An Up-Regulation of Renal α₂A-Adrenoceptors Is Associated with Resistance to Salt-Induced Hypertension in Sabra Rats

MOSTAFA KHALID, YVES GIUDICELLI, and JEAN-PIERRE DAUSSE
Department of Biochemistry and Molecular Biology, Faculté de Médecine de Paris-Ouest, Université René Descartes, Paris, France
Received May 17, 2001; accepted August 10, 2001 This paper is available online at http://jpets.aspetjournals.org

ABSTRACT
This study investigates the incidence of high-salt diet in blood pressures, renal α₂-adrenoceptor subtypes distribution, and gene expression in salt-sensitive (SBH) and salt-resistant (SBN) Sabra rats. Comparisons have been made between SBH and SBN rats submitted to a normal or a high-salt diet for 6 weeks. Only α₂B-adrenoceptors are detected in kidneys of SBH rats, whatever the diet. In contrast, mRNA corresponding to α₂A- and α₂B-subtypes are found in this strain. In these rats, high-salt diet increases blood pressures and up-regulates gene expression and density of only α₂B-adrenoceptors. Inversely, α₂A- and α₂B-adrenoceptors and corresponding mRNA are found in kidneys of SBN rats. In these rats, a high-salt diet does not affect blood pressures but increases gene expression and densities of both α₂A- and α₂B-adrenoceptors. If the up-regulation of renal α₂B-adrenoceptor subtypes is indicative of the hypertensive phenotype, the present study shows that this mechanism is also present in normotensive salt-resistant Sabra rats. In fact, the absence of α₂A-adrenoceptors in SBH could be responsible for the lack of adequate receptor-mediated renal functions predisposing to salt-sensitivity and consequently the development of hypertension. Conversely, the presence of this receptor in SBN rats and its up-regulation could be protective change against the increase of α₂B-adrenoceptors induced by the salt overload and could consequently be responsible for the resistance to salt-induced hypertension.

The kidney plays a major role in the chronic regulation of blood pressure via modulation of sodium and water excretion (Hall et al., 1990; Guyton, 1991). Several authors have focused on the role of the renal α₂-adrenoceptors in the modulation of water clearance and sodium excretion (Strandhoy et al., 1982; Gellai and Ruffolo, 1987), and a common characteristic among genetic models of hypertension is an increase in renal α₂-adrenoceptor density (Pettinger et al., 1982; Parrini et al., 1983, 1987). Because the physiologic activity of α₂-adrenoceptors depends on their density (Duzic et al., 1992), alteration in renal α₂-adrenoceptor density could account for disruption in blood pressure control.

Two different isoforms of α₂-adrenoceptors have been described in rodent kidney (Uhlen and Wikberg, 1991). The α₂A-adrenoceptor plays a crucial role in the hypotensive response (MacMillan et al., 1996) and is able to increase urine flow rate solely by increasing renal osmolar clearance (Intengan and Smyth, 1997a). On the other hand, the α₂B-adrenoceptor subtype mediates the α₂-adrenoceptor agonist-induced increase in blood pressure (Link et al., 1996), increases the renal free water clearance (Intengan and Smyth, 1996), and is overexpressed in the kidney of spontaneously hypertensive rats (Gong et al., 1994, 1995).

