Mechanisms Mediating the Vasoactive Effects of the B$_1$ Receptors of Bradykinin

Irena Duka, Arvi Duka, Ekaterina Kintsurashvili, Conrado Johns, Irene Gavras, Haralambos Gavras

Abstract—Bradykinin normally exerts its vasodilatory effect via the B$_2$ receptor (B$_2$R), but in this receptor’s absence, the B$_1$ receptor becomes expressed and activated. To explore the mechanism of B$_1$R-mediated vasodilation, 8 groups of B$_2$R gene–knockout mice received a 2-week infusion of a B$_1$R antagonist (300 μg · kg$^{-1}$ · d$^{-1}$) or vehicle (groups 1 and 2), B$_1$R antagonist or vehicle plus NO inhibition with N$	ext{-}$nitro-L-arginine methyl ester (groups 3 and 4), B$_1$R antagonist or vehicle plus cyclooxygenase inhibition with indomethacin (groups 5 and 6), or B$_1$R antagonist or vehicle plus blockade of vasoconstricting prostaglandin (PG) H$_2$ and thromboxane A$_2$ (TxA$_2$) with SQ29548 (groups 7 and 8). The B$_1$R antagonist produced significant ($P<0.05$) blood pressure increases of 17.7 ± 3.1 mm Hg in group 1 and 10.4 ± 3 mm Hg in group 3, whereas their vehicle-treated respective control groups 2 and 4 had no significant blood pressure changes. Indomethacin abolished the capacity of the B$_1$R antagonist to raise blood pressure, as did blockade of the receptors of PGH$_2$ and TxA$_2$. Injection with the B$_1$R agonist produced a hypotensive response (12 ± 1.3 mm Hg), which was further accentuated by TxA$_2$ blockade (21.7 ± 4.1 mm Hg). Analysis of B$_1$R gene expression by reverse transcription–polymerase chain reaction (PCR) in cardiac and renal tissues revealed marked expression at baseline, with further upregulation by 1.5- to 2-fold after various manipulations. Expression of the TxA$_2$ receptor gene in renal tissue by quantitative real-time PCR was significantly lower in mice treated with the B$_1$R antagonist, consistent with increased levels of agonist for this receptor. The data confirm that the B$_1$R becomes markedly expressed in the absence of B$_2$R and suggest that it contributes to vasodilation by inhibiting a vasoconstricting product of the arachidonic acid cascade acting via the PGH$_2$/TxA$_2$ receptor. (Hypertension. 2003;42:1021-1025.)

Key Words: receptors, bradykinin • mice • nitric oxide • prostaglandins • vasorelaxation

Bradykinin is a potent vasodilatory nonapeptide$^1$ that acts via 2 types of receptors: B$_1$ and B$_2$. The B$_2$ receptors (B$_2$Rs) are widely distributed in the vasculature$^2$ and account for most of its vasodilatory effects. Their activation leads to release of prostaglandins (PGs) and/or nitric oxide (NO),$^3$–$^5$ whereas their blockade by selective B$_2$R antagonists causes a small but significant hypertensive effect.$^6$

The B$_1$Rs are normally not expressed under physiologic conditions but are inducible by inflammation, lipopolysaccharides, cytokines, vascular trauma, etc.$^7$–$^9$ Once induced, the B$_1$Rs also mediate vasodilation. Indeed, the selective B$_1$R agonist des-Arg(9)-bradykinin was shown to reduce blood pressure in rabbits pretreated with lipopolysaccharides, but not in controls,$^{10}$ and to relax an in vitro preparation of rabbit mesenteric arteries.$^{11}$

In previous studies, we have shown that the normally nonexpressed B$_1$R gene becomes expressed in B$_2$R gene–knockout mice, in which the B$_2$R assume some of the hemodynamic properties of the B$_2$R and is further upregulated in response to hypertensive maneuvers.$^{12}$ These findings suggest a role for the B$_1$R in vascular tone regulation, but the extent to which these receptors are involved and the mechanism of B$_1$R-mediated vasodilation are not clearly understood. The current study was designed to explore this mechanism. For this purpose, we used B$_2$R gene–knockout mice (B$_2$R$^{-/-}$)$^{13}$ and assessed the involvement of NO and/or PGs in B$_1$R-mediated vasorelaxation by blocking the synthesis or the receptors of these autacoids and measuring the changes in blood pressure induced by a B$_1$R antagonist.

