Regulation of Renin Secretion and Expression in Mice Deficient in β1- and β2-Adrenergic Receptors

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Abstract—The present experiments were performed in β1/β2-adrenergic receptor–deficient mice (β1/β2ADR−/−) to assess the role of β-adrenergic receptors in basal and regulated renin expression and release. On a control diet, plasma renin concentration (in ng angiotensin I per mL per hour), determined in tail vein blood, was significantly lower in β1/β2ADR−/− than in wild-type (WT) mice (222±65 versus 1456±335; P<0.01). Renin content and mRNA were 77% and 65±5% of WT. Plasma aldosterone (in picograms per mL) was also significantly reduced (420±36 in β1/β2ADR−/− versus 692±59 in WT). A low-salt diet (0.03%) for 1 week increased plasma renin concentration significantly in both β1/2(679,776),(735,796)(735,776),(775,796)ADR−/− and WT mice (to 733±54 and 2789±555), whereas a high-salt diet (8%) suppressed it in both genotypes (to 85±24 in β1/β2ADR−/− and to 676±213 in WT). The absolute magnitude of salt-induced changes of plasma renin concentration was markedly greater in WT mice. Acute stimulation of renin release by furosemide, quinaprilat, captopril, or candesartan caused significant increases of plasma renin concentration in both β1/β2ADR−/− and WT mice, but again the absolute changes were greater in WT mice. We conclude that maintenance of normal levels of renin synthesis and release requires tonic β-adrenergic receptor activation. In the chronic absence of β-adrenergic receptor input, the size of the releasable renin pool decreases with a concomitant reduction in the magnitude of the plasma renin concentration changes caused by variations of salt intake or acute stimulation with furosemide, angiotensin-converting enzyme, or angiotensin type 1 receptor inhibition, but regulatory responsiveness is nonetheless maintained. (Hypertension. 2007;50:103-109.)

Key Words: plasma renin ■ salt intake ■ aldosterone ■ furosemide ■ angiotensin-converting enzyme inhibition ■ candesartan ■ sympathetic nervous system

The juxtaglomerular cells in the media of renal afferent arterioles are the major sites of synthesis of the aspartic protease renin, the rate-limiting enzyme in the formation of angiotensin II. Renin is stored in dense core vesicles and released in response to specific tubular and vascular signals transduced by the epithelial cells of the macula densa or by pressure-sensitive cells in the arteriolar wall. In addition, juxtaglomerular (JG) cells are in contact with sympathetic nerve varicosities and express postjunctional β1-adrenergic receptors. Activation of β1-adrenergic receptors directly increases renin secretion, even in the absence of changes in renal vascular tone or macula densa signals.1 Although the directional effects of the main determinants of renin release are known, the contributions of the baroreceptor, the macula densa, and the renal sympathetic nerves to complex disturbances such as changes in body salt content have been difficult to untangle. For example, the change in renin release that results from varying dietary NaCl intake could be mediated by a change of luminal NaCl concentration at the macula densa, a change of baroreceptor activity, or a change of sympathetic nerve activity, because dietary salt intake can influence glomerular filtration rate (GFR) and macula densa salt delivery, arterial pressure, and renal sympathetic nerve activity.2

The aim of the present experiments was to study the regulation of renin expression and release in the absence of β-adrenergic receptors. Because the effect of β-adrenergic stimulation on renin release is believed to be mediated by both postjunctional β1 receptors and prejunctional β2 receptors, mice deficient in both β1- and β2-adrenergic receptors (β1/β2ADR−/−) were used as an experimental model devoid of direct adrenergic input to JG cells.1 Our results show that the absence of β1- and β2-adrenergic receptors was associated with a very marked reduction of basal renin expression and release. Nevertheless, the regulation of renin release by alterations of dietary salt intake was maintained, albeit at a reduced level. Furthermore, acute furosemide administration, or angiotensin-converting enzyme and angiotensin type 1 receptor inhibition, stimulated renin release in the receptor-deficient mice, although the magnitude of the responses was significantly in both β1/β2ADR−/− and WT mice (to 733±54 and 2789±555), whereas a high-salt diet (8%) suppressed it in both genotypes (to 85±24 in β1/β2ADR−/− and to 676±213 in WT). The absolute magnitude of salt-induced changes of plasma renin concentration was markedly greater in WT mice. Acute stimulation of renin release by furosemide, quinaprilat, captopril, or candesartan caused significant increases of plasma renin concentration in both β1/β2ADR−/− and WT mice, but again the absolute changes were greater in WT mice. We conclude that maintenance of normal levels of renin synthesis and release requires tonic β-adrenergic receptor activation. In the chronic absence of β-adrenergic receptor input, the size of the releasable renin pool decreases with a concomitant reduction in the magnitude of the plasma renin concentration changes caused by variations of salt intake or acute stimulation with furosemide, angiotensin-converting enzyme, or angiotensin type 1 receptor inhibition, but regulatory responsiveness is nonetheless maintained. (Hypertension. 2007;50:103-109.)