The Sabra rat is a genetic model of salt-induced hypertension (Ben-Ishay and Yagil, 1994). In contrast to the Sabra salt-resistant (SBN) rat, Sabra salt-sensitive (SBH) rats fed a regular diet, have borderline hypertension at an early age, maintain a slightly elevated blood pressure in adult life, and become invariably hypertensive in response to relevant stimuli such as a deoxycorticosterone acetate-salt or a high-sodium diet. On a normal diet, urinary flow and the excretion of sodium, potassium, and total solutes are significantly lower in SBH than in SBN rats. However, the urine osmolality of the SBH rat is approximately 2-fold higher than that of the SBN rat. It has been suggested that these findings in SBH rats are compatible with an impaired renal excretion of sodium in the presence of a slight increase in blood pressure (Ben-Ishay and Yagil, 1994). This peculiar feature in the Sabra model is consistent with renal alteration in the distribution of α₂-adrenoceptor subtypes. As a matter of fact, SBH rats fed a regular diet, in contrast to SBN rats, exhibit high-renal α₂B-adrenoceptor densities and the absence of the α₂A-adrenoceptor subtype (Le Jossec et al., 1995). Recently, it has been shown that mice lacking one copy of the α₂B-adrenoceptor gene are unable to develop salt-induced hypertension (Makaritsis et al., 1999a). These data suggest the potential importance of α₂B-adrenoceptors to control blood pressure in response to dietary salt loading.

ABBREVIATIONS: SBH, salt-sensitive Sabra rats; SBN, salt-resistant Sabra rats; RT-PCR, reverse transcription-polymerase chain reaction; PCR, polymerase chain reaction; bp, base pair(s).
The aims of this study were to determine whether an hypertensive stimulus such as high-salt diet alters the renal distribution of \( \alpha_2 \)-adrenoceptor subtypes in Sabra rats and, if so, to establish whether such alterations reflected changes in the expression of their encoding genes.

**Experimental Procedures**

**Animals.** We used original SBH and SBN male Sabra rats (aged 3 weeks) bred at the Centre de Sélection et d’Elevage des Animaux de Laboratoires (Orléans, France). Four groups of rats were studied, two of each substrain: one with normal (0.2%) and one with high (8%)-NaCl laboratory chow. Water was given ad libitum, and rats were maintained at a constant room temperature (24°C) on a 12-h light/dark cycle. After 6 weeks, systolic blood pressure was measured between 9 and 11 AM using the tail-cuff method, with an electro-sphygmomanometer (Physiograph MK III; Narco-Bio-System, Inc., Houston, TX) on unanesthesized, restrained rats warmed to 38°C for 10 min. Two days later, rats were killed by decapitation, and their kidneys were carefully removed and rapidly frozen in liquid nitrogen. All experimental protocols were approved by the University Animal Use and Care Committee.

**Radioligand Binding Studies.** Renal membranes were prepared from whole kidney and radioligand-binding studies performed, as described previously (Le Jossec et al., 1995), with the specific radiolabeled \( \alpha_2 \)-adrenoceptor antagonist, \([^3]H\)RX821002. Briefly, 300 \( \mu \)g of renal membranes was incubated with 0.3 to 30 nM \([^3]H\)RX821002, 1 mM EDTA-K, 100 \( \mu \)M 5’-guanylylimidodiphosphate, 140 mM NaCl, and 50 mM Tris-HCl (pH 7.4), in a final volume of 300 \( \mu \)l for 45 min at 25°C. Reactions were stopped by dilution with ice-cold incubation buffer and rapid vacuum filtration through Whatman GF/C filters (Whatman, Maidstone, UK). The filters were washed twice with ice-cold incubation buffer and the radioactivity retained on filters was quantified by liquid scintillation counting. Nonspecific binding was determined in the presence of 20 \( \mu \)M phentolamine and represented 10% of the total binding. For competition studies, membranes were incubated for 45 min at 25°C with 2 nM \([^3]H\)RX821002 (a concentration near \( K_d \) value) and either 0.1 nM to 1 mM guanfacine, a selective \( \alpha_2A \)-adrenoceptor agonist (Uhlen and Wikberg, 1991), or 0.1 nM to 1 mM prazosin, which is selective for the \( \alpha_2B \)-adrenoceptor (Bylund et al., 1988). The resultant saturation and competition curves were analyzed using a nonlinear least-squares curve fitting program (GraphPad PRISM; GraphPad Software, Inc., San Diego, CA). Protein concentrations were determined according to Bradford (1976) using \( \gamma \)-globulin as the standard.

