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Regulation of Cardiovascular Signaling by Kinins and Products of Similar Converting Enzyme Systems

Decreased renal NO excretion and reduced glomerular tuft area in mice lacking the bradykinin B₂ receptor

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Schanstra, Joost P., Johan Duchene, Françoise Praddaude, Patrick Bruneval, Ivan Tack, Jacques Chevalier, Jean-Pierre Girolami, and Jean-Loup Bascands. Decreased renal NO excretion and reduced glomerular tuft area in mice lacking the bradykinin B₂ receptor. *Am J Physiol Heart Circ Physiol* 284: H1904–H1908, 2003. First published January 30, 2003; 10.1152/ajpheart.01150.2002.—Bradykinin B₂ receptor knockout mice (B₂^{-/-}) have been useful to study the role of bradykinin under pathological conditions. With the use of these mice, it was shown that bradykinin plays an important role in angiogenesis, heart failure, salt-induced hypertension, and kidney fibrosis. Data on the role of the bradykinin B₂ receptor under physiological conditions using these mice are controversial and scarce, because these mice have no typical phenotype. For this reason, we have studied, under physiological conditions, renal hemodynamics as well as a number of morphometric glomerular parameters of B₂^{-/-} mice on a homogenized genetic background and on mice bred in a pathogen-free environment. Backcrossed B₂^{-/-} mice had normal blood pressure and normal apparent renal hemodynamics and morphology. However, reduced renal nitrite excretion and glomerular cGMP content were found, which was associated with a reduced glomerular capillary surface area. These differences had, however, no detectable effects on renal hemodynamics. These differences between B₂^{-/-} and wild-type mice might become important under pathological conditions as shown by a number of studies using these bradykinin B₂ receptor knockout mice.

kidney; hemodynamics; nitric oxide; backcross; genetic background

THE DEVELOPMENT of genetically engineered mice lacking the bradykinin B₂ receptor (B₂^{-/-}) (4) has allowed to better define the physio(patho)logical actions of bradykinin. The nonapeptide bradykinin is generated by the proteolytic action of the serine protease kallikrein from kininogen (3). Pharmacological studies have shown that kinins exert their biological effects through the

activation of two seven-transmembrane domain G protein-coupled receptors named B₁ and B₂ receptor (20). The natural agonist of the B₂ receptor is bradykinin and its degradation by a carboxypeptidase produces the B₁ receptor agonist [des-Arg⁹]bradykinin (20). The B₁ receptor is weakly detectable under physiological conditions but is strongly expressed in pathological states (16). The B₂ receptor, which is constitutively expressed, mediates most of the known effects of bradykinin.

It is now generally admitted that bradykinin plays an essential role in renal homeostasis (23, 24). In the kidney, the most pronounced effects of bradykinin are the reduction of vascular resistance (RVR), the increase in renal blood flow (RBF) with no change in the glomerular filtration rate (GFR), and augmentation of natriuresis and diuresis (2, 13, 27). These natriuretic and diuretic effects of bradykinin are due, at least in part, to the activation of B₂ receptors in the medullary thick ascending limb of the loop of Henle (9).

B₂^{-/-} mice do not display a specific phenotype. For example, because bradykinin is a well-known vasodilator peptide, a higher blood pressure (BP) under basal conditions was expected in B₂^{-/-} mice. However, the majority of the papers studied thus far showed no difference in BP between B₂^{-/-} and wild-type mice (1, 6, 18) except for one study, which reported a higher BP in the B₂^{-/-} mice (15).

When fed a high-salt diet, B₂^{-/-} mice developed salt-sensitive hypertension, which was absent in wild-type mice. This salt-sensitive hypertension was associated with a reduced RBF and an increased RVR (1). This salt-sensitive hypertension was confirmed in another study using B₂^{-/-} mice (15); however, renal function was not studied. In contrast, a more recent study showed that increasing dietary salt intake did not modify BP and RBF in B₂^{-/-} mice, whereas the diet increased RBF in wild-type mice (18).

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As recently reviewed, it is now well admitted that differences in genetic background of genetically modified mice leads to divergent results between different laboratories (25). The observed differences for B₂^{-/-} mice might thus originate in differences in the genetic background of the used mice strains and therefore might not be due to the absence of the B₂ receptor. The current study was setup to investigate, under physiological conditions, renal hemodynamics as well as some morphometric glomerular parameters of B₂^{-/-} mice on a homogenized genetic background and on mice bred in a pathogen-free environment.

