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Effect of angiotensin II and telmisartan, an angiotensin$_1$ receptor antagonist, on rat gastric mucosal blood flow

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SUMMARY

Background: Angiotensin II (ATII) has been suggested to contribute to shock-induced dysfunction of the gastric circulation.

Aim: To substantiate this conjecture, the effects on gastric mucosal haemodynamics and the hyperaemic response to acid back-diffusion of ATII and the angiotensin AT_1 receptor antagonist, telmisartan, were examined in normal rats and in animals subjected to haemorrhage.

Methods: Gastric mucosal blood flow in phenobarbital-anaesthetized rats was recorded with the hydrogen clearance technique, and acid back-diffusion was induced by perfusing the stomach with ethanol (25%) in HCl (0.05 M).

Results: Intravenous infusion of ATII (0.3–10 nmol/min/kg) led to dose-dependent hypertension and a reduction of blood flow and vascular conductance in the gastric mucosa. The gastric hyperaemia caused by acid back-diffusion was attenuated by ATII (1 nmol/min/kg). These effects of ATII were antagonized by intravenous injection of telmisartan (1–10 mg/kg) which *per se* caused hypotension and dilated the gastric mucosal vasculature, but did not modify the gastric mucosal hyperaemia evoked by acid back-diffusion. Hypotension induced by haemorrhage (1.3 mL blood per 100 g body weight) failed to alter the hyperaemia due to acid back-diffusion, but caused gastric mucosal vasoconstriction, an effect that was left unaffected by telmisartan.

Conclusions: ATII constricts the rat gastric microvasculature via an action involving AT_1 receptors. The effects of telmisartan indicate that endogenous ATII contributes to the homeostatic regulation of gastric vascular tone but does not compromise the ability of the gastric microvasculature to react to influxing acid. These results negate the concept that ATII contributes to the gastric vascular perturbances in haemorrhagic shock.

INTRODUCTION

The vasoconstrictor peptide angiotensin II (ATII) plays an important role in cardiovascular homeostasis and hence in the control of organ perfusion. ATII is formed by the renin–angiotensin system, whose components angiotensinogen, renin and angiotensin-converting enzyme (ACE) are present not only in the systemic circulation but also in the gastric wall. Thus, angiotensinogen,[1] renin[2] and ACE[3, 4] are expressed in the gastric tissue as is chymase, another enzyme capable of angiotensin I conversion.[5] These findings suggest that ATII may be formed within the stomach to control local blood flow, a conjecture that is consistent with the ability of ATII to constrict the gastric vascular bed *in vitro*[6, 7] and the left gastric artery *in vivo*.[8]

The beneficial effect of ACE inhibitors in gastric dysfunction due to cardiogenic or haemorrhagic

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shock[9, 10] has been taken to suggest that ATII plays an adverse role in the maintenance of gastric mucosal perfusion. It should be taken into consideration though, that the effects of ACE inhibitors arise from both the inhibition of ATII formation and the inhibition of bradykinin breakdown.[11, 12] As a consequence, conclusive information on the role of ATII in gastric pathophysiology can only be obtained by the use of specific ATII receptor antagonists. The aim of the current study was therefore: (i) to characterize the effects of ATII and the AT_1 receptor antagonist telmisartan (BIBR 277)[13] on the gastric mucosal microcirculation of the rat, (ii) to examine whether endogenous ATII participates in the regulation of gastric mucosal blood flow (GMBF), (iii) to test whether ATII interferes with the vasodilation which is evoked in the gastric mucosa by acid back-diffusion, and (iv) to elucidate the role of ATII in the perturbances of the gastric circulation in haemorrhagic shock. Because AT_1 receptor antagonists are developed as antihypertensive therapeutics,[14] these studies were also conducted to survey the potential influence of this novel class of drugs on gastric vascular homeostasis.

METHODS

Surgical preparation

All experiments were approved by the Federal Ministry of Science and Research of the Republic of Austria. Female Sprague–Dawley rats, weighing 180–220 g, were fasted for 20 h but were allowed free access to water. After inducing anaesthesia with phenobarbital (250 mg/kg, i.p.) the rats were placed on a heated table, in order to maintain a rectal temperature of 37 °C, and fitted with a tracheal cannula, to facilitate spontaneous respiration and to allow for the administration of hydrogen. An arterial cannula was inserted into the right carotid artery and connected to a pressure transducer (ISOTEC; HSE, March-Hugstetten, Germany). The amplified signal from the pressure transducer was fed into a personal computer via an analogue–digital converter and mean arterial pressure and heart rate were calculated online. A second cannula was placed in the left jugular vein for continuous infusion of saline (1.5 mL/h), to avoid dehydration, and for the i.v. administration of drugs. The stomach was exposed by a midline laparotomy and fitted with an inflow cannula placed in the forestomach and an outflow cannula inserted through the pylorus.[15] Fluid (for composition see experimental protocol) kept at room temperature was perfused through the stomach at a rate of 0.7–0.8 mL/min throughout the experiment.

