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Biochemical and Pharmacological Characteristics of a Newly Synthesized H^+/K^+-ATPase Inhibitor, YJA20379-8, 3-Butyryl-4-[*R*-1-methylbenzylamino]-8-ethoxy-1,7-naphthyridine, in pigs and rats

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Abstract

We have investigated the effect of the newly synthesized proton-pump inhibitor YJA20379-8, 3-butyryl-4-[*R*-1-methylbenzylamino]-8-ethoxy-1,7-naphthyridine, on gastric mucosal proton pump (H^+/K^+-ATPase) activity, gastric acid secretion and gastric lesions in experimental animals.

In lyophilized pig gastric microsomes, YJA20379-8 was shown to inhibit H^+/K^+-ATPase activity; the inhibitory effect was not affected by pH, the IC50 (dose resulting in 50% inhibition) being 28·0 μM and 30·0 μM at pH 6·4 and pH 7·4, respectively. The effect was fully reversed by dilution and subsequent washing of the incubation mixtures of H^+/K^+-ATPase and YJA20379-8, suggesting the reversible nature of the enzyme inhibition. In pylorus-ligated rats, YJA20379-8 administered by different routes (intraduodenal, subcutaneous, intravenous or oral) resulted in dose-dependent suppression of basal gastric acid secretion. The duration of antisecretory action of 30 mg kg^{-1} YJA20379-8 given intraduodenally was very brief (less than 7 h). Pretreatment with YJA20379-8 also dose-dependently prevented gastric lesions induced by absolute ethanol and water-immersion stress in rats.

These results suggest that YJA20379-8 might exert its antiulcer activity partly by reversible suppression of acid secretion and partly by protecting the gastric mucosa against ulcerative stimuli.

Gastric H^+/K^+-ATPase, a proton pump located on the luminal membrane of parietal cells, mediates the final stage of gastric acid secretion (Hersey & Sachs 1995); it has, therefore, been regarded as a pharmacological target for the development of antiulcer drugs.

Substituted benzimidazoles such as omeprazole and lansoprazole are highly effective in the treatment of peptic ulcer disease in man (Classen et al 1985; Tytgat et al 1985) and are currently used clinically (Parsons et al 1995). These agents inactivate the H^+/K^+-ATPase by covalently binding to the sulphydryl groups of the enzyme, resulting in long-lasting acid suppression (Sachs et al 1988); subsequent restoration of acid secretion probably requires replacement of the enzyme by de-novo synthesis (Im et al 1985). Discovery of reversible inhibitors of H^+/K^+-ATPase might be desirable, because such drugs would enable greater flexibility in the optimization of the duration of acid suppression. Although several structural classes of reversible H^+/K^+-ATPase inhibitor have been described, none has been successfully used clinically (Pope et al 1995).

In this study, the effects of YJA20379-8, a newly synthesized naphthyridine derivative, were

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investigated on H^+/K^+-ATPase in pig gastric microsomes. Its effects on gastric acid secretion in pylorus-ligated rats and on cytoprotection were also examined and compared with those of omeprazole.

Materials and Methods

Test compounds

YJA20379-8, 3-butyryl-4-[*R*-1-methylbenzylamino]-8-ethoxy-1,7-naphthyridine and omeprazole were synthesized in the Department of New Drug Development of Yung Jin Pharmaceutical (Seoul, Korea) (Figure 1). For in-vitro studies, YJA20379-8 and omeprazole were dissolved in dimethylsulphoxide (DMSO) (International Specialty Chemical, Chicago, IL) at an appropriate concentration and further diluted with distilled water. The maximum concentration of DMSO contained in the assays was 0·5%; this had previously been shown to have no effect on enzyme activity. For in-vivo studies, except for the gastric secretion experiment with intravenous administration, YJA20379-8 was suspended in 1% (w/v) carmellose sodium. In the gastric secretion experiment by intravenous administration YJA20379-8 was dissolved in corn oil. In all in-vivo experiments, omeprazole was suspended in 1% carmellose sodium.

H^+/K^+-ATPase activity in pig gastric microsomes

Preparation of H^+/K^+-ATPase-enriched pig gastric microsomes. Gastric microsomes were prepared from pig fundic mucosa by a modification of the method described by Saccomani et al (1977).