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reduced. Thus, tonic β-adrenergic input is a major determinant of the size of the releasable renin pool. The absence of β-adrenergic receptors causes a reduction of the magnitude of the change in plasma renin by a number of physiological regulators, but it does not abrogate their regulatory ability.

Methods

Animals
β1/β2ADR−/− mice, originally generated by Rohrer et al., were obtained from Jackson Laboratories (Bar Harbor, Maine) and were interbred to generate subsequent generations. The background of these animals contains genetic contributions from FVB, C57Bl6, and 129svJ strains and was originally chosen to reduce prenatal mortality. Wild-type (WT) animals were generated from the F2 generation of crosses of β1/β2ADR−/− animals with C57Bl6 mice. We observed that, even in the mixed background, the average litter size of β1/β2ADR−/− crosses was only 5.1 (46 litters), whereas in control mice it was 9.2 (24 litters). Genotyping was performed on tail DNA using standard protocols. All of the mice were maintained on a standard rodent chow with free access to tap water. Animal care and experimentation was approved and carried out in accordance with National Institutes of Health principles and Guidelines for the Care and Use of Laboratory Animals.

Chronic Study Protocols
To study the effect of variation of NaCl intake, mice (2 to 3 months old) were placed on normal, high-, or low-salt diet (0.4%, 8%, and 0.03% NaCl, respectively) for 7 days. At the end of the experiments, kidneys were harvested under ketamine/xylazine anesthesia. For the low NaCl and enalapril protocol, mice (2 to 3 months old) were placed on a low-NaCl diet (0.03% NaCl) and received drinking water containing the angiotensin-converting enzyme inhibitor enalapril at 15 mg/100 mL, to provide ~30 mg/kg per day.

Acute Study Protocols
In mice pretreated with the different NaCl diets, furosemide was given IP at a dose of 40 mg/kg. The acute effect of renin–angiotensin blockade was tested by giving quinaprilat (50 μg/kg), captopril (800 μg/kg), or candesartan (50 μg/kg). All of the acute responses were assessed by collecting blood before and 1 hour after the drug injection.

Blood Collection and Renin Determination
For determination of plasma renin concentration (PRC), ∼50 μL of blood were collected into EDTA-containing 75-μL microhematocrit tubes from conscious mice by tail vein puncture. Red cells and plasma were separated and frozen until they were used for renin determination. PRC was determined as described in detail recently.

Determination of renal renin content. Samples of kidney cortex were dissected under the microscope, frozen in liquid nitrogen, and stored at −80°C until assay. For renin analysis, tissue was weighed, homogenized with two 30-second pulses in a 100-fold excess of homogenization buffer (5% [vol/vol] glycerol, 0.1 mmol/L of PMSF, 10 mmol/L of EDTA, and 0.1 mmol/L of 4-[2-amino-methyl]benzenesulfonyl fluoride) using a Polytron homogenizer (Kinematica), and centrifuged at 4°C at 14 000g for 5 minutes. The supernatants were frozen at −20°C and then thawed 3 times by alternation between the temperature between −20°C and 4°C. Supernatants were incubated with saturating concentrations of rat renin substrate, and angiotensin I generation was assayed by radioimmunoassay (DiaSorin). The supernatant protein concentration was assayed by Coomassie Plus protein assay (Pierce).

Renin mRNA
To quantify the level of renin mRNA expression in mice, real-time RT-PCR analysis was performed on whole kidney cDNA (whole kidney was used because initial studies showed that renin mRNA levels in the renal medulla are extremely low). RT-PCR amplification was performed using the ABI Prism 7900 Sequence Detection System (Applied Biosystems). Cycling conditions were 50°C for 2 minutes and 95°C for 10 minutes followed by 40 cycles of 95°C for 0.15 minutes and 60°C for 1 minute. Relative amounts of mRNA, normalized by β-actin, were calculated from threshold cycle numbers, that is, 2−ΔΔCt. Primer sequences were as follows: renin–sense: 5′-CACACTCAGCG ATACGGAATCTGTC-3′ and antisense: 5′-CATGGGTGTGGGAGTGGC-3′; β-actin was assessed with primers and probes by Applied Biosystems.