Gastric mucosal blood flow

Gastric mucosal blood flow was measured with the hydrogen clearance technique.[15–17] The washout of hydrogen gas was estimated by a needle-type platinum electrode inserted from the serosa into the basal portion of the gastric corpus mucosa and positioned at the submucosal border of the muscularis mucosae.[15] The determination of blood flow was discontinuous, as the experimental protocol involved alternating 15-min periods of saturation and desaturation, of the tissue with hydrogen gas. The current representing the actual hydrogen concentration at the site of the electrode was amplified, digitized and recorded on a personal computer. The washout curve was then fitted to a mono-exponential curve, the power of which was used to calculate the average gastric mucosal blood flow (mL/min/100 g) during the 15-min period of desaturation.[17] Average values of mean arterial pressure and heart rate were calculated for the same time periods. Since some of the experimental perturbations studied here altered the mean arterial pressure, all changes in gastric mucosal haemodynamics were also expressed as percentage changes of gastric mucosal vascular conductance (calculated as gastric mucosal blood flow divided by mean arterial pressure).

Experimental protocols

After completion of surgery, gastric mucosal blood flow was allowed a period of at least 60 min to settle at a stable baseline value. Thereafter, the first period of hydrogen saturation (0–15 min) and desaturation (15–30 min) was recorded to determine basal gastric mucosal blood flow. The alternating cycle of hydrogen saturation and desaturation was then continued to study the effects of ATII, telmisartan, gastric acid back-diffusion and haemorrhage on gastric mucosal blood flow.

Four studies were performed. In studies 1–3 the stomach was perfused with saline throughout the experiment. In Study 1 the effects of different doses of ATII or its vehicle on mean arterial pressure, heart rate and gastric mucosal blood flow were examined. To this end, graded doses of ATII in the range of 0.3–10 nmol/

min/kg were infused i.v., only one dose being tested in each animal. The infusion of ATII and its vehicle, which was made at a rate of 10.5 μL/min, started at t = 30 min, when the first cycle of hydrogen saturation and desaturation had been completed. The infusion was continued for 60 min, during which time two hydrogen saturation and desaturation curves were recorded to determine the effects of ATII or its vehicle on gastric mucosal blood flow.

Study 2 was carried out to investigate the effect of vehicle or telmisartan (1 and 10 mg/kg), and for comparison the α-adrenoceptor antagonist prazosin (0.1 mg/kg), on mean arterial pressure, heart rate and gastric mucosal blood flow. For this purpose, vehicle, telmisartan or prazosin was injected i.v. as a 1 mL/kg bolus at t = 30 min. After this, three cycles of hydrogen saturation and desaturation were performed to monitor gastric mucosal blood flow.

Study 3 was performed to assess the effect of telmisartan (1 and 10 mg/kg) or its vehicle on the haemodynamic changes caused by the i.v. infusion of ATII (1 and 3 nmol/min/kg). In this instance, telmisartan or its vehicle was injected as an i.v. bolus at t = 0 before recording the baseline haemodynamic parameters. At t = 30 min the i.v. infusion of ATII was started and continued over two periods of hydrogen saturation and desaturation.

Study 4 tested the hypothesis that endogenous ATII is involved in the circulatory disturbances of the gastric mucosa in haemorrhagic hypotension. This question was addressed in two stages. First, the effects of telmisartan, ATII, or a combination of telmisartan plus ATII, on the gastric mucosal vasodilator response to acid back-diffusion were investigated in normal rats. To this end, rats were pre-treated with an i.v. injection of telmisartan (1 mg/kg) or its vehicle (1 mL/kg) after which one cycle of hydrogen saturation/desaturation was recorded while the stomach was perfused with 0.05 M HCl. Thirty minutes after the injection of telmisartan or its vehicle, an i.v. infusion of ATII (1 nmol/min/kg) or vehicle (10.5 μL/min) was started and another saturation/desaturation cycle monitored, while 0.05 M HCl was perfused through the stomach. While the ATII/vehicle infusion continued, gastric acid back-diffusion was induced by perfusing the stomach with 25% ethanol in 0.05 M HCl,[15] and one additional saturation/desaturation curve recorded.

