J. Pharm. Pharmacol. 1995, 47: 493–498
Received June 27, 1994
Accepted December 7, 1994

Role of Acid Back-diffusion in the Formation of Mucosal Ulceration and Its Treatment with Drugs in Diabetic Rats

CHEN-ROAD HUNG AND ENG-YEN HUANG

Department of Pharmacology, College of Medicine, National Cheng Kung University, Tainan, 70101 Taiwan, Republic of China

Abstract

We have studied the role of acid back-diffusion in the formation of gastric mucosal ulceration and its treatment with several drugs in streptozotocin-induced diabetic rats. After vagotomy, the stomach of 1–8 week-old diabetic rats and age-matched control rats were irrigated with acid solutions of graded concentrations (50–150 mM HCl) for 1 or 3 h.

A marked increase in acid back-diffusion and in haemorrhagic ulceration was found in diabetic rats. The extent of acid back-diffusion and the severity of mucosal ulceration were dependent on the concentration and the time of contact of acid solutions with the gastric mucosa. A high correlation ($r = -0.9227$) between acid back-diffusion and mucosal ulceration was found in 3-h acid-irrigated diabetic rats.

In the 2-week diabetic rat, intragastric cimetidine (300 mg kg^{-1}) or $NaHCO_3$ (52 mg kg^{-1}) significantly ($P < 0.05$) reduced both acid back-diffusion and haemorrhagic ulcer formation, while atropine (1.0 mg kg^{-1}) or bupivacaine (0.5%, 0.4 mL/rat) was ineffective. High blood glucose levels in diabetic rats were not influenced by these agents. Acid back-diffusion and ulceration in the diabetic rat were markedly reduced by daily administration but not single injection of insulin (50 units kg^{-1}, s.c.).

Taken together, in the early stage of diabetes development, chronic insulin deficiency rather than nerve degeneration or hyperglycaemia may be responsible for the disruption of mucosal barriers. It is concluded that acid back-diffusion played an important role in the formation of acute haemorrhagic ulceration that can be inhibited by intragastric cimetidine, $NaHCO_3$ or daily injection of insulin.

Gastric neuropathy in diabetic patients and streptozotocin-induced diabetic animals has been well documented (Hikins et al 1975; Barrett & Sherwin 1983; Feldman & Schiller 1983; Piyachaturawat et al 1983; Tomlinson et al 1992). Research on the pathophysiological changes in the gastric mucosa in diabetes, however, is rare. It is reported that gastric dysfunction is more common in diabetic patients than in the general population (Lennart et al 1961). The complications of ulcer are more frequent and more severe in diabetic patients (Goyal & Spiro 1971), although this has been disputed (Wood 1947; Saltzman & McCallum 1983). It is probable that the gastric mucosa itself in diabetic patients may also be impaired in addition to neuropathy. The hypoglycaemia which may be encountered under various conditions in diabetic patients, can result in profound enhancement of gastric acid secretion (Hirschowitz 1967). When gastric mucosal barriers are disrupted, the luminal free acid may back-diffuse into the gastric mucosa, while other cations, including Na^+ and K^+ may move to the lumen. Mucosal ulceration and haemorrhage can be exacerbated by this acid back-diffusion, which is considered a sensitive index for the integrity of gastric mucosal barriers (Davenport et al 1964). Whether gastric acid back-diffusion may play a role in the formation of acute haemorrhagic ulceration in the diabetic rat is of special interest.

Correspondence: C.-R. Hung, Department of Pharmacology, College of Medicine, National Cheng Kung University, Tainan, 70101 Taiwan, Republic of China.

Materials and Methods

Animals

Male Wistar rats, 200–250 g, were fasted overnight. Under light ether anaesthesia, streptozotocin (65 mg kg^{-1}) dissolved in buffered saline (pH 7.4) was injected immediately into the femoral vein for induction of diabetes. An age-matched control group received the same volume of saline. Both diabetic and control rats were housed separately in a 12-h light–dark cycle room (25°C, 70% humidity), with free access to pelleted rodent diet (The Richmond standard, PMI Feeds, Inc., USA) and water. The blood glucose concentration was determined using a chemistry analyser (Technicon, Ames; RA-50, USA) on the day following administration of streptozotocin and at the time when the animals were killed. Blood glucose levels over 250 mg% were considered indicative of the diabetic state. The manifestations of diabetes, such as polyuria, polydipsia, polyphagia and body weight loss in diabetic rats were recorded every day. After 1, 2, 4, and 8 weeks of induction, the study was begun.

Before the experiments, all animals were deprived of food but were allowed free access to water for 24 h.

Surgical procedures

Under light ether anaesthesia, the stomach was surgically exposed for the ligation of pylorus and lower oesophagus. To prevent the spontaneous gastric secretion, bilateral diaphragmatic vagotomy was conducted. A polypropylene tube (1.0 mm i.d. × 20 mm) was inserted through an incision which was made in the forestomach. The tube was secured with a ligature.