Methods

Animals and Protocols

Eight groups of B$_2$R$^{-/-}$ mice derived from breeders provided to us by the Jackson Laboratories (Bar Harbor, Me) were used in these experiments.$^{12}$ When they were 8 to 12 weeks old and weighed 21 to 31 g, the mice were housed in the animal quarters with a 12-hour light/dark cycle and maintained on a standard chow diet (Purina Rodent Chow 5002) and distilled water ad libitum. All experiments were conducted in accordance with the guidelines for the Care and Use of Animals approved by the Boston University Medical Center.

Group 1 (n=10) received an infusion of a B$_1$ antagonist, whereas group 2 (n=9) received vehicle solution. Groups 3 and 4 (n=10 each) were given the NO synthase inhibitor N$	ext{-}$nitro-L-arginine methyl ester (l-NAME) in their drinking water. Group 3 received the B$_1$ antagonist, whereas group 4 served as a control, receiving only vehicle solution. Groups 5 and 6 were treated with subcutaneous
daily indomethacin; 1 received the B1 antagonist (n=7), and the other received a vehicle solution (n=9). Groups 7 and 8 (n=10 each) were treated with the thromboxane A2 (TxA2)/PGH2 receptor antagonist SQ29548. Group 7 received the B1 antagonist, and group 8, a vehicle solution.

All treatments lasted for a 2-week period. Systolic blood pressure (SBP) and heart rate were determined with a noninvasive, computerized, tail-cuff system (BP-2000 Visitech Systems), as described elsewhere.14 At the end of the experiments, the mice were euthanatized by CO2 inhalation; their hearts and kidneys were removed and prepared for tissue expression of the B1R gene, as described previously.12

Two other groups of B2R+/−/− mice (n=8 and 7) were anesthetized with pentobarbital (50 mg/kg IP) and had a modified polyethylene catheter introduced into the right iliac artery for direct BP recording, and silicone elastomer (Silastic) tubing was placed in the right iliac vein for drug administration, as described elsewhere. After an overnight recovery period, the arterial line was connected to a BP transducer, and the mean direct BP was recorded with a computerized data-acquisition system (Power Laboratory/400, AD Instruments, Bella Vista, NSW, Australia). In groups 1 and 2, with or without infusion of the B1 antagonist, the BP rose from 123.8±1.6 to 141.5±4.2 mm Hg (P<0.05) at the end of the 2-week period. In the vehicle-treated group 2, BP did not increase (124±1.8 vs 125±4.4 mm Hg; P=NS).

Figure 1B shows the time course of SBP in groups 3 and 4 treated with L-NAME, with or without the B1 antagonist. In group 3, the B1 antagonist increased the BP from 123.6±1.5 to 133.9±3.2 mm Hg (P<0.05), whereas in group 4, BP did not change significantly from baseline (123.4±1.7 vs 127.9±4.7 mm Hg; P=NS).

Figure 2A shows the time course of SBP in groups 5 and 6 treated with indomethacin, with or without the B1 antagonist. Neither group increased their BP significantly at the end of the 2-week period: In group 5, treated with the B1 antagonist, BP changed from 113.3±4.01 to 119.4±5.2 mm Hg, and in the vehicle-treated group 6, from 114.1±3.8 to 117.1±3.9 mm Hg (both P=NS).

Figure 2B presents the time course of SBP in the 2 groups of B1R−/−/− mice that received treatment with the TxA2/PGH2 antagonist SQ29548, with or without the B1 antagonist. Neither group increased their BP at the end of the 2-week period: In group 7 treated with the B1 antagonist, BP changed from 125±2.1 to 131±5.3 mm Hg, and in the vehicle-treated group 8, from 126.1±2 to 126.7±7.7 mm Hg.

