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Induction of kinin B_1 receptor-dependent vasoconstriction following balloon catheter injury to the rabbit carotid artery

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1 Balloon catheter injury to the rabbit carotid artery damaged the endothelium and induced neointima formation over 7 days. The area of intima, expressed as a percentage of the media, was 16.2 ± 4.2% and 8.2 ± 0.1% in balloon catheter-injured and sham-operated arteries.

2 Seven days after arterial injury, carotid arteries were isolated and set up as ring preparations in organ baths for isometric tension measurements. Balloon catheter-injured arteries first contracted with noradrenaline (0.01–0.1 μM), contracted further in a concentration-dependent manner to bradykinin (BK; pD_2, 5.98 ± 0.22; E_{max}, 41.3 ± 5.2% of KCl) and to des-Arg^9-BK (pD_2, 7.12 ± 0.36; E_{max}, 46.0 ± 9.9% of KCl). In contrast, vessel segments with endothelium either intact or acutely removed were unresponsive to both BK receptor agonists.

3 The concentration-contraction curves for BK and for des-Arg^9-BK were shifted to the right by the B_1 receptor antagonist, [Leu^8]des-Arg^9-BK (3 μM), but not by the selective B_2 receptor antagonist, Hoe 140 (1 μM).

4 Thus, BK and its metabolite, des-Arg^9-BK act as vasoconstrictor agents following balloon catheter injury. These effects appear to be mediated by activation of B_1 receptors.

Keywords: Vascular injury; kinin B_1 receptor; des-Arg^9-BK; bradykinin; rabbit carotid artery

Introduction

As proposed by Regoli & Barabé in 1980, kinin receptors have been divided in two types, B_1 and B_2. Endothelial B_2 receptor-mediated vasodilatation is one of the most important cardiovascular effects of the nonapeptide, bradykinin (BK) (Regoli & Barabé, 1980; Bonner & Schunk, 1986; Pelc *et al.*, 1991). In contrast with B_2 receptors, vascular B_1 receptors are thought to be absent under normal conditions but can be induced *in vitro* by prolonged incubation (Deblois & Marceau, 1987; Pruneau & Bélichard, 1993) or *in vitro* and *in vivo* by treatment with endotoxin (Regoli *et al.*, 1981; Deblois & Marceau, 1987).

Balloon catheter angioplasty produces major mechanical injury to the arterial wall with ultimate death of endothelial cells and to some extent smooth muscle cells (Liu *et al.*, 1989; Schwartz *et al.*, 1992). The resultant inflammation which develops at the site of vascular damage is characterized by the release of cytokines, growth factors and the expression of nuclear oncogenes (Liu *et al.*, 1989; Schwartz *et al.*, 1992). These factors stimulate migration and proliferation of smooth muscle cells from the media to form a neointima (Liu *et al.*, 1989; Schwartz *et al.*, 1992).

We hypothesized that injury to a blood vessel such as that produced by angioplasty, induces the expression of B_1 receptors in the vascular wall. To test this possibility, we investigated the response to BK and to des-Arg^9-BK in balloon catheter-injured and sham-operated carotid arteries of the rabbit. In addition, the responses to various dilators (acetylcholine, ionophore A 23187, sodium nitroprusside) were obtained in the same vascular preparations to determine a possible involvement of the endothelium.

Methods

Balloon catheter injury

Male New-Zealand White rabbits weighing 2.5 to 3.5 kg each were anaesthetized with ketamine (35 mg kg^{-1}, i.m.) and xylazine (5 mg kg^{-1}, i.m.). An arterial embolectomy catheter (2F Fogarty, Baxter, CA, U.S.A.) was inserted into the right common carotid artery through a branch of the internal carotid artery. The balloon on the catheter was then inflated with 0.05 ml of distilled water and the inner surface of the artery rubbed three times from the aortic arch up to the external carotid artery branch. After withdrawal of the catheter, the internal carotid artery was ligated and the wound closed. Penicillin G (200,000 iu) was applied locally to the wound and the animals allowed to recover. Other rabbits that were sham-operated without the ballooning procedure were controls. Because the embolectomy catheter was re-used in consecutive rabbits and thus could have been contaminated with lipopolysaccharides (LPS), three rabbits were operated under sterile conditions and a newly purchased embolectomy catheter used only once for each animal.

