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Protective Effects of Arginine-vasopressin on Aspirin-induced Gastric Mucosal Damage in Anaesthetized Dogs

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Abstract—The protective effects of graded doses of arginine-vasopressin (AVP) on acidified acetylsalicylic acid (ASA) solution-induced changes in gastric prostaglandin E_2 (PGE_2) secretion, mucus production, acid back-diffusion and mucosal damage were studied in the bilateral truncal vagotomized stomach of anaesthetized dogs. After 1–4 h intragastric irrigation of the stomach with AVP (1–100 ng kg^{-1}) plus 20 mM acidified ASA solution, a significant ($P < 0.05$) inhibition in gastric mucosal lesions and acid back-diffusion produced by acidified ASA solution was observed. The reduction in the gastric PGE_2 secretion and in mucus production provoked by the same dose of acidified ASA solution was also diminished. Furthermore, a correlation ($r = 0.883$; $P < 0.01$) between AVP-induced inhibition in ASA-provoked reduction in gastric PGE_2 secretion and in mucus production was found. During the experiment, the heart rate, the peripheral arterial blood pressure and the gastric arterial blood pressure were not altered by AVP (1–100 ng kg^{-1}). Thus, intragastric AVP protects gastric mucosa against ASA-induced damage without producing cardiovascular side effects. The inhibitory effects of AVP (100 ng kg^{-1}) on acidified ASA-induced reduction in PGE_2 and mucus secretion, as well as on ASA-induced enhancement in acid back-diffusion and erosion production were dose-dependently reversed by a specific V_1 antagonist, 1-(β-mercapto-β,β-cyclopentamethylene-propionic acid), 2-(*o*-methyl)tyrosine-Arg^8-vasopressin. From the above results, it is suggested that the protective effects of intragastric AVP on gastric mucosa against acidified ASA-induced damage is at least partly due to stimulation of the biosynthesis of gastric PGE_2, which may contribute to the increase in the gastric mucus secretion and to the decrease in acid back-diffusion. Furthermore, the endogenous PGE_2 stimulated by AVP may be mediated by V_1-receptor activation.

Arginine-vasopressin (AVP), which is found in various regions of the mammalian brain, can be released by hyperosmolality and haemorrhage (Dunn et al 1973; Liard 1988; Wang et al 1988). Pharmacologically, AVP shows both vasoconstriction and antidiuretic actions. The receptors involved in these effects are defined as V_1- and V_2-receptor, respectively (Gilman et al 1990). In the clinic, AVP is widely used in the treatment of patients with gastrointestinal haemorrhage or with polyuria (Robertson 1977; Mathias et al 1986). In most cases, these drugs are given parenterally. In the therapy of gastric haemorrhage, high doses of AVP may be needed to obtain the local effect, because of wide distribution and extensive degradation. However, systemic administration of high doses of AVP may cause severe adverse effects; particularly there is a high risk to patients with heart disease or hypertension. Direct application of AVP on the gastric mucosa by oral administration seems more convenient and effective. Nevertheless, studies on the effect of intragastric administration of AVP on the gastric mucosa have not been reported. Therefore, instead of peripheral injection, the intragastric administration of AVP was performed in the present study. On the other hand, AVP has been reported to be able to stimulate the biosynthesis of prostaglandin E_2 (PGE_2) in the kidney (Walker et al 1978). PGE_2 exerts gastric mucosal cytoprotection in a variety of animals and in man (Miller 1983). The cytoprotective effects include an enhancement of gastric mucus secretion and reduction in the back-diffusion of gastric acid (Moody 1978).

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In our laboratory, we had observed that AVP can stimulate gastric PGE_2 secretion in the Heidenhain pouch of conscious dogs. However, it was not clear whether the endogenous PGE_2 stimulated by AVP is sufficient to protect gastric mucosa against injury produced by ulcerogenic drugs such as acetyl salicylic acid (ASA). This study was designed to investigate this point.

