Sympathetic activity in early renal posttransplantation hypertension in rats

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Received 13 March 2000; accepted in final form 13 June 2000

Grisk, Olaf, Bernd A. J. Frey, Andreas Uber, and Rainer Rettig. Sympathetic activity in early renal posttransplantation hypertension in rats. Am J Physiol Regulatory Integrative Comp Physiol 279: R1737–R1744, 2000.—The contribution of elevated sympathetic activity to the development of renal posttransplantation hypertension was investigated. F1 hybrids (F1H) from spontaneously hypertensive rats (SHR) and Wistar-Kyoto rats (WKY) were transplanted with either an SHR or a F1H kidney and bilaterally nephrectomized. Three weeks after transplantation, sympathetic activity was assessed by measuring adrenal tyrosine hydroxylase (TH) mRNA content and recording splanchnic nerve activity (SNA) in conscious animals. To investigate the dependence of arterial pressure on sympathetic activity, animals were treated with the α2-adrenoceptor agonist guanabenz intracerebroventricularly. Mean arterial pressure (MAP) was 145 ± 4 mmHg in recipients of an SHR kidney (n = 15) versus 110 ± 3 mmHg in recipients of an F1H kidney (n = 10; P < 0.001). Adrenal TH mRNA content was 1.93 ± 0.15 fmol/μg total RNA in recipients of an SHR kidney versus 1.96 ± 0.17 fmol/μg total RNA in recipients of an F1H kidney (not significant). SNA did not differ significantly between recipients of an SHR kidney (n = 8) and recipients of an F1H kidney (n = 7) in terms of frequency and amplitude of synchronized nerve discharges. In response to cumulative intracerebroventricular administration of 10 and 20 μg guanabenz, SNA fell to 51 ± 5% of control in recipients of an SHR kidney versus 44 ± 6% of control in recipients of an F1H kidney (not significant) accompanied by a slight fall in MAP in either group. The results suggest that elevated sympathetic activity is not a major contributor to the development of renal posttransplantation hypertension.

spontaneously hypertensive rats; renal transplantation; sympathetic nervous system; tyrosine hydroxylase; guanabenz

SYSTEM ANALYSES OF ARTERIAL pressure regulation revealed the importance of the renal capacity to excrete sodium and water for the level of sustained arterial pressure of an organism (17). Support for the important role of the kidney for long-term arterial pressure regulation and for the pathogenesis of genetic forms of arterial hypertension comes from renal transplantation studies (reviewed in Ref. 34). Several groups have demonstrated that transplantation of a kidney from genetically hypertensive rats into histocompatible normotensive recipients induces arterial hypertension (34). Furthermore, we could recently demonstrate that transplantation of a kidney from normotensive donor rats into bilaterally nephrectomized spontaneously hypertensive rats (SHR) combined with immunosuppression lowers arterial pressure in SHR (30).

In addition to intrarenal mechanisms, the sympathetic nervous system is implicated to be involved in the pathophysiology of primary and secondary forms of hypertension (37). In human primary hypertension, sympathetic activity to the kidneys, to the heart, and to skeletal muscles was found to be increased (10, 37). Furthermore, in human renovascular hypertension, increased muscle sympathetic nerve activity has been reported (20). Also, in experimental forms of hypertension, increased sympathetic activity (23, 29, 35) or increased dependence of arterial pressure on sympathetic activity has been shown (1, 7, 18, 19, 29). Elevated efferent sympathetic activity to the kidneys may be especially important for the development of hypertension due to its potential to contribute to increased renal sodium and water retention (4, 8).

After transplantation of a kidney from young SHR donors into normotensive histocompatible recipients, hypertension develops within a few weeks and reaches a stable level within 6–8 wk after renal transplantation (33). The development of renal posttransplantation hypertension is associated with increased renal sodium retention (12). Other mechanisms involved in the pathophysiology of posttransplantation hypertension remain unclear. Studies on renal plasma flow and glomerular filtration rate (33), renal and plasma renin-angiotensin systems (32), and renal α-adrenoceptor density (25) do not show deviations in the respective traits that could be associated with this form of hypertension. Furthermore, there is no sympathetic reinnervation of the grafted kidney during the development of renal posttransplantation hypertension, thus excluding renal sympathetic nerves as a contributing factor (16).

