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Nitric oxide modulates captopril-mediated angiotensin-converting enzyme inhibition in porcine iliac arteries

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Abstract

The influence of the angiotensin-converting enzyme inhibitor captopril on bradykinin-and angiotensin I-induced responses with special regard to nitric oxide (NO) was studied. Auxometric tension and angiotensin-converting enzyme activity was studied in isolated porcine iliac arteries. Captopril potentiated bradykinin-induced contraction of preparations with intact endothelium; this potentiation was not seen with the kininase I inhibitor mergepta or a bradykinin B_1-receptor antagonist. Captopril did not affect bradykinin-induced relaxation. The captopril-mediated increase of bradykinin-induced contraction was only seen in preparations with intact endothelium, while captopril did not affect arterial strips treated with *N*ω-nitro-L-arginine. Angiotensin I-induced contractions was less reduced by captopril when the strips were pretreated with *N*ω-nitro-L-arginine. Both captopril and the NO donor *S*-nitroso-*N*-acetyl-penicillamine inhibited angiotensin-converting enzyme activity. An additional reduction in angiotensin-converting enzyme activity was seen when *S*-nitroso-*N*-acetyl-penicillamine was added to captopril-treated preparations. In conclusion, captopril increased bradykinin-induced contraction in a NO-dependent manner. This potentiation is probably mediated by the increased metabolism of bradykinin by kininase I, and the additive angiotensin-converting enzyme inhibitory effect of captopril and NO.

Keywords: Angiotensin-converting enzyme activity; Bradykinin; Captopril; Contraction; Nitric oxide (NO); Relaxation

1. Introduction

Angiotensin-converting enzyme inhibitors are today commonly used in the treatment of hypertension and congestive heart failure. Apart from preventing the conversion of angiotensin I to angiotensin II, angiotensin-converting enzyme inhibitors also reduce bradykinin degradation (Bhoola et al., 1992; Skidgel, 1992). This increase in bradykinin content is believed to be responsible for part of the cardiovascular effects of angiotensin-converting enzyme inhibitors (Mombouli and Vanhoutte, 1992; Linz et al., 1995).

Angiotensin-converting enzyme (also called kininase II or E.C. 3.4.15.1) is a Zn^{2+}-containing dipeptidyl carboxypeptidase with two catalytic sites. It is found both circulating in plasma and membrane-bound in tissues. Angiotensin-converting enzyme acts on several peptides, like angiotensin I, bradykinin, enkephalins and substance P (Johnston, 1994; Corvol et al., 1995).

Bradykinin acts as an important regulator of blood flow, especially during inflammation (Hall, 1992). Bradykinin is a potent vasodilator, but may act as a contractile agent in higher concentrations (Regoli and Barabé, 1980; Hall, 1992) or in the presence of endothelial injury (Briner et al., 1993; Pruneau et al., 1994). Bradykinin-induced relaxation is endothelium-dependent and most often mediated by bradykinin B_2-receptor activation (D'Orléans-Juste et al., 1985; Schini et al., 1990) with the subsequent production of nitric oxide (NO), prostacyclin and/or endothelium-derived hyperpolarization factor (EDHF) (De Nucci et al., 1988; D'Orléans-Juste et al., 1989; Mombouli and Vanhoutte, 1995; Busse and Fleming, 1996). Bradykinin-induced contraction is mediated by bradykinin B_1 and/or B_2 receptors located in the vascular media (Regoli and Barabé, 1980). In virtually all species, the bradykinin B_1 receptor is not normally present but is up-regulated (induced) during, for instance, inflammation (Hall, 1992) and experimental conditions (Regoli and Barabé, 1980; Bouthillier et al., 1987).

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Angiotensin-converting enzyme inhibitors have been shown to potentiate both bradykinin-induced relaxation and contraction (Félétou et al., 1992; Mombouli et al., 1992; Hecker et al., 1994).

This study examines the effect of the angiotensin-converting enzyme inhibitor captopril on bradykinin-induced responses in isolated porcine iliac arteries, with special reference to endothelial function, NO and angiotensin-converting enzyme activity.