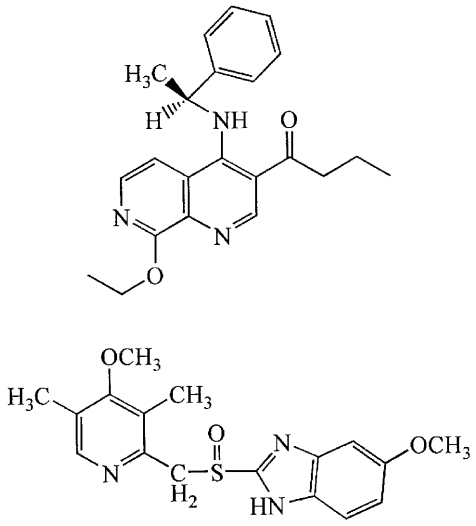

Figure 1. The structural formulae of YJA20379-8 (upper) and omeprazole.

Briefly, tissue was homogenized in isotonic medium and a microsomal fraction obtained by differential centrifugation. This material was separated on a discontinuous density gradient and the fraction at the interface between the 0·25 M sucrose and 0·25 M sucrose plus 7% Ficoll layers was taken. The interface fraction was diluted in 2 vols homogenization buffer, spun down and freeze-dried overnight. The lyophilized vesicles were resuspended in unbuffered 0·25 M sucrose and stored at −70°C. Protein concentration was determined by the method of Lowry et al (1951), with bovine serum albumin as standard.

Assay procedures. H^+/K^+-ATPase was pre-incubated for 30 min in 5 mM imidazole buffer (pH 6·4 and 7·4) containing different concentrations of inhibitor. Enzyme activity was determined at 37°C in the presence of 2 mM $MgCl_2$, 2 mM Na_2ATP and 20 mM imidazole buffer (pH 7·4), with or without 10 mM KCl. At the end of the incubation (15 min), the reaction was terminated by addition of ice-cold 22% trichloroacetic acid (1 mL). The inorganic phosphate formed by hydrolysis of ATP was measured spectrophotometrically by the method of Fiske & Subbarow (1925).

Reversibility of inhibition of gastric H^+/K^+-ATPase

Gastric microsomes were pre-incubated at 37°C for 30 min in imidazole buffer (pH 6·4, 5 mM) containing YJA20379-8 (28·0 μM) and omeprazole (25·0 μM), and samples of the medium were taken for determination of H^+/K^+-ATPase activity. The remaining medium was centrifuged at 100 000 *g* for 1 h and the supernatant removed. The resulting pellets were resuspended in the same volume of assay buffer without inhibitor and H^+/K^+-ATPase activity was measured.

Gastric acid secretion

All animal experiments were approved by the Committee on Research Animal Care of the Yung-Jin Research Centre and performed according to the principles and guidelines outlined by the Regulation of Maintenance and Care of Laboratory Animals (Korea). Male Sprague–Dawley rats, 180–220 g, were deprived of food for 24 h but allowed free access to water. Gastric secretion was determined by use of pylorus-ligated rats (Shay et al (1954).

Basal secretion. Under ether anaesthesia the abdomen was incised and the pylorus was ligated.

YJA20379-8 (3, 10 or 30 mg kg^{-1}) was administered intraduodenally immediately after pylorus ligation. The antisecretory effects of YJA20379-8 administered by other routes were also determined. YJA20379-8 was administered orally (5, 15 or 50 mg kg^{-1}) or subcutaneously (3, 10 or 30 mg kg^{-1}) 30 min before pylorus ligation. For intravenous dosing YJA20379-8 (0·5, 1·5 or 5 mg kg^{-1}) was injected into the tail vein immediately after ligation. Rats were killed by cervical dislocation 4 h after pylorus ligation. The gastric contents were collected and the volume and acidity determined. Acidity was determined with a pH meter (Orion, USA) by titration against 0·01 M NaOH to pH 7·0.

Duration of antisecretory action. To study the duration of antisecretory action, YJA20379-8 (30 mg kg^{-1}) was administered intraduodenally 0, 1, 3, 6 and 12 h before ligation.

Acute experimental lesions

Ethanol-induced gastric lesions. Male Sprague–Dawley rats, 180–200 g, were deprived of food but allowed free access to water for 24 h before the experiment. Absolute ethanol (1 mL/200 g) was given orally to rats and the rats were killed 1·5 h later. The stomach of each rat was removed and inflated by injecting 3% formalin (10 mL) for 10 min to fix the inner and outer layers of the gastric wall. The stomach was then incised along the greater curvature and examined for lesions in the glandular portion. Drugs (YJA20379-8 or omeprazole: 3, 10 or 30 mg kg^{-1}) or vehicle were administered orally 30 min before ethanol treatment.