In the present study, we investigated whether the development of renal posttransplantation hypertension is associated with elevated extrarenal sympathetic activity. Furthermore, we studied whether the
arterial pressure depends to a greater extent on sympathetic activity in recipients of a kidney from genetically hypertensive donors than in syngenically transplanted controls. This would indicate a role for sympathetic activation in the pathophysiology of renal posttransplantation hypertension. As an indicator of chronic sympathetic activity, the adrenal tyrosine hydroxylase (TH) mRNA content was measured. This was done because elevations of adrenal TH gene transcription rate, TH mRNA content, and TH enzyme activity are dependent, to a great extent, on increased preganglionic sympathetic nerve activity to the adrenals (3, 11, 27, 36). In addition, direct recordings of splanchnic sympathetic nerve activity (SNA) were performed in conscious, freely moving animals. The responses of arterial pressure and SNA to a sympathoinhibitory intervention were examined. To inhibit the centrally generated sympathetic tone, we administered the α2-adrenoceptor agonist guanabenz into the cerebroventricles of the experimental animals. In hypertensive states, such as primary hypertension (7, 18) and sodium chloride-induced hypertension (7, 19, 29), sympathetic nerve activity and arterial pressure fall to a greater extent in response to centrally administered α2-adrenoceptor agonists compared with the respective normotensive controls. Simultaneous recordings of sympathetic nerve activity and arterial pressure in response to centrally administered α2-adrenoceptor agonists provide a means to demonstrate increased dependence of elevated arterial pressure on sympathetic nerve activity.

METHODS

Animals. Experiments were performed in male F1-hybrids (F1H) obtained from breeding male spontaneously hypertensive rats (SHR) and female normotensive Wistar-Kyoto rats (WKY). SHR were purchased from Mollegard Breeding and Research Center (Skensved, Denmark). WKY were obtained from Charles River (Sulzfeld, Germany). F1H were bred in our institution’s animal facility. Animals were kept in a humidity- and temperature-controlled environment with lights on from 6:00 AM to 6:00 PM. They had free access to standard rat chow (Ssniff, Soest, Germany) and tap water. The experiments were started in 8-wk-old animals. All experiments were approved by a governmental committee on animal welfare.

Transplantation surgery. Renal transplantation was performed as previously described (12, 16, 30, 33). F1H were chosen as histocompatible graft recipients for SHR kidneys. SHR and F1H served as kidney donors. Donor and recipient were operated simultaneously by two investigators applying microsurgical techniques. Cold ischemia time of the grafts did not exceed 45 min. Recipients of a kidney graft were bilaterally nephrectomized. For nephrectomy in the recipients, the renal capsule was opened at the caudal pole and bilaterally nephrectomized. For nephrectomy in the recipients, the renal capsule was opened at the caudal pole and bilaterally nephrectomized.

Animal instrumentation. For arterial pressure recordings and intravenous drug administration, catheters (PE-10 fused to PE-50) were inserted into the aorta and inferior vena cava via the right femoral vessels and exteriorized and fixed at the back of the neck under either ether anesthesia (protocol 1) or methohexital anesthesia (Brevimytal, Lilly, Giessen, Germany) (protocol 2). The catheters were filled with isotonic saline containing 250 IU/ml heparin and plunged. For cerebroventricular cannulation, rats were anesthetized with ketamine 70 mg/kg ip and placed in a stereotaxic apparatus (model 900, David Kopf Instruments, Tujunga, CA). A 23-gauge stainless steel cannula was placed into the right lateral cerebral ventricle according to coordinates from the atlas of the rat brain (31). The cannula was fixed to the skull with dental cement and anchored to the bone with two jeweller’s screws. Proper placement of the intracerebroventricular cannula was verified by positive backflow of cerebrospinal fluid on cannula insertion and on the day of the experiment after removal of the obturator from the cannula. Animals without proper backflow of cerebrospinal fluid from the cannula were excluded from further experimentation. Popliteal nerve recordings, animals were anesthetized with methohexital (50 mg/kg ip) and supplemental anesthetic was given intravenously. A bipolar recording electrode (36-gauge stainless steel, Cooner Wire Chatsworth, CA) was placed around a splanchnic nerve branch caudally from the adrenal nerves via a left flank incision. After a clear signal was obtained, the electrode was fixed with silicone (Wacker Sil-Gel 601, Wacker Chemie, Munich, Germany) and exteriorized at the back of the neck together with a subcutaneously placed grounding wire. The flank incision was closed in layers. After animals were instrumented, they were placed in their home cages on fresh bedding for recovery from surgery and anesthesia.