2. Material and methods

2.1. Tension studies

Iliac arteries from domestic pigs were obtained at the local slaughterhouse and transported to the laboratory in Krebs' buffer. The Krebs' buffer had the following composition in mM: 137 Na^+, 5.89 K^+, 2.50 Ca^{2+}, 1.20 Mg^{2+}, 134 Cl^-, 18.0 HCO_3^-, 1.20 $H_2PO_4^-$ and 5.6 glucose, and was gassed with 95% O_2 + 5% CO_2 and kept at 37°C. The arteries were carefully cleaned of adipose tissue, cut into rings of 3–5 mm and then cut open, forming arterial strips. In some experiments, the endothelium was removed by gently rubbing the luminal side of the strips with a wooden stick, as previously described (Persson and Andersson, 1998). The strips were mounted between a fixed point in organ chambers containing Krebs' buffer, and a Grass FT 03 strain gauge transducer connected to a Grass Polygraph (Grass Instrument, Quincy, MA, USA), allowing continuous measurement of auxometric tension. The strips were then stretched to 2–2.5 g and allowed to equilibrate for 45 min, resulting in a passive tension of 0.5–1.0 g (the optimal passive tension for these vessels). After wash, endothelial function of each strip was tested by precontraction with 10^{-6} M phenylephrine and adding 10^{-6} M acetylcholine. Only strips relaxing more than 50% in response to acetylcholine were considered having an intact endothelium. As for the rubbed strips, the removal of the endothelium was regarded as complete when no relaxation or a slight contraction was seen. Then, the preparations were submitted to several washes which made tension return to basal value. Angiotensin I- and bradykinin-induced responses were then examined as described below. The preparations were washed every 45 min throughout the experiments.

2.1.1. Bradykinin-induced contraction

Experiments were performed on arterial strips with intact (with or without pretreatment with 10^{-4} M *N*ω-nitro-L-arginine for 15 min) or removed endothelium. All strips were preincubated for 5 h prior to bradykinin stimulation; the reason for this was to avoid discrepancies in results due to de novo synthesis of the bradykinin B_1 receptor (in a preliminary study we found a maximal bradykinin-induced contraction at 5 h; data not shown). Preparations preincubated with captopril for different time periods showed the most significant effect on bradykinin-induced responses when captopril was present for 3 h prior to bradykinin stimulation; therefore this preincubation time was used in all the following experiments. Captopril concentrations used were 10^{-7}, 10^{-6} or 10^{-5} M. When the kininase I carboxypeptidase inhibitor mergepta or the brady kinin B_1-receptor antagonist des-Arg^9-[Leu^8]bradykinin was used, they were added 10 min before bradykinin.

After stimulation with bradykinin, the strips were submitted to several washes and then maximal contraction of each strip was determined by using a Krebs' buffer with a high K^+ concentration (128 mM K^+, 15.4 mM Na^+ and other ions as described in Section 2.1).

2.1.2. Bradykinin-induced relaxation

In order to study bradykinin-induced relaxation, arterial strips with intact endothelium were used. Prior to bradykinin stimulation, strips were pretreated for 3 h with captopril; concentrations as described in Section 2.1.1. Each strip was then precontracted with 10^{-6} M phenylephrine and bradykinin was cumulatively added in the concentration range 10^{-11} to 3×10^{-8} M. To avoid any contractile response to bradykinin, 10^{-6} M indomethacin was added to all strips 10 min before phenylephrine-precontraction. After bradykinin stimulation, the strips were washed and tension allowed to return to basal value. Then, 10^{-6} M phenylephrine was added followed by 10^{-6} M nitroprusside.

2.1.3. Angiotensin I-induced contraction

Angiotensin I (10^{-5} M)-induced contractions were examined in arterial strips with intact endothelium with or without 10^{-4} M *N*ω-nitro-L-arginine for 15 min. Preparations were preincubated for 10 min with captopril (10^{-7}, 10^{-6} and 10^{-5} M) prior to adding angiotensin I. Finally, maximal contraction of each strip was examined by replacing the Krebs' buffer surrounding the preparations with a Krebs' buffer with high K^+ concentration as described in Section 2.1.1.

2.2. Angiotensin-converting enzyme activity

Iliac arteries were homogenised with a glass/glass homogeniser in 10 vol 0.1 M potassium phosphate buffer, pH 7.8. After centrifugation ($1000 \times g$ for 20 min), the supernatant was incubated with captopril and/or *S*-nitroso-*N*-acetyl-penicillamine (a NO donor) for 10 min, and then angiotensin-converting enzyme activity was analysed with a commercial radioenzymatic assay (ACE-direct REA, Bühlmann Laboratories, Allschwil, Switzerland). The

experiments were performed in darkness due to the instability of *S*-nitroso-*N*-acetyl-penicillamine when exposed to light. The effect of 10^{-4} M *N*ω-nitro-L-arginine on angiotensin-converting enzyme activity was also studied.