Water-immersion stress-induced gastric lesions. Male Sprague–Dawley rats, 180–200 g, were deprived of food but allowed free access to water for 24 h before the experiment. Rats were placed in a restraint cage and then immersed vertically to the level of the xiphoid process in a water bath (21–23°C) for 7 h, then killed. The stomach was treated with formalin as above, incised along the greater curvature and examined for lesions in the glandular portion. Drugs (YJA20379-8 or omeprazole: 3, 10 or 30 mg kg^{-1}) or vehicle were administered orally 30 min before stressing.

Lesion index

The lengths (mm) of lesions induced by ethanol and water-immersion stress were measured macroscopically, summed for each stomach, and the total was used as the lesion index.

Statistical analysis

Data are expressed as means ± s.e.m. In the biochemical study IC50 values (doses resulting in 50% inhibition) were calculated by the method of linear least squares. In pharmacological studies Student's *t*-test was used to determine the statistical significance of the data at the levels of $P < 0.05$ and $P < 0.01$. ED50 values (doses affording 50% protection) and 95% confidence limits were calculated by the probit method.

Results

Effects on H^+/K^+-ATPase activity in pig gastric mucosal microsomes

YJA20379-8 in the presence of 10 mM KCl inhibited H^+/K^+-ATPase activity in a concentration-dependent manner with IC50 values of 30 μM at pH 7·4 and 28 μM at pH 6·4 (Figure 2). The inhibitory potency of YJA20379-8 was almost equal to that of omeprazole at pH 6·4, but more potent at pH 7·4; the IC50 values of omeprazole were 25 and 99 μM at pH 6·4 and 7·4, respectively.

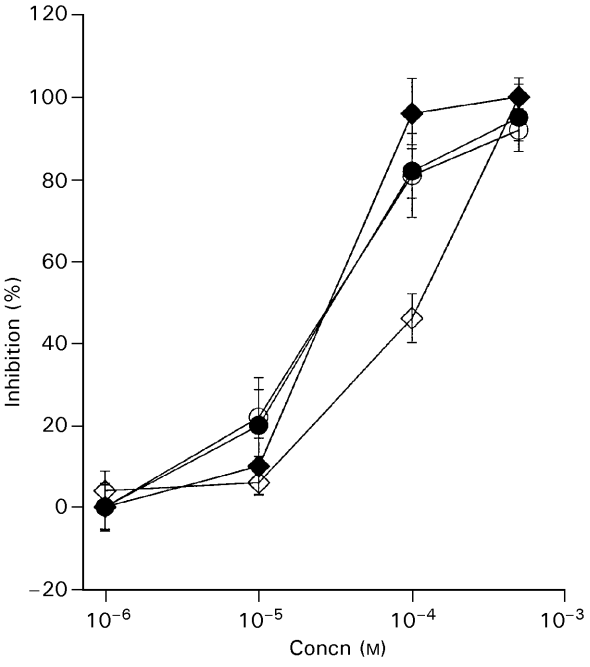

Figure 2. Effects of YJA20379-8 on the H^+/K^+-ATPase activity of pig gastric microsomes. The enzyme was pre-incubated for 30 min with different concentrations of YJA20379-8 (●, ○) and omeprazole (◆, ◇) at pH 6·4 (●, ◆) and 7·4 (○, ◇). Activity without inhibitor was taken as 100%. The results are means ± s.e.m. from four different experiments.

Reversibility of inhibition of gastric H^+/K^+-ATPase

Gastric microsomes were incubated in 5 mM imidazole buffer (pH 6·4) containing YJA20379-8 or omeprazole. The buffer was then removed by centrifugation and replaced by fresh buffer without inhibitor. YJA20379-8 (28 μM) and omeprazole (25 μM) inhibited H^+/K^+-ATPase activity by 48 and 55%; after the drug was removed enzyme activities were inhibited by 3 and 50%, respectively (Table 1). The results indicate that inhibition of H^+/K^+-ATPase by YJA20379-8, but not omeprazole, is almost completely reversed by removing the drug from the medium.

Effects on basal secretion and duration of antisecretory action

YJA20379-8 administered intraduodenally, subcutaneously, intravenously or orally caused dose-dependent inhibition of gastric secretion. The ED50 values after treatment were 14·5 (intraduodenal), 19·0 (subcutaneous), 2·5 (intravenous) and 44·3 (oral) mg kg^{-1}, respectively (Table 2). In the study of the duration of action, the duration of the antisecretory effect of YJA20379-8 (30 mg kg^{-1}) administered intraduodenally was extremely brief, with 50% pre-dose levels being regained within ca 5 h. Inhibition of gastric secretion 4, 5, 7, 10 and 16 h after administration of YJA20379-8 were 72·1, 58·0, 49·0, 28·5 and 14·6%, respectively (Table 3).