Materials and Methods

Animals

Adult mongrel dogs of either sex, 8–12 kg, were fasted but allowed free access to water for 18 h, and were anaesthetized with pentobarbitone (30 mg kg^{-1}, i.v.). A polyethylene tube (5·0 mm i.d.) connected to a ventilator (New Eng. Med. Inst. Model 110, USA) was inserted into the trachea. Polyethylene tubes (0·86 mm i.d.) connected to a blood pressure monitor (Life Scope 12,BSM-8500J, Nihon Hohden), were inserted into the femoral artery and the gastric epiploic artery enabling simultaneous measurement of the heart rate and the blood pressure. An incision was then made on the abdomen and the stomach was exposed. The lower oesophagus and the pylorus sphincters were ligated, taking great care not to injure blood vessels. A stainless-steel fistula (8·5 mm i.d. × 30 mm) connected to a 20-mL syringe by a rubber tube, was inserted into an incision on the transitional region of the stomach. The wound was securely ligated and the stomach was rinsed meticulously with double-distilled water (37°C). The luminal residue was expelled. Care was taken to avoid distension and mechanical stimulation of the stomach.

Study of acid back-diffusion

The stomach was irrigated with 50 mL vehicle with or

Table 1. Time course of the effect of AVP on ASA-induced gastric acid back-diffusion, PGE_2 secretion, mucus production and mucosal ulceration in the dog stomach. The stomach was irrigated either with a solution of acidified ASA or AVP or AVP+ ASA for 2 h.

		Gastric content			Mucosa	
Time (h)	Treatment	H^+ net flux (μM h^{-1})	Na^+ net flux (μM h^{-1})	PGE_2 (ng h^{-1})	AB binding (μg (g wet wt tissue)$^{-1}$)	Ulcer area (mm^2)
1	ASA	−2869·6±130·4	1235·3±353·0	64·4±15·6	62·2±11·1	175·0±17·9
	ASA+AVP	−2543·5±456·5	1294·1±205·9	64·4±20·6	64·4±20·6	164·3±7·1
2	ASA	−2087·3±21·8	911·0±58·8	43·5±2·5	28·9±6·7	228·6±10·7
	ASA+AVP	−1608·7±87·0*	676·5±14·7*	145·2±12·6*	108·9±15·5*	53·6±16·1*
4	ASA	−913·0±43·5	470·6±29·4	8·8±3·5	46·7±13·3	219·6±16·1
	ASA+AVP	−913·0±87·0	441·2±117·6	12·5±6·3	95·6±24·4*	69·3±12·8*

*$P<0·05$. Each test used six dogs. AB = alcian blue.

without drugs using a 50-mL disposable syringe through the fistula. Phenol red was used as a volume marker. The volume was measured to the nearest 0·1 mL. The luminal contents were mixed by repeated injection and aspiration for 30 s. Five millilitres of the luminal contents was then withdrawn. During the experiment the stomach content was mixed, using a syringe, every 15 min. After 1, 2 or 4 h the animal was killed by intravenous injection of KCl. The stomach was removed and the luminal contents were collected.

Morphological study

After the final sample was collected, the stomach was excised and opened along the greater curvature. The specimen was then gently washed with tap water and examined for gross evidence of ulceration by an investigator unaware of the group to which the animal had been assigned. The width and the length of lesions on the gastric mucosa were measured by a planimeter under a dissecting microscope (0·7 × 3·0 American Optical Scientific Instruments, USA). The area of the ulcer (mm^2) was considered as an ellipse and calculated by width (mm) × length (mm) × $\pi/4$ as described by Kauffman & Grossman (1978). The ulcer areas on each stomach were summed.

Histological study

After gross examination, specimens were blocked and immersed in 10% neutral formalin for two days. Blocks were then dehydrated in alcohol, cleared in xylene and embedded in paraffin. Sections (7 μm) were cut and stained with haematoxylin and eosin using routine histological procedures. Sections were then examined under the light microscope.