Back diffusion of gastric acid

The acid back-diffusion was quantitated as previously described (Hung & Lee 1991). Briefly, the stomach was rinsed meticulously with double distilled water (37°C). Seven millilitres of acid solution containing 100 mM HCl and 54 mM NaCl was injected with a syringe into the lumen. The lumen content was well mixed for 30 s, and 3 mL of the fluid was taken as the initial sample. The incision in the forestomach was tightly closed. The abdominal wound was also sutured.

After 1 or 3 h, the animal was killed with an overdose of ether. The gastric sample (final sample) was collected and centrifuged at 3000 rev min^{-1} for 20 min. The initial and final samples were analysed for titratable acidity and Na^+ concentration. After the stomach was filled with 1·0% formalin for 10 min, the mucosa was exposed by opening the stomach along the greater curvature. The length (mm) and the width (mm) of the ulcers on the gastric mucosa were measured by a planimeter under a dissecting microscope (×0·7–×3·0; American Optical Scientific Instruments 569, USA). The ulcer area (mm^2) for each stomach was calculated and summed. The mucosal damage was determined by a person unaware of the schedules. Histological studies of the stomach were conducted by the methods previously described (Hung et al 1994). Briefly, after gross examination, the specimens were blocked and immersed into 10% neutral formalin for two days. Blocks were then dehydrated in a series of alcoholic solutions, cleared in xylene and embedded in paraffin. Sections (7-mm thick) were cut and stained with haematoxylin and eosin according to standard histological procedures. Sections were then examined under the light microscope.

Quantitation of gastric samples

The volumes of the initial and final samples were measured to 0·1 mL. The acidity was measured by titrating 1 mL of a sample of gastric contents with 0·1 M NaOH to pH 7·0 on an autoburrette titrator (Radiometer, Copenhagen, Denmark). The concentrations of Na^+ were measured using a flame photometer (Eppendorf, FCM 6341, Germany). The net flux of ions through gastric mucosa was calculated as follows:

$$\text{Net flux} = F_c \times F_v - I_c \times (7 - 1_v) \quad (1)$$

Where F_c and I_c are the concentration (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.

Drug administration

Streptozotocin (65 mg kg^{-1}) (Sigma) was dissolved in buffered saline, and injected into the femoral vein. Acid solutions of graded concentrations (50–150 mM HCl) were added with an adequate amount of NaCl for isotonicity. Cimetidine (300 mg kg^{-1}) (Sigma) and $NaHCO_3$ (52 mg kg^{-1}) (Sigma) were dissolved in physiological acid solution containing 100 mM HCl and 54 mM NaCl, and irrigated into the stomach for 3 h. Atropine sulphate (1·0 mg kg^{-1}) (Sigma) and insulin (50 units kg^{-1}) (Insulin Nordisk Retard NPH, Denmark) were given by subcutaneous injection (s.c.). Bupivacaine (0·5%) (Abbott Pharmaceutical Co., USA) was administered by injection of 0·4 mL per rat into both serosal sides of the stomach. Each solution was used freshly.

Statistics

Data are presented as the mean ± s.e.m. per group. Unless otherwise indicated, the statistical analysis was performed by the Student's *t*-test for unpaired comparison, and values of $P < 0·05$ were considered significant.

Results

Streptozotocin-induced diabetes

During the induction of diabetes from 1–8 weeks, the manifestations of diabetes were observed in the diabetic rat. The degeneration and atrophy of pancreatic β-tissue was also found one week after streptozotocin injection. The stomach appeared atonic and enlarged. The regurgitation of duodenal bile salts was also observed inside the stomach.

Influence of acid solutions on the gastric mucosa in diabetic rats

Intragastric irrigation of normal saline (154 mM NaCl) did not produce visible ulceration in either diabetic or age-matched control rats (data not shown). However, when the stomach of the diabetic rat was irrigated with physiological acid solutions of graded concentrations for 3 h, an acid concentration-dependent increase in the luminal H^+ loss and Na^+ output was obtained. This enhancement in acid back-diffusion was accompanied by severe mucosal haemorrhagic ulceration (Fig. 1). High correlations ($r = -0·9879$ and $-0·9227$ in 1- and 3-h acid solution perfusion studies, respectively) between back-diffused H^+ and haemorrhagic ulceration were found. The correlation obtained from the