Isolated carotid artery reactivity

At 7 days following balloon catheter injury, rabbits were killed by an overdose of i.v. sodium pentobarbitone. The right carotid artery was then carefully dissected out and transferred to a Krebs solution of the following composition (in mM): NaCl 119, KCl 4.7, KH_2PO_4 1.18, $MgSO_4$ 1.17, $NaHCO_3$ 25, $CaCl_2$ 2.5, ethylenediaminetetracetic acid (EDTA) 0.026, glucose 5.5, bubbled with 95% O_2 plus 5% CO_2. Carotid arteries of control animals were obtained and kept under the same conditions. Three rings of 3 mm in length were prepared from each carotid segment and were suspended on wire hooks (0.3 mm in diameter) in 20 ml jacketed organ baths maintained at 37°C. In some control carotid arteries, the vascular endothelium was rubbed off *in vitro* with a catheter which was introduced into the vessel lumen and gently moved back and forth several times. One hook was suspended from a Gould-Statham UC_2 or UTC_2 transducer, and the other was fixed to a plastic support leg. Changes in isometric tension were recorded continuously on two-channel recorders (Gould BS272 or Linseis Type 7025). Rings were left unstretched for 15 min and were then gradually stretched to a passive tension of 2 g. Preliminary experiments showed that a 2 g resting tension was at the

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optimal plateau of the length-tension relationship for potassium chloride (KCl, 75 mM).

After 1 h of equilibration, arterial rings were contracted with noradrenaline (NA, 0.01 to 0.1 μM) or angiotensin II (AII, 0.003 to 0.01 μM). At the plateau of contraction, the responses to cumulative concentrations of des-Arg^9-BK (0.001 to 3 μM) or of BK (0.001 to 3 μM) were obtained in the presence or absence of [Leu^8]des-Arg^9-BK (3 μM) or D-Arg-[Hyp^3, Thi^5, D-Tic^7, Oic^8]-BK (Hoe 140, 1 μM). After washing, the maximum contractile responses were obtained with KCl (75 mM) and the bath washed. The vessels were then re-contracted to a stable level of active force with NA (0.01 to 0.1 μM) to determine relaxation responses to cumulative addition of acetylcholine (ACh, 0.001 to 1 μM), the calcium ionophore, A 23187 (0.001 to 1 μM) or sodium nitroprusside (SNP, 0.001 to 1 μM). Responses to des-Arg^9-BK and to BK in the absence and presence of antagonists were also obtained in vessels maintained under resting conditions for 1 h. Indomethacin (3 μM) was present throughout all experiments.

Morphology of the intraluminal surface

Two different methods were used to assess the integrity of the endothelium. First, *en face* preparations of vessel segments were prepared according to the method of Gabaldon (1987). In brief, perfusion fixation of the carotid artery was performed *in situ* at 100 mmHg via a catheter inserted into the abdominal aorta. Perfusion was as follows: (1) fixative for 10 min (1% paraformaldehyde, 2% glutaraldehyde, 6 mM NaCl in 0.1 M phosphate buffer, pH 7.4); (2) washing solution for 1 min (8.9% sucrose in 20 mM HEPES buffer, pH 7.4); (3) 0.05% $AgNO_3$ in washing solution for 1 min; (4) washing solution for 1 min; (5) fixative for 2 min. The carotid artery was then dissected out, mounted flat on a glass slide with the endothelium facing upward and exposed to light for 4 h.

The second method used to determine the presence of endothelium was the global *en face* technique of Kohler & Jawien (1992). The carotid arteries were fixed at 100–120 mmHg perfusion pressure by infusion of 2.5% glutaraldehyde in 0.1 M phosphate buffer (pH 7.4). Evans blue dye in phosphate buffer saline (60 mg kg^{-1}) was infused intravenously 15 min before fixation to allow identification of endothelium-denuded (blue) regions as distinct from regions in which the endothelium had regenerated (white).