Sample assay

The initial sample and the final sample taken from the stomach were centrifuged at 3000 rev min^{-1} for 30 min and volumes, acidity, Na^+ concentration, and PGE_2 content were measured. The amount of mucus on the corpus mucosa was also determined. The acidity was measured by titrating 1-mL sample with 0·1 M NaOH to pH 7·0 on an autoburette titrator (Radiometer, Copenhagen, Denmark) The concentration of Na^+ was measured using a flame photometer (Eppendorf, FCM 6431, Germany). The net flux of ions through gastric mucosa was calculated as:

$$F_c \times F_v - I_c \times (50 - I_v)$$

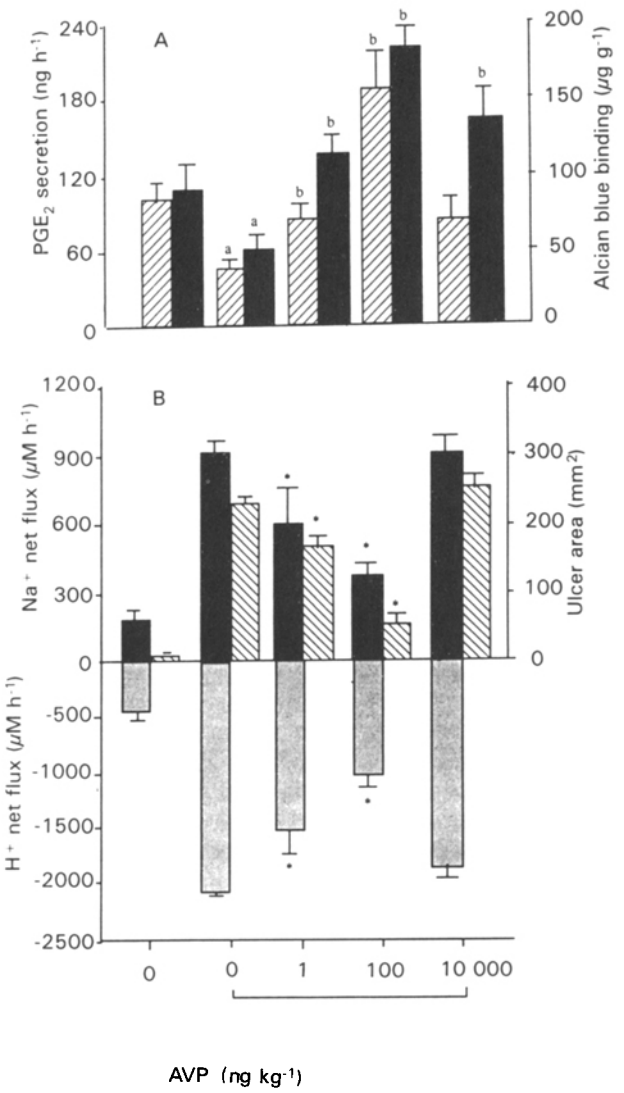

FIG. 1. A. Effect of graded doses of AVP on ASA-induced PGE_2 secretion (▨) and mucus production (■). B. Effect of graded doses of AVP on ASA-induced gastric mucosal permeability to electrolytes, Na^+ (■) and H^+ (▨), and mucosal ulceration (▧) in dog stomach. The stomach was irrigated with either vehicle solution (100 mM HCl+54 mM NaCl) or with AVP (1–1000 ng kg^{-1}) plus acidified ASA (20 mM) solution for 2 h. Gastric mucus production was expressed by the amount of alcian blue binding on the gastric mucosa. Each group used six dogs. Data are presented as mean ±s.e.m. $^aP<0·05$ compared with acid solution, $^bP<0·05$ compared with ASA. *$P<0·05$ compared with control.