Analytical methods. For measurement of TH mRNA content with a competitive RT-PCR, total RNA was isolated from the adrenals (5). Primers (Amersham Pharmacia Biotech, Freiburg, Germany) were upstream (ACGCCTAGCTCCTCGGAACCTG) spanning nucleotides 185–207 and downstream (CGACGCTTGCCGATACACCTGGTC) spanning nucleotides 600–622 of the rat TH cDNA sequence (13). This resulted in a PCR fragment of 438-base pair length. For construction of a competitor mRNA, the PCR fragment was cloned into pCR2.1 vector (TA Cloning, Invitrogen, Leek, The Netherlands). The cDNA sequence was truncated at the restriction enzyme Sma I after nucleotides 600–622 of the rat TH cDNA sequence (13). The truncated cDNA was inserted into Sma I sites of pGEM-4z vector (Promega, Mannheim, Germany) and the plasmid was linearized with Pvu I (Promega, Mannheim, Germany). The Pvu II linearized plasmid was linearized with Nhe I and Bam H I and linearized with Nhe I and Bam H I and inserted into the restriction sites Bam HI/Hind III of pGEM-4z vector (Promega, Mannheim, Germany). The Pvu II linearized pGEM-4z construct was then linearized with T7-RNA polymerase (Epicentre, Madison, WI) to generate the competitor mRNA.

A standard curve was established using 0.5 μg adrenal RNA pooled from several rats and adding varying amounts of competitor RNA to the PCR reaction mixture for calculation of TH mRNA amounts in the test samples (Fig. 1). For measurement of adrenal TH mRNA content via competitive RT-PCR (One Tube RT-PCR system, Roche Diagnostics, Mannheim, Germany), a 5'-digoxigenin-labeled upstream primer was used. If necessary, the amount of total adrenal RNA from the experimental animals added to the reaction mixture was adjusted to remain in the linear part of the standard curve. RT-PCR was performed with a thermal cycler (Touch Down, Hybaid, Teddington, UK). The program profile was as follows: 48°C × 45 min reverse transcription, 94°C × 4 min initial denaturation, 26 cycles 94°C × 1 min-61°C × 1 min-68°C × 1 min, final extension 68°C × 5 min. The PCR products were separated with polyacrylamide
The amplified and filtered signal was displayed on an oscilloscope. SNA was analyzed as mean integrated voltage and with the help of the sympathetic peak detection algorithm (24), as described in detail previously (14, 15). Analysis of full wave-rectified and integrated SNA with the sympathetic peak detection algorithm gives frequency and amplitude of synchronized discharges in which amplitude is determined by the number of simultaneously active nerve fibers (28). To allow for comparison of multifiber recordings between animals, amplitude of synchronized discharges is given as relative amplitude in percent maximum amplitude under control conditions. Therefore, the ratio of the 95th percentile of the absolute values for peak amplitude obtained in each animal during control conditions was set equal to 100%. Nerve recordings were corrected for background noise obtained 30 min after the animals were killed with an overdose of methohexital intravenously.