### Expression of B1R and TxA2 Receptors in Tissues

Total RNA was prepared from heart and kidney tissue with TRIzol reagent (GIBCO BRL). The expression of B1R was examined by reverse transcription–polymerase chain reaction (PCR) techniques, as previously described,13 whereas the expression of TxA2 receptors in kidneys was examined by quantitative real-time PCR. Real-time PCRs were performed with an ABI prism 7900 HT sequence detection system with a SYBR Green–based protocol (Applied Biosystems). Oligonucleotide primers for TxA2 and glyceraldehyde 3-phosphate dehydrogenase (GAPDH, used as a control) were designed with Primer Express Software version 2.0 (Applied Biosystems) and manufactured by Invitrogen and IDT. TxA2 receptor transcripts were amplified with forward primer AGCACCAGCTGCTCATCTACC-3’ and reverse primer 5’-GACCGGCGAAAGAGGATATAGAC-3, producing a 34-bp product. GAPDH was amplified with forward primer 5’-TGCCACCAACAGTCTTAGA-3’ and reverse primer 5’-GGATGCAAGGATGATGTTC-3’, producing a 117-bp product.

The final concentration of the primers for both genes was 300 nM/μL. After an initial denaturation step at 95°C for 10 minutes, the cDNA products were amplified for 40 cycles, consisting of denaturation at 95°C for 15 seconds and a single step of annealing and extension at 60°C for 1 minute. All reactions were run in triplicate and included negative controls. The SDS 2.0 software generated standard curves from 10-fold cDNA dilutions.

### Drugs

The B1 antagonist R-892 (AcLys[ε-caproic][D-β-Nal][leucine]-des-Arg9-bradykinin; a gift from Dr. Dominique Rolgoli, Sherbrooke, Canada)15 was infused subcutaneously at a dose of 300 μg · kg−1 · d−1 through an osmotic minipump (Durect). L-NAME (Sigma) at 50 mg/L was given in the drinking water. Indomethacin (Sigma) at 2 mg · kg−1 · d−1 was injected subcutaneously. SQ29548, a TxA2/PGH2 antagonist (a gift from Bristol-Myers Squibb, Princeton, NJ), was infused subcutaneously at 0.2 mg · kg−1 · h−1 through an osmotic minipump. The B1 agonist des-Arg10-Lys-bradykinin (Peninsula Laboratories Inc) was injected intravenously at a dose of 200 μg/kg.

### 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 factors. Differences within and between groups were determined by paired and unpaired Student t tests, respectively, and Tukey test was used for multiple comparisons. Differences at P<0.05 were considered significant.

### Results

Figure 1A presents the time course of systolic BP in groups 1 and 2, with or without infusion of the B1 antagonist. In the B1 antagonist–treated group 1, BP rose from 123.8±1.6 to 141.5±4.2 mm Hg (P<0.05) at the end of the 2-week period. In the vehicle-treated group 2, BP did not increase (124±1.8 vs 125±4.4 mm Hg; P=NS).

Figure 1B shows the time course of SBP in groups 3 and 4 treated with L-NAME, with or without the B1 antagonist. In group 3, the B1 antagonist increased the BP from 123.6±1.5 to 133.9±3.2 mm Hg (P<0.05), whereas in group 4, BP did not change significantly from baseline (123.4±1.7 vs 127.9±4.7 mm Hg; P=NS).

Figure 2A shows the time course of SBP in groups 5 and 6 treated with indomethacin, with or without the B1 antagonist. Neither group increased their BP significantly at the end of the 2-week period: In group 5, treated with the B1 antagonist, BP changed from 113.3±4.01 to 119.4±5.2 mm Hg, and in the vehicle-treated group 6, from 114.1±3.8 to 117.1±3.9 mm Hg (both P=NS).

Figure 2B presents the time course of SBP in the 2 groups of B1R−/−/− mice that received treatment with the TxA2/PGH2 antagonist SQ29548, with or without the B1 antagonist. Neither group increased their BP at the end of the 2-week period: In group 7 treated with the B1 antagonist, BP changed from 125±2.1 to 131±5.3 mm Hg, and in the vehicle-treated group 8, from 126.1±2 to 126.7±7.7 mm Hg.
A significant drop in BP (12/110 mm Hg) was observed following the addition of the TxA2/PGH2 receptor antagonist, similar to the drop observed in mice injected during a concurrent infusion of saline. On the contrary, when the second dose of the B1 agonist was administered without a TxA2/PGH2 receptor antagonist or saline on arterial BP, as shown in A, the first injection of the B1 agonist (200 μg/kg) elicited a significant drop in BP (12 ± 1.4 mm Hg; P < 0.05). Infusion of the TxA2/PGH2 receptor antagonist SQ29548 by itself did not cause any change in BP, but repeated injection of the B1 agonist produced a drop in BP by 21.7 ± 4.1 mm Hg, which was significantly more (P < 0.05) than with the first injection of the B1 agonist (before the TxA2/PGH2 receptor antagonist). On the contrary, when the second dose of the B1 agonist was injected during a concurrent infusion of saline, it again produced a BP drop of 9.4 ± 1.2 mm Hg, similar to the 10.2 ± 0.8 mm Hg produced by the first dose. These results corroborate those of groups 7 and 8, suggesting that the activation of B1R inhibits a vasoconstricting component of the arachidonic acid cascade, whereas blockade of the B1R releases this component. To further illustrate this, we infused 1 B1R−/− mouse for 90 minutes with the B1 agonist at 0.2 μg/min, which produced a 9-mm Hg fall of BP from baseline. Addition of the TxA2/PGH2 receptor antagonist as a concurrent infusion for another 120 minutes produced a 25-mm Hg fall in BP from baseline. This sequence is shown in B of Figure 3.