**Analysis of Renal \( \alpha_2 \)-Adrenoceptor mRNA.** Total renal RNA was isolated using guanidium thiocyanate-phenol-chloroform extraction with the TRIzol reagent (Invitrogen, Cergy-Pontoise, France) and used for RNA-directed complementary cDNA synthesis and DNA amplification as previously described (Le Jossec et al., 1995), except that HotStarTaq DNA polymerase (Qiagen S.A., Courtaboeuf, France) and used for RNA-directed complementary cDNA synthesis and DNA amplification as previously described (Le Jossec et al., 1995), except that HotStarTaq DNA polymerase (Qiagen S.A., Courtaboeuf, France) was used according to the conditions provided by the supplier and that 1 \( \mu \)l of \([^3]H\)dCTP was added to the PCR reaction. PCR mixtures of cDNA and respective primers (Table 1) were amplified using a program temperature control system (Appligene Oncor, Illkirch, France). One cycle of PCR consisted of 1 min at 94°C, 1 min at 57°C, and 1 min at 72°C for \( \alpha_2 \)-adrenoceptor subtypes cDNA and was performed for a total of 33 cycles. For \( \beta \)-actin, similar experimental conditions were used, except that the annealing temperature was 53°C and the number of amplification cycles was 30. Primers used for \( \beta \)-actin amplification (Nudel et al., 1983) were chosen to span two introns to discriminate the cDNA amplification products from genomic DNA contamination. Each reaction mixture was separated on a 1.5% low melting point agarose (Invitrogen) gel stained with ethidium bromide and documented on Polaroid 665 film (Polaroid UK, Ltd., St. Albans, UK). For quantification, respective bands for \( \alpha_2A \), \( \alpha_2B \), and \( \beta \)-actin signals were excised and agarose-melted at 70°C, and the incorporated radioactivity was determined by scintillation counting in Aquasafe 300 Plus (Lumiscan Analytic, Frankfurt, Germany). The incorporated radioactivity was normalized with respect to the length of the three cDNA, and \( \alpha_2A \) and \( \alpha_2B \) messenger RNA levels were expressed versus \( \beta \)-actin mRNA content.

**Materials.** \([^3]H\)RX821002 (2.29 \( \times \) 10^12 Bq/mmol), \([^3]H\)dCTP (1.92 \( \times \) 10^12 Bq/mmol), and DNA molecular weight markers (100-bp ladder) were purchased from Amersham Pharmacia Biotech (Les Ulis, France). Oligonucleotides were synthesized by Eurogentec (Herstal, Belgium). The following drugs were supplied by the indicated companies: prazosin (Pfizer Central Research, Sandwich, Kent, UK), guanfacine (Novartis, Basel, Switzerland). All other materials were obtained from Sigma Aldrich (Saint-Quentin-Fallavier, France).

**Statistical Analysis.** All results were expressed as the mean \( \pm \) S.E.M. Statistical analyses were performed using analysis of variance followed by the Student-Neuman-Keuls multiple comparison test. Data from DNA amplification were analyzed using the nonparametric one-way procedure of the SAS system (SAS Institute Inc., Cary, NC), and comparison between groups were made using the \( \chi^2 \) and Kolmogorov-Smirnov tests. \( P < 0.05 \) was considered as statistically significant.

**Results**

**Physiological Data.** At 6 weeks of regimen, blood pressures were in normal diet (133 \( \pm \) 9; 108 \( \pm \) 10 mm Hg, \( n = 6 \)), \( P < 0.001 \) SBH versus SBN and in sodium overload (161 \( \pm \) 19; 112 \( \pm \) 14 mm Hg, \( n = 6 \), \( P < 0.005 \) SBH versus SBN). Body weights were for SBH (238 \( \pm \) 6; 234 \( \pm \) 16 g, 0.2% versus 8.0% NaCl) and for SBN (221 \( \pm \) 7; 220 \( \pm \) 13 g, 0.2% versus 8.0% NaCl).

