Vasoactive Potential of the B₁ Bradykinin Receptor in Normotension and Hypertension

Irena Duka, Ekaterina Kintsurashvili, Irene Gavras, Conrado Johns, Margaret Bresnahan, Haralambos Gavras

Abstract—The B₁ type receptor of bradykinin (Bk B₁R) is believed to be physiologically inert but highly inducible by inflammatory mediators and tissue damage. To explore the potential participation of the Bk B₁R in blood pressure (BP) regulation, we studied mice with deleted Bk B₁R gene with induced experimental hypertension, either salt-dependent (subtotal nephrectomy with 0.5% NaCl as drinking water) or renin/angiotensin-dependent ( renovascular 2-kidney–1-clip). Compared with the wild-type controls, the B₁R gene knockout mice had a higher baseline BP (109.7±1.1 versus 101.1±1.3 mm Hg, P=0.002), developed salt-induced hypertension faster (in 19.3±2.3 versus 27.7±2.4 days, P=0.024), and had a more severe end point BP (148±3.7 versus 133±3.1 mm Hg, P<0.05). On the contrary, renovascular hypertension developed to the same extent (149.7±4.3 versus 148±3.6 mm Hg) and in the same time frame (14±2.2 versus 14±2.1 days). A bolus infusion of a selective B₁R antagonist at baseline produced a significant hypertensive response (by 11.4±2 mm Hg) in the knockout mice only. Injection of graded doses of a selective B₁R agonist produced a dose-dependent hypertensive response in the knockout mice only. Assessment of tissue expression of B₁R and B₂R genes by reverse transcription–polymerase chain reaction techniques revealed significantly higher B₁R mRNA levels in the B₂R knockout mice at all times (normotensive baseline and hypertensive end points). At the hypertensive end points, there was always an increase in B₁R gene expression over the baseline values. This increase was significant in cardiac and renal tissues in all hypertensive wild-type mice but only in the clipped kidney of the renovascular knockout mice. The B₂R gene expression in the wild-type mice remained unaffected by experimental manipulations. These results confirm the known vasodilatory and natriuretic function of the Bk B₂R; they also indicate that in its absence, the B₁R can become upregulated and assume some of the hemodynamic properties of the B₂R. Furthermore, they indicate that experimental manipulations to produce hypertension also induce upregulation of the B₁R, but not the B₂R, in cardiac and renal tissues. (Circ Res. 2001;88:275-281.)

Key Words: bradykinin receptors ■ gene knockout mice ■ blood pressure ■ tissue gene expression

Clinical observations and experimental studies have suggested that the kallikrein-kinin system may participate in the maintenance of normotension and the development of various hypertensive processes. An association between kallikrein and sodium handling was reported years ago in hypertensive patients,1–3 and low urinary kallikrein excretion has been used as a marker of salt sensitivity in normotensive as well as essential hypertensive subjects.4–6 Studies in animals have reported that when this system was either genetically deficient7,8 or pharmacologically impaired,9 it led to an abnormal blood pressure (BP) response to different stimuli, such as excessive salt intake or chronically infused vasoconstrictive substances. Physiopharmacological studies in the past have attributed the hemodynamic and metabolic effects of bradykinin to the B₂ receptor.10 Recently, experiments using genetically engineered mice with targeted disruption of the bradykinin B₂ receptor (Bk B₂R) gene11 have further reinforced this notion. Indeed, Bk B₂R gene knockout mice have shown an exaggerated BP response to high salt diet,11,12 deoxycorticosterone acetate (DOCA) salt-induced hypertension,13 or exogenous angiotensin II infusion.14 On the contrary, bradykinin B₁ receptors (Bk B₁Rs) appear to be absent under physiological conditions, and their expression is only induced by inflammation, cytokines, or tissue trauma.15,16 Different authors have tried to investigate the function of Bk B₁Rs under conditions of pharmacological blockade or absence of Bk B₂ receptors,17,18 but the role of these receptors, if any, in cardiovascular regulation is poorly understood.