2.3. Calculations

Angiotensin I- and bradykinin-induced contractions were calculated as percent of K^+-induced contraction. Bradykinin- and nitroprusside-induced relaxations were calculated as percent of phenylephrine-induced precontraction. 1 unit (U) of angiotensin-converting enzyme activity is defined as the amount of enzyme required to release 1 μmole of hippuric acid per minute and liter. Results are given as mean ± S.E.M. and statistical calculations were done with one-way analysis of variance (ANOVA) repeated measures for matched data, followed by Dunett's post-hoc test, or Student's *t*-test for unpaired or one sample data. pD_2 values for the concentration–relaxation curves were estimated with a nonlinear regression analysis using GraphPad Prism™ 2.0 and are given with a 95% confidence interval in parenthesis, and differences in maximal relaxation were estimated by one-way ANOVA or Student's *t*-test for unpaired values. Statistical significance is defined as $^*P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$.

2.4. Drugs

Acetylcholine, angiotensin I, bradykinin, des-Arg^9-[Leu^8]bradykinin, indomethacin, phenylephrine, *N*ω-nitro-L-arginine and nitroprusside were purchased from Sigma (St. Louis, MO, USA). The kininase I carboxypeptidase inhibitor mergepta (DL-2-mercaptomethyl-3-guanidino ethylthiopropanoic acid) from Calbiochem (La Jolla, CA, USA). Captopril was a gift from Bristol-Myers Squibb (Princeton, NJ, USA). *S*-nitroso-*N*-acetyl-penicillamine was obtained from GEA Pharmaceutical (Copenhagen, Denmark). All drugs were dissolved in distilled water except indomethacin where 5% $NaHCO_3$ was used, resulting in a final concentration of 0.005% $NaHCO_3$ in the organ baths.

3. Results

3.1. Tension studies

No significiant difference was seen in basal tension, acetylcholine-induced relaxation (except between strips with and without endothelium) or K^+-induced contraction in any of the experimental series described below (data not shown).

3.1.1. Bradykinin-induced contraction

In preparations with intact endothelium, captopril (10^{-7}, 10^{-6} and 10^{-5} M) dose-dependently increased bradykinin-induced contractions (Fig. 1A). No such captopril-induced effect was seen, with any of the concentrations used, when strips with intact endothelium were treated with *N*ω-nitro-L-arginine (Fig. 1B) or in preparations with removed endothelium (Fig. 1C). *N*ω-nitro-L-arginine slightly increased bradykinin-induced contractions compared to control (Fig. 1A and B: control curves), but this effect did not reach significance ($P < 0.07$). The kininase I carboxypeptidase inhibitor mergepta (10^{-6} M) significantly decreased bradykinin-induced contraction (Fig. 2A). Moreover, the captopril-induced potentiation was not seen in the presence of mergepta (Fig. 2B). The bradykinin B_1-recep-