Morphometric measurements

One week following surgery, rabbits were anaesthetized and killed with an overdose of sodium pentobarbitone. A catheter was placed in the thoracic aorta and the vascular system was first rinsed with heparinized saline (100 iu ml^{-1}) for 2 min then fixed for 20 min with Bouin's fluid (Rhône Poulenc, France) under a perfusion pressure of 100 mmHg. The right carotid artery was removed, cleaned of connective tissue, placed in Bouin's fluid for 2 days for further fixation, and embedded in paraffin. The artery segments were divided in four equal parts and a cross-sectional ring (4 mm) was cut from each part and stained with haemotoxylin and eosin (Ridray *et al.*, 1991).

Computer-assisted morphometry was performed with a Samba Image Analysis System (Alcatel, France) with 256 levels of grey and a 512 × 512 pixel grid. For each carotid cross-sectional ring (4/carotid artery), eight to fifteen microscopic fields, in order to cover the entire vessel circumference, were analysed in a blind manner with a 75 × final magnification on the video screen. A specific programme was developed (C. Robert, Lab. Fournier, France) to trace automatically the boundary limits between adventitia, media and intima. The observer hand using the computer's mouse was needed to separate structures only when the field image did not allow the programme to identify the different arterial structures. Intima and media areas (mm^2 after internal calibration of the pixel size) and intima/media area ratios were automatically calculated.

Drugs

A 23187, acetylcholine chloride, angiotensin II acetate, bradykinin acetate, des-Arg^9-bradykinin acetate, [Leu^8]des-Arg^9-bradykinin acetate, indomethacin, noradrenaline hydrochloride and sodium nitroprusside were obtained from Sigma