Second, the effect of AT_1 receptor blockade with telmisartan on gastric mucosal hyperaemia induced by acid back-diffusion was examined in rats subjected to haemorrhage. Following slow withdrawal through the carotid cannula of 1.3 mL blood per 100 g body weight (t = 0) baseline mean arterial pressure, heart rate and gastric mucosal blood flow were recorded (15–30 min). After the i.v. injection of telmisartan (1 mg /kg) or its vehicle (1 mL/kg) and an additional saturation/desaturation cycle the gastric perfusion was changed from 0.05 M HCl to 25% ethanol in 0.05 M HCl and the effect of acid back-diffusion on gastric mucosal blood flow recorded.

Materials

Phenobarbital was dissolved in saline at a concentration of 33 mg/mL. Stock solutions of ATII (Bachem, Bubendorf, Switzerland) were prepared in distilled water (1 mM) and further dilutions ready for infusion were prepared with saline. Telmisartan (BIBR 277, 4′-[(1,4′-dimethyl-2′-propyl-[2,6′-bi-1H-benzimidazol]-1-yl) methyl]-[1,1′-biphenyl]-2-carboxylic acid; Boehringer Ingelheim Pharma KG, Biberach, Germany) was dissolved by placing 20 mg of the drug in a vial and adding, step by step, 800 mg distilled water, 44 mg 1 M NaOH, 900 mg distilled water and 100 mg mannitol, the emerging solution being stirred and heated to 90 °C. To obtain a concentration of 10 mg/mL telmisartan, the solution was made up to a final volume of 2 mL by adding distilled water, the pH then being adjusted to ≈ 9.5 with 1 M HCl. The 1 mg/mL telmisartan solution and the blank vehicle were prepared in an analogous manner.

Statistical analysis

The data are presented as mean ± S.E.M. Statistical comparisons between groups were made with the Kruskal–Wallis H-test or the Mann–Whitney U-test. Probability values of $P < 0.05$ were regarded to be significant.

RESULTS

Effects of ATII and telmisartan on gastric haemodynamics in the absence of acid back-diffusion (Studies 1–3)

Intravenous ATII infusion at rates of 0.3–10 nmol/min/kg caused a dose-dependent increase in mean arterial pressure and decrease in gastric mucosal blood flow, while in contrast, the vehicle had no effect (Figure 1,

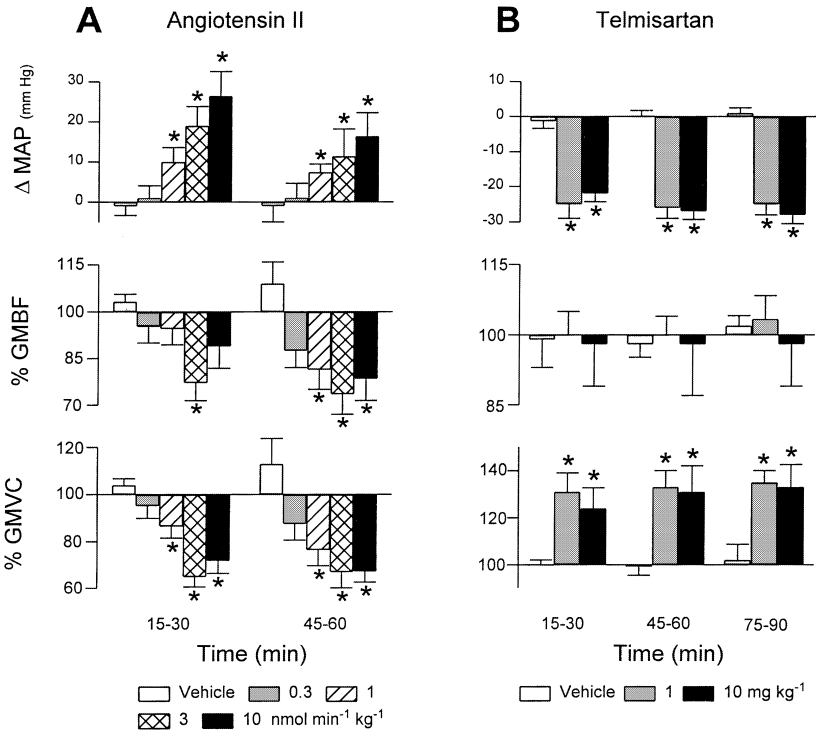

Figure 1. Effect of (A) angiotensin II (ATII) and (B) telmisartan on mean arterial blood pressure (MAP), gastric mucosal blood flow (GMBF) and gastric mucosal vascular conductance (GMVC). ATII or its vehicle was infused i.v. for a period of 60 min, whereas telmisartan or its vehicle was injected as i.v. bolus. The bars depict changes in the haemodynamic parameters relative to baseline values, the abscissa indicating the recording periods after the start of the ATII infusion or telmisartan injection. Mean ± S.E.M., $n = 6–7$; *$P < 0.05$ vs. vehicle.

