower panel: the action of the drugs on the total acid output. Bars represent means ± S.E.M. $*P<0.05$, $**P<0.01$; (a) compared with saline-vehicle control group, (b) compared with the same drug in vehicle-treated group, (c) compared with saline-glibenclamide group.

pounds were intracerebroventricularly (i.c.v.) injected according to Noble et al. (1967) in the volume of 10 μl 10 min after pylorus ligation. After 4 h, the animals were sacrificed by overdose of ether, the stomachs were removed; the gastric juice was collected, and centrifuged to remove residual debris. The gastric volume was measured, and the samples were analysed for gastric acidity by titration with 0.1 N sodium hydroxide to pH 7.0 in a TTT85 Titrator (Radiometer, Copenhagen). The results were expressed as gastric volume (in ml), and total acid output (in μEq/4 h).

2.3. Materials

The compounds used in the present study were obtained from the following sources: clonidine HCl, glibenclamide, and β-endorphin (Sigma, USA), oxymetazoline (RBI Natick, USA). The compounds for i.c.v. administration were dissolved in saline with the exception of glibenclamide which was dissolved in 5% Tween 80/saline. Control animals received the drug solvent.

2.4. Statistical analysis

Results are presented as means ± S.E.M. The significance of differences was evaluated by analysis of variance (ANOVA) followed by Tukey test for multiple comparison. A probability of $P < 0.05$ was considered statistically significant.

3. Results

3.1. The effect of clonidine, oxymetazoline, and β-endorphin on the gastric acid secretion in pylorus ligated rats

Clonidine (11.25, 23.5, 47 nmol/rat i.c.v.), oxymetazoline (8.4, 16.8, 67.5, 168.9 nmol/rat i.c.v.), and β-endorphin (0.1, 0.2, 1, and 2 nmol/rat i.c.v.) exerted a dose-dependent inhibition on the gastric acid secretion. The ED_{50} values of clonidine, oxymetazoline, and β-endorphin were 20, 7.5, and 0.25 nmol/rat i.c.v., respectively (Table 1).

3.2. The action of i.c.v. injected glibenclamide on the antisecretory effect of clonidine, oxymetazoline, and β-endorphin in pylorus-ligated rats

Clonidine (47 nmol/rat i.c.v.) reduced both the volume and the total acid output of gastric juice in a highly significant manner (the total acid output was unusually high in the daily control-saline-treated-group (first column, lower panel), this did not affect the antisecretory activity of clonidine). Similarly, both oxymetazoline (16.8 nmol/rat i.c.v) and β-endorphin (1 nmol/rat i.c.v.) reduced the gastric acid secretion significantly. When the rats were pretreated with the K_{ATP}^+ channel blocker glibenclamide (10 nmol/rat i.c.v.), the antisecretory effect of clonidine and oxymetazoline, as well as that of β-endorphin, was antagonized (Fig. 1).

4. Discussion

Data of the literature show that the non-selective α_2-adrenoceptor agonist clonidine, injected subcutaneously, exerts a dose-dependent antisecretory effect in pylorus-ligated rats. (Cheng et al., 1981; Kuchandy et al., 1985; Gyires et al., 1996; Nakadate et al., 1982). However, the inhibitory effect of clonidine is only partly due to the action of α_2-adrenoceptors on the presynaptic vagal fibers in the stomach. It was supposed that central components also might be involved in the gastric antisecretory response of clonidine. Nevertheless, the effective doses of clonidine, given either intracerebroventricularly or intracistenally, was similar to that injected subcuteaneously (Pascaud and Roger, 1976; Pascaud et al., 1982). Consequently, the central and peripheral action cannot be distinguished on the basis of these results.

Our present experimental data showed that the α_2-adrenoceptor agonist clonidine ($ED_{50} = 20$ nmol/rat) and the α_{2A}-adrenoceptor subtype selective oxymetazoline ($ED_{50} = 7.5$ nmol/rat), injected i.c.v., inhibited the gastric acid secretion in a dose-dependent manner in pylorus-ligated rats. These results suggest that—in contrast with the gastroprotective effect, where central α_{2B}-adrenoceptor subtype is supposed to mediate mucosal protection (Gyires et al., 2000b)—the antisecretory action may be due to the activation of central α_{2A}-type adrenoceptors (Blandizzi et al., 1995). The intracerebroventricularly effective doses of these α_2-adrenoceptor stimulants, given subcutaneously, failed to affect the acid secretion indicating that the antisecretory effect was not due to the leakage of the substances to the periphery but to the activation of central α_2-adrenoceptors.

Moreover, we found (Müllner et al., 2001) that the antisecretory effects of clonidine and oxymetazoline were blocked by the opioid receptor antagonists naloxone and naltrindole, indicating the involvement of endogenous opioids in the antisecretory action of α_2-adrenoceptor agonists. On the other hand, data of the literature suggested that β-endorphin—equipotent at μ- and δ-opioid receptors (Akil et al., 1981)—may be involved in the antihypertensive and gastroprotective effects of clonidine (Farsang and Kunos, 1979; Ramirez-Gonzales et al., 1983; Van Giersbergen and De Jong, 1987; Gyires et al., 2000c). This prompted us to examine the effect of β-endorphin on the gastric acid secretion.