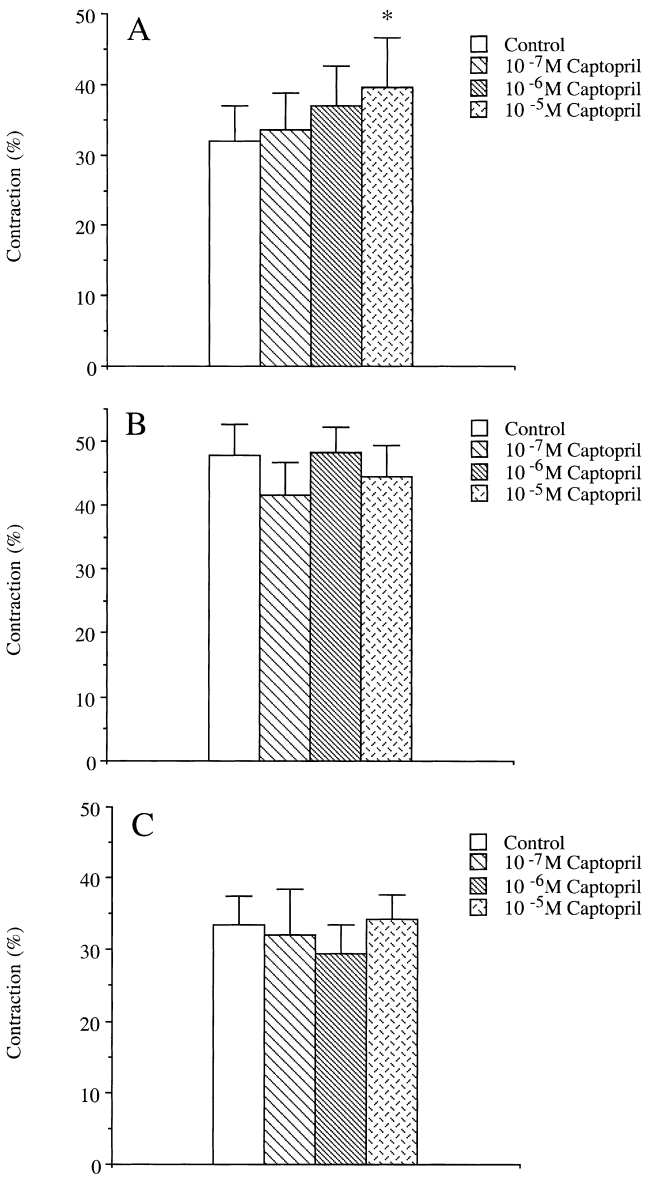

Fig. 1. Bradykinin (10^{-5} M)-induced contraction of isolated porcine iliac arteries. Preparations were pretreated with captopril for 3 h. Arterial strips with intact endothelium, without (A; $n = 12$) or with 10^{-4} M *N*ω-nitro-L-arginine (B; $n = 6$), or strips with removed endothelium (C; $n = 6$). Significance is calculated with one-way ANOVA and denoted as $^*P < 0.05$.

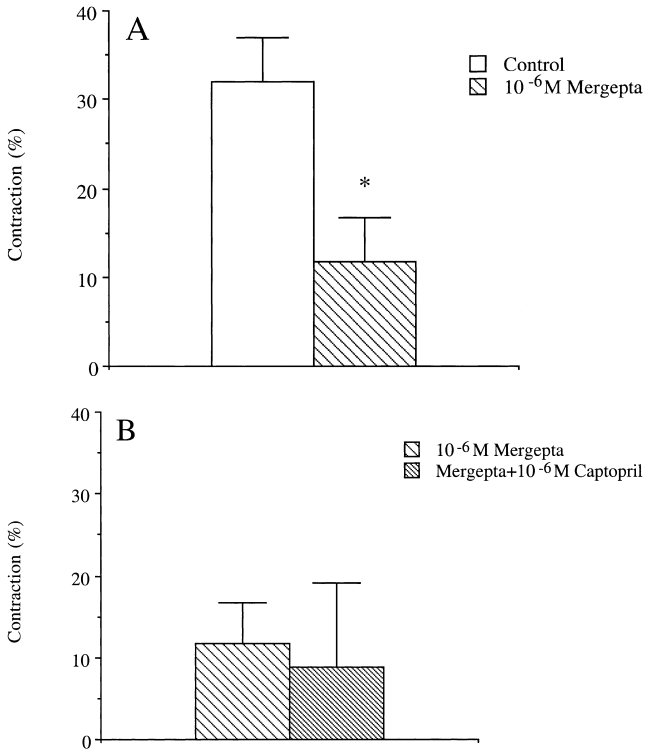

Fig. 2. Bradykinin (10^{-5} M)-induced contraction of isolated porcine iliac arteries with intact endothelium. Bradykinin was added after pretreatment with 10^{-6} M mergepta for 10 min (A; $n=12$ for control and 5 for mergepta-treated) or 10^{-6} M captopril for 3 h (B; $n=5$). Significance is calculated with Student's *t*-test for unpaired values and denoted as $^{*}P<0.05$.

tor antagonist des-Arg^{9}-[Leu^{8}]bradykinin signficantly reduced the contractions and attenuated the captopril-induced potentiation (Fig. 3).

