Effect of endogenous angiotensin II on the frequency response of the renal vasculature

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DiBona, Gerald F., and Linda L. Sawin. Effect of endogenous angiotensin II on the frequency response of the renal vasculature. Am J Physiol Renal Physiol 287: F1171–F1178, 2004.—The frequency response of the renal vasculature was evaluated using pseudorandom binary sequence renal nerve stimulation, and the role of angiotensin II was evaluated by the administration of the angiotensin II AT$_1$-receptor antagonist losartan. These results suggested that the renal vascular frequency response in normal rats might be affected by physiological alterations in the activity of the endogenous renin-angiotensin system. This hypothesis was tested by examining the renal vascular frequency response in normal rats consuming a low-, normal-, or high-sodium diet after acute administration of either vehicle or losartan.

METHODS

Sprague-Dawley rats were housed in individual metabolic cages and divided into three dietary groups. All three dietary groups were given nominally sodium-free pellet food (ICN) ad libitum. The low-sodium group (LNa) received sodium-free distilled water as drinking fluid, the normal-sodium group (NNa) received 50 meq/l NaCl as drinking fluid, and the high-sodium group (HNa) received 154 meq/l NaCl as drinking fluid. The rats equilibrated on these different dietary sodium intake regimens for at least 1 wk. Based on the average amount of drinking fluid taken with each diet, the NNa group had a sodium intake of 1.70 meq/day, the HNa group had a sodium intake of 9.10 meq/day, and the LNa group had a sodium intake of 0.0 meq/day. As previously demonstrated in this laboratory (4), this dietary regime produces significant increases and decreases in plasma renin activity in LNa and HNa rats, respectively, compared with NNa rats.

All animal procedures were performed in compliance with the University of Iowa Policies and Guidelines Concerning the Use of Animals in Research and Teaching and the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Rats were anesthetized with pentobarbital sodium (50 mg/kg ip); an oral endotracheal tube was inserted, and mechanical ventilation with room air was instituted. A jugular vein was catheterized for the administration of additional anesthetic (10 mg·kg$^{-1}$·h$^{-1}$ iv) and isotonic saline at 0.05 ml/min. A carotid artery was catheterized for the measurement of arterial pressure [AP; pulsatile and mean (MAP)] and heart rate. Via a left flank incision, the left renal nerve bundle was dissected free and placed on a silver wire bipolar electrode to which it was fixed with Silgel (Wacker Chemie, Munich, Germany). The electrode was connected to an electrical stimulator (Grass S88) or the output of a computer-controlled stimulator, and the nerve bundle was sectioned between the electrode and the neuraxis, ensuring that the only activity passing to the left kidney was derived from the stimulator. A noncannulating electromagnetic flow probe (1.5-mm circumference) was placed around the left renal artery and connected to an electromagnetic flowmeter (Carolina Medical Electronics). The flow probe was calibrated in situ by pumping heparinized rat blood at known flow rates through the cannulated rat renal artery (with the flow probe in place) at the end of the experiment.

After surgery, a 45-min period was allowed for equilibration and stabilization.

Conventional renal nerve stimulation. For each rat, a supramaximal voltage was determined as follows. At a frequency of 2 Hz and a
rectangular pulse duration of 0.5 ms, stimulation voltage was progressively increased until further increases in stimulation voltage did not result in further decreases in RBF. For further studies, rectangular pulses of 0.5-ms duration and supramaximal voltage (as determined for each rat) at frequencies of 0, 0.5, 1.0, 1.5, and 2.0 Hz were used. Each 60-s period of renal nerve stimulation was preceded by a 5-min control period and followed by a 5-min recovery period.

This experimental protocol was used in rats from each of the three dietary sodium groups both before and 30 min after the administration of losartan (10 μmol/kg iv).