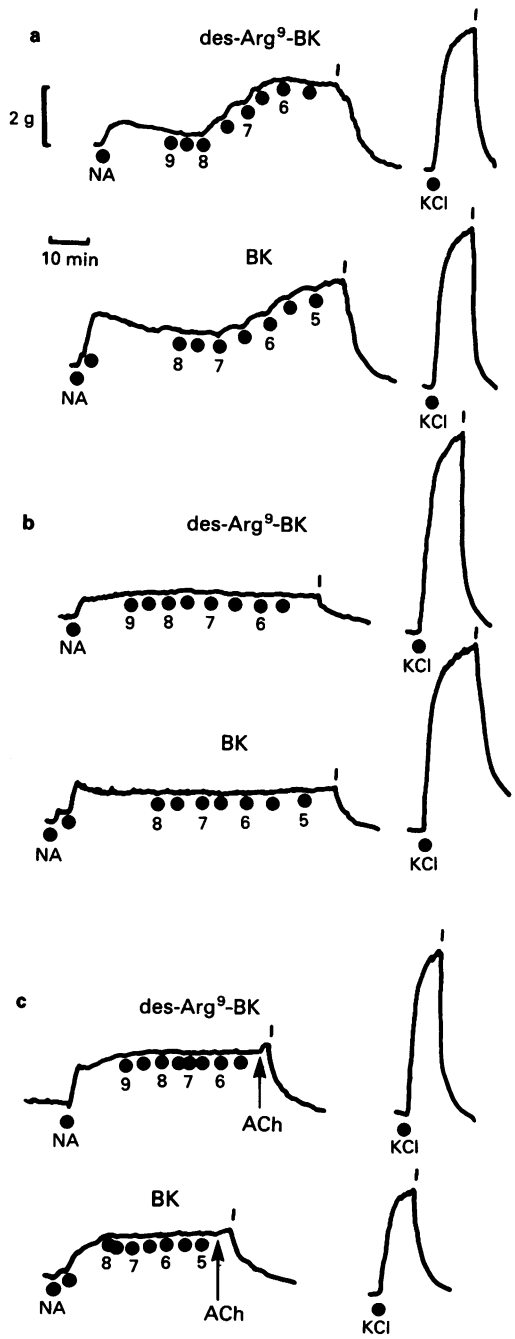

Figure 1 Representative recordings showing the effects of des-Arg^9-bradykinin (des-Arg^9-BK) and bradykinin (BK) on precontracted rings from balloon catheter-injured (a), control (b) and acutely denuded (c) carotid arteries. Precontraction was induced by noradrenaline (NA, 0.01 to 0.1 μM). Potassium chloride (KCl) was used at 75 mM. In acutely denuded arteries (c), 10 μM acetylcholine (ACh) produced a contraction (see arrow), confirming the absence of endothelium. Vertical black bars indicate washes (2 ×) with a fresh Krebs solution.

Chem. Co. (St Louis, MO, U.S.A.). D-Arg-[Hyp^3, Thi^5, D-Tic^7, Oic^8]-bradykinin (Hoe 140) was a generous gift from Dr K. Wirth (Hoechst AG, Frankfurt, Germany). All drugs made up in distilled water or dimethylsulphoxide and kept on ice were protected from light.

Statistical analysis

Data are given as mean ± s.e.mean. Contraction responses are measured as a % of the maximum contraction obtained with KCl (75 mM). The negative logarithm of the concentration of agonist needed to reach 50% of its maximal response (pD_2) was calculated by using least square analysis (Tallarida & Murray, 1981). After testing for linearity and parallelism, pD_2 values and maximal responses were compared by Student's t test. The level of significance was $P<0.05$.

Results

Vascular reactivity

Stable precontractions of arteries were obtained with NA (0.01 to 0.1 μM) (Figure 1). The levels of precontraction before addition of des-Arg^9-BK were not significantly different between groups and represented 31 ± 7%, 35 ± 7% and 29 ± 8% of the response to KCl (75 mM) in vehicle-, [Leu^8]des-Arg^9-BK- and Hoe 140-treated arteries, respectively. Similarly, the contractile response to NA before addition of BK was not different and reached 36 ± 9%, 31 ± 9% and 26 ± 6% of KCl in vehicle-, [Leu^8]des-Arg^9-BK- and Hoe 140-treated arteries. Des-Arg^9-BK and BK caused further contractions only in the balloon-injured artery (Figures 1 and 2). This was not dependent on the precontracting agent (NA) since similar responses to des-Arg^9-BK and BK were obtained when the arteries were precontracted with AII (data not shown). Under similar conditions (NA precontraction), both agonists neither contracted nor relaxed acutely denuded and control arteries (Figure 1). The endothelium-dependent