Figure 3 shows the effect of an intravenous injection of the B1 agonist with or without concurrent infusion of the TxA2/PGH2 receptor antagonist or saline on arterial BP. As shown in A, the first injection of the B1 agonist (200 μg/kg) elicited a significant drop in BP (12 ± 1.4 mm Hg; P < 0.05). Infusion of the TxA2/PGH2 receptor antagonist SQ29548 by itself did not cause any change in BP, but repeated injection of the B1 agonist produced a drop in BP by 21.7 ± 4.1 mm Hg, which was significantly more (P < 0.05) than with the first injection of the B1 agonist (before the TxA2/PGH2 receptor antagonist). On the contrary, when the second dose of the B1 agonist was injected during a concurrent infusion of saline, it again produced a BP drop of 11.4 ± 1.2 mm Hg, similar to the 10.2 ± 0.8 mm Hg produced by the first dose. These results corroborate those of groups 7 and 8, suggesting that the activation of B1R inhibits a vasoconstricting component of the arachidonic acid cascade, whereas blockade of the B1R releases this component. To further illustrate this, we infused 1 B1R−/− mouse for 90 minutes with the B1 agonist at 0.2 μg/min, which produced a 9-mm Hg fall of BP from baseline. Addition of the TxA2/PGH2 receptor antagonist as a concurrent infusion for another 120 minutes produced a 25-mm Hg fall in BP from baseline. This sequence is shown in B of Figure 3.

There were no differences in body weight among groups at baseline or at end point. B1R mRNA expression was already evident at baseline in the hearts and kidneys of all animals, as shown in the past for B2R−/− mice. Administration of L-NAME produced no changes in B1R mRNA expression in heart and kidney tissues, as shown in the Table. Indomethacin alone also produced additional increases in B1R mRNA, by 1.5- to 2-fold, in heart and kidney tissues, as did administration of the TxA2/PGH2 receptor antagonist whether given alone or concurrently with the B1 antagonist.

TxA2 receptor expression in kidneys of groups 1 and 2, treated with the B1 antagonist and vehicle, respectively, was determined by quantitative real-time PCR. The slopes of the standard curve for TxA2 and for GAPDH, were −3.28 and −3.4, respectively, where −3.33 corresponds to 100% efficiency of the PCR. The copy numbers for TxA2 were normalized with the data obtained from GAPDH. We found that the expression of TxA2 in mice treated with the B1 antagonist was downregulated by 50% (P < 0.05), consistent with increased levels of agonist for these receptors.

**Discussion**

In previous studies, we have demonstrated that in B2R gene– knockout mice, the B1R becomes overexpressed and appears to take over some of the hemodynamic properties of the missing B2R, namely, vasorelaxation and contribution to the hypotensive action of angiotensin-converting enzyme inhibitors. The current experiments were designed to explore the mechanism(s) of B1R-mediated vasorelaxation. By evaluating the BP responses to the selective B1R antagonist R89215 administered in B2R−/− mice concurrently with inhibition of PG or NO synthesis, we sought to dissect the contribution of each of these factors in mediating the actions of the upregulated B1R. As expected, these mice had a slightly elevated BP at baseline and, consistent with our previous data, responded with further BP rises when treated with a B1R antagonist. The present study suggests that NO is not responsible for B1R-mediated vasorelaxation, because the B1R antagonist increased BP to the same extent in the presence or absence of L-NAME, which blocks formation of NO. This is in contrast to other studies in different species, which have shown that stimulation of the B1R with an agonist failed to produce vasodilation in pigs or dogs when NO synthesis had also been blocked, suggesting that those responses were dependent on the release of NO from the endothelium. It has also been suggested that responses to bradykinin can be mediated by the release of other factors, such as an endothelium-derived hyperpolarizing factor or the activation of muscarinic receptors.