Table 1. Haemodynamic effects of angiotensin II (ATII), telmisartan and prazosin

		Mean arterial pressure (mmHg)		Heart rate (beat/min)		Gastric mucosal blood flow (mL/min/100 g)	
Drug	Dose	pre	post	pre	post	pre	post
Vehicle (ATII)	10.5 μL/min	101 ± 5	101 ± 4	402 ± 21	412 ± 20	43.0 ± 6.4	44.4 ± 6.7
ATII	0.3 nmol/min/kg	107 ± 4	107 ± 3	379 ± 22	383 ± 19	36.5 ± 3.5	34.4 ± 2.8
ATII	1 nmol/min/kg	109 ± 4	121 ± 6†	386 ± 21	397 ± 12	35.5 ± 5.5	32.5 ± 4.0
ATII	3 nmol/min/kg	109 ± 2	130 ± 4†	386 ± 14	414 ± 14	36.8 ± 4.2	28.4 ± 4.1†
ATII	10 nmol/min/kg	100 ± 6	122 ± 5†	385 ± 17	408 ± 13†	33.9 ± 2.4	30.0 ± 3.1
Vehicle (telmisartan)	1 mL/kg	105 ± 5	103 ± 6	386 ± 18	389 ± 18	37.1 ± 2.3	36.6 ± 2.7
Telmisartan	1 mg/kg	108 ± 6	83 ± 5†	389 ± 25	383 ± 28	36.0 ± 3.1	36.1 ± 3.7
Telmisartan	10 mg/kg	107 ± 3	85 ± 4†	379 ± 17	376 ± 19	38.2 ± 3.0	36.4 ± 2.0
Vehicle (prazosin)	1 mL/kg	98 ± 7	99 ± 6	337 ± 6	337 ± 4	34.2 ± 4.4	32.3 ± 4.6
Prazosin	50 μg/kg	102 ± 4	67 ± 3†	331 ± 12	326 ± 21	34.7 ± 4.5	30.1 ± 4.0

Mean arterial blood pressure, heart rate and blood flow in the gastric mucosa were determined during the 15-min period before, and the 15–30-min period after the i.v. infusion of angiotensin II (ATII) or its vehicle had been started or telmisartan, prazosin or the respective vehicle had been injected i.v., respectively. Data shown are mean ± S.E.M.; $n = 6–7$. †$P < 0.05$ vs. pre-infusion.

Table 1). The hypertensive action of ATII was biphasic at the initial pressor response, which with higher ATII doses reached peak values of up to 60 mmHg (data not shown), and declined within 10 min, giving way to a lower but sustained hypertension (Figure 1, Table 1). The initial pressor effect of ATII was usually accompanied by a parallel increase in heart rate, but the elevation of heart rate seen at later periods was not statistically significant (Table 1). The ATII-induced decrease in gastric mucosal blood flow pointed to gastric mucosal vasoconstriction, which was most obvious when the gastric mucosal haemodynamics were expressed as gastric mucosal vascular conductance (Figure 1).

Table 2. Effect of telmisartan on angiotensin II (ATII)-induced haemodynamic changes

	Mean arterial pressure (mmHg)		Heart rate (beat/min)		Gastric mucosal blood flow (ml/min/100 g)	
Agonist/antagonist	pre	post	pre	post	pre	post
ATII 1 nmol/min/kg						
Vehicle 1 mL/kg	99 ± 6	113 ± 7†	357 ± 16	361 ± 17	33.8 ± 2.4	30.4 ± 2.2†
Telmisartan 1 mg/kg	75 ± 6	79 ± 6	350 ± 16	362 ± 14	29.1 ± 1.9	28.0 ± 2.1
Telmisartan 10 mg/kg	78 ± 6	81 ± 6	372 ± 8	379 ± 11	32.2 ± 2.6	30.3 ± 1.8
ATII 3 nmol/min/kg						
Vehicle 1 mL/kg	106 ± 5	131 ± 3†	384 ± 13	426 ± 16†	36.8 ± 7.3	30.4 ± 5.7†
Telmisartan 1 mg/kg	76 ± 6	91 ± 5†	391 ± 16	418 ± 13†	40.4 ± 7.1	40.8 ± 5.6
Telmisartan 10 mg/kg	76 ± 4	82 ± 3	386 ± 12	392 ± 9	37.0 ± 2.4	35.9 ± 2.8