The purpose of the current experiments was to further explore the potential participation of the Bk B₁R in BP regulation in normotension and hypertension, in the presence or absence of the Bk B₂R. To this aim, we studied mice lacking the gene encoding for the Bk B₂R and their wild-type

Original received August 8, 2000; revision received December 7, 2000; accepted December 8, 2000.
From the Hypertension and Atherosclerosis Section of the Department of Medicine, Boston University School of Medicine, Boston, Mass.
Correspondence to Haralambos Gavras, MD, Chief, Hypertension and Atherosclerosis Section, Boston University School of Medicine, 715 Albany St, Boston, MA 02118. E-mail hgavras@bu.edu
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counterparts, by developing 2 pathogenically different experimental hypertensive models, 1 salt-dependent (subtotal nephrectomy with dietary salt loading) and 1 renin-dependent (2-kidney–1-clip renovascular hypertension).

Materials and Methods

Animals
Bk B1R gene knockout mice (Bk B1R−/−) and their wild-type controls (Bk B1R+/+) were used in this study. Bk B2R−/− mice were derived from a breeding pair of homozygous knockout mice, generated by gene targeting and homologous recombination11 provided to us by The Jackson Laboratories (Bar Harbor, ME) and bred in our Mouse Facility. The strain is maintained on a mixed 129/Sv×C57BL/6J genetic background by mating of homozygotes. As controls we used wild-type B6129SvF2 mice, which were derived from mating C57BL/6J female with 129S3/SvImJ male and were also obtained from The Jackson Laboratories. The animals, 8 to 12 weeks old and weighing 21 to 30 g, were housed in the animal quarters with a 12-hour light/dark cycle and were fed a standard diet (Chow 5002) and distilled water ad libitum. After subtotal nephrectomy, drinking water was replaced with 0.5% saline. All experiments were conducted in accordance with the guidelines for the care and use of animals approved by the Boston University Medical Center.

Subtotal Nephrectomy
Two groups of mice, a group of Bk B2R knockout mice (Bk B2R−/−) (n=16) and a group of their wild-type counterparts (n=10), were subjected to subtotal nephrectomy. The procedure was performed in anesthetized mice (pentobarbital 50 mg/kg IP). The left kidney was exposed via flank incision, and both poles were excised (approximately two thirds of the kidney), leaving a small amount of renal tissue around the left ureter and hilar vessels. After a 7-day recovery period, again under anesthesia, the right kidney was removed, leaving 20% to 25% of the total renal mass. Twenty-four hours after the second operation, the animals were placed and maintained on 0.5% NaCl as drinking water for the entire period of the experiment.

Renovascular Hypertension
Two groups of animals (n=12 each), Bk B2R gene knockout and wild-type mice, were anesthetized with pentobarbital (50 mg/kg IP), and the procedure was performed as described elsewhere.15 Briefly, a midline incision was made in the abdominal wall and a U-shaped silver clip (0.076 mm) was placed around the left renal artery. In our previous studies, we found this clip size optimal to induce high BP without producing renal infarction. Mice were sutured and returned to a warm cage until they were fully recovered.

BP and Heart Rate (HR) Monitoring
Systolic BP (SBP) and HR were determined using a noninvasive computerized tail-cuff system (BP-2000 Visitech Systems). Mice were trained for 1 week, and control BP was recorded as described elsewhere.15 After the baseline measurements and the subsequent surgical procedure (subtotal nephrectomy or renal artery clipping), the mice were followed for a maximal period of 35 days or until they became hypertensive. Hypertension was defined as a SBP greater than 150 mm Hg or an increase by $100 mm Hg from baseline sustained for 3 consecutive days. BP measurements of the last 3 days were averaged, and the mean was considered the end point tail-cuff BP for the animal.

Determination of Plasma Catecholamine Levels
At the end of the experiment, the iliac artery was catheterized for blood drawing. On the day after catheterization, with the animals conscious and quiet, 100 μL of blood was drawn slowly from the arterial line into a syringe presurized with EGTA (90 mg/mL) and reduced glutathione (60 mg/mL) solution RPN532 (Amersham Life Science), which was used as an antioxidant and antioxidant. The blood was expelled through the needle into an Eppendorf tube, and plasma was separated by spinning at 900g to 1000g in a variable-speed centrifuge. The plasma was transferred to fresh tubes, sealed, and stored at −80°C until assay. Mouse plasma 10 to 20 μL was diluted to 50 μL with sterile water to produce the 50 μL volume needed in the assay. Plasma norepinephrine and epinephrine were measured by the BioTrak catecholamine Research Assay System TRC 995 (Amersham Life Science). The assay is sensitive to ~2 pg norepinephrine or epinephrine per tube.