Table 1. Reversibility of H^+/K^+-ATPase inhibition by YJA20379-8 in pig gastric microsomes.

Incubation condition	Test compound	H^+/K^+-ATPase activity (μmolPi (mg protein)$^{-1}$ h^{-1})	Inhibition (%)
Original medium	Control	35·2 ± 1·9	–
Original medium	YJA20379-8 28·0 μM	18·2 ± 1·5	48·3
Original medium	Omeprazole 25·0 μM	16·0 ± 0·7	54·3
Resuspended medium	Control	33·2 ± 1·2	–
Resuspended medium	YJA20379-8 28·0 μM	32·1 ± 2·6	3·3
Resuspended medium	Omeprazole 25·0 μM	16·5 ± 0·9	50·3

Gastric microsomes were pre-incubated at 37°C for 30 min in 5 mM imidazole buffer (pH 6·4) containing 28·0 μM YJA20379-8 and 25·0 μM omeprazole, and samples of the medium were taken for determination of H^+/K^+-ATPase activity. The remaining medium was centrifuged at 100 000 *g* for 1 h and the supernatant was removed. The resulting pellets were resuspended in the same volume of the assay buffer without inhibitor and H^+/K^+-ATPase activity was measured. All values are means ± s.e.m. of results from three different experiments.

Table 2. Inhibitory effects of YJA20379-8 on basal gastric secretion in pylorus-ligated rats.

Route	Dose (mg kg^{-1})	Gastric secretion		Inhibition (%)	ED50 (mg kg^{-1})
		Volume (mL/4 h)	Total acid output (mEq/4 h kg^{-1})		
	0	5·40 ± 1·05	2·64 ± 0·80	–	
	3	4·68 ± 1·42	2·61 ± 0·90	1·1	
Intraduodenal	10	2·30 ± 0·67*	1·15 ± 0·52	56·4	14·5
	30	1·65 ± 0·84**	0·73 ± 0·48*	72·3	
	0	4·62 ± 0·77	2·33 ± 0·69	–	
	3	4·15 ± 1·09	1·98 ± 0·82	15·0	
Subcutaneous	10	3·02 ± 1·36	1·20 ± 0·80	48·5	19·0
	30	2·75 ± 0·73*	1·09 ± 0·51	53·2	
	0	6·12 ± 0·25	4·18 ± 0·26	–	
	0·5	5·34 ± 0·63	3·69 ± 0·71	11·8	
Intravenous	1·5	5·24 ± 0·62	3·16 ± 0·53*	24·5	2·5
	5	2·48 ± 0·35**	1·01 ± 0·19**	76·0	
	0	5·97 ± 1·07	4·16 ± 1·15	–	
	3	5·08 ± 2·15	3·33 ± 1·42	20·0	
Oral	10	4·85 ± 0·71	3·05 ± 0·56	26·7	44·3
	30	3·68 ± 0·52*	1·88 ± 0·60*	54·8	

Drug or vehicle was administered intraduodenally or intravenously immediately after pylorus ligation. For subcutaneous or oral treatment, drug or vehicle was administered 30 min before pylorus ligation. Gastric contents were collected 4 h after ligation and analysed for acid output. All values are means ± s.e.m. of results from three experiments (n = 7). *$P < 0·05$, **$P < 0·01$ compared with respective control.

Table 3. Effects of YJA20379-8 on basal gastric secretion in pylorus-ligated rats at different times before pylorus ligation.

Time before pylorus ligation	Dose ($mg\,kg^{-1}$)	Gastric secretion		Inhibition (%)
		Volume (mL/4 h)	Total acid output ($mEq/4\,h\,kg^{-1}$)	
−0 h	0	5·33 ± 1·68	3·73 ± 0·80	–
	30	1·78 ± 0·54*	1·04 ± 0·36**	72·1
−1 h	0	5·36 ± 1·12	3·14 ± 0·66	–
	30	2·77 ± 0·97*	1·32 ± 0·52*	58·0
−3 h	0	5·48 ± 1·54	4·55 ± 0·01	–
	30	2·92 ± 0·97	2·32 ± 0·13**	49·0
−6 h	0	4·97 ± 1·31	4·31 ± 0·38	–
	30	3·13 ± 1·15	3·08 ± 0·77	28·5
−12 h	0	4·32 ± 0·60	2·94 ± 0·43	–
	30	3·48 ± 1·23	2·51 ± 0·71	14·6

Drug or vehicle was administered once, intraduodenally, 0, 1, 3, 6 or 12 h before pylorus ligation. The animals were killed 4 h after ligation. All values are means ± s.e.m. of results from three experiments. $*P < 0.05$, $**P < 0.01$ compared with respective control.