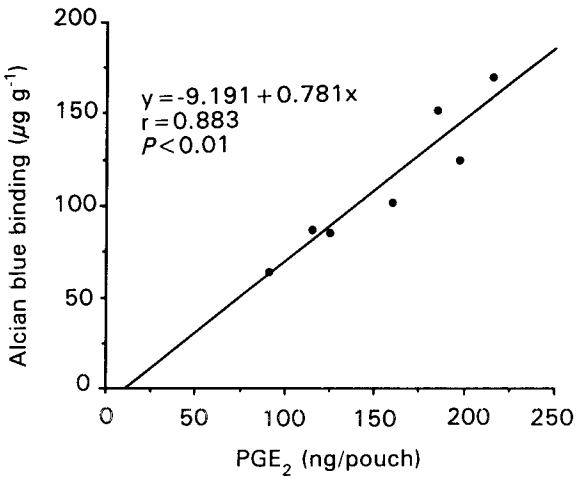

FIG. 2. Correlation between AVP-induced inhibition in ASA-provoked gastric PGE_2 secretion and in mucus production. Dog stomach was irrigated for 3 h with an acid solution containing AVP (100 ng kg^{-1}) and ASA (20 mM). Alcian blue binding was measured in 1 g corpus tissue.

where F_c and I_c are the ionic concentrations (mM) of the final sample and the initial sample, respectively, and F_v and I_v are the volumes (mL) of the final sample and the initial sample, respectively; the volume instilled into the pouch at the beginning of the experiment was 50 mL.

PGE_2 assay

The amount of PGE_2 contained in the gastric juice was determined by a specific radioimmunoassay (RIA) as previously reported (Chang 1988). The specific antiserum against PGE_2 was developed in our laboratories, and the cross-reaction of the antibodies with other prostaglandins, such as $PGF_{2\alpha}$, 6-keto $PGF_{1\alpha}$ and PGD_2 was at least two orders of magnitude lower than PGE_2. The sensitivity was comparable with other prostaglandin RIA methods and picogram levels could be measured quantitively. Antiserum, labelled antigen, [5,6,8,11,12,14,15 (n)$-^3$H]PGE_2 (147 Ci $mmol^{-1}$, NEN, USA) and PGE_2 standards (Sigma) were diluted in the standard RIA buffer, 0·05 M Tris-HCl, pH 7·5, containing 0·1% gelatin. The incubation mixture (0·4 mL) contained 0·2 mL PGE_2 standards of sample, 0·1 mL antiserum (final dilution, 1:5000), and 0·1 mL [^{3}H]PGE_2 (approx. 10 000 counts min^{-1}). The incubation was carried out for 1 h at room temperature (21°C). All samples were run in duplicate. Separation of bound from free antigen was achieved by γ-globulin plus dextran-coated charcoal. Interpolation of sample values from the standard curve was performed using the built-in program of a β-counter (Beckman Inst. LS 5000 TA, USA). Sensitivity of the RIA was in the range 15–300 pg.

Measurement of gastric mucus

The measurement of mucus production was as described by Corne et al (1974). In brief, 1 g corpus mucosa was excised and immersed for 2 h in a buffer solution containing 0·1% alcian blue, 0·16 M sucrose and 0·05 M sodium acetate. The pH was adjusted to 5·8 with 1 M HCl. The unbound dye was removed by two subsequent washings of 15 and 45 min in 0·25 M sucrose solution. The mucus-bound dye was extracted by immersing the mucosa in 0·5 M $MgCl_2$ for 2 h. The resulting solution was mixed and shaken vigorously with diethylether. The optical density of the aqueous solution was determined at 605 nm in a spectrophotometer (Hitachi, U 3210 Japan).

