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Pharmacology of kinins in the arterial and venous mesenteric bed of normal and B_2 knockout transgenic mice

Nathalie Berthiaume [a], Fred Hess [b], Airu Chen [c], Domenico Regoli [a], Pedro D'Orléans-Juste [a,*]

[a] *Department of Pharmacology, Medical School, Université de Sherbrooke, Sherbrooke, Que., Canada J1H 5N4*
[b] *Department of Human Genetics, WP26-265, Merck Research Lab, P.O. Box 4, Sumneytown Pike, West Point, PA 19486, USA*
[c] *Department of Genetics and Molecular Biology, R80T-150, Merck Research Lab, P.O. Box 2000, Rahway, NJ 07065, USA*

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Abstract

We have tested the vasoactive effects of kinins in addition to various other endothelium-dependent or independent agonists in the arterial and venous perfused mesenteric circuits of the mouse. Bradykinin (0.1 pmol–100 nmol), but not des–Arg^9–bradykinin (10 nmol) induced a dose-dependent vasodilation of the precontracted arterial and venous mesenteric vasculature of the mouse. Furthermore, acetylcholine (2.5 nmol) also induced a marked arterial vasodilation but was without effect on the venous side. Other endothelium-dependent vasodilators, such as platelet-activating factor (PAF) (1 nmol), tachykinin NK_1 selective agonist ([Sar^9,Met(O_2)^{11}]substance P) (0.5 nmol) and adenosine diphosphate (5 nmol), were without effect on either side of the mesenteric bed of the mouse. The bradykinin B_2 receptor selective antagonist (HOE 140) abolished the arterial and venous vasodilation induced by bradykinin without affecting that of acetylcholine or sodium nitroprusside. In addition, the bradykinin B_1 receptor antagonist des–Arg^9–[Leu^8]bradykinin was without effect on the responses induced by bradykinin. A nitric oxide synthase inhibitor N^{ω}-nitro-L-arginine methyl ester (L-NAME) markedly reduced, whereas removal of the endothelium with 3-[3-cholamidopropyl)dimethylammonio]-1-propane sulfonate (CHAPS) abolished dilatation to bradykinin and acetylcholine (arterial side only) without affecting that induced by sodium nitroprusside in the mouse arterial and venous mesenteric circuits. In the same two circuits of transgenic B_2 knockout mice, the vasodilatory responses to bradykinin were absent, whereas the arterial circuit still responded to acetylcholine by a L-NAME-sensitive vasodilation. Our results suggest the exclusive contribution of B_2 receptors located on the endothelium in the vasodilatory effects of bradykinin in the arterial and venous mesenteric circuits of the mouse. © 1997 Elsevier Science B.V.

Keywords: Vasodilation; Vasoconstriction; Bradykinin; Bradykinin receptor; Mesenteric bed; B_2 knockout mice

1. Introduction

The pre and post-capillary mesenteric circuits of rats and guinea pigs respond in a qualitatively different manner to many vasoactive peptides and autacoids (D'Orléans-Juste et al., 1996). One of those peptides, bradykinin, induces a marked vasodilation in the arterial and venous mesenteric vasculature of both species (D'Orléans-Juste et al., 1991; Berthiaume et al., 1995).

Bradykinin is a nonapeptide which predominantly induces its hypotensive effect in vivo through the activation of B_2 receptors (Regoli and Barabé, 1980). In addition to the previously mentioned receptor population, kinins also act via B_1 receptors which expressions are upregulated by various cytokines (Marceau, 1995). Both B_2 and B_1 human receptor types have been cloned and functionally expressed in various host cells (Hess et al., 1992; Bacharov et al., 1996).

On the other hand, Borkowski et al. (1995) have developed a genetically modified transgenic B_2 knockout mouse in which model Alfie et al. (1996) have recently demonstrated the absence of hypotensive effects of intravenously administered bradykinin. However, it remains to be determined whether the endothelium, nitric oxide or B_1 receptors are involved in the hypotensive effects of kinins

* Corresponding author. Tel.: (1-819) 564-5344; Fax: (1-819) 564-5400; e-mail: labpdj@courrier.usherb.ca

administered systemically in the wild-type or B_2 knockout mouse.