3.1.2. Bradykinin-induced relaxation

Captopril alone did not affect bradykinin-induced relaxation (neither pD_2 values nor maximal relaxation) in any of the concentrations used (Fig. 4). Mergepta significantly

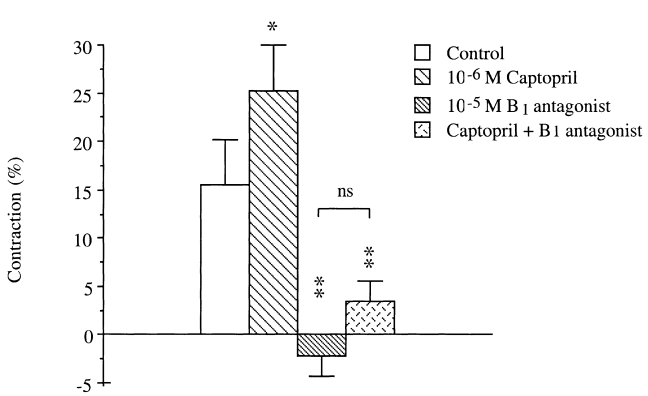

Fig. 3. Bradykinin (10^{-5} M)-induced contraction of isolated porcine iliac arteries with intact endothelium. Bradykinin was added after pretreatment with 10^{-5} M des-Arg^{9}-[Leu^{8}]bradykinin for 10 min, $n=5$. Significance is calculated with one-way ANOVA and denoted as $^{*}P<0.05$ and $^{**}P<0.01$.

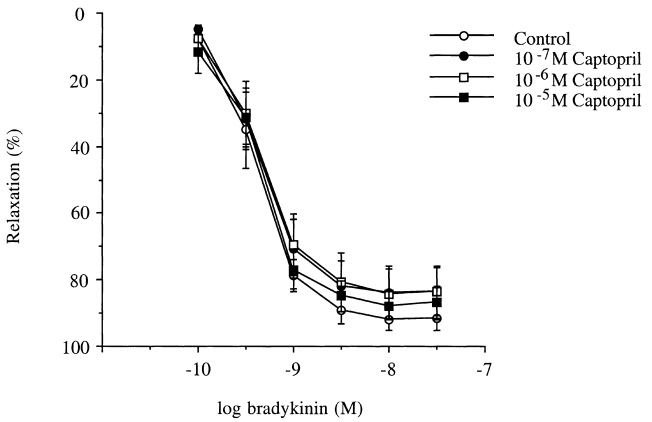

Fig. 4. Bradykinin-induced relaxation of isolated porcine iliac arteries with intact endothelium after pretreatment with captopril for 3 h. 10^{-6} M indomethacin was present in all preparations and added 10 min prior to phenylephrine-induced precontraction. No significant difference was seen in pD_2 values or maximal relaxation, $n=8$.

augmented bradykinin-induced relaxation when compared to control; pD_2 was 9.39 (9.50–9.28) and 9.11 (9.20–9.02) respectively (Fig. 5A; no change in maximal bradykinin-induced relaxation was seen). When 10^{-6} M captopril was added to strips treated with 10^{-6} M mergepta, there was no significant change of the concentration–relaxation curve; pD_2 9.42 (9.52–9.32) and 9.31 (9.39–9.24) respectively (Fig. 5B). Nitroprusside-induced relaxation was neither affected by mergepta nor captopril treatment (data not shown).

3.1.3. Angiotensin I-induced contraction

In preparations with intact endothelium, angiotensin I-induced contraction was significantly inhibited by 10^{-6} and 10^{-5} M captopril, while 10^{-7} M had no effect. Arterial strips pretreated with *N*ω-nitro-L-arginine were significantly less sensitive to captopril (Fig. 6). No significant difference was seen in control compared to *N*ω-nitro-L-arginine treated strips. A time delay (of 4–8 min) in obtaining maximal response was seen in all preparations treated with captopril compared to controls (results not shown).

3.2. Angiotensin-converting enzyme activity

The iliac arteries exhibited a low angiotensin-converting enzyme activity, 5.7 ± 0.7 U. As expected, captopril dose-dependently and highly significantly inhibited angiotensin-converting enzyme activity. Also, both 10^{-5} and 10^{-4} M *S*-nitroso-*N*-acetyl-penicillamine inhibited angiotensin-converting enzyme (Fig. 7A). The concomitant addition of *S*-nitroso-*N*-acetyl-penicillamine and captopril to the preparations resulted in a further reduction of enzyme activity. This additional inhibition was evident when 10^{-7} and 10^{-6} M captopril was used, but was significant only with the lower concentration (Fig. 7B).