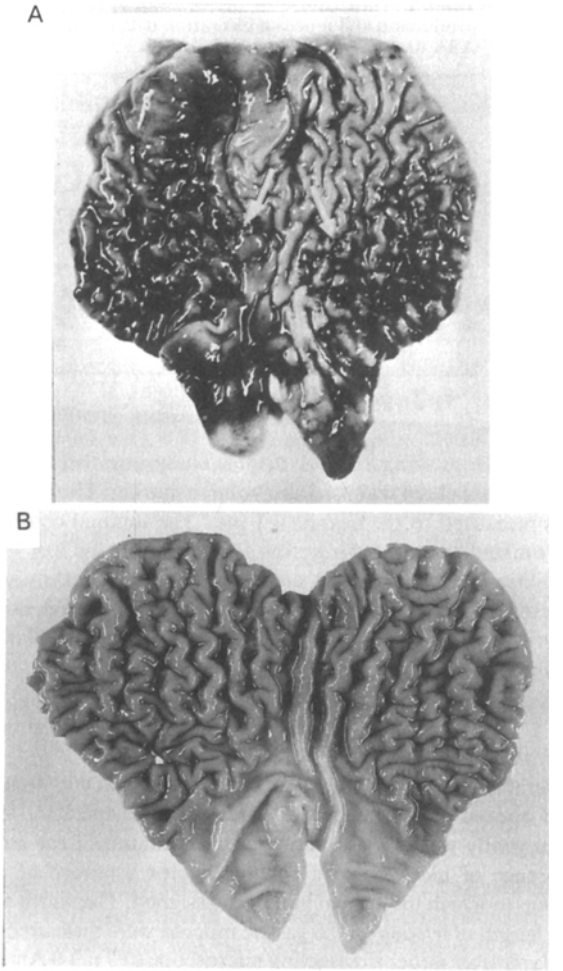

FIG. 3. Gross appearance of the gastric mucosa. A. The stomach was irrigated with 20 mM acidified ASA solution for 2 h. Note that severe haemorrhage and numerous erosions (indicated by arrows) occur on both fundic and antral mucosa. B. AVP (100 ng kg^{-1}) was added to the acidified ASA solution used for irrigation of the stomach for 2 h; the mucosal erosions and haemorrhage are markedly inhibited.

Drug administration

Acetyl salicylic acid (ASA, Sigma) was dissolved in the vehicle (100 mM HCl + 54 mM NaCl.) Arginine vasopressin (AVP, Peninsula Lab., USA) or the V_1 antagonist, 1-(β-mercapto-β,β-cyclopentamethylene-propionic-acid),2-(*o*-methyl)tyrosine-Arg^8-vasopressin (Peninsula Lab., USA) was given concomitantly with the acidified ASA solution. All solutions were freshly prepared before each experiment.

Statistical analysis

Data were expressed as mean ± s.e.m. and were analysed for statistical significance by Student's unpaired *t*-test. $P < 0.05$ was considered significant.