We suggest as a working hypothesis that kinins induce their vasoactive effects in the pre and post-capillary mesenteric circuits of the mouse through the sole activation of B_2 receptors located on the endothelium, as previously demonstrated in the rat and guinea-pig mesenteric circuits (Berthiaume et al., 1995; D'Orléans-Juste et al., 1996).

Therefore, the aims of the present study are to develop a model of endothelium intact vascular circuits in which it is possible to (1) assess the effects of vasoactive agents both in pre and post-capillary circuits in the mouse, (2) pharmacologically characterize the arterial and venous responses of the same circuits to bradykinin and compare these responses in circuits isolated from B_2 knockout transgenic mice, (3) assess the contribution of the endothelium and of nitric oxide endothelium-derived relaxing factor (EDRF) in the response to bradykinin of both mesenteric circuits in the mouse.

On the other hand, it was also of interest to determine whether B_1 receptor activation would be present in vascular circuits of control mice and whether that phenomenon may be upregulated in transgenic B_2 knockout mice. Allogho et al. (1995) have recently shown B_1 receptor-dependent contractile responses of non-vascular tissues derived from normal mice.

To our knowledge, this is the first study demonstrating the important contribution of the endothelium-derived relaxing factor in the vasoactive effects of bradykinin in intact vascular circuits of mice. Furthermore, our results suggest that the absence of hypotensive effects of bradykinin seen by Alfie et al. (1996) in B_2 knockout transgenic mice is due to the absence of functional B_2 receptors on the endothelium of various vascular circuits, including the mesenteric arterial and venous beds.

2. Materials and methods

2.1. Experimental protocols

Tissues were obtained from normal C57Bl/6 (Charles River) or J129sv X C57Bl/6 wild type (agouti color) and B_2 knockout transgenic J129sv X C57Bl/6 (agouti color) mice (Merck, Rahway, NJ, USA)(Borkowski et al., 1995).

2.1.1. Mouse vascular bed perfused simultaneously through the arterial and venous sides

Male mice (18–30 g) were killed by stunning and exsanguination. The abdomen was opened and the ileo–colic and colic branches of the superior mesenteric artery were tied. The portal mesenteric vein was freed of connective and adipose tissues and this vessel and the superior mesenteric artery cannulated with hypodermic needles (23G1, Becton Dickinson). The mesentery was then perfused (200 μl/min for 5 min) via the mesenteric artery with warmed (37°C, 95% O_2, 5% CO_2) and oxygenated Kreb's solution containing heparin (100 U/ml). Following this initial perfusion period, the mesentery was separated from the intestine by cutting close to the intestinal border and the venous and arterial vasculature perfused independently at flow rates of 200 μl/min with Kreb's solution containing indomethacin (5 μM). The responses of the vasculature to the different agonists tested, administered intraluminally through lateral injection ports, were measured with pressure transducers (Statham, Model P-23A) and recorded on a Grass physiograph (Model 7-D).

2.1.2. Arterial and venous contractions of the mesenteric vasculature in response to various peptides

The optimal perfusion flow rate was established at 200 μl/min and chosen following preliminary experiments where vascular reactivity to endothelin-1 (both sides) was monitored at rates of 100, 200 or 400 μl/min. The constrictor effects induced by endothelin-1 (0.5 nmol) at the above-mentioned flow rates were averaged on the arterial side at 4.2 ± 2; 4.8 ± 0.9; 3.2 ± 0.3 mmHg ($n = 3–15$) and on the venous side 2.4 ± 0.5, 2.6 ± 0.3, 3.1 ± 0.8 mmHg ($n = 3–10$). Thereafter, all other experiments were performed under a constant perfusion flow of 200 μl/min. When steady increase of perfusion pressure had been obtained on both sides of the circulation, the various peptides were administered as bolus injections. Following an equilibration period of 50 min, the pressor effects of bradykinin (10 nmol), des–Arg^9–bradykinin (10 mol), angiotensin II (5 nmol) and endothelin-1 (0.5 nmol) were assessed on arterial and venous sides of non-precontracted mesenteric beds. Agonists were administered in volumes of 1 to 10 μl. Individual drugs were administered consecutively at time intervals of 10 to 90 min to avoid tachyphylaxis.