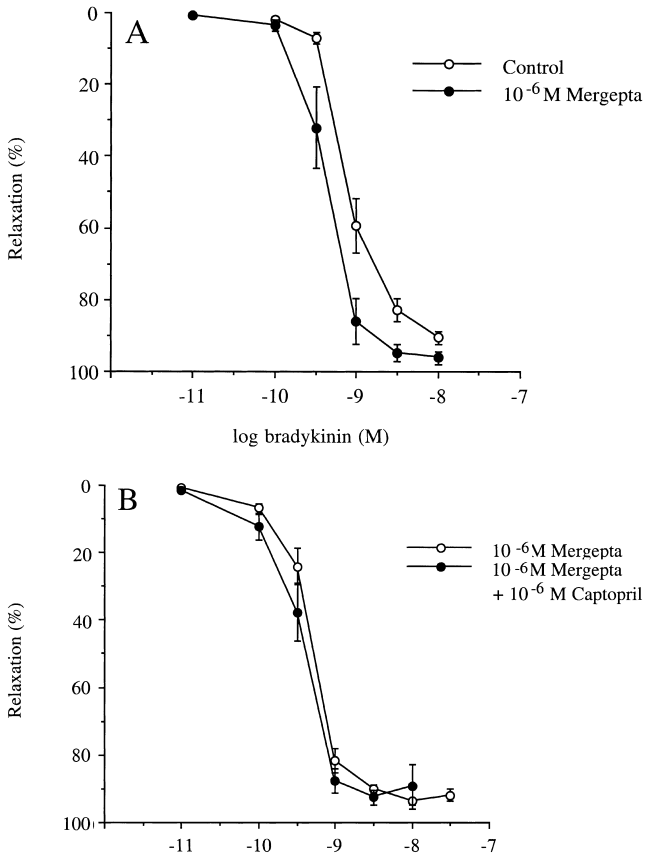

Fig. 5. Bradykinin-induced relaxation of isolated porcine iliac arteries with intact endothelium. Arterial strips were treated with 10^{-6} M mergepta for 10 min, without (A) or with (B) 10^{-6} M captopril for 3 hs prior to phenylephrine-induced precontraction. 10^{-6} M indomethacin was present in all preparations, $n = 6–7$. No difference was seen in maximal relaxation. (A) pD2 values were significantly different ($P < 0.05$) between control, 9.39 (9.50–9.28), and mergepta treated, 9.11 (9.20–9.02). (B) pD2 values were slightly (but not significantly) different between mergepta and mergepta + captopril treated, 9.42 (9.52–9.32) and 9.31 (9.39–9.24) respectively. pD2 values were estimated with a nonlinear regression analysis and given with a 95% confidence interval in parenthesis.

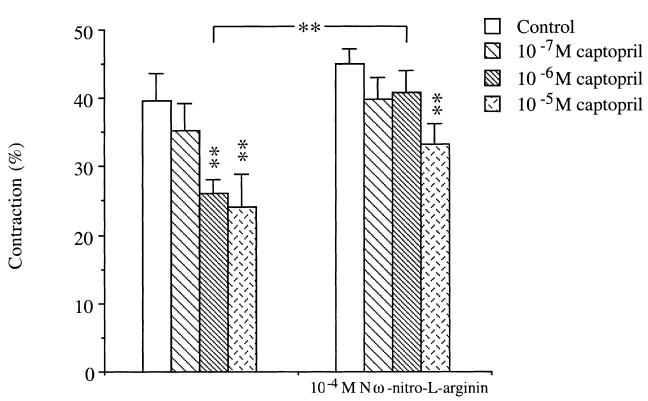

Fig. 6. Angiotensin I (10^{-5} M) -induced contraction of isolated porcine iliac arteries with intact endothelium or intact endothelium treated with 10^{-4} M $N\omega$-nitro-L-arginine for 15 min. Preparations were pretreated with captopril for 10 min. Significance is calculated with one-way ANOVA and denoted as $^{**}P < 0.01$, $n = 6$.