Plasma Aldosterone
Plasma aldosterone concentrations were determined in 20 μL of plasma using a radioimmunoassay kit (Coat-a-count; DPC).

Physiological Phenotyping Methods
GFR was measured in awake animals by a single injection of fluorescein isothiocyanate inulin clearance using the method of Qi et al with modifications in our laboratory that have been described previously. For measurement of renal blood flow (RBF), the right renal artery was approached from a flank incision and carefully dissected free to permit placement of a 0.5-PSB peripheral nanobase connected to an ultrasonic TS420 flowmeter module (Transonic Systems). Superficial RBF was measured simultaneously using a laser Doppler perfusion probe (418–2 Master Probe +B500 straight microtip) with a PF 5010 LDPM flowmeter unit/Periflux system 5000 (Perimed AB). Measurements are expressed as arbitrary perfusion units. The probes were held in place with micromanipulators. RBF and superficial RBF signals were digitized and analyzed using PowerLab software (ADInstruments).

Statistical Analyses
Data are expressed as mean±SE. Statistical comparisons were done by paired t test for comparisons of PRC before and after an intervention in the same animals. Unpaired t test was used to compare 2 values between different animals. P<0.05 was considered to indicate a significant difference.

Results

Basal Levels of PRC and Renal Renin mRNA Expression
Initial studies confirmed that the changes in blood pressure caused by isoprotenerol or propranolol were largely absent in β1/β2ADR−/− mice and that propranolol did not cause the reduction of PRC seen in WT animals (data not shown). Baseline levels of PRC were significantly reduced in conscious β1/β2ADR−/− (n=17) compared with WT mice (n=16; Figure 1A). To test whether the difference in PRC reflects a differential stress response, we also assessed baseline PRC levels during short-term anesthesia (Figure 1B). As shown in conscious mice, PRC of β1/β2ADR−/− mice was reduced to ~15% of WT mice (407±74 versus 2606±224 ng angiotensin I per mL per hour; n=7 for both groups).

Effect of Dietary Salt Intake on PRC, Renal Renin Content, and Renin mRNA Expression
To address the role of β-adrenergic receptors in the regulation of renin during changes in dietary NaCl intake, we compared the effect of varying NaCl intake on renin secretion in β1/β2ADR−/− and WT mice. As shown in Figure 2, PRC increased significantly during low-salt feeding and decreased significantly during high-salt feeding in both genotypes. However, β1/β2ADR−/− mice remained relatively hyporeninemic at all of the levels of salt intake. The absolute changes of PRC caused by changes of salt intake were smaller.
in $\beta_1/\beta_2$ADR$^{-/-}$ than WT mice. Thus, whereas adrenergic input through $\beta_1$ or $\beta_2$ receptors is not required for the response of renin release to changes in salt intake, it determines the magnitude of the response.

Measurements of renal mRNA expression and renin content are summarized in Figure 3. Renal renin mRNA was markedly lower in $\beta_1/\beta_2$ADR$^{-/-}$ compared with WT mice at low- and normal but not high-salt intake. Renin mRNA was not significantly altered by a low-salt diet in either WT or adrenergic-deficient mice, whereas a high-salt diet caused comparable reductions of renin mRNA in both genotypes. Renal renin content was significantly lower in $\beta_1/\beta_2$ADR$^{-/-}$ compared with WT mice at normal ($P<0.02$), as well as low- ($P=0.0009$) and high-salt intake ($P<0.02$). There was a significant reduction in renin content at high-salt intake in both genotypes ($P<0.001$), whereas the increase in renin content with low NaCl intake did not reach significance.

**Effect of Low-Salt Diet and Enalapril**

To determine the magnitude of the possible stimulation of renin expression without $\beta$-adrenergic input, mice were treated for 1 week with a low-salt diet in combination with enalapril (10 mg/kg per day). As can be seen in Figure 5A,
PRC (in nanograms of angiotensin per milliliter per hour) increased from 1923±97 to 66 680±4598 in wild type (n=9; P<0.001) and from 313±87 to 29 566±7157 in β1/β2ADR-/− mice (n=8; P<0.001). Thus, whereas the increase of PRC caused by low salt/enalapril pretreatment was greater in WT mice, PRC of β1/β2ADR-/− mice animals also showed a major stimulatory response. As shown in Figure 5B, renal renin mRNA after treatment with low salt and enalapril increased significantly in both WT (by 635±39%) and β1/β2ADR-/− mice (from 25% of WT control to 87±19%; P<0.01; n=8).