MATERIALS AND METHODS

Animals. B₂^{-/-} mice were generously provided by Drs. F. Hess and T. MacNeil (Merck; Rahway, NJ) (4). B₂^{-/-} mice were originally on a mixed genetic background (J129sv × C57Bl/6J). B₂^{-/-} mice were backcrossed for 10 generations against a C57Bl/6J background, and the homogeneity of the background was verified by microsatellite analysis (Nucleis; Angers, France; Table 1). Furthermore, mice were housed in a pathogen-free environment.

Experimental protocols. Male mice at the age of 8 wk were used in these experiments, 10 mice in each group. Mice were maintained on a standard mouse chow and tap water. For the metabolic study, mice were housed individually in metabolic cages (Marty Technologie) in a temperature (20°C) and photoperiod (7 AM to 7 PM)-controlled room. They were allowed free access to standard chow and water. Food and water consumption and urine secretion were determined gravimetrically once a day for each mouse during 3 days. Nitrite concentrations in urine samples were determined colorimetrically (Roche Molecular Biochemicals; Meylan, France). Na⁺ and K⁺ concentrations were determined by flame photometry. In vivo renal hemodynamic measurements on mice were performed as previously described for rats with minor modifications (21). Arterial blood samples were taken at the end of the urine collection period. Renal hemodynamic parameters were calculated as described (19). Measurement of blood pressure was performed in anesthetized mice by the tail-cuff plethysmography method as described (17). All experiments reported were conducted as stated in the National Institutes of Health *Guide For The Care And Use Of Laboratory Animals* (Institute of Laboratory Animal Resources,

National Academy Press, Washington DC, 1996) and were approved by a local animal care and use committee.

Histological and morphometric analysis. For histological studies, kidneys were fixed in alcoholic Bouin's solution, embedded in paraffin, sectioned at 4 μm, and stained with hematoxylin according to routine histological staining (22). Morphometric measurements of the different glomerular and capillary surfaces were performed by using an automated image-analyzing system as previously described in detail (10).

Isolation of glomeruli and cGMP measurements. Glomeruli were obtained as described previously (14). cGMP content was measured as previously described (28) using an EIA-kit from Cayman Chemical (Ann Arbor, MI).

Statistical analysis. Values are expressed as means ± SD. Data were compared using SPSS software (SPSS Science; Chicago, IL). ANOVA with post hoc Tukey's α-test was performed for comparison between groups. *P* values <0.05 were considered as significant.

RESULTS

B₂^{-/-} mice are genetically comparable to C57Bl/6J mice. After homogenization of the genetic background of B₂^{-/-} mice by 10 backcrosses, microsatellite analysis showed that B₂^{-/-} mice are now genetically comparable to C57Bl/6J mice (Table 1). C57Bl/6J mice were used as control mice in all experiments.

B₂^{-/-} mice display normal renal and systemic hemodynamic parameters. It is well known that bradykinin, via the B₂ receptor, induces vasodilatation and is natriuretic and diuretic. However, no difference was observed in BP, heart rate (HR), renal plasma flow (RPF), GFR, and RVR between wild-type and B₂^{-/-} mice (Fig. 1). A 3-day metabolic study (Table 2) showed that body weight, food and water intake, urinary flow, urine sodium and potassium excretion, as well as osmolality, did not differ significantly between both groups. However, nitrite excretion was significantly reduced in B₂^{-/-} mice (0.13 ± 0.01 μmol/24 h) compared with wild-type mice (0.79 ± 0.12 μmol/24 h, *P* < 0.01).

B₂^{-/-} mice have a decreased glomerular capillary surface area. No difference in the histological structure of the kidney was observed between B₂^{-/-} and wild-type mice. Wild-type and B₂^{-/-} mice had the same