Tissue Weight
After the blood withdrawal, mice were killed with pentobarbital; the heart was excised and washed with saline. The heart and the remnant kidney weight in subtotally nephrectomized mice or the left (clipped) and right (nonclipped) kidney weight (in renovascular hypertension) were determined.

Preparation of RNA
Total RNA was prepared from 2 tissues, kidneys and hearts, of Bk B1R knockout and wild-type mice at baseline and end point, using TRizol reagent (GIBCO BRL). To increase the purity of the RNA samples, we performed an additional step, a DNase digestion step, to eliminate DNA with Total RNA Isolation Kit S.N.A.P. (Invitrogen).

Expression of Bradykinin Receptors in Tissues
The expression of Bk B1 and B2 receptors in the heart and kidney was examined by reverse transcription–polymerase chain reaction (RT-PCR) techniques. From each tissue, 1 μg of total RNA was converted to cDNA, using a RNA PCR Kit (Perkin-Elmer), and PCR was performed with oligonucleotide primers complementary to mouse Bk B1 and B2 receptor cDNA and 18S rRNA in the same tube. Bk B1R transcripts were amplified with forward primer 5′-TGACTTTCTTTTTGCCCTG-3′ and reverse primer 5′-ACGACTTCTGACGGAAACGC-3′, producing a 391-bp product. Bk B2R receptor transcripts were amplified using the forward primer 5′-GAGTGTGGATGATGTCTGAAGT-3′ and reverse primer 5′-CACGGCACATCCGGAGCGAGT-3′, producing a 300-bp fragment. For internal standard, we chose 18S rRNA, RT-PCR, a product of 185 rRNA-specific primers (Ambion), produced a 488-bp fragment. To establish conditions that allow comparison of the amounts of cDNA produced by RT-PCR, we varied the number of cycles from 24 to 40; a cycle number of 30 was chosen to compare the different levels of expression of the various mRNAs. PCR was performed using the following conditions: 120 seconds at 95°C and annealing 60 seconds at 60°C, followed by 7 minutes at 72°C. Each of the PCR products was separated on a 2% agarose gel and visualized by ethidium bromide staining. The resulting gels were scanned with the pdi 420 image scanner (pdi Inc, Huntington Station, NY) and analyzed with NIH Image J software program.

Functional Assessment of the Bk B1Rs
To confirm that overexpression of B1 receptors in the knockout animals is functionally important, 4 groups of mice, 2 Bk B1R gene knockout mice and 2 of their wild-type controls, were tested with a Bk B1 agonist and a Bk B1 antagonist. After being maintained on a regular diet for a period of 7 days, the animals were anesthetized with sodium pentobarbital (50 mg/kg IP). A modified polyethylene catheter was introduced in the right iliac artery for direct BP recording, and silastic tubing was placed in the right iliac vein for drug administration, as described elsewhere.16 After surgery the animals were returned to their cages and allowed an overnight recovery period. On the day after catheterization, the arterial line was connected to a BP transducer, and mean BP was recorded with a computerized data-acquisition system (Power Laboratory/400, AD Instruments Pty Ltd). The baseline BP was recorded for at least 30 minutes or until it became stable. At this point, one group of knockout mice and one of wild-type controls (n=8 each) received injection of a 100-μL bolus of 0.8 mg/kg of the Bk B1R antagonist, des-Arg9-[Leu8]-bradykinin (Peninsula Laboratories, Inc), and had their BP recorded over the next 30 minutes, until it returned to baseline. In 2 other groups (n=7 each), the dose–BP response curve
to the Bk B,R agonist des-Arg10-Lys-bradykinin (Peninsula Laboratories, Inc) was assessed. The doses were graded from 20 to 200 μg/kg. Each dose was injected in a random order, and sufficient time was allowed (at least 1 hour) for BP to return to baseline.

**Statistical Analysis**

All data are expressed as mean±SEM. Two-way ANOVA for repeated measures was used to test for interaction between time and grouping factor. Differences within and between groups were determined using paired and unpaired Student t tests, respectively. A Tukey test was used for multiple comparisons. Differences at P<0.05 were considered significant.