2.1.3. Endothelium-dependent vasodilation

In order to evaluate the endothelium-dependent relaxant effects of bradykinin (0.1 pmol–100 nmol), des–Arg^9–bradykinin (10 nmol), acetylcholine (2.5 nmol), the tachykinin NK_1 receptor agonist [Sar^9,$Met(O_2)^{11}$]substance P (0.5 nmol), platelet-activating factor (PAF) (1 nmol), adenosine diphosphate (5 nmol) or sodium nitroprusside (1 nmol), the perfusion pressure on both sides of the mesenteric circulation was increased by infusing on the venous side the thromboxomimetic 9,11-dideoxy-9α,11α-epoxymethano prostaglandin $F_{2\alpha}$ (U46619) (14.2 μM) and on the arterial side the selective α_1-adrenoceptor agonist, methoxamine (200 μM) (Warner, 1990; Berthiaume et al., 1995).

In some experiments, HOE 140 (5×10^{-7} M, arterial; 10^{-7} M, venous), a B_2 selective antagonist and des–Arg^9[Leu^8]bradykinin (5×10^{-7} M, arterial; 10^{-7} M, venous), a bradykinin B_1 receptor antagonist or N^w-nitro-L-

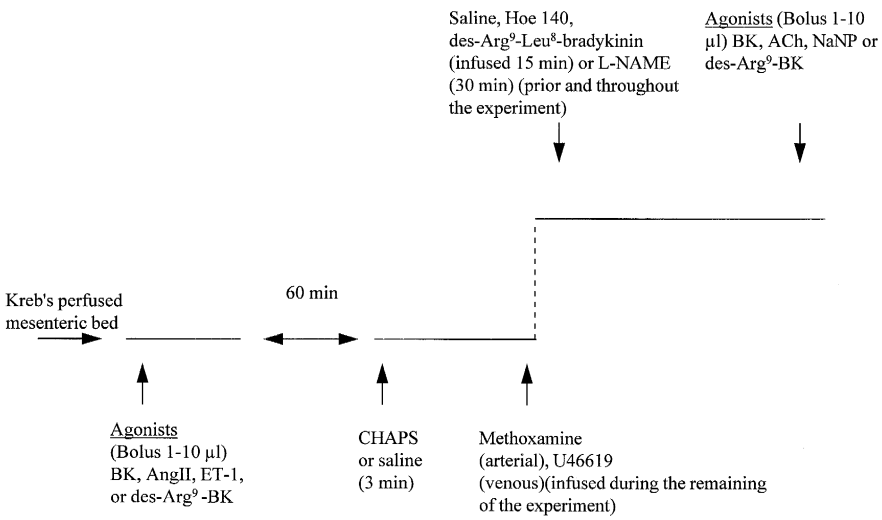

Fig. 1. Diagrammatic representation of experimental designs. The arterial and venous mesenteric circuits were perfused (200 μl) independently. All agonists, bradykinin (BK), des–Arg^9–BK, angiotensin II (Ang II), endothelin-1 (ET-1), acetylcholine (ACh) or sodium nitroprusside (NaNP) were administered intraarterially or intravenously.

arginine–methyl ester (L-NAME (200–400 μM)) were infused 15, 15 and 30 min, respectively, prior to a challenge with the various agonists. Finally, vasodilatory responses to acetylcholine, bradykinin and sodium nitroprusside were monitored in mesenteric circuits pretreated with 3-[3-cholamidopropyl)-dimethylammonio]-1-propane sul-