**Acute Effects on PRC: Furosemide**

To determine the acute release response, we examined the effect of furosemide on PRC in WT and β1/β2ADR-/− mice pretreated with high- and low-NaCl diets. Data are summarized in Figure 6. Furosemide (40 mg/kg IP) increased PRC in both WT and β1/β2ADR-/− mice regardless of dietary regimen. The relative change of PRC was somewhat greater in β1/β2ADR-/− mice at all of the salt intakes, but the absolute changes of PRC correlated closely with basal values and were greater in WT than in β1/β2ADR-/− mice at low-salt and normal salt intakes.

**Acute Effects on PRC: Angiotensin Blockade**

Acute angiotensin-converting enzyme inhibition with quinaprilat (50 μg IP) or captopril (30 mg/kg), as well as acute AT1 blockade with candesartan (50 μg IP), caused the expected increase of PRC in both strains (Figure 7). The relative changes, expressed as fold increase, were comparable between genotypes, but the absolute change of PRC was much greater in WT than in β1/β2ADR-/− mice. As measured by telemetry, the acute reduction of blood pressure caused by quinaprilat (∼10 mm Hg) and candesartan (∼15 mm Hg) was comparable in WT and β1/β2ADR-/− mice (data not shown).

**RBF and GFR**

RBF averaged 1.6±0.1 mL/min (6.6±0.5 mL/min per gram of kidney weight; n=8) in WT and 0.81±0.04 mL/min (4.4±0.2 mL/min per gram of kidney weight; n=9) in β1/β2ADR-/− mice (P<0.0001 versus WT), a 48% reduction. Superficial blood flow measured simultaneously averaged 325±20 perfusion units in WT and 240±32 perfusion units in β1/β2ADR-/− mice (P<0.05), a 26% reduction. Mean femoral blood pressure of these anesthetized mice was 88±2.4 mm Hg in WT and 97±4.8 mm Hg in β1/β2ADR-/− mice (P<0.001). Thus, renal vascular resistance (millimeters of mercury times minutes per milliliter) was 57.4±5.2 in WT and 121.3±7.5 in β1/β2ADR-/− mice (P<0.0001). Mean body weights were 35±2.1 g in WT and 35±1.3 g in β1/β2ADR-/− mice. Despite identical body weights, kidney weights were significantly greater in WT than in β1/β2ADR-/− animals (484±39 versus 369±13 mg; P<0.01).

GFR of conscious WT mice had a mean value of 360.1±18.4 μL/min (n=7), whereas GFR of β1/β2ADR-/− mice was significantly lower, averaging 265.5±28.3 μL/min (n=7; P<0.05). Mean body weight (30.7±2.2 g in WT and 30.1±1.6 g in β1/β2ADR-/− mice) did not differ. Because the relative change of GFR was smaller than that of RBF, estimated filtration fraction was higher in β1/β2ADR-/− than in WT mice (29% versus 20.4%).
The main purpose of this study was to examine the effect of chronic absence of β-adrenergic receptor input on basal renin expression and release and to assess the responsiveness of the renin system to chronic and acute regulatory challenges without β-adrenergic control. As an experimental model, we used mice with targeted deletion of both β1- and β2-adrenergic receptors, the 2 receptor subtypes expressed in the kidney and cardiovascular system.8 β1-Adrenergic receptors have been shown to colocalize with renin at the glomerular vascular pole, and intense expression of both β1 and β2 receptors has been observed in larger renal arteries.9 As has been demonstrated earlier, heart rate and blood pressure responses to isoproterenol or epinephrine are markedly attenuated or abolished in this strain.3 Furthermore, we observed that propranolol does not alter PRC in the β1/β2-receptor–deficient mice, indicating that the “atypical” β3-adrenergic receptor does not have a major effect on either renin or the cardiovascular end points.

The present studies demonstrate a major impact of β-adrenergic tone on basal levels of circulating renin and renal renin expression. One factor that could contribute to this difference in conscious animals is a differential response to the acute stress of blood withdrawal, because the stress effect might be blunted in the β1/β2ADR−/− mice. However, the difference in PRC between β1/β2ADR−/− and WT mice was maintained when blood samples were obtained under isoflu-
cells. A detailed assessment of 24-hour blood pressure measurements using telemetry in \(\beta\)-adrenergic–deficient mice has shown that mean arterial blood pressure is significantly reduced in this strain over the entire 24-hour cycle (to be published). Thus, renal baroreceptors cannot be invoked as contributing to the inhibition of renin observed in the \(\beta\)-adrenergic–deficient animals. An increase of NaCl concentration at the macula densa is also unlikely in view of the significantly reduced GFR.