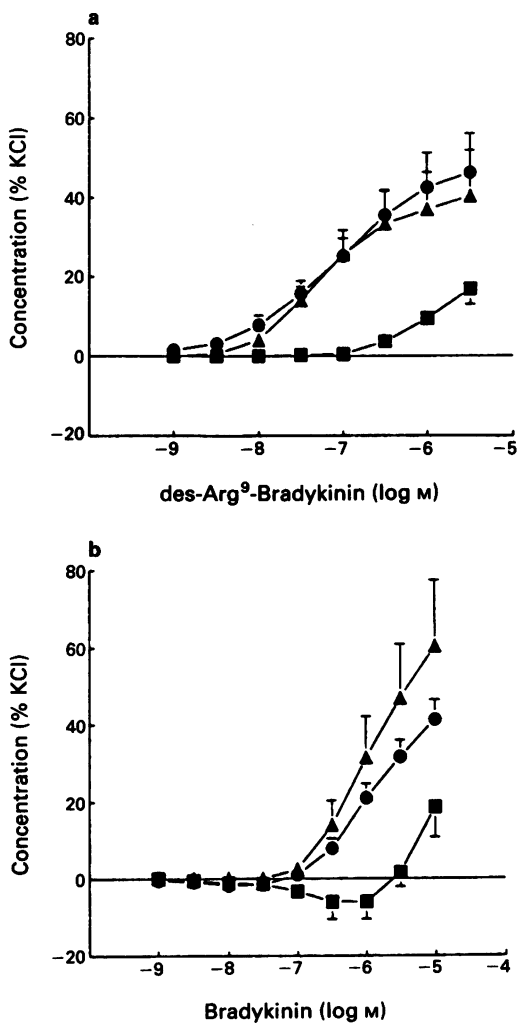

Figure 2 Concentration-contraction curves for des-Arg^9-bradykinin (a) and bradykinin (b) in balloon catheter-injured arteries precontracted with noradrenaline. Control responses (●) and responses in the presence of 3 μM [Leu^8]des-Arg^9-bradykinin (■) or 1 μM Hoe 140 (▲). Each point represents the mean ± s.e.mean of 6–9 animals. '0%' represents the level of contraction at the plateau of noradrenaline-induced response (see Results section for details).

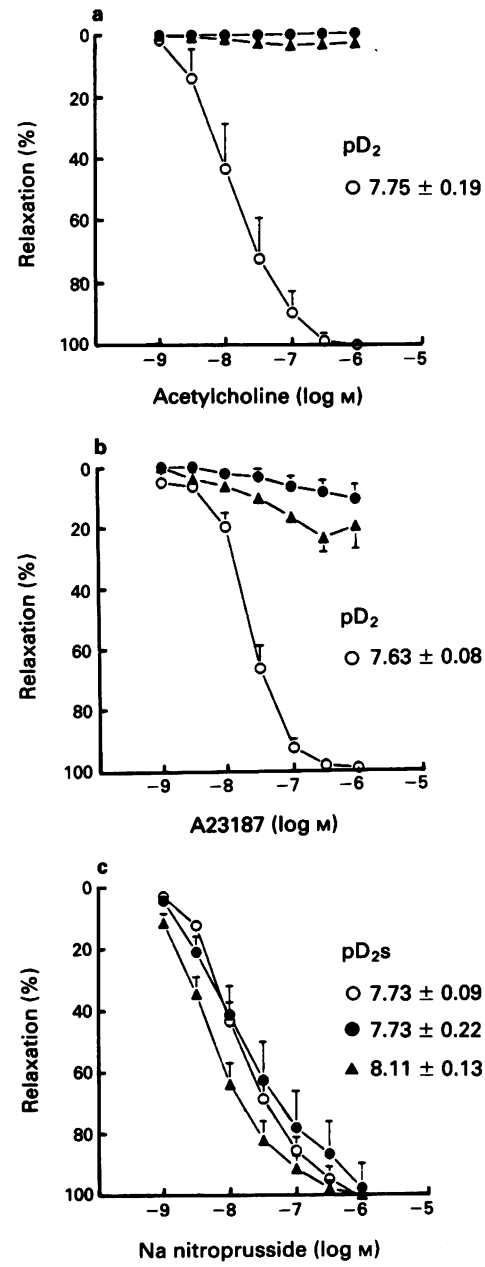

Figure 3 Cumulative concentration-relaxation curves for acetylcholine (a), A 23187 (b) and sodium nitroprusside (c) in balloon catheter-injured (▲), acutely denuded (●) and control (○) carotid arteries. Arterial rings were precontracted with noradrenaline (NA, 0.01 to 0.1 μM). Relaxation responses are expressed as percentages of contractions to NA. Each point represents the mean ± s.e.mean of 6 animals.