**Renal \( \alpha_2 \)-Adrenoceptor Densities and Subtype Distribution.** Specific binding of \([^3]H\)RX821002 to kidney membranes isolated from SBH and SBN rats was a saturable process (Fig. 1). Scatchard plots of \([^3]H\)RX821002 binding were monophasic, suggesting only one component of binding (data not shown). In all experiments, Scatchard plots were best analyzed by a model with only one high-affinity class of sites for both SBH and SBN rats and whatever the diet. However, under normal diet, renal \( \alpha_2 \)-adrenoceptor-binding capacities were significantly higher in SBH (169.7 \( \pm \) 7.2 fmol/mg protein, \( n = 6 \)) than in SBN (116.8 \( \pm \) 4.6 fmol/mg protein).

---

**TABLE 1**

<table>
<thead>
<tr>
<th>Locus</th>
<th>Primers (5′ - 3′)</th>
<th>Size (bp)</th>
<th>Position</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \alpha_2 )A</td>
<td>GGGCCCCAGACACCCTTCCT</td>
<td>311</td>
<td>196</td>
<td>Chalberg et al. (1990)</td>
</tr>
<tr>
<td>( \alpha_2 )B</td>
<td>AGTGGCGGAGGAGGATAGAC</td>
<td>407</td>
<td>705</td>
<td>Le Jossec et al. (1995)</td>
</tr>
<tr>
<td>( \beta )-Actin</td>
<td>GTTTGGGGTACATTTGTC</td>
<td>1112</td>
<td>1112</td>
<td>Nudel et al. (1983)</td>
</tr>
<tr>
<td>( \alpha_2 )A</td>
<td>TACCACACCTGTCAGCCTCC</td>
<td>281</td>
<td>1453</td>
<td>Nudel et al. (1983)</td>
</tr>
</tbody>
</table>
protein, n = 6) (Fig. 2). Under sodium overload, binding capacities were significantly increased in both SBH (216.7 ± 8.5 fmol/mg protein, n = 6) and SBN (165.4 ± 5.1 fmol/mg protein, n = 6) rats and with no significant difference in the magnitude of this effect between SBH and SBN. In addition, no differences in binding affinities were observed between SBH and SBN and between normal and high-salt diet (Table 2).

Competition binding experiments were performed to discriminate the α2-adrenoceptor subtypes using prazosin (selective for α2B-adrenoceptor) and guanfacine (selective for α2A-adrenoceptor). In kidney membranes of SBN rats after normal or high-salt diet, the competition curves for prazosin and guanfacine were shallow (Fig. 3, bottom). Using the iterative curve-fitting program, the curves were best fitted with the model of two classes of sites. The analysis further shows that under normal diet, the proportion of the high-affinity site for prazosin is 75% to 85% and the high-affinity site for guanfacine is 15% to 25%, corresponding to the characteristics of α2B- and α2A-adrenoceptor subtypes, respectively (Table 2). From these results, the calculated α2A- and α2B-adrenoceptor densities in SBN represent, 19.5 ± 1.1 and 99.2 ± 5.4 fmol/mg protein, respectively. Interestingly, under high-salt diet, the proportion of α2A-adrenoceptor subtype reached 30% to 40% of the total [3H]RX821002-binding capacity. Therefore, the increase in α2-adrenoceptor density observed in SBN rats after high-salt loading appears due to both enhanced α2A- and α2B-adrenoceptor subtype densities, 48.0 ± 1.6 and 132.8 ± 4.3 fmol/mg protein, respectively (P < 0.05 n = 6). In contrast, in kidneys of SBH rats under normal or high-salt diet, competition curves for prazosin and guanfacine were steep and monophasic (Fig. 3, top). In all experiments, the curves were best fitted with a one-site model. Computer analysis of all curves indicated indeed that prazosin binds to membranes with only high affinity and guanfacine with low affinity (Table 2), thus showing that [3H]RX821002 binding sites have the characteristics of the α2B-adrenoceptor subtype. As a consequence, the α2A-adrenoceptor subtype was undetectable in SBH rats and the increase in α2B-adrenoceptor density observed under high-salt diet in these rats resulted only from a raise in the α2B-adrenoceptor subtype.