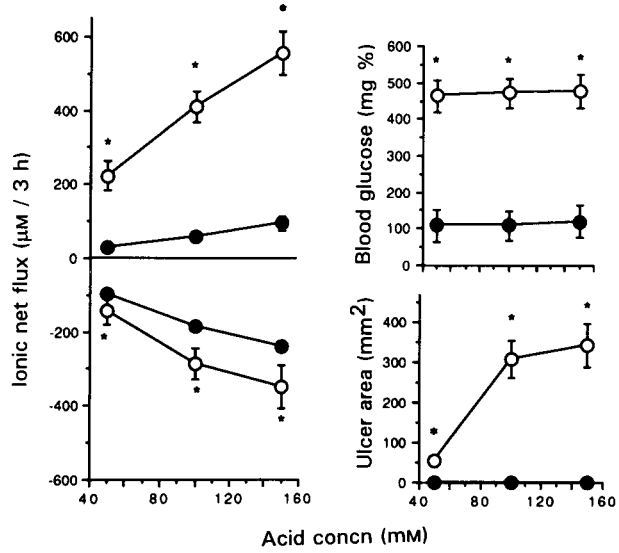

FIG. 1. Effects of acid solutions of graded concentrations on acid back-diffusion, mucosal ulceration and blood glucose in the diabetic and age-matched control rat. Acid solutions of graded concentrations (50–150 mM HCl plus adequate amount of NaCl for isotonicity) were irrigated in the stomachs of 2-week diabetic rats (○) or age-matched control rats (●) for 3 h. Severe haemorrhage was also observed in the gastric contents and on the diabetic rat gastric mucosa. Each test used 10 rats. *$P < 0·05$.

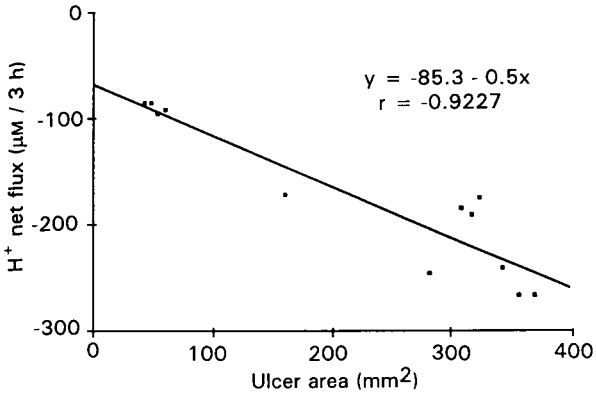

FIG. 2. Correlation between acid back-diffusion and mucosal ulceration in diabetic rats. The stomach of the diabetic rat was irrigated with acid solution containing 100 mM HCl and 54 mM NaCl for 3 h.

3-h gastric irrigation study is illustrated in Fig. 2. In these diabetic animals, high blood glucose concentrations remained unchanged. Fig. 3 demonstrates that when the 2-week diabetic rat stomach was irrigated with acid solutions containing 100 mM HCl and 54 mM NaCl for 1 and 3 h, the acid back-diffusion and the mucosal ulceration were more severe in the 3-h experiment than in the 1-h experiment. The morphological changes in gastric mucosa after 3-h acid irrigation in the diabetic rat are shown in Fig. 4a. It could be observed that numerous irregular ulcers accompanied by severe haemorrhage were produced in the gastric mucosa. Ulcers were predominately produced on the gastric fundus and corpus but seldom on the forestomach or on the antrum. Histological study also indicated that the upper part of the mucosal cells, including epithelial cells and mucus secreting cells were greatly damaged. In some cases, the damage even reached to the muscular layer. In addition, severe gastric oedema was also produced (Fig. 4b).

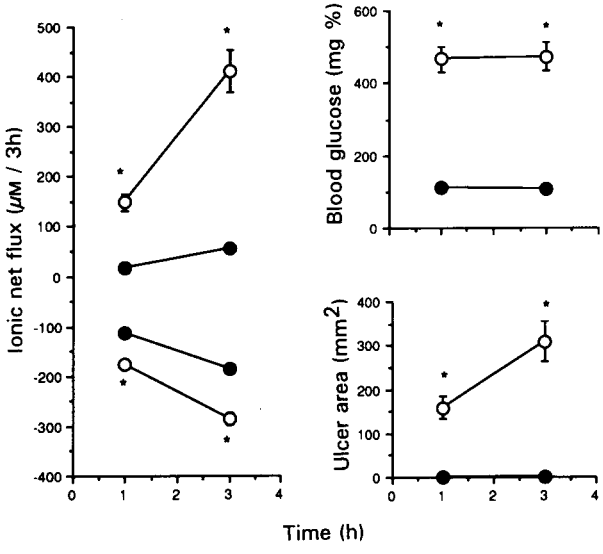

FIG. 3. Influences of acid-irrigation time on acid back-diffusion, mucosal ulceration and blood glucose levels. Acid solution containing 100 mM HCl and 54 mM NaCl was irrigated in the rat stomach for 1 and 3 h in either 2-week diabetic rats (○) or control rats (●). Each experiment used 10 rats. $*P < 0.05$.