Results

The effect of AVP on ASA-induced reduction in PGE_2

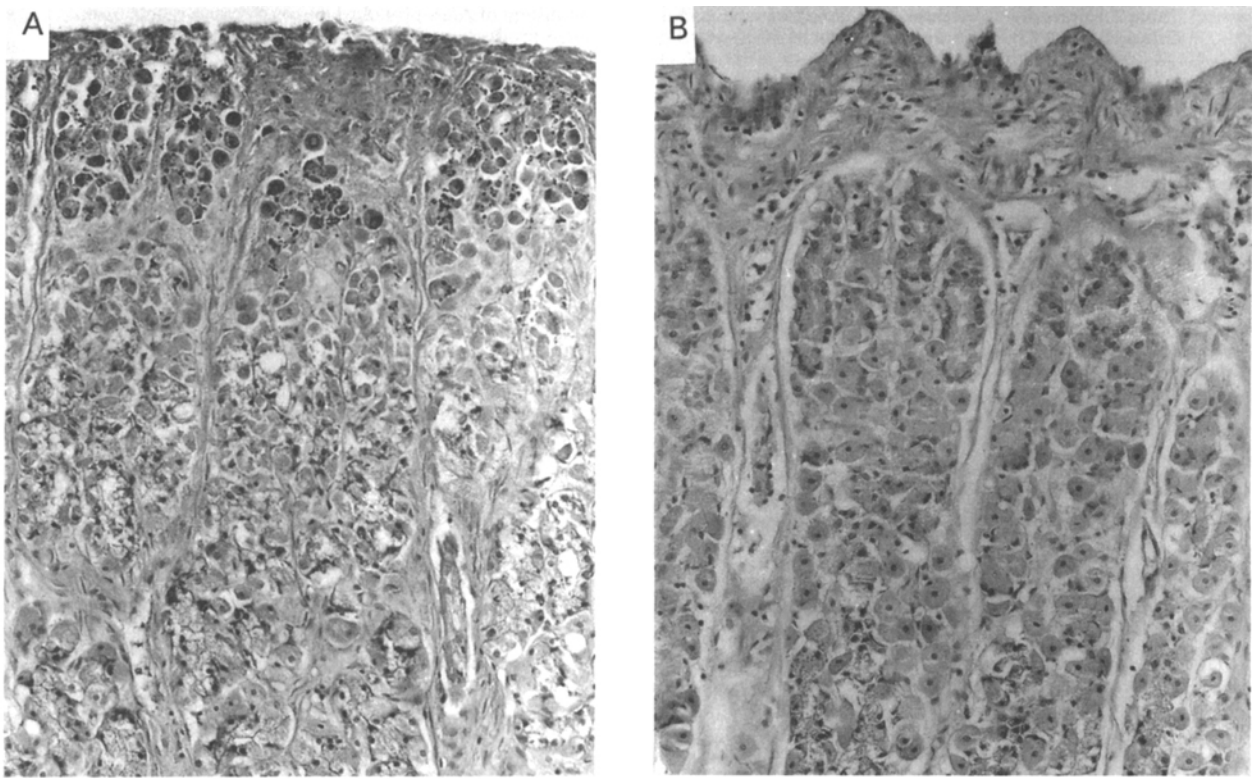

FIG. 4. Histological studies of the gastric mucosa. A. The stomach was irrigated with 20 mM acidifed ASA for 2 h. Note that the upper part of the mucosal cells are severely damaged by acidified ASA. The damaged cells are characterized by karyorrhexis and dense homogenous acidophylic cytoplasm. The epigastric layer is completely disrupted. B. The stomach was irrigated with AVP (100 ng kg^{-1}) plus 20 mM acidified ASA solution for 2 h; the epigastric layer remains intact and the upper part of mucosal cells looks normal.

secretion, mucus production and acid back-diffusion is shown in Table 1.

The effects of graded doses of AVP on ASA-induced decrease in PGE_2 secretion, mucus production, acid back-diffusion and ulcer formation are shown in Fig. 1.

AVP (1–100 ng kg^{-1}) produced a graded inhibition in gastric acid back-diffusion and in mucosal ulceration induced by 20 mM ASA. However, there was no significant change in these parameters when the dose of AVP was increased to 10 μg kg^{-1}. The ASA-produced decrease in gastric PGE_2 and in mucus secretion were significantly reversed by AVP (1–100 ng kg^{-1}). There was a good correlation ($r=0{\cdot}883$, $P<0{\cdot}01$) between this effect and mucus production (Fig. 2).

The morphological changes of acidified ASA (20 mM)-treated mucosa is shown in Fig. 3. Severe gastric bleeding accompanied by numerous erosions of the mucosa was observed. Histological studies indicated that the upper gastric cells, including epithelial cells and mucus cells, were necrotized by acidified ASA (Fig. 4). Concomitant intragastric irrigation with AVP (100 ng kg^{-1}) protected gastric mucosa against 20 mM acidified ASA-induced haemorrhage and erosions (Fig. 3). The damage to epithelial cell and mucus cell induced by acidified ASA was markedly diminished when the same dose of AVP was administered (Fig. 4).