Table 1. Results of microsatellite sequence analysis

Code: Motif: Size:	D3mit49 GA 124 bp	D5mit10 CA 190 bp	D11mit14 GT 151 bp	D11mit130 CA 197 bp	D14mit203 GT 146 bp	D16mit5 CA 156 bp	D17mit16 CA 120 bp	Ngfg TC 140 bp
n°1	119 ± 5	187 ± 5	150 ± 5	195 ± 5	144 ± 5	152 ± 5	118 ± 5	137 ± 5
n°2	119 ± 5	186 ± 5	150 ± 5	195 ± 5	144 ± 5	150 ± 5	117 ± 5	139 ± 5
n°3	117 ± 5	186 ± 5	150 ± 5	195 ± 5	145 ± 5	150 ± 5	116 ± 5	139 ± 5
n°4	117 ± 5	187 ± 5	150 ± 5	196 ± 5	147 ± 5	150 ± 5	114 ± 5	140 ± 5
n°5	123 ± 5	187 ± 5	151 ± 5	196 ± 5	145 ± 5	149 ± 5	116 ± 5	138 ± 5
n°6	123 ± 5	188 ± 5	151 ± 5	196 ± 5	146 ± 5	150 ± 5	117 ± 5	135 ± 5
n°7	123 ± 5	188 ± 5	151 ± 5	196 ± 5	147 ± 5	150 ± 5	118 ± 5	139 ± 5
n°8	123 ± 5	187 ± 5	152 ± 5	196 ± 5	147 ± 5	150 ± 5	118 ± 5	139 ± 5
n°9	131 ± 5	186 ± 5	152 ± 5	196 ± 5	147 ± 5	151 ± 5	119 ± 5	140 ± 5
n°10	127 ± 5	187 ± 5	150 ± 5	196 ± 5	147 ± 5	150 ± 5	119 ± 5	141 ± 5

First line indicates the code of the microsatellite (where for example D3mit49 represents satellite mit49 on chromosome 3), the motif, and the expected size in C57Bl/6J mice. NgFg, nerve growth factor, gamma. Eight microsatellites from 10 different B₂^{-/-} mice (n°1 to n°10) were analyzed. Numbers indicate the size obtained in the B₂^{-/-} DNA. As shown, no significant difference was observed when compared with the respective expected size of the C57Bl/6J strain-standard.

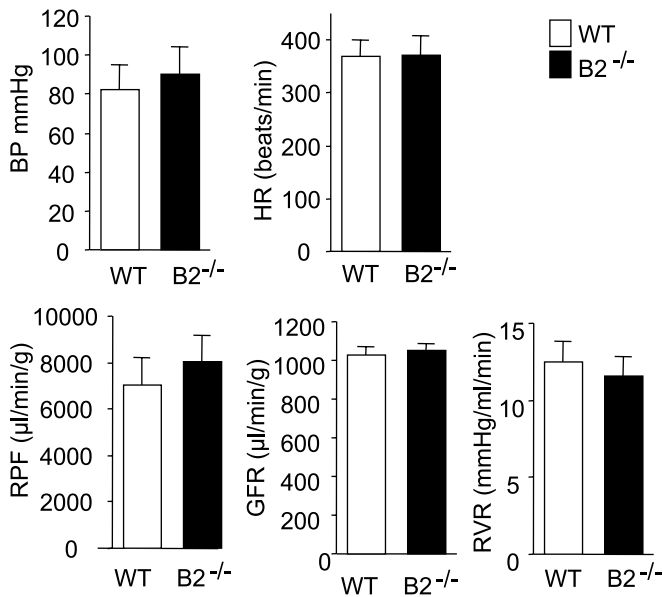


Fig. 1. Tail-cuff blood pressure (BP), heart rate (HR), renal plasma flow (RPF), glomerular filtration rate (GFR), and renal vascular resistance (RVR) in male bradykinin B₂ receptor knock-out (B₂^{-/-}) and wild-type (WT) mice. *n* = 10 mice in each group. Values are presented as means ± SD.

number of glomeruli (respectively 88.8 ± 6 and 88.3 ± 5 per kidney section, *n* = 10). However, morphometrical analysis of at least 40 glomeruli per kidney section showed that the B₂^{-/-} mice have a reduced glomerular tuft area, which is caused by a decreased capillary surface area of $25 \pm 8\%$ (Fig. 2). In contrast, the glomerular surface area was not different between both mice strains.

Glomeruli of B₂^{-/-} mice have reduced cGMP levels. As shown by the metabolic study, B₂^{-/-} mice had a decreased urinary nitrite excretion, which was associated with a decrease in the glomerular capillary surface area, suggesting a precontracted mesangium due to decreased vasodilatory factor levels. To further explore this hypothesis, we studied basal and the stimulated production of cGMP in isolated mouse glomeruli. As shown in Fig. 3, a significant (50%) decrease in basal cGMP levels was observed in isolated glomeruli of B₂^{-/-} mice compared with wild-type mice. When the