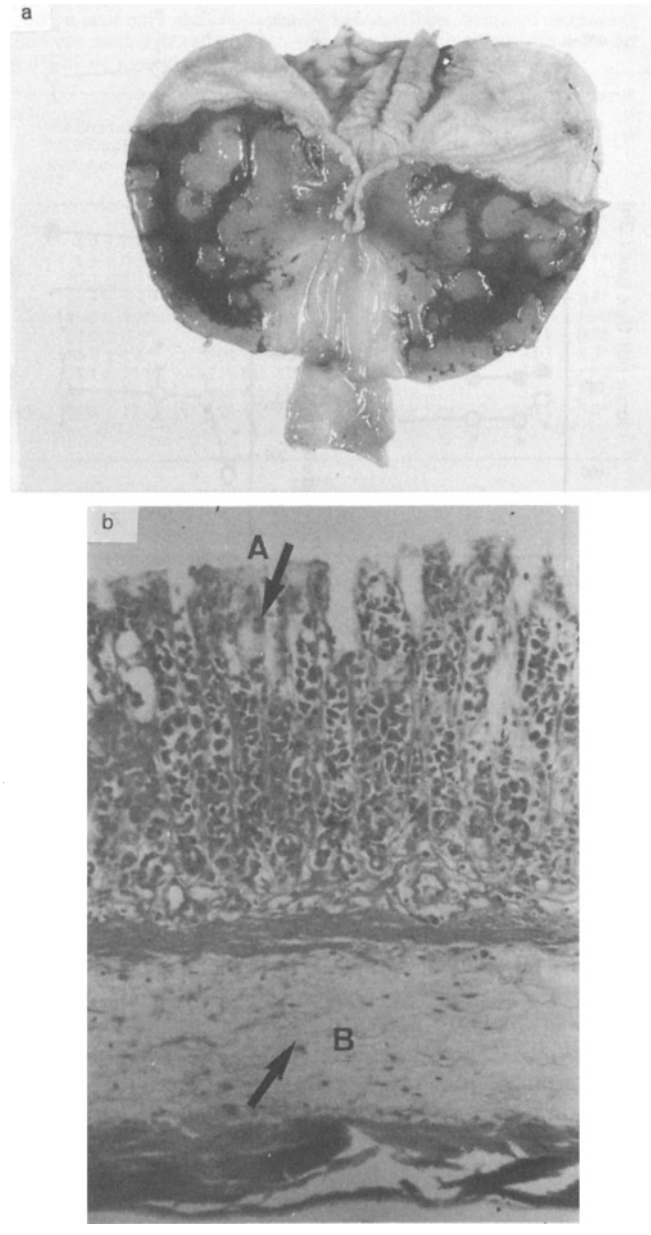

FIG. 4. a. Macroscopic study of 2-week diabetic rat gastric mucosa damaged by acid solution containing 100 mM HCl and 54 mM NaCl. The stomach of the animal was irrigated with acid solution for 3 h. Note that numerous and irregular severe ulcers are located on the corpus but not on the antrum. These ulcers are accompanied by severe haemorrhage. b. Microscopic investigation of diabetic rat gastric mucosal cells. The epigastric lining cells are completely disrupted (A); both mucosal and submucosal cells are greatly damaged and characterized by karyoclasis, and gastric oedema is also produced (B).

Influence of induction time on the gastric mucosa in diabetic rats

Fig. 5 indicates that after a single injection of streptozotocin (65 mg.kg^{-1}, i.v.) at 1, 2, 4, and 8 weeks, the stomach of the diabetic rat produced a substantial increase in acid back-diffusion and haemorrhagic ulcer than the age-matched control rat. The maximal values of either acid back-diffusion or mucosal ulceration were obtained at 2 weeks after streptozotocin was given. The same level was maintained until the

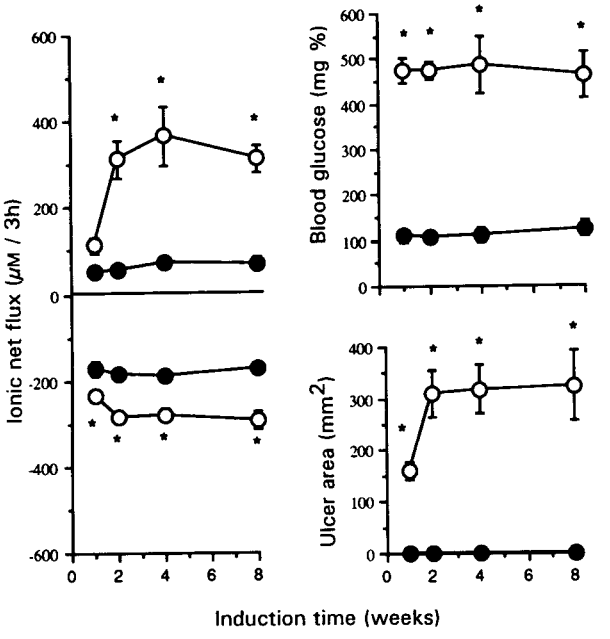

FIG. 5. Effects of induction time on acid back-diffusion and mucosal ulceration and blood glucose levels. The rat stomachs were irrigated with acid solution containing 100 mM HCl and 54 mM NaCl for 3 h in either 2-week diabetic rats (○) or control rats (●). Each test used 10 rats. $^*P < 0.05$.