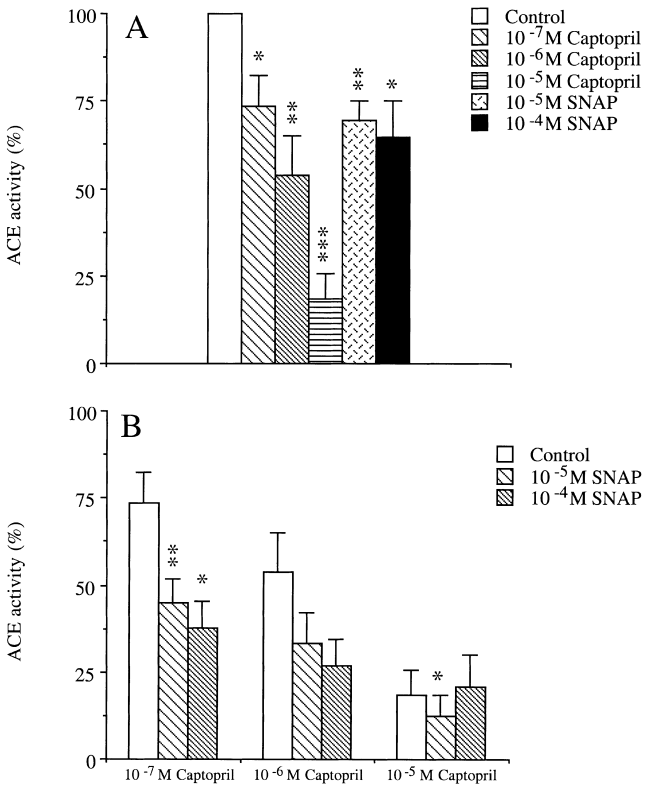

Fig. 7. Angiotensin-converting enzyme activity in homogenate of porcine iliac arteries with intact endothelium. Preparations were pretreated for 10 minutes with captopril and/or *S*-nitroso-*N*-acetyl-penicillamine (SNAP). Significance is calculated with Student's *t*-test for one sample (A) or paired data (B), and denoted as $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$, $n = 7$.

A 10^{-4} M $N\omega$-nitro-L-arginine had no significant effect on angiotensin-converting enzyme activity, 128.8 ± 24.5% of control.

4. Discussion

We have previously shown that bradykinin stimulation of porcine iliac arteries results in a biphasic response. Low concentrations of bradykinin ($< 3 \times 10^{-8}$ M) elicit a relaxing effect, while higher concentrations result in a contraction. The relaxation is mediated by bradykinin B_2 receptor and the subsequent production of NO. Both bradykinin B_1 and B_2 receptors located in the vascular media seem to be responsible for the contraction (Persson and Andersson, 1998).

Several enzymes are responsible for bradykinin degradation e.g. angiotensin-converting enzyme, neutral endopeptidase and carboxypeptidase M (kininase I) (Skidgel, 1992). The action of angiotensin-converting enzyme on bradykinin renders inactive peptide fragments, while kininase I activity results in the bradykinin B_1-receptor agonist des-Arg^9-bradykinin. des-Arg^9-bradykinin is, in turn, metabolized by angiotensin-converting enzyme (Sharma et

al., 1996). Previous results from our group suggest that kininase I is the main enzyme responsible for bradykinin degradation in porcine iliac arteries (Persson and Andersson, 1998). This is in accordance with the present study, as the kininase I inhibitor mergepta and the bradykinin B_1-receptor antagonist markedly reduced bradykinin-induced contraction. Also, the bradykinin concentration–relaxation curve was significantly shifted to the left by treatment with mergepta, implying an accumulation of bradykinin. In addition, treatment with captopril increased bradykinin-induced contraction but not relaxation. As an angiotensin-converting enzyme inhibitor augments bradykinin content, this bradykinin instead would be degraded by kininase I resulting in an increase in des-Arg^9-bradykinin. Such an increase in des-Arg^9-bradykinin concentration by angiotensin-converting enzyme inhibitors has been shown in other in vitro studies on rats and humans (Lamontagne et al., 1995; Décarie et al., 1996). In the present study, this is confirmed with two experiments. First, when mergepta was present captopril did not increase bradykinin-induced contraction, and second, if des-Arg^9-[Leu^8]bradykinin was added to the preparations the captopril-induced effect was not seen. Since captopril exerts small (albeit significant) effects on bradykinin-induced responses, angiotensin-converting enzyme seems to be of relatively low importance compared to carboxypeptidase M regarding bradykinin metabolism in these vessels.