**Results**

**Subtotal Nephrectomy**

Figure 1 presents BPs obtained by the tail-cuff method in subtotally nephrectomized salt-fed Bk B,R−/− and Bk B,R+/+ mice. Baseline SBP was higher in mice lacking the B,R gene than in their wild-type controls (109.7±1.1 versus 101.1±1.3 mm Hg, P=0.002). After subtotal nephrectomy and salt loading, both groups became hypertensive, but BP increased more and faster in Bk B2 R−/− mice. On the first week after treatment, SBP was 125±6 versus 110±3.5 mm Hg in knockout and wild-type mice, respectively (NS). At the end of the second week, SBP was 140±5.5 mm Hg in Bk B,R−/− versus 119±3.2 in Bk B,R+/+ mice (P<0.05); on the third week it was 140±4.3 versus 127±4 mm Hg, and on the fourth week, 148±3.7 versus 133±3.1 mm Hg (P<0.05 from each other and from baseline).

At baseline, Bk B,R−/− mice had accelerated HR compared with their wild-type counterparts (641±14.3 versus 592.6±17.5 bpm, P<0.05). Subtotal nephrectomy and 0.5% NaCl as drinking water increased the HR further in both groups, so that end point HR was still higher in Bk B,R−/− versus their controls (699.4±10.5 versus 671.9±7 bpm, P<0.05).

There was no difference in body weight and no weight gain over the period of the experiment in the genetically altered mice and their wild-type controls, although the knockout mice tended to be always a little smaller (at end point 24.2±0.7 versus 27.7±0.2 g, respectively, NS). Subtotal nephrectomy and salt loading increased heart weight-to-body weight ratio in both groups, but Bk B,R−/− showed a greater increase than Bk B,R+/+ (6.02±0.22 versus 5.2±0.1 mg/g, respectively, P<0.05). Also, the ratio of remnant kidney weight to body weight was significantly higher in knockout mice (6.74±0.38 versus 5.6±0.2 mg/g, respectively, P<0.05). No difference was found in catecholamine levels between the 2 groups, with norepinephrine levels ranging between 1596 and 1672 pg/mL and epinephrine levels between 317 and 514 pg/mL. The knockout mice became hypertensive in 19.3±2.3 days, which was significantly faster than the wild-type mice (27.7±2.4 days, P<0.05).

**Renovascular Hypertension**

Figure 2 presents the time course of SBP after renal artery clipping in both Bk B,R−/− and Bk B,R+/+ mice. At baseline tail-cuff BP was higher in the knockout mice compared with their wild-type counterparts (109.7±1.08 versus 101.5±0.83 mm Hg, P<0.001). However, both groups became equally hypertensive within 1 week after renal artery clipping (150±4.2 versus 144±3.5 mm Hg at 2 weeks and 149.7±4.29 versus 148±3.64 mm Hg at 4 weeks for the knockout mice and their wild-type controls, respectively).

Baseline HR was higher in knockout mice (637.2±5.3 versus 592.8±9.2 bpm, P<0.001); after 4 weeks it had increased significantly in both groups but did not differ between groups (665.8±10.6 versus 639.8±9.5 bpm in knockout mice and wild-type mice, respectively). There were no significant differences between knockout mice and their controls in terms of their body weight at baseline and end point or ratio of heart or kidney weight to body weight at end point. Both groups required an average of 14±2 days to become hypertensive.

**Expression of Bk B1 and B2 Receptor mRNA in Tissues**

The Bk B,R and B2,R mRNA expression in tissues was determined using a semiquantitative RT-PCR assay. The data of Bk B,R mRNA expression in kidneys of baseline normotensive, subtotally nephrectomized, or renovascular hypertensive mice are presented in Figure 3. At all times, the amount of Bk B,R mRNA expression was higher in the knockout mice compared with their wild-type controls (P<0.05). Sub-
total nephrectomy and salt loading induced a 2.5-fold increase (P<0.05) in Bk B1R expression over the baseline in wild-type, but no further increase in knockout mice. The Bk B1R mRNA levels in the clipped kidney of renovascular mice were greatly elevated compared with those measured both in the contralateral (nonclipped) kidney and in the kidneys from normotensive baseline animals for both groups of mice. Figure 4 shows no differences in Bk B2 R mRNA levels in kidneys of wild-type mice at hypertensive end point of subtotal nephrectomy or renovascular hypertension compared with normotensive baseline. As expected, there was no Bk B2 R mRNA expression in knockout mice.