When the stomach was irrigated with AVP, a significant decrease in acid back-diffusion was observed (Table 2) and an enhancement in gastric PGE_2 secretion and mucus production was obtained. Furthermore, mucosal ulceration was not found in the stomachs irrigated with AVP alone. The specific V_1 antagonist, 1-(β-mercapto-β,β-cyclopentamethylene-propionic acid), 2-(o-methyl)tyrosine-Arg^8-vasopressin, given alone, did not cause significant influence on the vehicle solution (100 mM HCl + 54 mM NaCl)-induced gastric PGE_2 secretion or mucus production. The erosions and acid back-diffusion were also unaffected. The effects of AVP (100 ng kg^{-1}) on 20 mM acidified ASA-induced mucosal erosions and acid back-diffusion were dose-relatedly reversed by 0·1–10 μg kg^{-1} of this specific V_1 antagonist. Furthermore, the inhibitory effects of AVP on the reduction in gastric PGE_2 secretion and in mucus production provoked by 20 mM acidified ASA solution were also significantly ($P<0{\cdot}05$) reversed by higher doses of V_1 antagonist (Table 2).

Discussion

The integrity of gastric mucosal barriers is important for protecting gastric mucosa against damage induced by ulcerogenic chemicals or gastric juice. Once the mucosal barriers are disrupted, the luminal H^+ will back-diffuse into the mucosa, with a Na^+ flux into the lumen. This back-diffusion of gastric acid is a sensitive index for the mucosal integrity (Davenport 1965). Chemicals, such as ASA, ethanol and bile salts can damage gastric mucosal barriers. In the present study, topical irrigation of the stomach with 20 mM acidified

Table 2. Effects of graded doses of V_1 antagonist on AVP-induced inhibition of ASA-provoked mucosal erosions, acid back-diffusion and AVP-induced enhancement of PGE_2 secretion and mucus production. The stomach was irrigated either with a solution of acidified ASA or AVP or AVP+ASA or V_1 antagonist +AVP+ASA for 2 h.

	Gastric content			Mucosa	
Treatment	H^+ net flux (μM h^{-1})	Na^+ net flux (μM h^{-1})	PGE_2 (ng h^{-1})	Mucus (μg (g wet wt tissue)$^{-1}$)	Ulcer area (mm^2)
Acid solution	−567·1±67·3	316·2±8·7	105·7±17·2	85·3±15·1	2·0±1·0
ASA (20 mM)	−2133·4±35·2[a]	900·4±50·1[a]	47·6±13·4[a]	33·2±4·4[a]	225·3±14·6[a]
AVP (100 ng kg^{-1})	−433·8±33·3[a]	116·6±16·4[a]	224·5±14·3[a]	183·0±33·2[a]	1·0±1·0
V_1 antagonist (10 μg kg^{-1})	−633·5±130·1	325·3±58·5	118·8±12·6	97·5±13·1	2·0±1·0
AVP (100 ng kg^{-1})+ASA (20 mM)	−1633·4±67·1	667·3±17·2	155·6±17·3	112·3±14·2	54·1±13·0
AVP (100 ng kg^{-1})+ASA (20 mM) + V_1 antagonist					
0·1 μg kg^{-1}	−1700·8±133·2	633·5±83·4	120·1±12·3	130·2±18·2	75·3±21·2
1·0 μg kg^{-1}	−1900·5±200·1	800·9±167·0	106·7±24·1	110·8±15·4	143·5±14·3[b]
10·0 μg kg^{-1}	−2067±33·3[b]	875·6±17·3[b]	72·3±1·7[b]	51·0±2·1[b]	166·9±4·1[b]

[a] $P<0·05$ compared with acid solutions, [b] $P<0·05$ compared with AVP+ASA. Each test used six dogs.