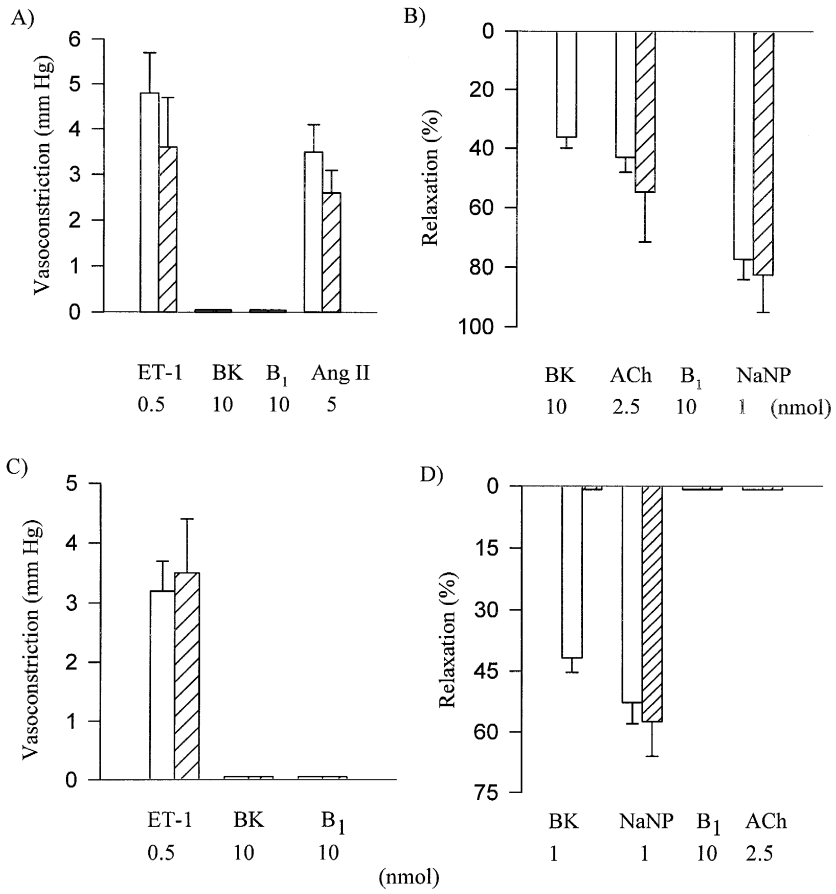

Fig. 2. Vasoactive effects of bradykinin (BK), acetylcholine (ACh), sodium nitroprusside (NaNP), des–Arg^9–bradykinin (B_1), endothelin-1 (ET-1) and angiotensin II (Ang II) on basally perfused arterial mesenteric circulation (A) or precontracted with methoxamine (200 μM) (B), on venous mesenteric circulation basally perfused (C) or precontracted with U46619 (14.2 μM) (D). Each column with a bar represents the mean ± S.E.M. of 5 to 15 experiments (open columns, normal mice; cross-hatched columns, transgenic B_2 knockout mice).

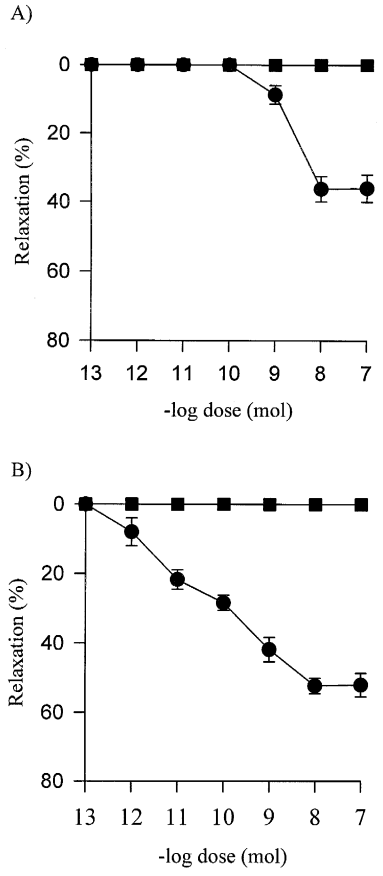

Fig. 3. Dose–response curves of the vasodilatory effects of bradykinin on the mouse arterial (A) and venous (B) mesenteric beds precontracted with methoxamine (200 μM) and U46619 (14.2 μM), respectively (●, control mice; ■, K.O. mice). Each point with a bar represents the mean ± S.E.M. of 4 to 10 experiments.

fonate (CHAPS) (20 mM, 3 min) to eliminate the endothelial layer (D'Orléans-Juste et al., 1991).