Mean arterial blood pressure, heart rate and blood flow in the gastric mucosa were determined during the 15-min period before and the 15–30-min period after the i.v. infusion of angiotensin II (ATII) had been started. Telmisartan or its vehicle were injected i.v. 30 min before the ATII infusion. Data shown are mean ± S.E.M.; $n = 6$–8. †$P < 0.05$ vs. preinfusion.

The intravenous injection of telmisartan (1 and 10 mg/kg) caused a prompt fall in mean arterial pressure, which was sometimes accompanied by a slight fall in heart rate (Figure 1, Table 1). Although the gastric mucosal blood flow did not change, gastric mucosal vasodilation was evident from the observation that gastric mucosal vascular conductance rose by about 30–40% following the telmisartan injection (Figure 1, Table 1). The effects of the ATII antagonist remained constant over the following 90 min, and responses to the two doses of telmisartan (1 and 10 mg/kg) did not differ from each other (Figure 1). The vehicle that the telmisartan was carried in failed to induce any haemodynamic alterations (Figure 1, Table 1). The haemodynamic effects of prazosin (50 μg/kg, i.v.), which were tested for comparison, were similar to those of telmisartan. The systemic hypotension was accompanied by an increase in gastric mucosal vascular conductance (134 ± 8% vs. 93 ± 5% in vehicle-treated rats; $n = 6$, $P < 0.01$) indicating a dilation of the gastric microvasculature, whereas gastric mucosal blood flow did not change (Table 1).

To examine the activity of telmisartan as an ATII antagonist, the effects of telmisartan (1 and 10 mg/kg) on the haemodynamic changes evoked by ATII were investigated. The two doses of ATII (1 and 3 nmol/min/kg) selected for these experiments reduced gastric mucosal vascular conductance to a half-maximal and maximal extent, respectively (Figure 1). Despite an obvious tendency towards inhibition, the moderate haemodynamic effects of the lower dose of ATII (1 nmol/min/kg) were too variable to allow for a significant inhibition by either dose of telmisartan (1 and 10 mg/kg), with the exception of the pressor response to ATII which was significantly antagonized by 10 mg/kg telmisartan (Figure 2, Table 2). In contrast, both doses of telmisartan (1 and 10 mg/kg) significantly attenuated the ability of the higher dose of ATII (3 nmol/min/kg) to decrease gastric mucosal blood flow and gastric mucosal vascular conductance (Figure 2, Table 2). The sustained phase of the hypertensive effect of ATII (3 nmol/min/kg) was also significantly reduced by the higher dose of telmisartan (10 mg/kg) but not by the lower dose of the antagonist (1 mg/kg) (Figure 2, Table 2). The initial peak increase in mean arterial pressure seen immediately after the start of the ATII infusion was completely abolished by both doses of telmisartan (data not shown).

Effects of ATII, hemorrhage and telmisartan on gastric haemodynamics under acid back-diffusion (Study 4)

To test for a pathophysiological role of ATII, the influence of exogenous and endogenous ATII on the gastric mucosal hyperaemic response to acid back-diffusion was examined under both normal conditions and during haemorrhage. The induction of acid back-diffusion by perfusing the stomach with 25% ethanol in 0.05 M HCl did not affect mean arterial pressure and heart rate (data not shown), but elicited a marked hyperaemia in the gastric mucosa. This was indicated by markedly elevated values of gastric mucosal blood flow after acid back-diffusion (Figure 3) as compared with the values at baseline (Table 3) and by a more