Pseudorandom binary sequence renal nerve stimulation. For each rat, a stimulus voltage was determined that produced the maximum decrease in RBF but was not supramaximal (i.e., a voltage that activated all nerve fibers). This was determined by stimulating the renal nerves at a frequency of 2 Hz, a duration of 0.5 ms, and voltages between 5 and 15 V in 1-V steps. The maximum voltage so determined was used for each pseudorandom binary sequence (PRBS) in each rat. After a 20-min equilibration period, losartan (10 μmol/kg iv) or vehicle (control; 0.2 ml isotonic saline iv) was administered. Thirty minutes later, the renal nerves were stimulated with a PRBS for 30 min. The PRBS (6–9) was composed of a basal pulse with a frequency of 2 Hz and a duration of 2 ms and a voltage that was switched between a low voltage (0.5 V) and the maximum voltage previously determined for each rat. Every 0.5 s, a decision was made to switch between the low voltage and the maximum voltage or to stay at the present voltage. This provided a signal with a flat power spectrum over the broad frequency range of interest, 0–0.7 Hz, a desirable feature of an input signal for systems analysis of frequency response (16).

After the administration of vehicle or losartan, MAP, RBF, and renal vascular resistance (RVR) reached stable values within 5–10 min. Data from the remaining 20–25 min of the 30-min postvehicle or -losartan period (i.e., before PRBS) were used to examine the dynamic relationship between AP and RBF, i.e., dynamic autoregulation of RBF.

This experimental protocol was used in rats consuming each of the three sodium diets, creating six experimental groups: LNa-control (n = 9), LNa-losartan (n = 7), NNa-control (n = 6), NNa-losartan (n = 6), HNa-control (n = 6), and HNa-losartan (n = 6).

The rats were killed with an overdose of pentobarbital sodium, and a 20-min recording of postmortem signals was made. The heart was removed and weighed.

Data analysis. The postmortem signals were subtracted from the recorded control and experimental period data. AP, both pulsatile and MAP, was recorded via an electronic pressure transducer (Statham). Heart rate was determined via a tachometer (Grass 7P4) driven by the pulsatile AP waveform. RBF, both pulsatile and mean, was recorded via the electromagnetic flowmeter, the output of which was low-pass filtered below 10 Hz by the built-in analog filter. The outputs of the pressure transducer, the tachometer, electromagnetic flowmeter, and the renal nerve stimulator were led to a Grass model 7D polygraph recorder for graphic output and to VHS tape via a pulse code modulation adapter (Vetter model 4000A PCM Recording Adapter) for later offline analysis.

For the conventional renal nerve stimulation data, the maximum change in RBF with each stimulation frequency was calculated as a %change from the mean value of the preceding 5-min control RBF value. For the PRBS stimulation data, analog AP, renal nerve stimulator, and RBF signals were sampled from tape at 500 Hz. Because the voltage required to activate all nerve fibers differed for individual rats, the amplitude of all PRBS stimuli was normalized to unity by dividing by the maximum voltage. Subsequent processing of the data was performed with Matlab software. The 500-Hz data files were digitally low pass filtered (3.5-Hz cut-off frequency, finite-impulse-response, order 50) and then decimated to a rate of 5 Hz. The period used for analysis (30 min) was split into segments of 4,096 points which permitted the analysis of fluctuations down to 0.0012 Hz. The transfer function spectra were calculated from PRBS (input) and RBF (output) during PRBS. The transfer function was taken as the quotient of the cross spectrum of input and output divided by the power spectrum of the output. The algorithm involved mean detrending and a Hanning window with 50% overlap of the blocks; there were two to four 50% overlapping blocks per rat. To permit comparison between rats, the transfer function gain (magnitude) values over the frequency range have been normalized to the value at 0 Hz frequency (DC). After conversion of the normalized transfer function gain values into decibels (20log[gain]), a mean spectrum was calculated from the consecutive spectra and averaged for all rats. The time delay was calculated from the slope of the plot of phase (radian) of the transfer function vs. frequency over its linear portion; time delay = change in phase angle (radian)/2π change in frequency (Hz).

Coherence is a frequency domain estimate of a linear correlation (i.e., squared coherence, akin to coefficient of determination) between two signals indicating the degree to which the variance in one signal can be explained by a linear operation on the other signal. The coherence spectra were calculated from PRBS or AP (inputs) and RBF (output). The coherence function was taken as the quotient of the square of the cross spectrum of input and output divided by the product of the power spectrum of the input times the power spectrum of the output. The algorithm involved mean detrending and a Hanning window with no overlap of blocks of 256 data points.