On the contrary, inhibition of PG synthesis by indomethacin abolished the hypertensive response to B1R blockade, suggesting that some component of the arachidonic acid cascade is a mediator of this response. There is a body of evidence supporting B1R-mediated vasodilation through PGs, such as in rabbit celiac and mesenteric arteries, in coronary arteries of the rat, and in dog mesenteric arteries. This vasodilation can be mediated by synthesis of PGs in the endothelium but might also involve release of endothelium-independent PGs. For example, in some endothelium-denuded vessels, such as in rabbit celiac and mesenteric arteries, activation of the B1R...
was reported to result in vasorelaxation that could be inhibited by indomethacin.24,25

The possibility that the B 1 R might interfere with the synthesis or activity of a vasoconstricting PG has not been considered so far. Our data are consistent with the notion that the B 1 R interferes with the vasoconstricting influence of some product of the arachidonic acid cascade (eg, TxA 2 , PGF, or PGH 2 ); blockade of the B 1 R would release this vasoconstricting product, whereas concurrent blockade of the synthesis of this product or antagonism of this product at the level of its receptor would negate the pressor response to B 1 R blockade. Indomethacin blocks cyclooxygenase and production of all downstream PGs, both the vasodilating ones as well as vasoconstricting ones, like PGH 2 and Tx. In our last 2 experimental groups, we decided to selectively block the receptors to these vasoconstricting products, ie, Tx and its precursor PGH 2 , which share the same receptor, with the compound SQ29548. The fact that this compound prevented the expected rise after B 1 R blockade would suggest that B 1 R activity might be suppressing these vasoconstricting substances. To further explore this hypothesis, a B 1 agonist was injected before and after TxA 2 /PGH 2 blockade. Expression of the TxA 2 receptor gene, assessed by real-time PCR in kidneys of mice treated with a B 1 antagonist, showed significant downregulation of the TxA 2 receptor gene, probably as a compensatory mechanism resulting from an increase in TxA 2 levels after B 1 R blockade.

Thus, our current data lead to the hypothesis of a possible dissociation between PG-mediated and NO-mediated vascular effects, so that vasorelaxation resulting from stimulation of B 1 Rs need not be NO mediated but rather might be attributable to B 1 R-mediated suppression of a vasoconstricting component of the arachidonic acid cascade. The accen-

### Variations of mRNA Coding for B 1 Rs in Kidneys and Hearts of B 2 R+/−/− Mice as a Function of Various Treatments

<table>
<thead>
<tr>
<th>Group</th>
<th>Kidney</th>
<th>Heart</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>0.97±0.04</td>
<td>1±0.1</td>
</tr>
<tr>
<td>L-NAME+B 1 A</td>
<td>1.32±0.19</td>
<td>0.78±0.15</td>
</tr>
<tr>
<td>L-NAME</td>
<td>1.17±0.19</td>
<td>0.75±0.16</td>
</tr>
<tr>
<td>Indomethacin+B 1 A</td>
<td>1.1±0.15</td>
<td>1.25±0.25</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>2±0.5*</td>
<td>1.72±0.05*</td>
</tr>
<tr>
<td>SQ29548+B 1 A</td>
<td>1.4±0.06*</td>
<td>2±0.05*</td>
</tr>
<tr>
<td>SQ29548</td>
<td>1.62±0.18*</td>
<td>1.5±0.18*</td>
</tr>
</tbody>
</table>

B 1 A indicates B 1 antagonist. Values are mean±SEM derived from 4 mice in each group. Mean densitometric data are expressed as a ratio of 18S mRNA, derived from reverse transcription–PCR.

*P<0.05 between treated and untreated mice.