Our results show that the absence of \(\beta\)-adrenergic activation of JG cells does not prevent the stimulation of renin release by low salt intake or the inhibition of both release and renal renin content by a high-salt diet. Thus, we conclude that salt-induced regulation of renin release and mRNA content is not primarily dependent on changes in \(\beta\)-adrenergic input. Most previous studies are in agreement with this conclusion, because neither renal denervation nor \(\beta\)-blockers prevented the rise of renin mRNA or plasma renin caused by a low-salt diet\(^{11,12,15}\) nor its inhibition by high-salt intake,\(^{12,15}\) though, in some studies, mostly in humans and dogs, propranolol has been found to reduce the stimulation of renin release during salt restriction to some extent.\(^{10}\) Although the current data show that the absence of \(\beta\)-adrenergic input does not prevent salt regulation of renin release, pre-existing expression levels of renin appear to be an important determinant of the change in PRC and the magnitude of the response to the dietary stimulus. Our data show that the switch to the high-salt diet caused roughly proportional, \(\sim 45\%\) to \(60\%\) reductions in renal renin mRNA, renin content, and PRC in both genotypes, suggesting that the fraction of renin released is largely constant at high-salt and normal salt intake with or without \(\beta\)-adrenergic input. In contrast, the fraction of renal renin released at low-NaCl intake in both WT and \(\beta1/\beta2ADR^{−/−}\) mice appears to be higher, because PRC increased much more than renin content. Thus, chronic upregulation of renin by a low salt intake or by a low-salt diet plus enalapril appears to augment the fraction of renin released under ambient conditions.

Previous studies have shown that the absolute renin secretion response to acute stimulation with furosemide or hydralazine was reduced in \(\beta1/\beta2ADR^{−/−}\) mice.\(^{16}\) The present studies confirm these observations and show, in addition, that the acute effect of furosemide is modified by salt intake in both WT and \(\beta1/\beta2ADR^{−/−}\) mice. These studies are in agreement with the findings that a low-salt diet enhanced the acute renin secretory effect of renal nerve stimulation in vivo and isoproterenol in vitro.\(^{17,18}\) In addition, the acute effects of captopril, quinapril, and candesartan were also markedly reduced in \(\beta1/\beta2ADR^{−/−}\) compared with WT mice. We have observed earlier that the release of renin to acute stimulation was markedly attenuated in cyclooxygenase-2–deficient mice, another situation where basal renin expression and release is suppressed.\(^{4}\) Thus, we believe that our observation of a direct relationship between the absolute magnitude of the acute renin release response and basal renin expression levels represents the general principle that the size of the releasable renin pool is a modulating and limiting factor for acute renin release.

A noteworthy aspect in our study is the observation that both RBF and GFR were significantly lower in \(\beta1/\beta2ADR^{−/−}\) than in WT mice. Previous studies of the renal hemodynamic effects of \(\beta\)-adrenergic stimulation and inhibition have been inconclusive. Intrarenal propranolol has been reported to decrease RBF in the dog in the absence of systemic alterations.\(^{19}\) On the other hand, micropuncture studies in the rat failed to show significant changes in either preglomerular or postglomerular arteriolar resistances during the administration of atenolol, though single naphron glomerular filtration rate decreased.\(^{20}\) Furthermore, isoproterenol did not significantly change GFR or glomerular resistances in either rats or dogs.\(^{21,22}\) In part, the reduction of renal function in our study may be a consequence of the significantly lower kidney weights in the \(\beta1/\beta2ADR^{−/−}\) mice, an observation that suggests the existence of a trophic influence of \(\beta\)-adrenergic receptors. The nature of this effect requires more studies, but there is evidence to show that \(\beta\)-adrenergic receptors stimulate ornithine decarboxylase, an enzyme that has been implicated in renal hypertrophy.\(^{23,24}\)

**Perspectives**

Chronic absence of \(\beta1-\) and \(\beta2\)-adrenergic receptors causes marked reductions of renin expression and PRC. Although the responses of renin to changes in chronic or acute modulatory inputs are maintained, their magnitude is consistently diminished in mice lacking \(\beta1-\) and \(\beta2\)-adrenergic receptors. Thus, tonic activation of \(\beta\)-adrenergic receptors in juxtaglomerular granular cells is required to maintain the releasable renin pool at a level that permits the full response to regulatory challenges.

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**Disclosures**

None.

**References**


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