Figure 5 shows the Bk B1 R mRNA expression in hearts of baseline normotensive, subtotally nephrectomized, and renovascular hypertensive mice. Bk B1 R expression was upregulated in Bk B2 R−/− mice at all times. Hypertensive procedures increased the expression of B1R by 2.4- and 2.6-fold, respectively, in hearts of wild-type subtotally nephrectomized and renovascular hypertensive mice, but produced no further increases in knockout mice. Figure 6 shows no significant changes in Bk B1 R mRNA expression in hearts of baseline normotensive, subtotally nephrectomized, and renovascular hypertensive mice. Bk B1 R expression was upregulated in Bk B2 R−/− mice at all times. Hypertensive procedures increased the expression of B1R by 2.4- and 2.6-fold, respectively, in hearts of wild-type subtotally nephrectomized and renovascular hypertensive mice, but produced no further increases in knockout mice.

Functional Assessment of the Bk B1 Receptors

Figure 7 shows the effect of an intravenous injection of the B1 antagonist des-Arg9-[Leu8]-bradykinin on the intra-arterial BP in knockout and wild-type mice fed a normal salt diet. The injection of des-Arg9-[Leu8]-bradykinin elicited within 5 minutes a significant (from 111.4±2.71 to 122.8±2.03 mm Hg, P<0.05) hypertensive response lasting about 15 minutes, only in the knockout mice, with no changes in the wild-type group (from 109.3± to 112.7±20.3 mm Hg, NS).

Figure 8 shows the BP changes caused by graded intravenous doses of the B1 agonist des-Arg10-Lys-bradykinin. The B1 agonist induced dose-related vasodepressor responses only in the Bk B2 R gene knockout mice. At 20 mg/kg the BP fall was 4.3±0.8 versus 2.4±1.0 mm Hg in knockout mice versus controls (NS); at 100 mg/kg, the BP fall was 7.3±0.7 versus...
2.3 ± 0.7, respectively (P < 0.05 between groups and from the effect of the previous dose in the knockout mice only); at 200 μg/kg, the BP fall was 13.1 ± 1.4 versus 4.7 ± 1.3, respectively (P < 0.05 between groups and from the previous dose in the knockout mice only).

**Discussion**

In the present studies, we demonstrated that loss of the B2R in genetically engineered mice causes a slight but significant rise in systemic BP already at baseline, before any experimental manipulations. This is in agreement with the literature of the past several years documenting by various means the B2R-mediated vasorelaxant contribution of bradykinin to maintenance of vascular tone; elevated BP has been reported in animals and humans genetically deficient in kallikrein,1,4,7,20 in animals treated acutely 21 or chronically 22 with selective B2R antagonists, and in genetically engineered animals with disrupted B2R gene.12,14 Likewise, rats23 and humans24 treated with angiotensin-converting enzyme inhibitors demonstrated a partial reversal of the BP-lowering effect of the angiotensin-converting enzyme inhibitors.

Subsequent experimental procedures to induce salt-dependent hypertension (ie, subtotal nephrectomy with dietary salt loading) revealed that the Bk B2R gene knockout mice had accelerated development and accentuated severity of salt-induced hypertension, as well as more pronounced cardiac hypertrophy than their wild-type controls. On the contrary, when angiotensin-dependent renovascular hypertension was induced by renal artery clipping, there was a similar BP rise in terms of magnitude and time frame in both the B2R gene knockout mice and wild-type mice. The exaggerated salt sensitivity, resulting from loss of both the vasodilatory and natriuretic effects of the B2R, 10 has also been reported by other investigators in various conditions with a genetically suppressed or otherwise impaired kallikrein-kinin system. Examples include the kininogen-deficient Brown Norway Katholiek rats; rats inbred for low urinary kallikrein; rats submitted to blockade of B2 receptors; and essential hypertensive patients with depressed urinary kallikrein, 4–9,22,25 as well as the Bk B2R gene knockout mice.12,14 Presumably, this vulnerability to salt-induced hypertension is attributable to loss of the B2R-dependent activation of endothelial autacoids. The very high catecholamine levels in the current experiments are similar to the hyperadrenergic state shown in other forms of salt-induced hypertension.26 However, there were no differences in magnitude of sympathetic stimulation between the knockout mice and wild-type mice.