Effects on acute experimental lesions

Effects on ethanol-induced gastric lesions. When absolute ethanol was given to the control animals, haemorrhagic band-like lesions were produced in the glandular portion of the stomach; the mean lesion index in control animals was 84·4 ± 12·2 mm (n = 7). YJA20379-8 (3, 10 or 30 $mg\,kg^{-1}$) administered orally dose-dependently inhibited these lesions; reduction of the lesion index for each dose was 34·5, 59·2 and 85·4% respectively (ED50, 9·6 $mg\,kg^{-1}$). Omeprazole also significantly inhibited lesion formation; the percentage reduction of the lesion index at each dose was 0·5, 34·2 and 72·7%, respectively (ED50, 17·1 $mg\,kg^{-1}$). The effect of YJA20379-8 was more potent than that of omeprazole (Table 4).

Effects on water-immersion stress-induced gastric lesions.Water-immersion stress for 7 h resulted in several instances of linear and dotted erosion of the glandular portion of stomach; the mean lesion index in the rats given vehicle was 55·6 ± 7·1 mm (n = 7). YJA20379-8 (3, 10 or 30 $mg\,kg^{-1}$) administered orally dose-dependently inhibited these lesions; inhibition of the lesion index at each dose was 28·5, 58·5 and 65·0% respectively (ED50, 9·4 $mg\,kg^{-1}$). Omeprazole also significantly inhibited lesion formation; inhibition of the lesion index at each dose was 19·9, 69·7 and 95·7% respectively (ED50, 6·4 $mg\,kg^{-1}$). The effect of YJA20379-8 was less potent than that of omeprazole (Table 5).

Discussion

This study has revealed that YJA20379-8, a new proton pump inhibitor, has potent anti-secretory effect and anti-gastric mucosal lesion activity.

In lyophilized pig gastric microsomes, YJA20379-8 resulted in direct and concentration-dependent inhibition of the H^+/K^+-ATPase

Table 4. Effects of YJA20379-8 on ethanol-induced gastric lesions in rats.

Treatment	Number of rats	Lesion index (mm; mean ± s.e.m.)	Inhibition (%)	ED50 ($mg\,kg^{-1}$) (95% confidence limits)
Vehicle	7	84·40 ± 12·20	–	
YJA203798, 3 $mg\,kg^{-1}$	7	55·28 ± 7·50*	34·5	9·6
YJA203798, 10 $mg\,kg^{-1}$	7	34·43 ± 4·70**	59·2	(3·1–28·4)
YJA203798, 30 $mg\,kg^{-1}$	7	12·32 ± 3·70**	85·4	
Vehicle	7	84·40 ± 12·20	–	
Omeprazole, 3 $mg\,kg^{-1}$	7	83·97 ± 1·10	0·5	17·1
Omeprazole, 10 $mg\,kg^{-1}$	7	55·50 ± 3·50*	34·2	(9·6–30·3)
Omeprazole, 30 $mg\,kg^{-1}$	7	23·00 ± 3·62**	72·7	

Drug or vehicle was given orally 30 min before administration of absolute ethanol. Rats were killed 1·5 h after treatment with ethanol and the lesion index was measured. All values are means ± s.e.m. of results from three experiments. $*P < 0.05$, $**P < 0.01$ compared with control.

Table 5. Effects of YJA20379-8 on water-immersion stress-induced gastric lesions in rats.