A similar analytic approach was used for the analysis of the dynamic relationship between AP and RBF during the 20–25 min of the 30-min postvehicle or losartan period (i.e., before PRBS) with AP as input and RBF as output; there were one-three 50% overlapping blocks of 4,096 data points/rat.

Statistical analysis was performed with analysis of variance with the subsequent use of Scheffé’s method for simultaneous comparisons within groups and the subsequent use of the F-ratio and modified statistic for nonsimultaneous comparisons between groups (22). A significance level of 5% was chosen. All data are expressed as means ± SE.

RESULTS

We have previously demonstrated that this dose of losartan abolishes the pressor responses (ΔMAP = +40–42 mmHg) and the renal vasoconstrictor responses (ΔRBF = −3.1–3.4 ml/min) to angiotensin II (100 pmol iv) (7).

Conventional renal nerve stimulation. Graded frequency renal nerve stimulation was performed before and after the administration of losartan. Before administration of losartan, there were no significant differences between the three dietary groups in the baseline values of MAP, RBF, and RVR (Table 1).

Administration of losartan resulted in decreases in MAP that were significantly greater in LNa (−25 ± 4 mmHg) than in either NNa (−10 ± 2 mmHg) or HNa animals (−1 ± 1 mmHg). After administration of losartan, MAP was significantly less in LNa than in NNa rats, which, in turn, was significantly less than in HNa rats. RBF was unaffected by losartan. RVR was significantly less in LNa than in NNa rats, which, in turn, was significantly less than in HNa rats.

Before losartan, graded frequency renal nerve stimulation did not significantly affect RBF at either 0.5 or 1.0 Hz in any of the three dietary groups but produced frequency-dependent decreases in RBF at both 1.5 and 2.0 Hz in all three dietary groups (Fig. 1, left). The decreases in RBF at 1.5 and 2.0 Hz were significantly greater in LNa than in either NNa or HNa rats (which did not differ from each other). After administration of losartan, graded frequency renal nerve stimulation did not significantly affect RBF at either 0.5 or 1.0 Hz in any of
three dietary groups but decreased in RBF at both 1.5 and 2.0 Hz that were similar in all three dietary groups (Fig. 1, right). After losartan administration, the renal vasoconstrictor responses were significantly attenuated at 1.5 (LNa: −54 ± 3%; NNa: −37 ± 2%; HNa: 0 ± 1%) and 2.0 Hz (HNa: −51 ± 3%; NNa: −38 ± 2%; HNa: −9 ± 1%). The degree of attenuation was significantly greater in LNa than in either NNa or HNa rats.

**PRBS renal nerve stimulation.** The baseline values of MAP, RBF, and RVR were similar in all groups of rats before and after losartan (Table 2). Administration of vehicle did not affect MAP, RBF, or RVR. Administration of losartan resulted in decreases in MAP that were significantly greater in LNa (−24 ± 3 mmHg) than in either NNa (−11 ± 3 mmHg) or HNa rats (−2 ± 1 mmHg). After administration of losartan, MAP was significantly less in LNa than in NNa rats, which, in turn, was significantly less than in HNa rats. RBF was unaffected by losartan. RVR was significantly less in LNa than in NNa rats, which, in turn, was significantly less than in HNa rats.

After the administration of vehicle or losartan, MAP, RBF, and RVR reached stable values within 10 min. Data from the remaining 20 min of the 30-min postvehicle or -losartan period (i.e., before PRBS) were used to examine the dynamic relationship between AP and RBF, i.e., dynamic autoregulation of RBF. In control rats (vehicle treated), transfer function gain exhibited a characteristic pattern consisting of a nadir between 0.02 and 0.06 Hz, representing the slower tubuloglomerular feedback (TGF) mechanism, a transition from negative to positive values at ~0.1 Hz, and a peak followed by a plateau between 0.1 and 0.2 Hz, representing the faster myogenic mechanism (Fig. 2). This pattern was apparent in each of the three dietary groups. The transfer function gain at frequencies <0.1 Hz was significantly lower in LNa rats and significantly higher in HNa compared with NNa rats. The lowest transfer function gain (and its frequency) was −17.8 ± 1.5 dB (0.02 Hz) in LNa, −11.8 ± 0.2 dB (0.01 Hz) in NNa, and −7.1 ± 1.8 dB (0.03 Hz) in HNa rats. Transfer function gain at frequencies >0.1 Hz was not significantly different among the LNa, NNa, and HNa groups.