8th week. However, the blood glucose levels did not significantly change over the induction time.

Effect of insulin

At the beginning of gastric acid irrigation, a single subcutaneous injection of 50 units kg^{-1} insulin, a dose which completely reversed hyperglycaemia in diabetic rats during its maximal effect, did not inhibit acid back-diffusion or haemorrhagic ulceration. Nevertheless, the blood glucose concentrations were significantly ($P < 0.05$) lowered. When the same dose of insulin was given once daily for two weeks (until the day of the gastric perfusion study), the acid back-diffusion and mucosal ulceration were greatly improved. The gastric haemorrhage and hyperglycaemia were also markedly reduced. Morphological study indicated that the haemorrhagic ulceration in the gastric mucosa of the diabetic rat was greatly diminished by this chronic administration of insulin (Fig. 6a). From the observation of histological specimens, the acid solution-induced damage of mucosal cells either in the epigastric layer or in the lamina propria was potently inhibited. Moreover, gastric oedema produced in these diabetic rats was also prevented (Fig. 6b).

Effects of drugs on acid back-diffusion and haemorrhagic ulcer in the diabetic rat

Table 1 demonstrates the effects of atropine, bupivacaine, cimetidine, $NaHCO_3$, and insulin on acid back-diffusion and mucosal damage induced by a 3-h irrigation of acid solution containing 100 mM HCl and 54 mM NaCl in 2-week diabetic rats. The changes in blood glucose concentration as well as gastric haemorrhage are also shown.

Effects of nerve blockers

Atropine (1·0 mg kg^{-1}) and bupivacaine (0·5%, 0·4 mL)

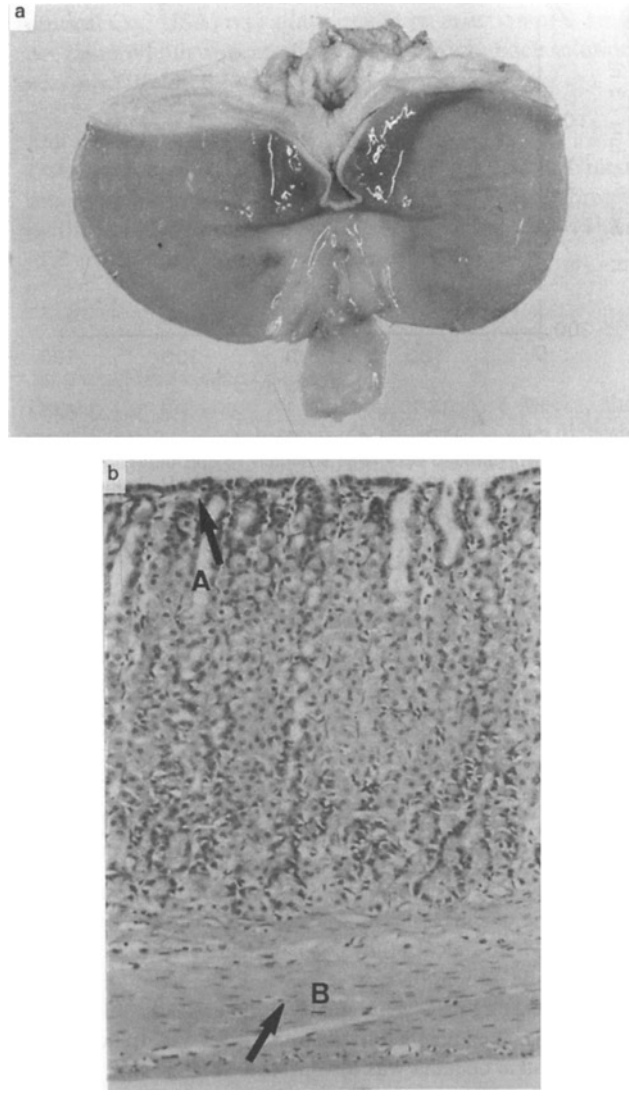

FIG. 6. Effect of daily subcutaneous injection of insulin (50 units kg^{-1}) on gastric mucosal damage induced by acid solution in the diabetic rat. The stomach of 2-week diabetic rat was irrigated with acid solution containing 100 mM HCl and 54 mM NaCl for 3 h. Morphological study (a) indicates that the mucosal haemorrhagic ulcer is potently protected. Histological investigation (b) shows that epigastric lining cells on the mucosa remain intact (A). Most of the mucosal and submucosal cells looked normal. Gastric oedema is also abolished (B).

were ineffective as inhibitors of acid back-diffusion and mucosal ulceration induced by acid solution. In contrast, the gastric volumes and haemorrhagic ulcerations were significantly exacerbated ($P < 0.05$). The hyperglycaemia in these diabetic rats was unaffected.