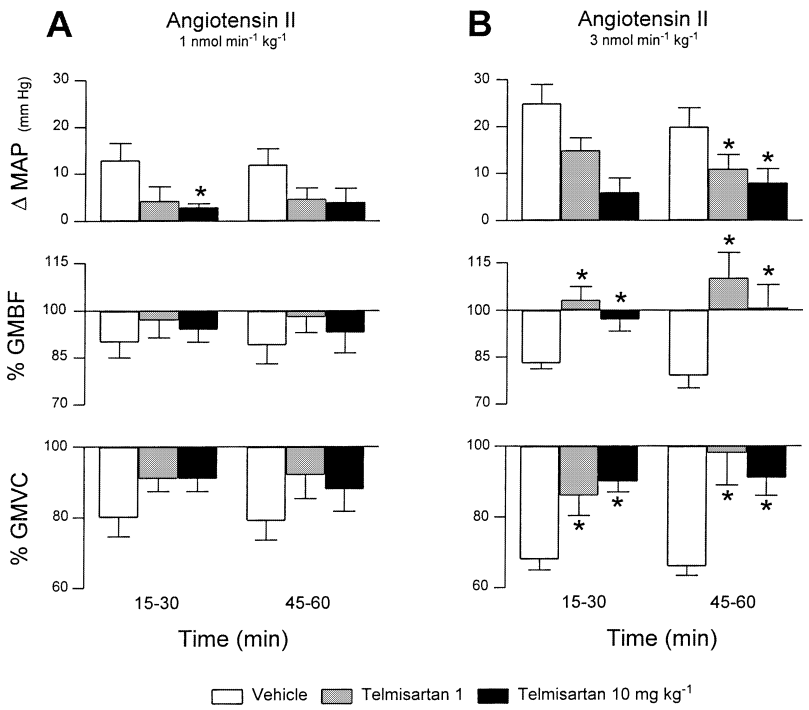

Figure 2. Effect of telmisartan on the ability of angiotensin II (ATII; 1 nmol/min/kg in (A) and 3 nmol/min/kg in (B)) to raise mean arterial blood pressure (MAP) and to lower gastric mucosal blood flow (GMBF) and gastric mucosal vascular conductance (GMVC). Telmisartan or its vehicle was injected i.v. 30 min before the i.v. infusion of ATII was started. The bars depict changes in the haemodynamic parameters relative to baseline values, the abscissa indicating the recording periods after the start of the ATII infusion. Mean ± S.E.M., $n = 7–8$. *$P < 0.05$ vs. vehicle.

than twofold increase in gastric mucosal vascular conductance relative to basal values in control animals (Figure 3). As in study 1, i.v. infused ATII (1 nmol/min/kg) caused hypertension and gastric mucosal vasoconstriction without affecting gastric mucosal blood flow. In addition, ATII reduced acid-evoked vasodilation, as indicated by a significantly diminished percentage rise of gastric mucosal vascular conductance (Figure 3).

The withdrawal from the rats of 1.3 mL blood per 100 g body weight lowered mean arterial pressure to 30–50 mmHg. After this initial fall, the mean arterial pressure readily recovered and reached stable values of 60–100 mmHg within 30 min (Table 3). Heart rate did not change, but gastric mucosal blood flow fell by 50%, which was in part due to vasoconstriction, as was demonstrated by a decrease in gastric mucosal vascular conductance (Table 3). While the relative increase in gastric mucosal vascular conductance in response to acid back-diffusion remained unchanged, the absolute values of gastric mucosal blood flow during acid back-diffusion were significantly decreased in haemorrhaged rats as compared with the control group (Figure 3).

Pre-treatment with telmisartan (1 mg/kg) caused hypotension and increased gastric mucosal vascular conductance without altering gastric mucosal blood flow (Table 3), as had been found in Study 2, but it did not significantly alter the gastric mucosal vasodilation (i.e. the increase in gastric mucosal vascular conductance) induced by acid back-diffusion, neither under control conditions nor after haemorrhage (Figure 3). In contrast, the inhibitory effect of ATII (1 nmol/min/kg) on the gastric mucosal dilator response to acid back-diffusion was abolished by telmisartan (1 mg/kg) pre-treatment (Figure 3).

DISCUSSION

The current study demonstrates, for the first time, that ATII is a factor in the physiological maintenance of gastric mucosal vascular tone. This conjecture is based on two observations. First, ATII constricted the gastric mucosal vasculature in a dose-dependent manner, as was demostrated by a decrease in gastric mucosal blood flow and gastric mucosal vascular conductance and, second, the AT_1 receptor antagonist telmisartan,[13, 18] dilated the gastric mucosal vasculature, as indicated by an increase in gastric mucosal vascular conductance. On the other hand, our data argue against a major role of ATII in the gastric perturbations during haemorrhagic hypotension, since telmisartan did not reverse the disproportionate hypoperfusion of the stomach after haemorrhage. Although our observations were made under anaesthesia, which is known to alter cardiovascular responsiveness, the major conclusions of this