**Renal α2-Adrenoceptor Subtype Gene Expression.** Experiments using reverse transcription-polymerase chain reaction (RT-PCR) were performed with specific α2-adrenoceptor subtype primers to determine whether alterations in renal α2-adrenoceptor subtype distribution could be associated with modifications in mRNA levels. cDNA amplifications with these specific primers show amplified products of predicted size [311 bp for α2A-adrenoceptor (Fig. 4, upper panel) and 407 bp for α2B-adrenoceptor (Fig. 4, middle panel)] in the kidney of SBH and SBN rats, whatever the salt diet. On the other hand, the fragment generated from β-actin primers (280 bp) (Fig. 4, bottom panel), which is present at comparable levels in the four groups, is the only fragment amplified, ruling out any genomic DNA contamination (Fig. 4A). After normal salt diet, analysis of the radioactivity incorporated into the α2-adrenoceptor products normalized to β-actin reveals (Fig. 5) higher α2B (P < 0.01) but equivalent α2A mRNA levels in SBH than in SBN rats. Under high-salt diet (Fig. 5), the α2B-adrenoceptor mRNA signal is increased in both SBH and SBN rats with a weaker magnitude in SBH yielding thus to equivalent levels in SBH and SBN rats. In contrast, the α2A-adrenoceptor signal remains unchanged in SBH rats, whereas it is markedly increased in SBN.

**Discussion**

The aim of the present study was to determine whether elevation in salt intake induces changes in renal α2-adrenoceptor subtype densities. To reach this target we have compared Sabra rats differing in their blood pressure response to high-salt diet. After 6 weeks of high-salt diet, salt-sensitive Sabra rats exhibit significant increases in blood pressures when compared with salt-resistant Sabra rats. In addition, based on radioligand-binding studies, high-salt diet produces a significant raise in α2B-adrenoceptor densities in kidneys of both SBH and SBN rats. Nevertheless, the total α2-adreno-
Receptor density remains significantly higher in SBH than in SBN rats.

Renal $\alpha_2$-adrenoceptors are heterogeneous (Uhlen and Wikberg, 1991), and altered distribution of their subtypes has been considered to predispose the development of hypertension in Sabra rats (Le Jossec et al., 1995). In fact, SBH rats fed a regular diet exhibit higher $\alpha_2$B-adrenoceptor densities in renal cortex than SBN rats (Le Jossec et al., 1995). These high levels, which appear to be the consequence of an overexpression of the encoding gene, have also been observed in spontaneously hypertensive rats (Gong et al., 1994; 1995). Inasmuch as this overexpression is a common feature of genetic models of hypertension, it has been hypothesized that the $\alpha_2$B-adrenoceptor overexpression could be controlled by genetic factors predisposing the rat to the onset of hypertension (Gong et al., 1994). A role for the $\alpha_2$B-adrenoceptor in the development of high blood pressure is further strengthened by the following recent studies. In $\alpha_2$B-adrenoceptor knockout mice, a lack of immediate hypertensive response to $\alpha_2$-adrenoceptor agonists has been observed (Link et al., 1996). Moreover, mice lacking a full complement of the $\alpha_2$B-adrenoceptor gene are unable to raise blood pressure in response to chronic salt loading after subtotal nephrectomy (Makaritsis et al., 1999a). In the present study, by the use of selective competitors, we find that high-salt diet increases renal $\alpha_2$B-adrenoceptor densities in both SBH and SBN rats with marked elevation of blood pressure only in SBH. In addition, our RT-PCR data indicate that these increases in $\alpha_2$B-adrenoceptor densities are secondary to the overexpression of the gene encoding this receptor subtype. However, after a high-salt diet, $\alpha_2$B-adrenoceptor densities are still higher in the SBH rat. Interestingly, we have recently reported a similar increase in renal $\alpha_2$B-adrenoceptor gene expression and density in cafeteria-fed rats, a nongenetic model of obesity-related hypertension (Coatmellec-Taglioni et al., 2000). Altogether, these observations lead us to postulate that a high density in renal $\alpha_2$B-adrenoceptors could be a determinant factor contributing in general to the hypertensive phenotype.