Effects of antiulcer agents

When the stomach of the diabetic rat was instilled with cimetidine (300 mg kg^{-1}), dissolved in acid solution, a potent inhibition of luminal H^+ loss and Na^+ output and gastric volume were obtained. This inhibition in acid back-diffusion induced by acid solution results from a decrease of H^+ concentration in the initial sample and an increase of that in the final sample. In addition, the ulcer formation and gastric haemorrhage were also potently inhibited by the

Table 1. Effects of atropine, bupivacaine, cimetidine, $NaHCO_3$ and insulin on acid back-diffusion, gastric haemorrhage, mucosal ulceration and blood glucose concentrations in diabetic rats. Two-week diabetic rats were used. The rat stomach was irrigated with either acid solution containing 100 mM HCl + 54 mM NaCl or acidified drug solution (drug dissolved in acid solution of the same concentration) for 3 h.

	Control	Atropine (1·0 mg kg^{-1}, s.c.)	Bupivacaine (0·5%, 0·4 mL serosal injection)	Cimetidine (300 mg kg^{-1}, intragastrically)	$NaHCO_3$ (52 mg kg^{-1}, intragastrically)	Single insulin (52 units kg^{-1}, s.c.)	Daily insulin (50 units kg^{-1}, s.c.)
Gastric content							
Initial volume	3·9 ± 0·0	4·0 ± 0·0	4·0 ± 0·0	4·0 ± 0·0	4·0 ± 0·0	4·0 ± 0·0	4·0 ± 0·0
Final volume	5·4 ± 0·3	5·8 ± 0·2*	6·2 ± 0·4*	4·5 ± 0·2*	5·0 ± 0·3*	5·2 ± 0·3	4·1 ± 0·1*
Initial [H$^+$] (mM)	100·0 ± 0·6	98·9 ± 1·0*	100·4 ± 0·6	70·2 ± 0·5*	70·9 ± 0·9*	99·6 ± 0·6	98·6 ± 0·3*
Final [H$^+$] (mM)	19·8 ± 2·4	19·8 ± 1·5	20·0 ± 2·0	29·9 ± 2·4*	14·8 ± 1·5*	18·6 ± 1·3	43·7 ± 3·8*
Net flux (μmol/3 h)	−287·5 ± 11·0	−280·0 ± 6·0	−276·1 ± 11·1	−145·0 ± 4·2*	−214·0 ± 7·2*	−300·6 ± 4·9*	−212·5 ± 16·0*
Initial [Na$^+$] (mM)	50·1 ± 1·0	50·9 ± 3·8	52·3 ± 0·4*	52·0 ± 0·5*	74·2 ± 0·7*	53·1 ± 0·2*	52·9 ± 0·5*
Final [Na$^+$] (mM)	99·5 ± 3·2	94·1 ± 3·6*	95·3 ± 3·2*	74·7 ± 1·6*	104·1 ± 1·3*	98·2 ± 2·5	74·3 ± 3·3*
Net flux (μmol/3 h)	344·7 ± 36·8	342·5 ± 32·4	393·7 ± 36·8*	135·1 ± 22·5*	219·8 ± 37·2*	304·5 ± 41·0	93·3 ± 15·2*
Blood glucose (mg%)	484·3 ± 26·9	476·0 ± 25·8	466·5 ± 25·3	458·1 ± 28·3	463·4 ± 24·5	86·5 ± 20·7*	72·8 ± 18·0*
Ulcer index (mm^2)	296·2 ± 42·3	328·0 ± 48·5	341·3 ± 50·2	76·5 ± 12·2*	96·4 ± 11·3*	274·8 ± 52·4	20·1 ± 5·0*
Gastric bleeding	7/7	7/7	7/7	0/7	2/7	7/7	0/7

Statistical differences were assessed by analysis of variance. *$P < 0·05$ vs control. Each test used seven animals.

same dose of cimetidine, despite the blood glucose level remaining unaltered. It can also be seen (Table 1) that 52 mg kg^{-1} $NaHCO_3$, which possesses almost the same acid-reducing capacity as 300 mg kg^{-1} cimetidine, produced a significant ($P < 0·05$) decrease in acid solution-induced acid back-diffusion and mucosal haemorrhagic ulceration. Nevertheless, the inhibitory effect of $NaHCO_3$ on these ulcerogenic parameters was less potent than that of cimetidine. Furthermore, the high blood glucose levels were not affected in either cimetidine- or $NaHCO_3$-treated diabetic rats.