Experimental protocol 1. Eight-week-old F1H were randomly assigned to one of the following three groups. The first group (n = 15) was transplanted with a kidney from age-matched SHR. After transplantation, animals were housed in individual cages. Animals were handled daily for control of body weight and water intake. On day 7, after renal transplantation, the right native kidney was removed. On day 18 after transplantation, animals were instrumented with an arterial catheter. On day 20, arterial pressure recordings were performed between 9:00 and 11:00 AM over 30 min in conscious animals allowed to move freely in their home cage. Arterial pressure, HR, and SNA were recorded for a 15-min baseline period. Thereafter, three intracerebroventricular injections were performed in the following order with 25-min intervals: vehicle, 10 μg guanabenz, 20 μg guanabenz. Injection volume was 1–2 μl/injection flushed with 1 μl isotonic saline. Guanabenz was 1–2 mg guanabenz, 20 mg guanabenz 403-nucleotide fragment with 0.125, 0.5, or 1 fmol of competitor (394-nucleotide fragment) for generation of a standard curve. B: linear regression relating the ratio between signal intensities of RT-PCR products of adrenal TH mRNA and of the competitor mRNA to the amount of competitor mRNA added to the RT-PCR reaction mixture. This relationship was used to calculate the amount of TH mRNA in the tissue sample. When the TH mRNA/competitor ratio is 1, the amount of competitor RNA equals the amount of TH mRNA in the tissue sample. Dotted lines mark the 95% confidence interval.

Fig. 1. Standard curve for estimation of the adrenal tyrosine hydroxylase (TH) mRNA content. A: images of competitive RT-PCR assays of 0.5 μg total adrenal RNA (438-nucleotide fragment) with 0.125, 0.5, or 1 fmol of competitor (394-nucleotide fragment) for generation of a standard curve. B: linear regression relating the ratio between signal intensities of RT-PCR products of adrenal TH mRNA and of the competitor mRNA to the amount of competitor mRNA added to the RT-PCR reaction mixture. This relationship was used to calculate the amount of TH mRNA in the tissue sample. When the TH mRNA/competitor ratio is 1, the amount of competitor RNA equals the amount of TH mRNA in the tissue sample. Dotted lines mark the 95% confidence interval.

Abnormalities in myocardial function caused by sympathetic hyperactivity after renal transplantation were evaluated. The heart rate (HR) was derived from the pulsatile arterial pressure signal. SNA was analyzed as mean integrated voltage and with the help of the sympathetic peak detection algorithm (24), as described in detail previously (14, 15). Analysis of full wave-rectified and integrated SNA with the sympathetic peak detection algorithm gives frequency and amplitude of synchronized discharges in which amplitude is determined by the number of simultaneously active nerve fibers (28). To allow for comparison of multifiber recordings between animals, amplitude of synchronized discharges is given as relative amplitude in percent maximum amplitude under control conditions. Therefore, the ratio of the 95th percentile of the absolute values for peak amplitude obtained in each animal during control conditions was set equal to 100%. Nerve recordings were corrected for background noise obtained 30 min after the animals were killed with an overdose of methohexital intravenously.

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Table 1. MAP, HR, body weight, and plasma creatinine and urea concentrations in animals of protocol 1

<table>
<thead>
<tr>
<th></th>
<th>Recipients of an SHR Kidney</th>
<th>Recipients of an F1H Kidney</th>
<th>Untreated Time Controls</th>
</tr>
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<tbody>
<tr>
<td>n</td>
<td>15</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>143 ± 4*</td>
<td>110 ± 3</td>
<td>ND</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>386 ± 8</td>
<td>374 ± 8</td>
<td>ND</td>
</tr>
<tr>
<td>Body wt on day 1 of the protocol, g</td>
<td>253 ± 9</td>
<td>247 ± 6</td>
<td>268 ± 4</td>
</tr>
<tr>
<td>Body wt on day 21 of the protocol, g</td>
<td>306 ± 7†</td>
<td>302 ± 6†</td>
<td>348 ± 7‡</td>
</tr>
<tr>
<td>Plasma creatinine concentration, μmol/l</td>
<td>55.4 ± 3.3†</td>
<td>49.8 ± 1.8†</td>
<td>38.4 ± 3.6</td>
</tr>
<tr>
<td>Plasma urea concentration, mM</td>
<td>14.6 ± 0.5†‡</td>
<td>10.8 ± 0.3†</td>
<td>8.0 ± 0.2</td>
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</table>

Values are means ± SE. *Significantly different vs. recipients of an F1 hybrid (F1H) kidney; †significantly different vs. time controls; ‡significantly different vs. respective value on day 1 of the protocol. MAP, mean arterial pressure; HR, heart rate; SHR, spontaneously hypertensive rat; ND, not determined.