In LNa and NNa (but not HNa) rats, the administration of losartan significantly increased transfer function gain (i.e., less negative) at frequencies ≤0.1 Hz while having no effect at frequencies >0.1 Hz. In LNa rats, gain was significantly increased over the frequency range 0.002–0.03 Hz while in NNa rats, gain was significantly increased over the frequency range 0.009–0.03 Hz. The lowest transfer function gain (and its frequency) before and after losartan administration were −17.8 ± 1.5 dB (0.02 Hz) vs. −11.8 ± 0.9 dB (0.02 Hz) in LNa (P < 0.05), −11.8 ± 0.2 dB (0.01 Hz) vs. −6.5 ± 0.7 dB (0.02 Hz) in NNa (P < 0.05), and −7.1 ± 1.8 dB (0.03 Hz) vs. −4.2 ± 2.79 dB (0.03 Hz) in HNa rats (not significant), respectively.

### Table 1. Baseline data in conventional renal nerve stimulation protocol before and after losartan administration

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>MAP, mmHg</th>
<th>RBF, ml/min</th>
<th>RVR, mmHg·ml⁻¹·min⁻¹</th>
<th>MAP, mmHg</th>
<th>RBF, ml/min</th>
<th>RVR, mmHg·ml⁻¹·min⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>LNa</td>
<td>8</td>
<td>108 ± 3</td>
<td>6.27 ± 0.28</td>
<td>17.64 ± 0.82</td>
<td>83 ± 2</td>
<td>6.01 ± 0.22</td>
<td>13.75 ± 0.74</td>
</tr>
<tr>
<td>NNa</td>
<td>6</td>
<td>114 ± 4</td>
<td>6.33 ± 0.29</td>
<td>18.15 ± 0.89</td>
<td>104 ± 3</td>
<td>6.76 ± 0.23</td>
<td>15.09 ± 0.77</td>
</tr>
<tr>
<td>HNa</td>
<td>6</td>
<td>120 ± 4</td>
<td>6.86 ± 0.38</td>
<td>17.80 ± 0.91</td>
<td>119 ± 3</td>
<td>6.98 ± 0.27</td>
<td>17.14 ± 0.79</td>
</tr>
</tbody>
</table>

Values are means ± SE. n, No. of rats; LNa, low-sodium diet; NNa, normal-sodium diet; HNa, high-sodium diet; MAP, mean arterial pressure; RBF, renal blood flow; RVR, renal vascular resistance. *P < 0.05 vs. control value.
In control rats (vehicle treated), phase was positive at frequencies \(0.2\) Hz in all three dietary groups and was not affected by administration of losartan (data not shown).

In control rats (vehicle treated), coherence was significantly less in LNa than in NNa and HNa rats over the frequency range \(0–0.4\) Hz and \(0–0.6\) Hz, respectively, whereas coherence was not significantly different between NNa and HNa rats over the entire frequency range (Fig. 3). The administration of losartan had no effect on coherence in any of the three dietary groups.

The transfer function gain during PRBS, i.e., PRBS to RBF, the renal vascular frequency response, is shown in Fig. 4. In control rats (vehicle treated), transfer function gain tended (not significant) to be less negative in LNa compared with either NNa or HNa rats. The administration of losartan had no effect on transfer function gain in NNa or HNa rats. However, in LNa rats, after the administration of losartan, transfer function gain was significantly more negative over the entire frequency range. After losartan administration, transfer function gain tended (not significant) to be more negative in LNa than in either NNa or HNa rats.