Contrary to the sodium-dependent hypertension, the renovascular angiotensin-dependent hypertension induced by clipping of one renal artery was not affected by the presence or absence of the B2R. Thus, angiotensin-induced vasoconstriction was apparently not being counteracted by the B2R. This is in agreement with similar findings by investigators using another angiotensin-dependent model,27 although others have reported an exaggerated BP response to angiotensin-dependent hypertension in B2R-deficient animals.14,28 These discrepancies are difficult to reconcile. A possible speculative explanation might be that genetic manipulations to delete the B2R gene might lead to constitutive expression of the inducible B2R in B2R gene knockout mice, and under certain conditions the B2R assumes a hemodynamic role. It should be
noted, however, that some investigators have failed to demonstrate upregulation of the B1R when the B2R was blocked or deleted.17–29 The inducible character of the B1R (a feature unusual for a G protein–coupled receptor) is well documented in the literature15 but has only been reported under conditions of inflammation and tissue damage. We hypothesized that certain experimental hypertension-inducing maneuvers might also induce upregulation of the B1R.

To explore this possibility, we assessed the tissue expression of the B1R gene and the vascular function of the B1R. One unexpected novel finding was that elimination of the B1R gene consistently resulted in significant increase of the B1R gene expression in the knockout mice in all tissues examined at both normotensive baseline and at hypertensive end points. Moreover, the upregulated B1R became further upgraded in cardiac and renal tissue after experimental manipulations to raise the BP. Indeed, in normotensive B2R knockout mice, it appeared to assume in part the hemodynamic function of the B1R. This was shown by both the hypertensive response to selective B1R blockade and the hypertensive dose-related response to a selective B1R agonist, both administered at doses commonly used in the literature.15–17 On the contrary, there was no BP response to either a B1R blocker or a B1R agonist in the wild-type animals, in keeping with what has been reported by other investigators.30 The hypertensive response to B1R blockade in the B2R knockout mice was similar to that observed after selective B2R blockade in normal animals,21–22 as mentioned earlier. It is notable that in wild-type animals, hypertensive or hypotensive responses to selective B1R agonists and antagonists, respectively, have been observed only after pretreatment of animals with inflammatory mediators such as lipopolysaccharides, interleukin-1, or bacterial toxins, ie, maneuvers known to produce B1R induction.15,16

Another unexpected new finding was the fact that, in normal (wild-type) mice, experimental manipulations to induce hypertension resulted also in a significant upregulation of the B1R gene expression in cardiac and renal tissues, even more pronounced than in the B2R gene knockout mice, whereas these manipulations produced no change in the B1R gene expression. This upregulation was maximal in the renal tissue of the clipped kidney in renovascular hypertension, the site known to be protected from hypertensive vascular damage. Actually, this was the only tissue that had a significant further increment in the already highly upregulated B1R gene expression of the B2R gene knockout mice. It is tempting to speculate that induction of B1R may be one of the mechanisms by which bradykinin exerts its tissue-protective effects under hypertensive conditions, whereas B2R activity participates in the equilibrium between vasoconstrictors and vasodilators at the resting state.

Although the hypertensive response to the B1R antagonist in the B2R gene knockout mice (but not in the wild-type mice) suggests that in the absence of the B2R, the vascular B2R seems to assume a B2R-like hemodynamic function, an alternative explanation is also plausible for the baseline BP elevation of the knockout mice, namely, that this hypertensive effect could be partly originating from the central nervous system (CNS). The CNS effects of Bk receptors may be opposite those of the peripheral vasculature. It has been reported that in genetically intact animals, central B1R stimulation tends to increase BP, whereas B2R blockade lowers BP.31,32 It is therefore possible that if excessive upregulation of B1R, such as detected in cardiac and renal tissues in our B2R knockout mice, occurs also in the CNS, the unopposed hypertensive influence of these receptors may be partly responsible for the baseline BP elevation in the B2R gene knockout mice.

In summary, the current data lend further support to the notion that the vasodilatory and natriuretic effects of bradykinin, which tend to counteract sodium-dependent hypertension, are exerted mainly via the B2 receptor. However, they also indicate that in its absence, the physiologically inert B1 receptor can become upregulated and, in the resting state, it can assume part of the hemodynamic properties of the missing B2 receptor. Furthermore, this is the first evidence to suggest that experimental manipulations to produce hypertension seem to also induce significant upregulation of the B1R, but not of the B2 receptor, in tissues that are particularly vulnerable to hypertensive damage. Whether the hemodynamic activity of the B2R is achieved via stimulation of downstream endothelial autacoids, as is the case with B2 receptor activation; via a direct centrally mediated mechanism; or both remains to be explored.

Acknowledgments
This work was supported by National Heart, Lung, and Blood Institute Grants R01 HL588807 and P50 HL55001.

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Circ Res. 2001;88:275-281
doi: 10.1161/01.RES.88.3.275

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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