relaxing agent, ACh, was without effect in balloon-injured and acutely denuded arteries but relaxed maximally the control carotid artery (Figure 3). The calcium ionophore, A 23187, produced a small relaxation of balloon catheter-injured arteries (E_{max}, 19.7 ± 7.4%) and of acutely denuded arteries (E_{max}, 10.7 ± 4.8%) but fully relaxed control arteries (Figure 3). SNP relaxed maximally arterial rings from all three groups with similar pD_2 values (Figure 3). Figure 2 also shows the effects of [Leu^8]des-Arg^9-BK and Hoe 140 on concentration-contraction curves for des-Arg^9-BK and BK. In the absence of antagonist, the calculated pD_2 values for des-Arg^9-BK and BK were respectively 7.12 ± 0.36 and 5.98 ± 0.22 and the E_{max} values 46.0 ± 9.9% and 41.3 ± 5.2%. The B_1 receptor antagonist, [Leu^8]des-Arg^9-BK (3 μM) shifted to the right by 74 × and 14 ×, respectively, the concentration-contraction curves for des-Arg^9-BK and for BK (Figure 2). In contrast, Hoe 140 (1 μM) was without effect on the curves for des-Arg^9-BK (pD_2, 7.14 ± 0.48) and for BK (pD_2, 6.04 ± 0.38). Similar contractile responses to des-Arg^9-BK and to BK were obtained in arteries injured with a newly purchased balloon catheter (data not shown). The contraction to 75 mM KCl of balloon catheter-injured, acutely denuded and control arteries were 3.2 ± 0.3 g, 3.6 ± 0.3 g and 6.5 ± 0.2 g ($P<0.05$), respectively.

Balloon-catheter injured arteries under resting conditions contracted in response to des-Arg^9-BK and to BK with respective pD_2 values of 6.14 ± 0.12 and 5.73 ± 0.15 and E_{max} values of 37.2 ± 4.0% and 41.1 ± 5.4% of KCl ($n = 6$ in each group). Under these conditions, the responses to des-Arg^9-BK and to BK were unaffected by Hoe 140 (1 μM) but were shifted 7 and 10 × by [Leu^8]des-Arg^9-BK (3 μM).

Silver nitrate and Evan's blue staining

The luminal surface of sham-operated carotid arteries did not stain blue after administration of Evan's blue dye (Figure 4). In contrast, balloon catheter-injured arteries were uniformly stained blue indicating that, 7 days after surgery, most of the endothelium had not regenerated (Figure 4). However, patches of artery not stained blue were observed along the arterial surface indicating focal regeneration of endothelial cells around orifices of small artery branches (Figure 4). Endothelial cell regeneration also occurred at both ends of the injured arterial segment. Silver nitrate staining revealed intact endothelial junctions in control arteries whereas no staining was observed in injured vessels (Figure 4).

Morphometry

Morphological data are summarized in Table 1. Seven days after balloon catheter injury, significant increases in the cross-section area of both the intima and media were observed. The area of intima to media, expressed as a ratio, however was significantly increased 2.1 fold in injured arteries as compared with controls (sham-operated).