As previously noted during PRBS (6, 7), the phase angle decreased linearly, indicating the presence of a pure time delay (data not shown). In control rats (vehicle treatment), the calculated values for time delay were similar in LNa (685 ± 18 ms), NNa (705 ± 20 ms), and HNa rats (698 ± 19 ms). There was no effect of losartan administration on the calculated values for time delay: LNa (701 ± 17 ms), NNa (709 ± 19 ms), and HNa (697 ± 18 ms).

The coherence between PRBS and RBF is shown in Fig. 5. In control rats (vehicle treated), coherence was similar among the three dietary groups. The administration of losartan did not significantly affect coherence in any of the three dietary groups.

**DISCUSSION**

The major finding of the current study is that physiological alterations in activity of the endogenous renin-angiotensin system influence both the renal vasoconstrictor response to graded frequency conventional renal nerve stimulation and the renal vascular frequency response to PRBS renal nerve stimulation.

During graded frequency conventional renal nerve stimulation, a relative insensitivity of the renal vasculature to low frequencies (0.5, 1.0 Hz) was observed both in the absence and presence of losartan. These observations are in agreement with multiple prior studies in several species, which also identified an effect of these low (nonvasoconstrictor) frequencies to
increase renal tubular sodium and water reabsorption and renin release (reviewed in Ref. 5). Conventional renal nerve stimulation at 1.5 and 2.0 Hz produced renal vasoconstriction which was greater in LNa than either NNa or HNa rats, suggesting that increased activity of the endogenous renin-angiotensin system augmented the renal vasoconstrictor response. This was confirmed by the observation that, after losartan administration, the renal vasoconstrictor responses to 1.5 and 2.0 Hz were attenuated in proportion to the level of activation of the endogenous renin-angiotensin system, i.e., LNa > NNa > HNa.

While losartan administration had no effect on the renal vascular frequency response in NNa and HNa rats, with normal and decreased activity of the renin-angiotensin system, respectively, it significantly increased the attenuation (gain became more negative) in LNa with increased activity of the renin-angiotensin system. Thus transfer function gain, which tended to be less negative in LNa than in either NNa or HNa rats before losartan administration, tended to become more negative in LNa than in either NNa or HNa rats after losartan administration. This was not associated with any change in either the phase (time delay) or coherence between PRBS and RBF.

These findings suggest that increased activity of the endogenous renin-angiotensin system within the kidney (i.e., during LNa) affects the frequency response characteristics of the renal vasculature. These results are similar to previous findings in
rats with CHF, wherein the abnormality in the frequency response characteristics of the renal vasculature was corrected by the administration of losartan (6, 7). In both LNa and CHF rats, the effect of losartan was to decrease the gain (i.e., more negative). However, while there is increased activity of the endogenous renin-angiotensin system within the kidney in both LNa and CHF rats, there are important differences. Compared with LNa normal rats, CHF rats have decreased basal RBF (−20%) and increased basal RVR; losartan administration decreased MAP with little change in RBF so that there was a reduction in RVR. The decreases in both MAP and RVR were greater in CHF than LNa normal rats. In LNa and NNa rats, basal MAP, RBF, and RVR are similar; losartan administration decreased MAP with little change in RBF so that there was a reduction in RVR. The decreases in both MAP and RVR were greater in LNa than in NNa rats. Thus the reductions in RVR produced by losartan are largely dependent on the reductions in MAP because RBF, being well autoregulated, was not greatly affected whether its basal level was decreased (CHF) or normal (LNa). These results suggest that the common abnormality associated with an altered frequency response of the renal vasculature is an angiotensin II-dependent contribution to basal RVR, whether it is increased (CHF) or normal (LNa). It is possible that the presence of a tonic level (normal or increased) of angiotensin II-dependent renal vascular constrictor tone altered the ability of the renal vasculature to effectively discriminate, i.e., filter, frequencies within the PRBS input signal.