Fig. 1 represents a diagrammatic scheme of the overall experimental procedures detailed above.

2.2. Drugs

All peptides were synthesized in our laboratories, except endothelin-1 (Peptides International, Louisville, KY, USA). Indomethacin, acetylcholine, adenosine diphosphate, CHAPS and methoxamine were purchased from Sigma (St. Louis, MO, USA). U46619 and PAF were purchased from Cayman (Ann Arbor, MI, USA). Sodium nitroprusside was purchased from Fisher Scientific (Fair Lawn, NJ, USA). All agents were dissolved in phosphate-buffered saline (PBS), except for indomethacin which was dissolved in Trizma base (pH 7.4; 0.2 M, Sigma).

2.3. Statistics

The Mann Whitney-*U* statistical test was used for non-parametric grouped data and the Student's *t*-test was used for parametric or grouped data. *P* values of 0.05 and lower were considered to be significant.

3. Results

3.1. Role of bradykinin B_2 receptors in the kinins-induced vasodilation of the mouse mesenteric circuit

When perfused at 200 μl/min, the basal perfusion pressures obtained in the mouse arterial and venous mesenteric bed of wild-type or B_2 knockout mice were 9.8 ± 1.5 ($n = 10$) or 11.0 ± 1.2 mmHg ($n = 5$) and 3.8 ± 0.4 ($n = 10$) or 3.7 ± 0.9 mmHg ($n = 6$), respectively.

In another series of experiments, in basally perfused mesenteric circuits of wild-type or B_2 knockout (KO) mice, bradykinin at the highest dose used (10 nmol) was inactive as a vasoconstrictor yet both sides of the vascular bed responded well to endothelin-1 (Fig. 2A and C). In addition, des–Arg^9–bradykinin (10 nmol) was inactive on both sides of the mesenteric bed in both wild-type and KO mice.

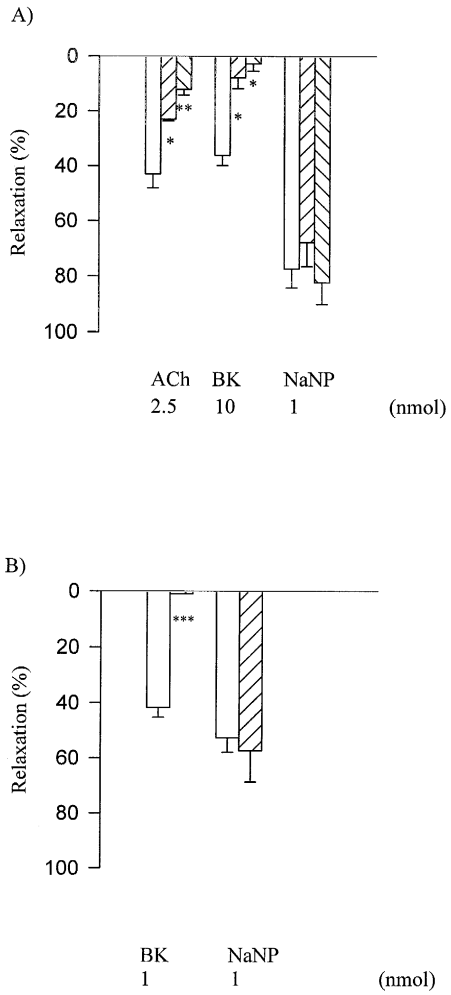

Fig. 4. Effect of L-NAME (upward cross-hatched columns, 200 μM; downward cross-hatched columns, 400 μM; 30 min) on the vasodilation (control, open columns) induced by bradykinin (BK), acetylcholine (ACh) or sodium nitroprusside (NaNP) on the mouse arterial (A) or venous (B) mesenteric bed. Each column with a bar represents the mean ± S.E.M. of 5 to 10 experiments. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