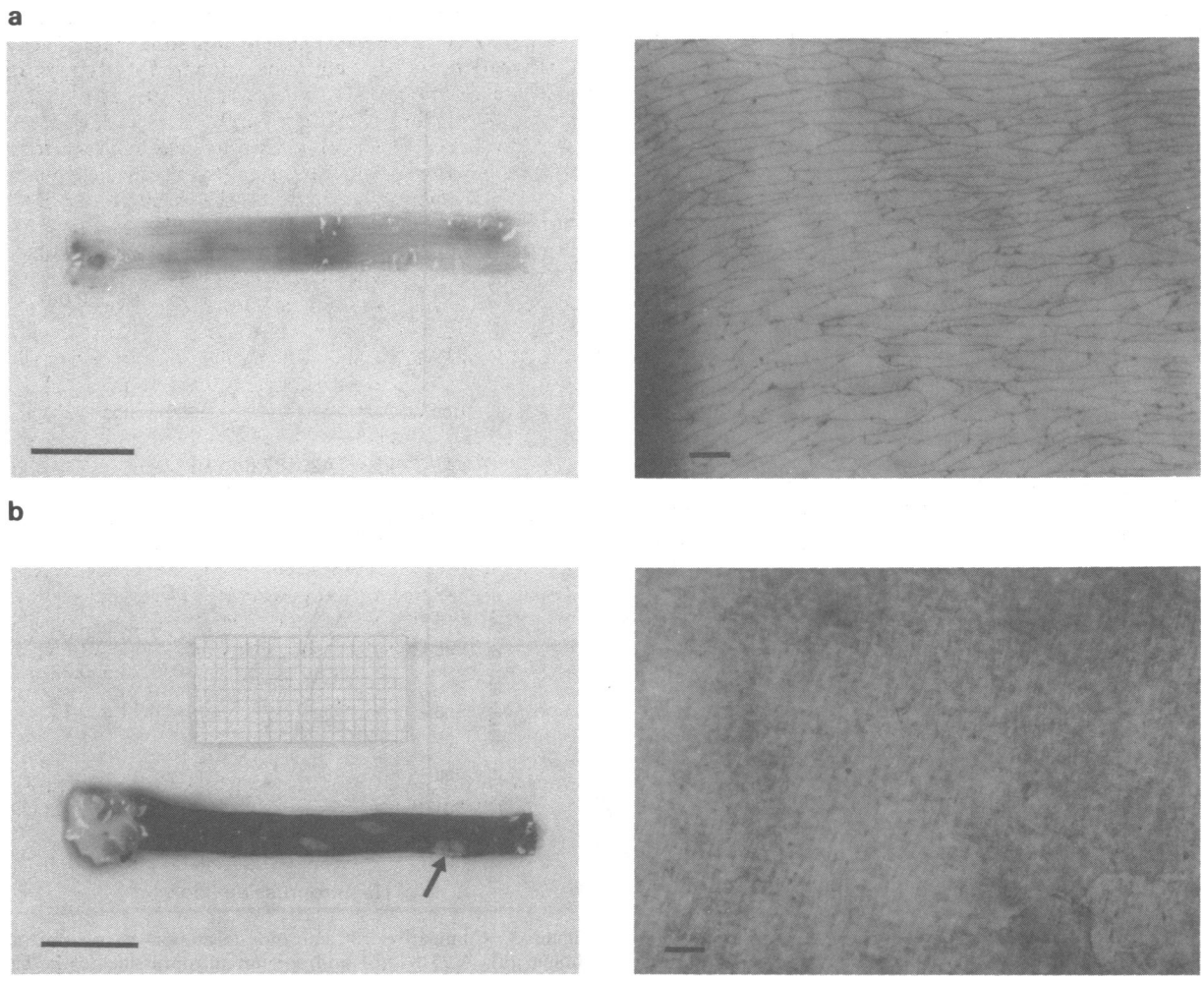

Figure 4 Intraluminal surface of a control (a) and a balloon catheter-injured (b) carotid artery stained with Evan's blue dye (left side) and silver nitrate (right side). See Methods for experimental details. Surfaces without endothelium which stained blue with Evan's blue dye appear black in the figure. The arrow indicates an area where the endothelium has regenerated. Note the absence of staining with silver nitrate in balloon catheter-injured arteries. Scale bar: 1 cm (left side) and 10 μm (right side).

Table 1 Morphological data obtained from vascular cross sections 7 days after angioplasty of the rabbit carotid artery

Group	*Intima area* (mm^2)	*Media area* (mm^2)	*Intima/media* (%)
Sham-operated (5)	0.030 ± 0.000	0.370 ± 0.007	8.2 ± 0.1
Balloon catheter-injured (9)	0.099 ± 0.018*	0.627 ± 0.032*	16.2 ± 4.2*

Results are given as mean ± s.e.mean. In parentheses are given the number of rabbits. See Methods section for details of histomorphometric techniques.
*Significantly different from sham-operated animals at $P<0.05$.