Treatment	Number of rats	Lesion index (mm; mean ± s.e.m.)	Inhibition (%)	ED50 ($mg\,kg^{-1}$) (95% confidence limits)
Vehicle	8	55·60 ± 7·06	–	
YJA203798, $3\,mg\,kg^{-1}$	8	39·75 ± 6·80*	28·5	9·4
YJA203798, $10\,mg\,kg^{-1}$	8	23·07 ± 1·17**	58·5	(3·2–31·4)
YJA203798, $30\,mg\,kg^{-1}$	8	19·46 ± 1·67**	65·0	
Vehicle	8	43·91 ± 3·17	–	
Omeprazole, $3\,mg\,kg^{-1}$	8	35·17 ± 2·18*	19·9	6·4
Omeprazole, $10\,mg\,kg^{-1}$	8	13·29 ± 1·90**	69·7	(3·8–10·8)
Omeprazole, $30\,mg\,kg^{-1}$	8	1·88 ± 0·83**	95·7	

Drug or vehicle was given orally 30 min before the start of water immersion. Rats were killed 7 h after immersion and the lesion index was measured. All values are means ± s.e.m. of results from three experiments. $*P < 0{\cdot}05$, $**P < 0{\cdot}01$ compared with control.

reported to play an important role in acid formation in parietal cells (Forte & Lee 1977; Berglindh et al 1980). The inhibitory activity of YJA20379-8 was not affected by pH (6·4 and 7·4), implying that YJA20379-8, unlike omeprazole, might not be transformed into an active form under acidic conditions. This suggestion is also supported by a previous report describing YJA20379-8 as stable in the pH range 1–14 (Chung et al 1998). In contrast, omeprazole was ca 4 times more potent at inhibiting H^+/K^+-ATPase at pH 6·4 than that at pH 7·4, confirming the pH-dependence of the inhibitory activity of omeprazole (Lindberg et al 1986). In the experiment performed to assess the nature of H^+/K^+-ATPase inhibition by YJA20379-8, the inhibitory effect was fully reversed simply by diluting and subsequently washing the incubation mixture of H^+/K^+-ATPase and YJA20379-8; inhibition by omeprazole could not be reversed by this physical method. This result suggests that YJA20379-8 might interact reversibly with the H^+/K^+-ATPase.

The in-vivo antisecretory effects of YJA20379-8 after administration by different routes (intraduodenal, subcutaneous, intravenous or oral) were investigated by measuring the inhibition of gastric acid secretion in pylorus-ligated rats. In this experiment the inhibitory potency (ED50 value) of YJA20379-8 after intravenous administration was at least sevenfold that after use of other routes. This result implies that YJA20379-8 has to reach the parietal cells in the stomach via the systemic circulation before it can exert effective antisecretory action. It should be also noted that oral administration of YJA20379-8 resulted in very weak inhibition of the basal gastric secretion. Because the compound is expected to be stable at the acidity of the rat stomach (Chung et al 1998), this poor potency might be ascribed to poor absorption from the gastrointestinal tract and the gastrointestinal first pass effect (Chung et al 1999; Kim et al 1999). Further investigation would elucidate the clear reason. In the duration study it was found that the antisecretory effect of YJA20379-8 was much shorter after intraduodenal administration. The pharmacological half-life of the antisecretory effect was estimated to be approximately 5 h. Considering that the potency of the effect of YJA20379-8 on the H^+/K^+-ATPase was similar to that of omeprazole, the short duration of the antisecretory action might reflect the reversible nature of enzyme inhibition by the compound. This characteristic of YJA20379-8 would be considered a beneficial property, potentially avoiding the side-effects associated with prolonged suppression of acid secretion seen with omeprazole (Wallmark et al 1984).

In general, antisecretory agents inhibit gastric and duodenal lesions in rats (Yamada et al 1996). In contrast, gastric lesions induced by necrotizing agents are not suppressed by inhibition of acid secretion, but rather by cytoprotective effects (Long et al 1983). In the current study oral administration of YJA20379-8 resulted in significant inhibition of ethanol-induced gastric lesions, suggesting that the compound has cytoprotective activity. The antilesion effect was ca twice that of omeprazole.

YJA20379-8 administered orally also prevented the acute gastric lesions induced by water-immersion stress, the pathogenesis of which is assumed to be mediated by increased gastric acid secretion and a relative reduction in blood supply (Kitagawa et al 1979). On the basis of ED50 values YJA20379-8 was shown to be ca half as potent as omeprazole. Because of the weak antisecretory effect of YJA20379-8 after oral administration, the antiulcer activity of the compound against water immersion stress might involve an increase in blood supply or another unknown mechanism in addition to its antisecretory activity.

Taken together, our results indicate that YJA20379-8 inhibits gastric H^+/K^+-ATPase in parietal cells probably by a reversible mechanism, resulting in relatively short-lasting antisecretory action. It has also been shown that YJA20379-8 potently prevented ethanol and water-immersion stress-induced gastric lesions by suppressing acid secretion and partly by protecting the gastric mucosa. These characteristics of YJA20379-8 could make the compound a sensitive and potent regulator of acid secretion.

Acknowledgements

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