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Benz was obtained from Sigma Chemicals (Deisenhofen, Germany). The drug was dissolved in distilled water containing 50 mM acetic acid, because the drug is insoluble in aqueous solutions at neutral pH. Final pH was 6.8. The solution administered as vehicle during the first injection consisted of 1 μl sodium acetate (50 mM) brought to pH 6.8 that was flushed with 1 μl isotonic saline. Five minutes after each intracerebroventricular injection, arterial pressure, HR, and SNA were recorded for 15 min. The doses of guanabenz were chosen on the basis of results from previous experiments (14) and a preliminary dose-finding study. In these experiments, doses of 40 μg guanabenz ictv and higher produced slight pressor responses in baroreceptor intact F1H that are in agreement with data obtained for α2-adrenoceptor agonists by others in normotensive animals (2, 18).

To ensure that recording conditions were stable over time, five 12-wk-old F1H were instrumented as described above without prior renal transplantation. Instead of guanabenz, they received three injections of 1 μl sodium acetate (50 mM) at pH 6.8 flushed with 1 μl isotonic saline in 25-min intervals.

Statistics. Comparisons between group means were performed with unpaired Student’s t-test or by one-way analysis of variance as appropriate. Comparisons on group means with repeated measurements were performed with one- or two-way analysis of variance for repeated measurements as appropriate. If analyses of variance showed significant effects of treatments, time, or interactions between treatment and time, a Student-Newman-Keuls test was performed to identify significant differences between individual group means. Differences were taken as significant at P < 0.05. Data in text, tables, and figures are presented as means ± SE.

RESULTS

Adrenal TH mRNA content. Three weeks after renal transplantation, mean arterial pressure (MAP) was increased by >30 mmHg in recipients of an SHR kidney compared with recipients of an F1H kidney (P < 0.001), whereas HR did not differ significantly between both groups. During the protocol, body weight gain was similar in both transplanted groups, whereas time controls gained more weight compared with transplanted animals. Data are summarized in Table 1. Adrenal TH mRNA content was similar in recipients of an SHR kidney and in recipients of an F1H kidney. In transplanted animals, adrenal TH mRNA content was increased by 45% compared with untreated time controls (Fig. 2).

Splanchnic nerve recordings. Under control conditions, synchronized SNA showed similar characteristics in recipients of an SHR kidney and in recipients of an F1H kidney when analyzed with the sympathetic peak-detection algorithm. Mean peak interval was 191 ± 11 ms in recipients of an SHR kidney versus 170 ± 4 ms in recipients of an F1H kidney (not significant). This corresponds to mean frequencies of 5.2 and 5.9 Hz, respectively. Mean relative amplitude of synchronized SNA was 59 ± 4% of maximum peak amplitude in recipients of an SHR kidney and 59 ± 3% of maximum peak amplitude in recipients of an F1H kidney (Fig. 3). In transplanted animals, SNA gradually fell in response to intracerebroventricular administration of guanabenz. The degree of sympathoinhibition did not differ between groups (Fig. 4). The fall in mean integrated SNA was paralleled by a reduction in amplitude of synchronized discharges, i.e., a decrease in simultaneously active fibers. Frequency of synchronized SNA was reduced only after cumulative administration of 10 and 20 μg guanabenz with no significant difference between groups (data not shown). After cumulative intracerebroventricular administration of 10 and 20 μg guanabenz, arterial pressure fell slightly in both groups by 4–5 mmHg accompanied by a reduction in HR (Fig. 4). Repeated intracerebroventricular administration of vehicle solution did not significantly change HR, MAP, and SNA in five time-control experiments in nontransplanted F1H (Fig. 5).

![Fig. 2. TH mRNA content in adrenals obtained 3 wk after renal transplantation from recipients of a spontaneously hypertensive rat (SHR) kidney (n = 15), recipients of a F1 hybrid (F1H) kidney (n = 10), and time controls (n = 11; *P < 0.05 vs. transplanted animals).](http://ajpregu.physiology.org/DownloadedFrom/10.1152/ajpregu.00728.2016)
DISCUSSION

The mechanisms leading to arterial hypertension after transplantation of a kidney from genetically hypertensive donors into normotensive recipients are largely unknown. We have previously demonstrated that reinnervation of transplanted SHR kidneys does not contribute to the development of renal posttransplantation hypertension (16). In the current study, we investigated whether increased activity of extrarenal parts of the sympathetic nervous system is involved in the pathophysiology of posttransplantation hypertension. We investigated the animals 3 wk after renal transplantation (2 wk after bilateral nephrectomy) when arterial pressure is still rising (33) and when neural activation is more likely to be of pathophysiological importance compared with later phases when secondary structural changes, including hypertensive renal damage, may influence arterial pressure to a greater extent.