Discussion

Balloon catheter injury to the rabbit carotid artery produced a significant intimal thickening which was already apparent 7 days after surgery (see also Azuma *et al.*, 1992). At this time, the intima was predominantly devoid of endothelium although some endothelial regrowth was observed at both ends of the injured intraluminal surface and around the orifices of arterial branches. In these vessels that were chronically without endothelium, B_1 receptor-mediated contractions occurred, whereas, control vessels and vessels acutely without endothelium were unresponsive to B_1 receptor activation. Des-Arg^9-BK was about 10 times more potent than BK which is in agreement with the order of potency of both agonists towards the B_1 receptor subtype in other tissues (Regoli *et al.*, 1990). In addition, the contractions to des-Arg^9-BK and BK were inhibited by [Leu^8]des-Arg^9-BK but not by the specific B_2 antagonist, Hoe 140. Thus, the appearance of B_1 receptor-mediated contractions was related to the balloon catheter-induced injury. In balloon catheter-injured arteries maintained under resting conditions, contractions also developed in response to des-Arg^9-BK and to BK but with a reduced sensitivity. Although we have no adequate explanation for such a reduction in sensitivity, we suggest that it might be due to the absence of precontraction, a condition which has been shown in other pharmacological preparations to enhance the response to contractile agonists (see Cocks *et al.*, 1993). Similar to the observations made in precontracted arteries, the response to both kinin receptor agonists was probably the result of stimulation of B_1 receptors since it was antagonized by [Leu^8]des-Arg^9-BK but not by Hoe 140.

The absence of endothelium in the balloon catheter-injured artery was confirmed both by staining with Evan's blue dye and silver nitrate. Furthermore, absence of an endothelial layer was functionally confirmed by loss of endothelium-dependent relaxation responses to ACh. No staining to Evan's blue dye was observed around the orifices of small artery branches indicating the presence of regenerated endothelial cells which may have been responsible for the modest relaxation observed with BK and A 23187 but not with des-Arg^9-BK. However, no endothelium-dependent relaxation responses mediated by B_2 receptor activation were found in either intact (Pruneau & Bélichard, 1993) or sham-operated rabbit carotid arteries (this study). The reason why regenerated endothelial cells appear to respond to a B_2 receptor agonist is unknown.

Injury to the arterial wall, as that produced by angioplasty, is known to create a chronic inflammatory state (Berk *et al.*, 1991) which is reinforced by thrombus formation at the site of injury (Schwartz *et al.*, 1992). Expression of functional B_1 receptors has been demonstrated to occur in many inflammatory conditions (Marceau *et al.*, 1983). In most vascular experiments either *in vitro* or *in vivo*, B_1 receptor up-regulation was induced with LPS (Regoli *et al.*, 1981; Deblois & Marceau, 1987; Nwator & Whalley, 1989). Thus, our results could be explained by contamination of the balloon catheter with LPS. Although we did not measure LPS levels, this possibility was indirectly ruled out since des-Arg^9-BK induced similar contractions in arteries previously injured with newly purchased balloon catheters which were assumed to be LPS-free. In addition, responses to kinins were studied 90 min following the dissection of the arteries to avoid induction of B_1 receptors in response to prolonged incubation *in vitro* (Deblois & Marceau, 1987; Pruneau & Bélichard, 1993).

The physiological significance of B_1 receptor induction after intraluminal balloon injury is unknown. Des-Arg^9-BK is however likely to be produced *in situ* from BK. Circulating carboxypeptidase N, membrane anchored carboxypeptidase M or the lysosomal enzyme deamidase are able to remove terminal Arg from BK (Skidgel, 1992; Campbell *et al.*, 1993). In addition, BK is generated during inflammatory reactions by the action of plasma kallikrein (for review, see Bhoola *et al.*, 1992). Sufficient amounts of des-Arg^9-BK or BK may then be locally produced to activate B_1 receptors and to induce vasoconstriction after endothelium removal (Briner *et al.*, 1993). Interestingly, it has been reported that both BK and des-Arg^9-BK stimulated protein synthesis and cell division in human cultured fibroblasts (Goldstein & Wall, 1984) and that expression of a mutant *ras* protein in Rat 13 cells increased the expression of BK receptors and their sensitivity to ligand stimulation of mitogenesis (Roberts & Gullick, 1989). It raises the possibility that BK receptors may be involved in smooth muscle cell proliferation which occurs in the arterial wall following endothelium denudation.

In conclusion, we have provided evidence to support the view that induction of B_1 receptors occurs that mediate contraction at the site of vascular injury. Because BK is an autocrine hormone in many vascular tissues throughout the body, BK and its metabolite, des-Arg^9-BK, may become potent vasoconstrictors at the site of vascular injury following angioplasty.

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