In precontracted mesenteric beds, methoxamine (200 μM, arterial side) or U46619 (14.2 μM, venous side) induced increases in perfusion pressure (arterial, wild-type: 2.7 ± 0.4 ($n = 9$); KO: 2.6 ± 0.3 mmHg ($n = 5$) venous, wild-type: 1.3 ± 0.3 mmHg ($n = 6$); KO: 1.4 ± 0.2 mmHg ($n = 10$), respectively. A single bolus of bradykinin (10 nmol, arterial; 1 nmol, venous), but not of des–Arg^9–bradykinin (10 nmol, both sides) induced a marked vasodilation of the arterial and venous mesenteric bed of control mice (C57B1/6 or J129sv X C57B1/6). In contrast, the vasoactive effects of bradykinin were absent in knockout vascular circuits (Fig. 2B and D), while those of acetylcholine (arterial side only) or sodium nitroprusside induced significant vasodilatory responses of either normal (wild type) or knockout mesenteric vessels.

Dose-dependent vasodilatory responses to bradykinin (0.1 pmol–100 nmol) on both sides of the mouse mesenteric vasculature are illustrated in Fig. 3A and B. Finally, both the [Sar^9,Met(O$_2$)^{11}]substance P (0.5 nmol), adenosine diphosphate (5 nmol) and PAF (1 nmol) were inactive as vasodilators on both sides of the mouse mesenteric circuit (results not shown).

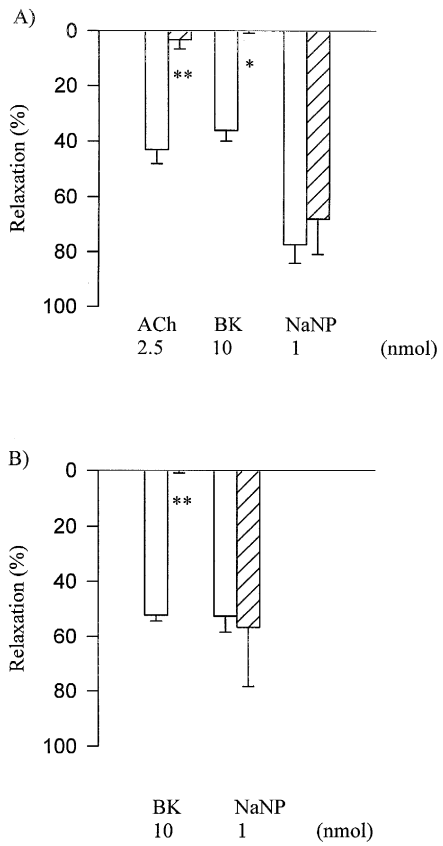

Fig. 5. Effect of CHAPS (cross-hatched columns; 20 mM; 3 min) on the vasodilation (control, open columns) induced by bradykinin (BK), acetylcholine (ACh) or sodium nitroprusside (NaNP) on the mouse arterial (A) or venous (B) mesenteric bed. Each column with a bar represents the mean ± S.E.M. of 3 experiments. * $P < 0.05$, ** $P < 0.01$.