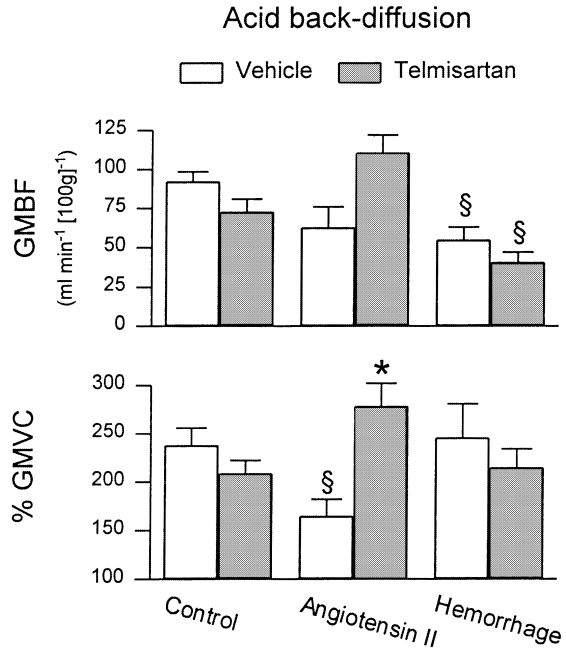

Figure 3. Effects of telmisartan, angiotensin II and haemorrhage on changes in gastric mucosal haemodynamics caused by acid back-diffusion, which was induced by perfusing the stomach with 25% ethanol in 0.05 M HCl. Gastric mucosal blood flow (GMBF) was recorded during period 15–30 min after acid back-diffusion had been induced. The changes in gastric mucosal vascular conductance (GMVC) in response to acid back-diffusion are expressed as percentage of the respective baseline values taken during the 15-min period before acid back-diffusion. Haemorrhage was induced by slowly withdrawing 1.3 mL blood per 100 g body weight from a carotid artery 75 min before acid back-diffusion was initiated. In control and haemorrhagic rats telmisartan (1 mg/kg) or vehicle (1 mL/kg) was injected i.v. 30 min before the induction of acid back-diffusion. The angiotensin II group received a telmisartan/vehicle injection 60 min and an infusion of angiotensin II (1 nmol/min/kg) starting 30 min before acid back-diffusion. Mean ± S.E.M.; $n = 14–6$. *$P < 0.05$ vs. vehicle, §$P < 0.05$ vs. control.

study promise to be relevant for the following reasons. The overall alteration of cardiovascular responses to drugs by anaesthesia is largely due to a depression of neural counter-regulatory mechanisms, as is exemplified by diminished pressor effects of drugs and a smaller depressor effect of haemorrhage in conscious rats as compared to anaesthetized rats.[19] However, from a pharmacological point of view, anaesthesia might be an even more appropriate experimental condition than consciousness in which to investigate cardiovascular reactivity to vasoactive drugs, since responses will be less obscured by counter-regularory mechanisms. Moreover, basal activity and responsiveness to hypotension of the renin-angiotensin system have been shown to be unaltered by anaesthesia.[20]

Since telmisartan effectively inhibited the haemodynamic responses to ATII (3 nmol/min/kg) it would appear that the dilatory action of the antagonist is mostly due to a blockade of AT_1 receptors. Given the specificity of telmisartan as an AT_1 antagonist[8, 13, 18] it can be ruled out that the nonspecific effects of the antagonist accounted for the changes in mean arterial pressure and gastric mucosal vascular tone, which were similar with the 1 and 10 mg/kg doses of telmisartan. The influence of telmisartan-evoked hypotension on gastric mucosal blood flow was compared with hypotension induced by the α-adrenoceptor antagonist prazosin and haemorrhage. The fall in mean arterial pressure seen after prazosin was likewise accompanied by a significant increase in gastric mucosal vascular conductance, whereas gastric mucosal blood flow did not change. In contrast, haemorrhagic hypotension caused a marked decrease in both gastric mucosal blood flow and gastric mucosal vascular conductance. This observation suggests that hypotension *per se* does not dilate the gastric mucosal vasculature and therefore that the telmisartan-evoked increase in gastric mucosal vascular conductance reflects the true gastric mucosal vasodilation which arises from antagonism of endogenous ATII. This inference is further supported by the ability of ATII to constrict the gastric vascular bed *in vitro*[6, 7] and the left gastric artery *in vivo*.[8]