On the other hand, a role for the renal $\alpha_2$A-adrenoceptor...
high-salt diet as presently shown. However, the normal salt diet (Le Jossec et al., 1995) as well as under subtype and is pharmacologically absent in SBH rats under binding technique, which is unable to detect low levels of DNA size markers, lanes 1 and 6; SBH under normal (lane 2) and high-salt diet (lane 3); SBN under normal (lane 4) and high-salt diet (lane 5). The upper panel for \( \alpha_2 \)-A products, middle panel for \( \alpha_2 \)-B products and bottom panel for \( \beta \)-actin products.

Fig. 4. Ethidium bromide staining of RT-PCR products using \( \alpha_2 \)-adrenoceptor subtypes or \( \beta \)-actin primers in kidney of SBH and SBN rats under normal and high-salt diet. Results are representative of one experiment performed at 33 cycles of amplifications for \( \alpha_2 \)-primers and 30 cycles for \( \beta \)-actin. DNA size markers, lanes 1 and 6; SBH under normal (lane 2) and high-salt diet (lane 3); SBN under normal (lane 4) and high-salt diet (lane 5). The upper panel for \( \alpha_2 \)-A products, middle panel for \( \alpha_2 \)-B products and bottom panel for \( \beta \)-actin products.

Fig. 5. Gene expression of \( \alpha_2 \)-adrenoceptor subtypes determined by RT-PCR normalized to corresponding \( \beta \)-actin levels and expressed as percent of SBH values under normal diet. Data for normal (open column) and high-salt diet (hatched column) are given as the mean \( \pm \) S.E.M. (n = 6).**, \( P < 0.01 \) for the comparison between SBH and SBN; *, \( P < 0.05 \); ***, \( P < 0.001 \) for the comparison between normal and high-salt diet.

subtypes should also be considered as it is also expressed in renal cortex of SBN rats to a lesser extent than the \( \alpha_2 \)-B subtype and is pharmacologically absent in SBH rats under normal salt diet (Le Jossec et al., 1995) as well as under high-salt diet as presently shown. However, the \( \alpha_2 \)-A-adrenoceptor mRNA is clearly present in the kidneys of SBH rats under both a normal and a high-salt diet. These discrepant findings could be explained by the limited sensitivity of the binding technique, which is unable to detect low levels of \( \alpha_2 \)-A-adrenoceptor sites, if any, in SBH rats. Another explanation could be that post-transcriptional or post-translational events occur in the kidney of SBH rats preventing detection of the receptor protein by binding studies. In contrast to \( \alpha_2 \)-B, \( \alpha_2 \)-A-adrenoceptor mRNA levels are completely insensitive to the high-salt diet in SBH rats. Interestingly, a similar situation has been found in the hypertensive cafeteria-fed rat model in which the renal \( \alpha_2 \)-A-adrenoceptor subtype is no longer pharmacologically detectable in spite of unaltered gene expression when compared with normal chow-fed rats (Coatmellec-Taglioni et al., 2000). Indubitably, the discrepancy between gene expression and undetectable \( \alpha_2 \)-A-adrenoceptor sites in hypertensive rats remains to be clarified. However, from these studies, it seems clear that high-renal \( \alpha_2 \)-A-adrenoceptor densities do not appear to be solely implicated in the hypertensive phenotype. It is indeed possible that high-\( \alpha_2 \)-B-adrenoceptor densities associated with a lack of adequately functional renal \( \alpha_2 \)-A-adrenoceptor may facilitate the onset of hypertension. Our present observations in SBN rats provide strong support to this hypothesis. As a matter of fact, a high-salt diet increases \( \alpha_2 \)-B-adrenoceptor densities in the kidney of SBN rats but fails to induce any change in blood pressure. As a contrast to SBH rats, high-salt diet markedly increases renal \( \alpha_2 \)-A-adrenoceptor mRNA and densities in SBN. It is thus tempting to speculate about the potential significance of this interstrain difference for renal \( \alpha_2 \)-adrenoceptors in terms of genetic pre-disposition to salt sensitivity and development of hypertension in Sabra rats.