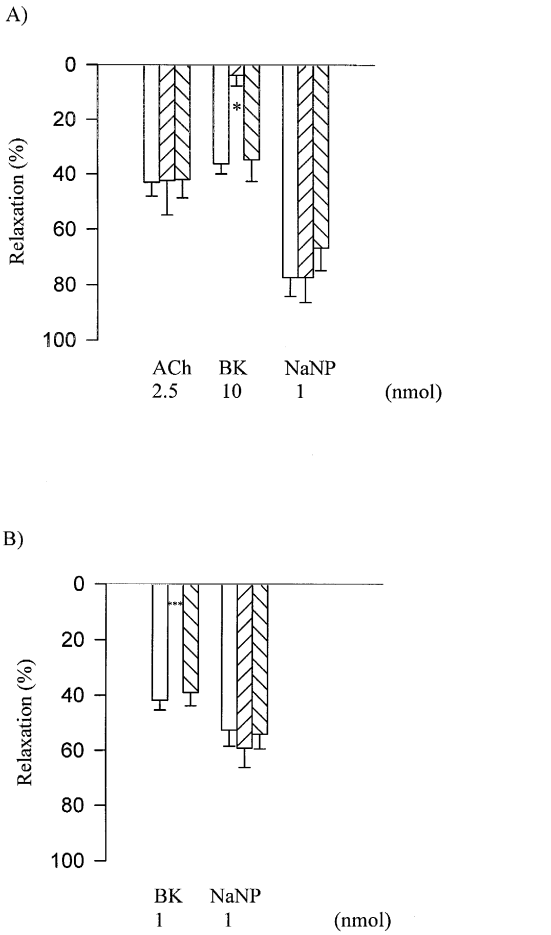

Fig. 6. Effect of Hoe 140 (upward cross-hatched columns, 5×10^{-7} M, arterial; 10^{-7} M, venous; 15 min) and des–Arg^9–[Leu^8]bradykinin (downward cross-hatched columns, 5×10^{-7} M, arterial; 10^{-7} M, venous; 15 min) on the vasodilation (control, open columns) induced by bradykinin (BK), acetylcholine (ACh) or sodium nitroprusside (NaNP) on mice arterial (A) or venous (B) mesenteric bed. Each column with a bar represents the mean ± S.E.M. of 4 to 5 experiments. * $P < 0.05$, *** $P < 0.01$.

3.2. Effect of L-NAME or CHAPS on the arterial and venodilatory effect of bradykinin

Fig. 4 illustrates the contribution of nitric oxide synthase in the vasodilatory properties of bradykinin. L-NAME (200–400 μM; 30 min) significantly reduced the vasodilatory response to bradykinin (10 nmol, arterial; 1 nmol, venous) in mesenteric circuits from control mice (wild type) (Fig. 4A and B). Furthermore, the response to acetylcholine (2.5 nmol, arterial side) but not to sodium nitroprusside (1 nmol, arterial and venous) was reduced in a concentration-dependent fashion by the treatment with L-NAME (200–400 μM) (Fig. 4A). It is also worthy of notice that L-NAME significantly reduced acetylcholine-induced vasodilation in B_2 knockout mice (controls: 54.7 ± 16.8%; in presence of L-NAME (200 μM): 19 ± 4%) ($P < 0.05$, $n = 4$–5 experiments, results not shown).

Fig. 5 shows that a 3 min treatment with CHAPS (20 mM) abolishes the responses to bradykinin and acetyl-

choline (arterial side only) without affecting the relaxation induced by sodium nitroprusside in both the arterial and venous circuits.

3.3. Effects of bradykinin B_1 and B_2 receptor antagonists on bradykinin-induced vasodilatory response of the mouse arterial and venous mesenteric beds

Fig. 6 illustrates the reduction of bradykinin-induced vasodilation in mesenteric arterial (Fig. 6A) and venous (Fig. 6B) vasculature by a 15 min pretreatment with the bradykinin B_2 receptor antagonist Hoe 140 (5×10^{-7} M, arterial; 10^{-7} M, venous). In contrast, a 15 min treatment with the selective B_1 receptor antagonist des–Arg^9–[Leu^8]bradykinin (5×10^{-7} M, arterial; 10^{-7} M, venous) was without effect. The specificity characteristic of Hoe 140 was shown by its lack of antagonism on acetylcholine (2.5 nmol) and sodium nitroprusside (1 nmol) induced arterial and venous vasodilation, respectively.

4. Discussion

Our results suggest that the arterial and venous responses of the mesenteric bed of the mouse to bradykinin are solely mediated by B_2 receptors located on the endothelium and which are blocked by the selective bradykinin B_2 receptor antagonist HOE-140 (Wirth et al., 1991). As illustrated as well in the present study, the vasodilatory effects of bradykinin are entirely dependent on the release of EDRF, since they are prevented by treatment with L-NAME (Radomski et al., 1990). On the other hand, in B_2 knockout mice this response to bradykinin is absent, suggesting the lack of functional B_2 receptors in the mesenteric vascular circuit of these transgenic animals. It is also of interest that no upregulation of B_1 receptors was found in vascular circuits of B_2 knockout transgenic mice, as assessed by the lack of effect of des–Arg^9–bradykinin. As previously demonstrated by Allogho et al. (1995), B_1 receptor activation has been shown to induce contraction of stomach strips derived from normal C57 Bl/6 mice. In contrast to the stomach where B_1 and B_2 receptors are constitutively present and in which tissue des–Arg^9–bradykinin and bradykinin both induce contractions, the arterial and venous mesenteric circuits of the mouse were devoid of B_1 receptor-dependent vasodilatory or vasoconstrictive effects.