Table 2. Three-day metabolic study

	WT Mice	B ₂ ^{-/-} Mice
Body weight, g	25.3 ± 0.5	26.2 ± 0.54
Kidney weight, g	0.259 ± 0.02	0.263 ± 0.019
Food intake, g/24 h	4.7 ± 0.39	4.26 ± 0.13
Water intake, ml/24 h	4.09 ± 0.24	4.08 ± 0.21
U _{vol} , ml/24 h	1.38 ± 0.02	1.25 ± 0.06
U _{Na} output, µmol/24 h	195 ± 27	206 ± 11
U _K output, µmol/24 h	448 ± 64	408 ± 20
U _{NO₂} output, µmol/24 h	0.79 ± 0.12	0.13 ± 0.01*
U _{osmol} , mosmol/kgH ₂ O	2,986 ± 124	3,036 ± 86

Values are means ± SD. Physiological parameters in wild-type (WT) and B₂^{-/-} mice. Male mice of 8 wk were used. U_{vol}, urine volume; U_{Na}, urine sodium; U_K, potassium urine; U_{osmol}, urine osmolality. **P* < 0.01.

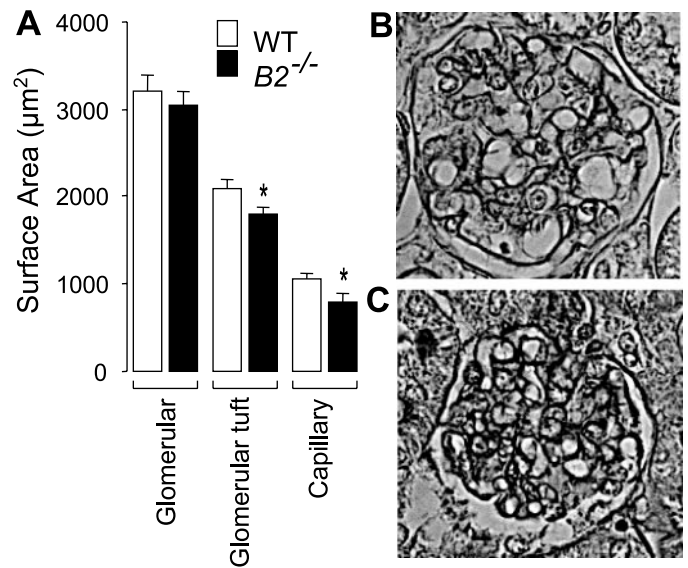


Fig. 2. Morphometric analysis of different glomerular domains. A: whole glomerular surface (glomerular), glomerular tuft area, and glomerular capillary surface. *n* = 10 mice in each group. Values are presented as means ± SD. Forty glomeruli were analyzed per kidney section. **P* < 0.01 compared with WT value. B: representative glomerular section showing glomerular capillary network and mesangium of wild-type mice. C: representative glomerular section showing glomerular capillary network and mesangium of B₂^{-/-} mice. Capillary lumens are larger in wild-type than those in B₂^{-/-} mice.

glomeruli were stimulated with calcium ionophore A23187, an increase in the cGMP content was observed in both wild-type and B₂^{-/-} mice. The ionophore-induced cGMP production was significantly higher in wild-type than in B₂^{-/-} mice, although the relative increase in cGMP levels between both mouse strains was comparable.

DISCUSSION

The main goal of this study was to determine, on a homogenized genetic background, renal function and morphology of B₂^{-/-} and wild-type mice. Consistent with previous reports (1, 6, 18, 29), we found that under physiological conditions B₂^{-/-} mice have normal BP and a normal HR. We thus confirm on a genetically controlled background that under physiological condi-

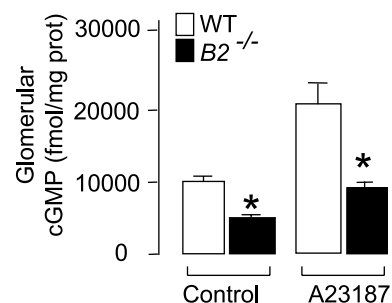


Fig. 3. Variations in cGMP content of isolated glomeruli from B₂^{-/-} and WT mice under basal conditions (control) and stimulated with the calcium ionophore (A23187). Values are presented as means ± SD of 6 distinct experiments. **P* < 0.01 compared with WT value.

tions, i.e. normal sodium diet, the bradykinin B₂ receptor plays a minor role in BP regulation. It is, however, difficult to exclude compensatory mechanisms for the absence of the B₂ receptor in these mice. However, on a mixed J129sv × C57Bl/6J genetic background, there was no modification of the renin-angiotensin system in B₂^{-/-} mice (15).