To shed light on the pathophysiological role of the renin–angiotensin system in the stomach, the influence of ATII and telmisartan on the gastric hyperaemia that occurs in response to acid back-diffusion was examined. This model was chosen because the hyperaemic response to gastric acid challenge is a protective reaction of the mucosa to influxing acid and thus proves particularly suitable to study gastric mucosal blood flow under pathophysiological circumstances.[15, 21, 22] The gastric vasodilation that is evoked by acid back-diffusion involves sensory neurones[15] and is mediated by calcitonin gene-related peptide and nitric oxide.[23, 24] The influence of telmisartan on gastric mucosal microcirculation and the presence of the renin–angiotensin system in the gastric wall[1–5] are compatible with the idea that endogenous ATII modifies gastric vascular homeostasis in the face of acid back-diffusion. However, while exogenous ATII reduced the hyperaemic response to acid back-diffusion by an AT_1 receptor-mediated mechanism, antagonism of endogenous ATII did not

Table 3. Haemodynamic effects of telmisartan in rats subjected to haemorrhage

	Mean arterial pressure (mmHg)		Heart rate (beat/min)		Gastric mucosal blood flow (mL/min/100 g)		Gastric mucosal vascular conductance (mL/min/g/mmHg)	
	pre	post	pre	post	pre	post	pre	post
Control								
Vehicle 1 mL/kg	106 ± 4	108 ± 4	338 ± 7	343 ± 8	43.1 ± 2.9	40.7 ± 2.7	41.6 ± 3.2	38.4 ± 2.8
Telmisartan 1 mg/kg	106 ± 4	87 ± 3*†	331 ± 12	328 ± 9	40.0 ± 2.9	40.6 ± 5	38.8 ± 3.2	49.7 ± 3.8*†
Hemorrhage								
Vehicle 1 mL/kg	89 ± 5§	88 ± 6§	311 ± 7	321 ± 9	21.5 ± 4.6§	24.6 ± 4.1§	25.9 ± 6.6§	29.6 ± 5.4†
Telmisartan 1 mg/kg	81 ± 6§	59 ± 3§*†	330 ± 15	336 ± 14	19.5 ± 3.6§	20.1 ± 3.6§	26.3 ± 5.5§	35.5 ± 6.7§†

Hemorrhage was induced by slow withdrawal of 3 mL blood from a carotid artery at 0 min. Telmisartan (1 mg/kg) or its vehicle (1 mL/kg) was injected i.v. at 45 min. Mean arterial blood pressure, heart rate, blood flow and vascular conductance in the gastric mucosa were determined during the periods 30–45 min (pre telmisartan/vehicle) and 60–75 min (post telmisartan/vehicle). Data shown are mean ± S.E.M.; n = 6–14. *$P < 0.05$ vs. vehicle, §$P < 0.05$ vs. control, †$P < 0.05$ vs. pre-infusion.

modify the mucosal hyperaemia due to gastric acid challenge. It hence appears that, despite its constrictor action on the gastric vasculature, endogenous ATII does not compromise the ability of the gastric microvasulature to dilate in response to influxing acid. It follows in addition, that ATII, should it be formed locally under conditions of acid back-diffusion, is unlikely to be a factor that causes gastric mucosal dysfunction by interfering with protective vasodilator reactions.

Gastric mucosal pathology is a frequent complication of cardiovascular shock and has been attributed to an enhanced activation of the renin–angiotensin axis and the resulting vasoconstriction.[9, 10, 25] The current results, however, do not support this concept because the gastric mucosal vasodilator response to acid back-diffusion, which was inhibited by exogenous ATII, was left unaltered by haemorrhage, and the blockade of AT_1 receptors with telmisartan failed to reverse the gastric mucosal vasoconstriction due to haemorrhage. Thus, endogenous ATII is unlikely to participate in the deleterious effects of haemorrhage on gastric circulatory homeostasis. Instead, a role for other vasoconstrictors is suggested. The protective effect of ACE inhibitors on gastric function during haemorrhagic shock[10] is probably due to their ability also to inhibit bradykinin breakdown.[11, 12]

In conclusion, the present data demonstrate that ATII is a potent constrictor of the rat gastric mucosal vasculature and contributes to the physiological maintenance of mucosal vascular tone. This homeostatic effect of the peptide depends on the activation of AT_1 receptors, since it is antagonized by telmisartan. Despite its vasoconstrictor action, however, endogenous ATII does not seem to hinder the protective rise of gastric mucosal blood flow in the face of acid back-diffusion. The AT_1 receptor antagonist telmisartan likewise does not have an adverse effect on the microcirculatory reaction to influxing acid and in fact improves gastric mucosal perfusion at baseline. This aspect is of pharmacotherapeutic relevance, given that AT_1 receptor antagonists are developed as antihypertensive drugs.[14] Furthermore, the present data negate the concept that ATII contributes to vascular dysregulation of the gastric mucosa in haemorrhagic shock.

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