ASA produced gastric lesions characterized by multiple erosions and bleeding. This result is consistent with previous investigations (Hung et al 1976). The acid back-diffusion was enhanced while gastric PGE_2 secretion and mucus production were decreased by ASA. The reduction in gastric PGE_2 secretion and in mucus production may partly result from the damage of epithelial cells and mucus cells by ASA. Subsequently, substantial luminal free H^+ diffused back to the gastric mucosa. Aspirin may also interfere with cyclo-oxygenase which catalyses the biosynthesis of PGE_2 (Flower et al 1972). PGE_2 can stimulate gastric mucus production (Bolton et al 1978). The inhibition in the activity of cyclo-oxygenase by ASA may result in the decrease of gastric mucus production. It is widely accepted that gastric mucus plays an important role in the protection of gastric mucosa (William & Turnberg 1980) and the decrease in mucus production is one of the ulcerogenic factors of ASA (Rainsford 1978). The significant correlation ($r=0·883$, $P<0·01$) between AVP-inhibited reduction in gastric PGE_2 secretion and in mucus production induced by ASA, observed in the present study, indicated that AVP-stimulated gastric PGE_2 may be involved in the production of gastric mucus. When the stomach was irrigated with low doses of AVP plus acidified ASA solution, the mucosal erosions and bleeding were markedly inhibited by AVP. Many reports demonstrate that PGE_2 is able to protect gastric mucosa against ethanol- (Konturek et al 1982), ASA- (Robert 1981), bile salt- (Teretz et al 1990; Mann 1976), cold stress- (Kawarada et al 1975), or indomethacin (Lippman 1974)-induced gastric mucosal damage. The anti-ulcer effects of PGE_2 are not merely due to its antisecretory action. The cytoprotection properties of PGE_2 include prevention of acid back-diffusion, enhancement in mucus secretion and increase of the mucosal blood flow. Both exogenous and endogenous PGE_2 provide the above mentioned cytoprotection requirements in a variety of animals and in man (Ligumski et al 1982; Allen et al 1986; Ligumski & Kauffman 1986). In the present study, the acid back-diffusion induced by ASA was significantly inhibited by AVP given concomitantly with ASA solution. In addition, it has been reported that PGE_2 can prevent gastric mucosal barrier damage (Cohen 1975, 1978). In the present study, a dose-related inhibition in ASA-induced reduction in PGE_2 secretion and in mucus production by AVP was obtained. It is concluded that AVP, given intragastrically, can act directly on its receptors on the mucosal cells and thus stimulate PGE_2 secretion. The release of PGE_2 by vasoconstrictors may cause dilation of resistance of blood vessels, reduction of the release of noradrenaline from sympathetic nerves, and attenuation of the vascular reactivity to pressor hormones (Alberto & Kafait 1982). Thus, vasodilative effects of AVP-stimulated endogenous PGE_2 may also contribute to the protection of the gastric mucosa against ASA-induced damaging effects. On the other hand, high doses (>10 μg kg^{-1}) of AVP were ineffective against mucosal erosion and acid back-diffusion induced by ASA. The vasoconstriction induced by high doses of AVP may mask the vasodilation caused by PGE_2. Thus, the functions of the gastric cells were reduced. The mechanisms of AVP-stimulated gastric PGE_2 secretion is not fully understood. Other vasoconstrictors, such as angiotensin II or noradrenaline also promote formation of PGE_2 from the kidney (Dunham & Zimmerman 1970), heart (Gunther & Cannon 1980; Junstad & Wennmalm 1973), or blood vessels (McGiff et al 1970; Bloomberg et al 1977; Malik 1978). The stimulation of PGE_2 biosynthesis by AVP may be due to the homeostatic response of blood vessel constriction. In the present study, we have also shown that intragastric irrigation of low doses of AVP can prevent gastric haemorrhage and ulceration produced by ASA, but systemic blood pressure, gastric blood pressure and heart rate were unaffected. The results suggested that oral AVP may be superior to parenteral administration. The inhibitory effect of AVP on ASA-induced erosions and acid back-diffusion as well as ASA-induced reduction in PGE_2 secretion and in mucus production were dose-relatedly reversed by the specific V_1 antagonist. These findings suggested that V_1 receptors of AVP may play an important role in regulating the biosynthesis of gastric PGE_2.

In conclusion, intragastric administration of low doses of AVP protected gastric mucosa against acidified ASA-induced damage without altering the systemic arterial pressure, gastric arterial pressure or heart rate. The protective effect of AVP is partly due to the increase in the gastric PGE_2 secretion and mucus production as well as the inhibition in acid back-diffusion. Furthermore, the stimulation of gastric

PGE_2 biosynthesis by AVP may be, at least in part, mediated by V_1-receptor activation.

Acknowledgements

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