To obtain more insight in the in vivo renal function and morphology of B₂^{-/-} mice, we performed a metabolic study, determined several renal parameters, performed classical histomorphology, and determined a number of glomerular morphological parameters. As previously reported (1, 7, 18), GFR, RPF, and RVR were not different between both strains. Furthermore, the majority of the urinary parameters was comparable between wild-type and B₂^{-/-} mice. However, a significantly lower urinary NO₂ excretion was observed in B₂^{-/-} mice. Classic kidney histomorphological analysis did not show any difference between B₂^{-/-} and wild-type mice. But glomerular morphology analysis of a large number of glomeruli showed a significant decrease in the size of the glomerular tuft area, which could be attributed to a decreased capillary surface of ~20%. Interestingly and consistent with our data, a reduction of the glomerular tuft area was found in mice having three copies of the angiotensin I-converting enzyme (ACE) (11). Indeed, because ACE has a higher affinity for bradykinin than for angiotensin I (12), overexpression of ACE could result in a decreased bradykinin concentration and, as a consequence, mimic the reduced glomerular tuft area observed in B₂^{-/-} animals. The decreased urinary nitrite concentration in B₂^{-/-} mice suggests impaired nitric oxide (NO) release in this strain, which could account for the observed reduced glomerular tuft area. In the B₂^{-/-} mice, it is possible that bradykinin, normally generating NO, is no longer able to counteract the action of endogenous vasoconstrictors, such as angiotensin II.

To verify that this decrease in the glomerular tuft area might be due to an impaired release of NO and not to anatomic abnormalities, we have measured the cGMP content in isolated glomeruli under basal and stimulated conditions. We found a net 50% decrease in basal cGMP content in the glomeruli of B₂^{-/-} mice compared with wild-type mice. Moreover, stimulation of the isolated glomeruli with the calcium ionophore A23187 produced a higher increase in cGMP content in wild-type glomeruli than in glomeruli of B₂^{-/-} mice, indicating a functional but reduced NO-cGMP pathway in the B₂^{-/-} animals. This lower cGMP production observed in isolated glomeruli under basal conditions can explain the decrease in capillary tuft area in the B₂^{-/-} mice, but it is without consequences on the renal function at least under physiological conditions. Interestingly, when stimulated by the calcium-ionophore, the cGMP content is still inferior in B₂^{-/-} compared with wild-type mice. These data reinforce the hypothesis suggested by others that impairment in the NO-cGMP pathway is an important reason why B₂^{-/-} mice are less resistant to pathological insults. Indeed, indirect evidence has suggested that the B₂^{-/-} mice have

an impaired ability to release NO. Alfie et al. (1) also proposed an impaired ability to release NO to explain the shift to the right of the mean arterial pressure curve in response to acetylcholine in B₂^{-/-} mice compared with control mice. Furthermore, based on data obtained after NO synthase blockade by N^G-nitro-L-arginine methyl ester, this impaired ability to release NO could also explain the enhanced susceptibility to angiotensin II-induced hypertension (7). Reduced NO release could also explain the increased RVR recently reported in B₂^{-/-} mice (29). We were, however, not able to detect any significant variation in the RVR. These authors, who have also homogenized the genetic background of their animals, have used female mice, whereas we have used male mice. Moreover their animals were 12 wk older than the animals that we used. It is thus possible that B₂^{-/-} mice develop, with age, an increased RVR, which is, at the kidney level, without functional consequence at 2 mo but becomes detectable at 5 mo. This progressive increase in RVR could be explained by the absence of the physiological tonic vasodilatory effect of bradykinin in these mice mainly due to this impaired NO-cGMP pathway. Consistent with the above data, it has been recently reported that transgenic mice overexpressing the B₂ receptor have increased renal hemodynamic parameters (increase in RBF and GFR), which was associated to an increased urinary NO₂ and NO₃ excretion (30).

In summary, we have shown that in our B₂^{-/-} mice, under physiological conditions, the B₂ bradykinin receptor was not necessary to maintain normal blood pressure, renal hemodynamics, and salt balance. Nevertheless, the B₂^{-/-} mice, compared with wild-type animals on the same genetic background, exhibit significant spontaneous differences in terms of reduced glomerular tuft area associated with a lower urinary NO₂ excretion.

Apparently, thus without significant consequence under physiological conditions, the bradykinin B₂ receptor has been shown, using B₂^{-/-} mice, to play an important role under different pathological conditions, including hypertension, heart failure, angiogenesis, and kidney fibrosis (5, 8, 22, 26, 31, 32).

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