For assessment of chronic sympathetic activity, we chose adrenal TH mRNA content as a marker. TH catalyzes the rate-limiting step of catecholamine synthesis, and its activity rises with increases in preganglionic nerve activity to the adrenals (36). This is accompanied by an increase in TH gene transcription rate and TH mRNA content (11, 27). Nerve-section experiments and administration of cholinergic blockers showed that increases in adrenal TH mRNA depend on preganglionic neural input in response to stimuli such as water deprivation (3), cold stress, and hypoglycemia (27), but not immobilization stress (27). Furthermore, increases in adrenal TH enzyme activity and catecholamine content (35), as well as elevated superior cervical ganglion TH immunoreactivity and TH mRNA content (26), have been reported in sodium chloride-induced hypertension.

Three weeks after renal transplantation, TH mRNA content was almost identical in recipients of an SHR kidney and recipients of an F1H kidney, suggesting...
that sympathetic activity to the adrenals did not depend on the source of the renal graft. In transplanted animals, TH mRNA content was increased by 45% of the time-control values. We have previously shown that transplantation of an F1H kidney does not increase blood pressure in bilaterally nephrectomized F1H recipients (16). Thus the moderate increase in adrenal TH mRNA content as seen in this study is not associated with an increment in blood pressure.

The increased adrenal TH mRNA contents in transplanted rats are most likely an effect of surgical stress imposed on the animals that underwent three surgical interventions within 3 wk. Surgical stress may also be reflected by reduced body weight gain compared with time controls. Other stressors were kept to a minimum. All animals were handled daily and were well accustomed to the laboratory conditions. It is unlikely that elevation of adrenal TH mRNA through surgery was near maximum and therefore prevented detection of possible differences between recipients of an SHR and an F1H kidney. Thus three- to fourfold elevations have been reported in response to restraint stress in Sprague-Dawley rats (22). Furthermore, threefold increases in superior cervical ganglion TH mRNA content have been found in sodium chloride-induced hypertension in Dahl salt-sensitive rats (26).

To further investigate the sympathetic nervous system, we performed splanchnic nerve recordings. For estimations of chronic sympathetic activity, this method has limitations because of the variability of absolute voltages between individual recordings and the extent of surgery influencing the system under investigation. To increase the amount of information obtained from multifiber recordings, we used the sympathetic peak-detection algorithm (24) for analysis of sympathetic nerve activity. This method provides data on the frequency of synchronized discharges and their amplitude that is determined by the amount of simultaneously active fibers (24, 28). Experiments performed under similar conditions as in the present study showed increases in frequency and amplitude of synchronized renal nerve discharges in SHR versus WKY and in sodium chloride-induced hypertension consistent with elevated sympathetic activity in these hypertensive states (6). Thus sympathetic peak detection appears suitable for detection of differences in sympathetic tone under these experimental conditions.

In the present study, we found almost identical mean peak amplitudes and similar mean peak intervals (inverse of frequency) in recipients of an SHR and of an F1H kidney. If anything, frequency of synchronized discharges tended to be somewhat lower in recipients of an SHR kidney compared with recipients of an F1H kidney. Under the assumption that maximum peak amplitude under control conditions reflected similar proportions of simultaneously active fibers of the splanchnic nerve in the two groups, data on relative amplitude and frequency of synchronized discharges indicate that SNA was not significantly different between recipients of an F1H kidney and recipients of an SHR kidney under control conditions.