Discussion

Streptozotocin, which possesses anti-tumour and diabetogenic effects, is commonly used as a diabetes inducer in experimental animals (Calabresi & Chabner 1991; Tomlinson et al 1992). In the present study, the manifestations of diabetes and the atrophy of pancreatic β-cells observed in 1–8 week streptozotocin-induced diabetic rats may indicate that diabetes was developed in those animals. The irrigation of the stomach with acid solutions of physiological concentrations (50–150 mM HCl) produced a concentration- and a time-dependent enhancement in the mucosal permeability to electrolytes and haemorrhagic ulceration in diabetic rats. Furthermore, a high correlation between the acid back-diffusion and ulcer formation was found in both the 1- and the 3-h gastric acid perfusion study. Taken together, the haemorrhagic ulceration produced in diabetic rats was mainly due to the enhancement in acid back-diffusion. Morphological and histological studies further supported this view by showing severe haemorrhagic ulceration and profound damage of mucosal cells in the gastric mucosa. Gastric oedema produced in the diabetic rat stomach was probably due to the increase in gastric vascular permeability induced by histamine release which resulted from acid back-diffusion. However, the high blood glucose concentration remained unchanged. Therefore, streptozotocin-induced diabetes may produce pathological changes in the gastric mucosa, and the intraluminal acid back-diffuses into gastric mucosa through the disrupted mucosal barriers. This back-diffusion of gastric acid, rather than hyperglycaemia, plays a more important role in the formation of gastric haemorrhagic ulcer and oedema in the diabetic rat. Hitherto, the initiation of the disruption of gastric mucosal barriers in diabetic rats has been unclear, as was the reason for the maximal increase in acid back-diffusion and ulceration two weeks after streptozotocin administration. Nevertheless, the decrease in gastric mucosal blood flow resulted from pathological changes in blood vessels and in haemodynamics; the impairment of hormonal controlling mechanisms as well as the regurgitation of bile salts produced by diabetes may partly be responsible. Other reports indicate that bile salts can damage gastric mucosal barriers (Davenport & Chavre 1968; Ritchie 1975; Whittle 1977). Atropine, an anticholinergic, and bupivacaine, a potent long-acting local anaesthetic, failed to inhibit acid back-diffusion and ulceration. The gastric volume and ulcer formation were significantly ($P < 0·05$) enhanced. These results suggest that the damage to gastric mucosal barriers, rather than impairment or degeneration of nerves, is more important for the occurrence of acid back-diffusion and acute haemorrhagic ulceration in the early stage of diabetes. Cimetidine, a histamine H_2-receptor antagonist, potently inhibits gastric secretion (Hirschowitz 1979; Hung et al 1979). Cimetidine is also effective in healing gastroduodenal ulcer (Bauer et al 1986; Feldman & Burton 1990). In the present study, intragastric cimetidine reduced the acid concentration in the initial sample and elevated that in the final sample. This may result from the buffering and neutralizing actions of cimetidine. It is reported that in the lumen, only free acid can back-diffuse into gastric mucosa (Hollander et al 1985). A previous report has demonstrated that the amount of acid back-diffused into gastric mucosa is dependent on the concentration of free acid in the lumen (Hung & Lee 1991). Taken together, the inhibitory effect of cimetidine on acid solution-induced gastric haemorrhagic ulceration and oedema in the diabetic rat results from the reduction of acid back-diffusion, which was achieved by neutralizing and buffering effects rather than from antisecretory action. On the other hand, $NaHCO_3$ at a dose (52 mg kg^{-1}) with the same acid-reducing effect as cimetidine (300 mg kg^{-1}) was also effective in protecting diabetic rat gastric mucosa against acid-induced damage. However, due to a lack of

buffering action, the inhibitory effect of $NaHCO_3$ was less than that of cimetidine.

It was also demonstrated that daily administration, but not single injection of long-acting insulin, potently inhibited acid back-diffusion and haemorrhagic ulceration in streptozotocin-induced diabetic rats. Morphological and histological studies also showed that chronic administration of insulin potently diminished the disruption of gastric mucosal barriers and effectively protected gastric mucosa cells against acid solution-induced damage. In addition, gastric oedema was also prevented (Fig. 6a, b). The insulin-induced modulation of rates of DNA, RNA and protein synthesis as well as of cellular growth and differentiation may be involved in the maintenance of the integrity of gastric mucosal barriers. Furthermore, the blood glucose concentrations in these acute and chronic insulin-treated diabetic rats were greatly reversed. Therefore, it seems likely that long-term deficiency of insulin or chronic hypo-insulinaemia may also be responsible for pathological changes in gastric mucosal barriers. This consequently renders gastric mucosa more susceptible to the acid-induced damaging effect.