Captopril increased bradykinin-induced contraction only in arterial strips with functionally intact endothelium. That captopril did not affect bradykinin-induced contraction of preparations with removed endothelium is expected since angiotensin-converting enzyme is mainly an endothelial enzyme. The lack of effect in arteries with intact endothelium treated with the NO synthase inhibitor *N*ω-nitro-L-arginine is rather surprising. An inhibitory effect on angiotensin-converting enzyme activity by *N*ω-nitro-L-arginine would have explained these results, but the NO-synthase inhibitor did not decrease angiotensin-converting enzyme activity.

Why is the captopril-induced increase dependent on NO synthesis? Recently, Ackermann et al. showed that NO and NO-releasing substances (NO donors) can competetively inhibit angiotensin-converting enzyme (Ackermann et al., 1998). Therefore, we investigated if the NO donor *S*-nitroso-*N*-acetyl-penicillamine could affect angiotensin-converting enzyme activity in our preparations and also if it could further reduce captopril-induced inhibition of the enzyme. *S*-nitroso-*N*-acetyl-penicillamine did indeed inhibit angiotensin-converting enzyme with approximately 30%, an obvious reduction albeit small compared to the captopril-induced inhibition. The concomitant addition of *S*-nitroso-*N*-acetyl-penicillamine to captopril-treated preparations further decreased angiotensin-converting enzyme activity by about 50%. This further reduction by *S*-nitroso-*N*-acetyl-penicillamine was only seen when 10^{-7} and 10^{-6} M captopril was used; 10^{-5} M captopril in itself reduced angiotensin-converting enzyme activity levels down to detection limit. In addition, angiotensin I-induced contraction of the arterial strips was more sensitive to captopril treatment when endothelial NO synthesis was left undisturbed. The difference in captopril potency concerning tension studies and angiotensin-converting enzyme activity is probably due to differences in methodology: tension studies are performed on whole tissue while angiotensin-converting enzyme activity is measured in crude homogenates. Thus, captopril augmented bradykinin-induced contraction only when the arterial strips had an intact NO synthesis. This could be due to the further reduction in angiotensin-converting enzyme activity by captopril when NO was present. Angiotensin-converting enzyme inhibitor treatment has been shown to increase endothelium-dependent relaxation (mediated mainly by NO) in both animals (Félétou et al., 1992; Mombouli et al., 1992; Hecker et al., 1994) and humans (Mancini et al., 1996; Hornig et al., 1997; Kuga et al., 1997). It has also been proposed that angiotensin-converting enzyme inhibitors can potentiate bradykinin-induced responses by a direct interaction at the bradykinin B_2 receptor level (Hecker et al., 1994). A direct effect on bradykinin contractile receptors in our study should have been seen as an increase in contraction in preparations both with and without *N*ω-nitro-L-arginine. As it was not, such an angiotensin-converting enzyme-independent effect of captopril is unlikely in our system.

It could be speculated that it exists a positive feedback loop concerning angiotensin-converting enzyme inhibition, where NO acts as an endogenous angiotensin-converting enzyme inhibitor resulting in an increase in bradykinin and a decrease in angiotensin II content. Whether this affects the result of angiotensin-converting enzyme inhibitor treatment in patients with endothelial dysfunction remains to be elucidated.

In conclusion, angiotensin-converting enzyme is of minor importance regarding bradykinin degradation in porcine iliac arteries. Captopril increases bradykinin-induced contraction probably due to the increased metabolism of bradykinin by kininase I carboxypeptidases forming the contractile metabolite des-Arg^9-bradykinin. Bradykinin-induced relaxation was only augmented by captopril in the presence of the kininase I carboxypeptidase inhibitor mergepta. Both captopril and the NO donor *S*-nitroso-*N*-acetyl-penicillamine inhibited angiotensin-converting enzyme activity. An additional reduction in captopril-mediated angiotensin-converting enzyme inhibition was seen with the concomitant addition of *S*-nitroso-*N*-acetyl-penicillamine. Also, captopril increased bradykinin-induced contraction only in arterial strips with an intact NO synthesis. It is suggested that NO acts as an endogenous inhibitor of angiotensin-converting enzyme and may be additive to the angiotensin-converting enzyme inhibitory effects of captopril. The importance of endothelial NO concerning the potency of angiotensin-converting enzyme inhibitor treatment in humans is not yet known.

Acknowledgements

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