Centrally administered \( \alpha_2 \)-adrenoceptor agonists, such as clonidine (18, 29) and guanabenz (7, 19), evoke exaggerated sympathoinhibition and decreases in arterial pressure in SHR (7, 18) and in sodium chloride-induced hypertension in borderline hypertensive rats, SHR, and Dahl salt-sensitive rats (7, 19, 29). This is possibly due to an increased \( \alpha_2 \)-adrenoceptor sensitivity in depressor regions of the central nervous system (29). Renal posttransplantation hypertension is associated with increased sodium retention (12), and the recipients used in the present study are genetically closely related to SHR and borderline hypertensive rats as used in other studies (7, 18, 29). Therefore, we applied intracerebroventricular guanabenz treatment to investigate whether arterial pressure depends to a greater extent on sympathetic activity in recipients of an SHR kidney as in syngenically transplanted controls.

Intracerebroventricular treatment with guanabenz induced a similar sympathoinhibition in both transplanted groups accompanied by a slight decrease in arterial pressure and bradycardia that did not differ between groups. The degree of sympathoinhibition was
on the same order of magnitude as reported in other studies for hypertensive (7, 19) and normotensive (7, 14) rats under almost identical experimental conditions with renal nerve recordings. The data indicate that the sensitivity of the sympathetic nervous system to inhibition with centrally administered guanabenz is not increased in renal posttransplantation hypertension. Furthermore, these results show that arterial pressure does not depend to a greater extent on sympathetic nerve activity in recipients of an SHR kidney than in syngeneically transplanted controls. We did not use higher doses of guanabenz, because they produced slight pressor responses as it was found by others for both guanabenz (2) and clonidine (18) in normotensive rats.

Renal posttransplantation hypertension can be caused by either a primary defect in the kidney of genetically hypertensive donors or by secondary renal damage due to arterial hypertension of the kidney donor (34). Transplantation of kidneys from 5-wk-old stroke-prone SHR without demonstrable hypertensive renal damage (21) and transplantation of kidneys from adult stroke-prone SHR with previous antihypertensive treatment (33) induced arterial hypertension in F1H recipients, indicating that primary renal defects rather than hypertensive renal damage play an important role for the development of this form of experimental hypertension. To minimize the potential effect of secondary renal damage on arterial pressure in recipients of an SHR kidney, we used young (8-wk-old) SHR as kidney donors. In SHR, hypertensive renal damage develops slowly, and, even at the age of 34 wk, differences between intact WKY and SHR with respect to proteinuria and glomerular sclerosis are rather moderate (9).

Taken together, the data suggest that there is no specific sympathetic activation in response to transplantation of an SHR kidney into an F1H recipient, and the development of renal posttransplantation hypertension does not depend on increased sympathetic tone. The present data, together with results obtained in previous experiments (16), led us to conclude that effects of the recipients’ sympathetic nervous system are of limited importance for the development of renal posttransplantation hypertension.

**Perspectives**

The activity of the sympathetic nervous system is important for rapid adjustments of cardiovascular and renal function in response to changing environmental conditions. Its involvement in long-term arterial pressure regulation remains unclear. This is due to a lack of reliable methods to chronically quantify sympathetic activity and adaptation of the nervous system to repeatedly applied stimuli (e.g., central and peripheral resetting of baroreflexes). In addition to short-lasting effects on organ function, the sympathetic nervous system may also induce chronic effects on target organs that may become manifest as altered DNA and protein synthesis as well as changes in organ morphol-

ogy. SHR are characterized by increased sympathetic innervation of their internal organs compared with normotensive rats. It has been demonstrated that selective surgical renal denervation in young SHR delays, but does not prevent, the development of arterial hypertension in these animals. However, complete neonatal sympathectomy induces a long-term reduction of arterial pressure in SHR. Thus the degree to which a reduction in sympathetic tone affects long-term blood pressure in SHR depends on the stage during ontogeny at which it is applied and on the extent to which sympathetic influences are removed. Furthermore, it may also depend on the specific organ affected. Because the kidney appears to be the major determinant of long-term blood pressure in SHR, future research should be directed toward the specific role of early sympathetic activation within this organ for the development of hypertension in this model.

We thank Doreen Block, Karin Niemann, and Brigitte Sturm for expert technical assistance. This work was supported by grants from the Deutsche Forschungsgemeinschaft (GR-14302/1 and RE-5527/3–9).

**REFERENCES**


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