---

**Figure 3.** A, Effect of a bolus injection of a B 1 agonist without and with infusion of the TxA 2 /PGH 2 receptor antagonist (solid line) or normal saline (dotted line) on direct intra-arterial BP in B 2 R−/− mice. **P<0.05, **P<0.001 between baseline and the peak effect of B 1 agonist injection; *P<0.05 between TxA 2 /PGH 2 receptor antagonist and saline-treated group. B, Representative BP tracing in 1 B 2 R−/− mouse infused with a B 1 agonist without and with concurrent infusion of the TxA 2 /PGH 2 receptor antagonist.
tuated hypotensive response to a B₁R agonist under concurrent blockade of the TxA₂/PGH₂ receptor further corroborates this interpretation.

The discrepancies between different studies indicate that the mechanism of B₁R-mediated vasodilation is heterogenous and might be species specific as well as vessel specific. The different experimental settings might also account for the differences between studies, as our study was conducted in vivo in conscious mice with a genetically deleted B₂R, whereas others were conducted in normal animals with various pharmacologic blockers or in vitro in isolated blood vessels. These experimental inconsistencies illustrate the complexity of the mechanisms involved in B₁R-mediated vasodilation.

In addition to the BP response, there was an upregulation of B₁R in kidney and heart tissues, in keeping with our previous findings in B₁R−/− subtotally nephrectomized mice. This upregulation is accentuated by hypertensive manipulations and might contribute to the lack of a significant BP rise in response to such manipulations in these animals with normal renal function. This is in contrast to the significant loss of insulin sensitivity in B₂R−/− animals with normal renal function. This is in contrast to the fact that TxA₂/PGH₂ receptor inhibition prevented the BP rise in response to such manipulations in these animals with normal renal function. This is in contrast to the complexity of the mechanisms involved in B₁R-mediated vasodilation.

The discrepancies between different studies indicate that the mechanism of B₁R-mediated vasodilation is heterogenous and might be species specific as well as vessel specific. The different experimental settings might also account for the differences between studies, as our study was conducted in vivo in conscious mice with a genetically deleted B₂R, whereas others were conducted in normal animals with various pharmacologic blockers or in vitro in isolated blood vessels. These experimental inconsistencies illustrate the complexity of the mechanisms involved in B₁R-mediated vasodilation.

In addition to the BP response, there was an upregulation of B₁R in kidney and heart tissues, in keeping with our previous findings in B₁R−/− subtotally nephrectomized mice. This upregulation is accentuated by hypertensive manipulations and might contribute to the lack of a significant BP rise in response to such manipulations in these animals with normal renal function. This is in contrast to the significant loss of insulin sensitivity in B₂R−/− mice, in which B₁R upregulation cannot compensate for this property.

**Perspectives**

The current findings corroborate and amplify previous data indicating that in the absence of the B₂R, bradykinin can still exert a tonic vasorelaxant effect via activation of B₁Rs, as shown by the hypertensive response to B₂R blockade. Preservation of the hemodynamic properties of bradykinin via the B₁R in the absence of a B₂R is of particular interest when considered in light of the fact that its metabolic (insulin-sensitizing) properties seem to be solely dependent on the B₂R and are lost in its absence. The vasorelaxant effect of the B₁R does not seem to be effected via NO release, because inhibition of NO synthesis by L-NAME did not accentuate the hypertensive response to B₂R blockade. The fact that indomethacin did abolish this response would suggest that some component of the arachidonic acid cascade might be involved in the B₁R-mediated vascular effects; this compound would be a vasoconstricting substance that is suppressed by B₂R activity and becomes apparent after B₁R blockade. The fact that TxA₂/PGH₂ receptor inhibition prevented the BP rise expected after B₂R blockade would corroborate this interpretation. Further elucidation of the complex relation between vasoconstricting and vasodilatory factors and their metabolic functions should enhance the tissue-protective efficacy of interventions aimed at lowering BP to improve perfusion and preserve nutrition of vital organs.

**Acknowledgments**

This study was supported in part by National Institutes of Health grants R01 HL 58807 and P50 HL 55001.

**References**


Mechanisms Mediating the Vasoactive Effects of the B1 Receptors of Bradykinin
Irena Duka, Arvi Duka, Ekaterina Kintsurashvili, Conrado Johns, Irene Gavras and Haralambos Gavras

Hypertension. 2003;42:1021-1025; originally published online October 13, 2003; doi: 10.1161/01.HYP.0000097550.98865.35
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/42/5/1021

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/