Targeted disruption of B_2 receptor gene in mice abolished the responses to bradykinin in non-vascular tissues (Borkowski et al., 1995). This is to our knowledge the first report showing a lack of vasodilatory effects of bradykinin in vessels derived from these animals and would support the absence of B_2 receptor-dependent release of endothelium-derived relaxing factor (EDRF) and thus hypotension triggered by the i.v. administered peptide in vivo. While this manuscript was in preparation, the group of Alfie et al. (1996) reported the lack of hypotensive effect of bradykinin in B_2 transgenic knockout as opposed to wild-type mice. The present study supports the observations made by Alfie et al. (1996), by illustrating (a) the essential contribution of the endothelium and of EDRF in the vasodilatory response of these vascular circuits to bradykinin and (b) the total lack of bradykinin induced a vasodilatory response in both the arterial and venous mesenteric beds of B_2 transgenic knockout animals.

Where PAF and endothelin-3 have been shown to be potent mesenteric arterial dilators (Warner et al., 1989; D'Orléans-Juste et al., 1993; Claing et al., 1994), bradykinin is an established vasodilator of both the arterial and venous mesenteric circuits of the rat and guinea pig (D'Orléans-Juste et al., 1991; Berthiaume et al., 1995). The marked vasodilatory properties of bradykinin can now be extended to the same two mesenteric circuits in the mouse. Alfie et al. (1996) has also shown that acetylcholine induced a hypotensive effect in B_2 transgenic

Table 1
Summary of the arterial and venous effects of various agonists in the mesenteric vascular circuits of wild-type (w.t.) or B_2 knockout (B_2 K.O.) transgenic mice

Animals	Agonists	Vasodilators [a]				Agonists	Vasoconstrictors	
		Endothelium intact		Endothelium impaired [b]			Arterial	Venous
		Arterial	Venous	Arterial	Venous			
Wild-type	BK	↓	↓	0	0	BK	0	0
	des–Arg^9–BK	0	0	0	0	des–Arg^9–BK	0	0
	Ach	↓	0	0	0	ET-1	↑	↑
	NaNP	↓	↓	↓	↓	Ang II	↑	↑
B_2 Knockout	BK	0	0	0	0	BK	0	0
	des–Arg^9–BK	0	0	0	0	des–Arg^9–BK	0	0
	Ach	↓	0	0	0	ET-1	↑	↑
	NaNP	↓	↓	↓	↓	Ang II	↑	↑

↓: Vasodilation.
↑: Vasoconstriction.
[a] Arterial and venous beds treated with methoxamine and U46619, respectively.
[b] Arterial and venous beds treated with L-NAME or CHAPS.

knockout mice and was not different from that observed in control animals. We found that acetylcholine induced a L-NAME and CHAPS-sensitive vasodilatory effect in the arterial mesenteric circuit of B_2 knockout mice. This illustrates the capacity of the arterial mesenteric circuit of B_2 transgenic mice to respond to other endothelium-dependent vasodilators. Although we further tested other endothelium-dependent vasodilators previously documented in the rat and guinea-pig mesenteric beds ([Sar^9,$Met(O_2)^{11}$]substance P, PAF, adenosine diphosphate and acetylcholine), none of these agents would induce a vasodilatory response in the venous mesenteric bed of the mouse. As we have recently suggested, qualitatively different pre- and post-capillary responses of the mesenteric circuits to a single vasoactive agent may contribute in changes in hydrostatic pressures and plasma extravasation phenomenon (D'Orléans-Juste et al., 1996).

In conclusion, our study supports the notion that the hypotensive effects of bradykinin in vivo in the mouse involve vasodilation of not only the high resistance, but the low resistance vascular circuits as well, through B_2 receptor-dependent release of EDRF, as summarized in Table 1. The double perfused mesenteric bed of the mouse may be useful to study the vasoactive properties of various peptides in endothelium-intact vascular circuits of transgenic animals knocked out for many receptor genes.

Acknowledgements

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