β-Endorphin was found to decrease the total acid output in pylorus-ligated rats; the ED_{50} value was 0.25 nmol/rat i.c.v. (Table 1). β-Endorphin, injected into the third ventricle, inhibited the basal gastric acid secretion also in rats with gastric fistula (Roze et al., 1980). Moreover, i.c.v. administration of β-endorphin was reported to decrease the pentagastrin and meal-stimulated gastric acid secretion in

conscious dogs, an action which was completely abolished by truncal vagotomy (Lenz et al., 1986).

μ-Opioid receptor and α_2-adrenoceptor stimulants were shown to hyperpolarize neurones by increasing K^+ conductance, evoking inhibitory postsynaptic potential (North et al., 1987). In accordance with these findings, the antinociceptive effect of morphine was antagonised by K_{ATP} channel blocker sulfonylureas (Ocana et al., 1990; Narita et al., 1992; Raffa and Martinez, 1995; Lohmann and Welch, 1999). Moreover, K_{ATP} channels are likely to play an important role as indirect modulators of the supraspinal analgesia induced by μ-opiod receptor agonists, since the analgesic activity and the activation of the descending noradrenaline system induced by i.c.v. injected morphine was antagonised by i.c.v. administrated glibenclamide (Narita et al., 1992). Selective agonists for μ-opioid receptors increased the conductance of K^+ channels in rat nucleus locus coeruleus (North et al., 1987) and substantia gelatinosa (Yoshimura and North, 1983). K_{ATP} channels were also suggested to be involved in the gastroprotective effect of morphine against ethanol-induced mucosal damage (Bhonsule et al., 1992). Furthermore, stimulants of δ-opioid receptors augmented the conductance of inwardly rectifying potassium channels and hyperpolarized the membrane in submucosus plexus of guinea pig (North et al., 1987).

Besides the opioids, K_{ATP} channels may also mediate the effects of α_2-adrenoceptor agonists. For example, α_2-adrenoceptors are coupled to K^+ channels, and α_2-adrenoceptor stimulants increased potassium conductance in guinea pig submucosus plexus (North and Surprenant, 1985), in rat locus coeruleus (Williams et al., 1985), and in substantia gelatinosa (North and Yoshimura, 1984). In addition, the clonidine-induced antinociceptive effect was decreased by different K_{ATP} channel blocker sulfonylureas, while the administration of K_{ATP} channel opener minoxidil and diazoxide potentiated the antinociception exerted by clonidine. These results indicate that K_{ATP} channels represent an important step in the transduction mechanism of central antinociception induced by the activation of α_2-adrenoceptors (Ocana and Baeyens, 1993; Raffa and Martinez, 1995; Galeotti et al., 1999).

On the basis of these data, we aimed to examine whether the central K_{ATP} channels are involved in the antisecretory effects of α_2-adrenoceptor and opioid receptor agonists by using glibenclamide which blocks selective K_{ATP} channels. High affinity binding sites for glibenclamide have been found in brain, pancreatic beta cells, and cardiovascular system (Castle et al., 1989).

Our recent findings suggest that K_{ATP} channels might be involved in the antisecretory action of α_2-adrenoceptor and opioid receptor stimulants since i.c.v. injection of glibenclamide significantly reduced the gastric antisecretory effect of clonidine, oxymetazoline, as well as that of β-endorphin. This assumption is highly supported by our very recent findings, which showed that diazoxide, an opener of K_{ATP} channels, induced antisecretory effect in the doses of 43 and 86 nmol/rat i.c.v. (Gyires, unpublished observation).

Data of the literature provided the evidence of interactions between α_2- and opioid systems (Bentley et al., 1983; Farsang and Kunos, 1979; Van Giersbergen and De Jong, 1987) and the induction of β-endorphin release by α_2-adrenoceptor stimulants (Ramirez-Gonzales et al., 1983; Gyires et al., 2000c). Therefore, the question remains to be clarified whether the increased potassium conductance is due to the direct action, of α_2-receptors on the K_{ATP} channels, or to an indirect action, by initiating the release of β-endorphin. Namely, according to the data of the literature, both α_2-adrenoceptors and opioid receptors can directly be coupled to membrane potassium channels through the intermediary action of guanine nucleotide-binding regulatory protein (North et al., 1987; Miyake et al., 1989).

In summary, the blockade of K_{ATP} channels by glibenclamide inhibited the antisecretory effect of α_2-adrenoceptor agonists and β-endorphin in a significant manner. This finding may suggest that the centrally initiated antisecretory action of the α_2-agonist clonidine and oxymetazoline, as well as that of β-endorphin, may involve K_{ATP} channel-dependent effector mechanisms in pylorus-ligated rats.

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