In normotensive rats, it has been shown that stimulation of the renal \( \alpha_2 \)-A-adrenoceptor subtype by the selective \( \alpha_2 \)-agonist guanfacine increases urine flow rate solely by increasing osmolar clearance (Intengan and Smyth, 1997a). In spontaneously hypertensive rats, however, guanfacine fails to increase osmolar clearance (Intengan and Smyth, 1997b), suggesting a defect in renal \( \alpha_2 \)-A-adrenoceptor capacity. When compared with SBN rats, SBH rats have a lower fractional sodium excretion in the presence of comparable free water clearance (Ben-Ishay and Yagil, 1994). Based on the natriuretic activity of the renal \( \alpha_2 \)-A-adrenoceptor shown in Wistar and Sprague-Dawley rats (Intengan and Smyth, 1996, 1997a), it can reasonably be postulated that the lack of this receptor in the SBH rats may be contributing to the sensitivity to sodium and thus predisposing these animals to develop hypertension when submitted to high-salt intake. In contrast, \( \alpha_2 \)-A-adrenoceptors present in the kidney of SBN rats are markedly increased by high-salt regimen. This phenomenon could be an protective and adaptive change in these animals in response to salt overload, resulting in an increase in sodium excretion and the maintenance of normal blood pressure when submitted to high-salt diet. However, this hypothesis must be supported by investigating the function of renal \( \alpha_2 \)-A-adrenoceptors in Sabra rats. Evidently, the key
question that remains to be answered is whether these alterations in renal α₂-adrenoceptor subtypes are relevant to the pathogenesis of hypertension in SBH rats. In fact, from a subsequent series of studies on salt-induced hypertension in mice deficient in each one of these α₂-adrenoceptor subtypes (Makaritsis et al., 1999a, 1999b, 2000) it has been suggested that adrenergically mediated hypertension is a function of the central α₂-B-adrenoceptor. Since we have shown central differences in α₂B-adrenoceptor densities between SBH and SBN rats (Parini et al., 1986), an investigation of the distribution of their subtypes merits future studies.

In conclusion, these results demonstrate that marked differences exist in expression levels of renal α₂-adrenoceptor subtypes between salt-sensitive and salt-resistant Sabra rats. If high-renin α₂B-adrenoceptor densities most probably contribute to the hypertensive phenotype, results of the present study also suggest that they are not implicated alone in the salt-induced hypertension of the SBH rat. In fact, the absence of the α₂A-subtype in SBH could also be responsible of the lack of adequate receptor-mediatedrenal functions, predisposing this rat strain to the onset of hypertension under high-salt diet. In contrast, the presence of the α₂A-subtype in SBN and its up-regulation under high-salt diet could protect this rat strain against the pressive effect of high-salt diet and consequently may explain the peculiar resistance to salt-induced hypertension of these rats.

References


Address correspondence to: Dr. Jean-Pierre Daussie, Department of Biochemistry and Molecular Biology, UFR Biomédicale, 45 rue des Saints-Pères, 75270 Paris cedex 06, France. E-mail: daussie@mailhost.paris-ouest.univ-paris5.fr