From the above results, it is suggested that acid back-diffusion plays an important role in the formation of the acute haemorrhagic ulcer and gastric oedema in streptozotocin-induced diabetic rats, and that intragastric cimetidine or $NaHCO_3$ or daily injection of insulin has potent protective effects on gastric acid-induced acid back-diffusion and mucosal haemorrhagic ulceration in these rats.

Acknowledgement

This research was supported by a grant (NSC 83-0412-B-006-028) from the National Sciences of Council in Taiwan, Republic of China.

References

Barrett, E. J., Sherwin, R. S. (1983) Gastrointestinal manifestations of diabetic ketoacidosis. Yale J. Biol. Med. 56: 175–178

Bauer, R. F., Bibach, R. G., Casler, J., Goldstein, B. (1986) Comparative mucosal protective properties of misprostol, cimetidine and sacralfate. Gastroenterology 31: 81s-85s

Calabresi, P., Chabner, B. A. (1991) Antineoplastic agents. In: Gilman, A. G., Rall, T. W., Nies, A. S. (eds) Goodman and Gilman's The Pharmacological Basis of Therapeutics. 8th edn, Macmillan, New York, pp 1209–1263

Davenport, H. W., Chavre, V. J. (1968) Destruction of the gastric mucosal barrier by detergents and urea. Gastroenterology 54: 175–181

Davenport, H. W., Warner, H. A., Code, C. F. (1964) Functional significance of gastric mucosal barrier to sodium. Gastroenterology 47: 142–152

Feldman, M., Burton, M. E. (1990) Histamine H_2-receptor antagonists. Standard therapy for acid-peptic diseases. (First of two parts.) N. Engl. J. Med. 323: 1672–1680

Feldman, M., Schiller, L. R. (1983) Disorders of gastrointestinal motility associated with diabetes mellitus. Ann. Intern. Med. 98: 378–384

Goyal, R. K., Spiro, H. M. (1971) Gastrointestinal manifestations of diabetes mellitus. Med. Clin. North Am. 55: 1031–1044

Hikins, D. J., Moody, F., Steward, I. M., Atkinson, M. (1975) Vagal impairment of gastric secretion in diabetic autonomic neuropathy. Br. Med. J. 2: 588–593

Hirschowitz, B. I. (1967) Continuing gastric secretion after insulin hypoglycemia despite glucose injection. Am. J. Dis. 12: 19–25

Hirschowitz, B. I. (1979) H_2-histamine receptor. Ann. Rev. Pharmacol. Toxicol. 19: 203–244

Hollander, D., Tarnauski, A. A., Krause, W. J., Gergely, H. (1985) Protective effect of sulcrafate against alcohol-induced mucosal injury in the rat. Gastroenterology 88: 366–374

Hung, C.-R., Lee, C.-H. (1991) Protective effect of cimetidine on tannic acid-induced gastric damage in rats. J. Pharm. Pharmacol. 43: 559–563

Hung, C. R., Okabe, S., Kasuya, Y. (1979) Gastric acid secretion in beagle dogs using intramuscular injection of stimulants. Jpn. J. Pharmacol. 29: 147–148

Hung, C.-R., Wang, J.-J., Chang, W.-C., Shen, C.-L. (1994) Protective effects of arginine-vasopressin on aspirin-induced gastric mucosal damage in anaesthetized dogs. J. Pharm. Pharmacol. 46: 276–281

Lennart, A., Gerhard, D., Lehmann, K. E. (1961) The gastric mucosa in diabetes mellitus — a functional and histopathological study. Acta Medica Scandinavica. 169, fasc. 3: 339–349

Piyachaturawat, P., Poprasit, J., Glinsukon, T., Wanichanon, C. (1983) Gastric mucosal lesions in streptozotocin-diabetic rats. Cell. Biol. Int. Rep. 12: 53–63

Ritchie, W. P. (1975) Acute gastric mucosal damage induced by bile salts, acid and ischemia. Gastroenterology 68: 699–704

Saltzman, M. B., McCallum, R. W. (1983) Diabetes and the stomach. Yale J. Biol. Med. 56: 179–185

Tomlinson, K. C., Gardiner, S. M., Herbden, R. A., Bennet, T. (1992) Functional consequences of streptozotocin-induced diabetes mellitus, with particular reference to the cardiovascular system. Pharmacol. Rev. 44: 104–150

Whittle, B. J. R. (1977) Mechanism underlying gastric damage induced by indomethacin and bile salts and the actions of prostaglandins. Br. J. Pharmacol. 60: 455–460

Wood, M. N. (1947) Chronic peptic ulcer in 94 diabetics. Am. J. Dig. Dis. 14: 1–11