However, in the anesthetized rabbit, when angiotensin II was infused into the renal artery in amounts sufficient to decrease basal RBF and increase basal RVR by 33%, the renal vasoconstrictor responses to graded frequency conventional renal nerve stimulation and the frequency response characteristics of the renal vasculature were not affected (10). It was concluded that decreases in basal RBF of ~30% appear to have little impact on the renal vascular responsiveness to renal sympathetic nerve stimulation or on the ability of the different frequencies within RSNA to modulate RBF. However, it was acknowledged that 1) these conclusions apply only to the effects of acute administration of exogenous angiotensin II and may not apply to the situation of chronic increases in endogenous angiotensin II as is the case here in LNa (and in CHF) rats; 2) additional important information is likely to be derived from the use of angiotensin II AT₁-receptor antagonists to more physiologically inhibit the effect of endogenous angiotensin II, such as losartan as used herein.

Basal MAP (i.e., renal perfusion pressure) was significantly reduced by losartan, more in LNa than in NNa rats. However, losartan did not affect the renal vascular frequency response in NNa rats. This argues against the level of basal MAP and its ability to influence basal RVR by the autoregulatory response as being a determinant of the renal vascular frequency response. Furthermore, in the isolated, perfused rabbit kidney, application of a wide range of renal perfusion pressure (60, 100, 135 mmHg) did not alter the renal vascular frequency response to PRBS (11).

During both conventional renal nerve stimulation and PRBS stimulation, the kidney receives its entire neural input according to investigator-chosen parameters. This means that the effects of endogenous angiotensin II and exogenous losartan on the renal vascular response are localized within the kidney. Possible sites for this interaction are the renal sympathetic nerve terminal and the renal vasculature. In this regard, increased renin angiotensin II can facilitate the release of norepinephrine from renal sympathetic nerve terminals via stimulation of angiotensin II AT₁ receptors located presynaptically on the renal sympathetic nerve terminals (1, 5). If the increases in renin angiotensin II content produced by a low-sodium diet are similar to those produced by chronic angiotensin II infusion, then an additional contribution may be derived from an increase in the density of renal vascular innervation (19). Conversely, losartan decreases the renal vasoconstrictor response to graded frequency renal nerve stimulation (but not to norepinephrine) in a dose-dependent manner, further identifying this effect as presynaptic and not postsynaptic (23). Thus in
response to an increase in renal sympathetic nerve activity, increased renal angiotensin II enhances the release of norepinephrine from renal sympathetic nerve terminals, resulting in a greater renal vasoconstrictor response, which, when represented in the frequency domain, may appear as an increase (i.e., less negative) in gain.

Using the data collected before PRBS permitted an analysis of dynamic autoregulation of RBF during physiological alterations in the activity of the endogenous renin-angiotensin system. In LNa and NNa rats, with increased and normal endogenous renin-angiotensin system activity, respectively, transfer function gain was significantly decreased (i.e., more negative) only in the frequency range of the TGF mechanism compared with in HNa rats with decreased endogenous renin-angiotensin system activity. Furthermore, losartan administration made transfer function gain significantly less negative in LNa and NNa (but not HNa rats) only in the frequency range of the TGF mechanism. Taken together, these results indicate that angiotensin II enhances the effectiveness of the TGF mechanism. These results confirm and extend the results from a prior frequency domain analysis in rats (presumably on a normal-sodium diet), showing that the administration of captopril, an angiotensin-converting enzyme inhibitor, increased the mean gain of the transfer function over the frequency band 0.005–0.05 Hz from $-6.9 \pm 1.2$ to $-1.9 \pm 1.6$ dB (11). It is well known from renal micropuncture studies that TGF is attenuated after treatment with an angiotensin-converting enzyme inhibitors (e.g., Ref. 18), an angiotensin II AT1-receptor antagonist (e.g., Ref. 2) or in angiotensin II AT1 knockout mice (21) and enhanced after angiotensin II infusion (e.g., Refs. 2 and 18).

It is noted that the values for coherence between AP and RBF at frequencies <0.03 Hz are somewhat higher than those observed by others in the rat (e.g., Ref. 14) and are more similar to those seen in the dog (15). This is not related to block size, as the values were similar with block sizes of 256, 512, and 1,024 (data not shown). The origin and significance of this difference are not clear.

Angiotensin II has been implicated in determining the range of renal artery pressure (RAP) over which stepwise autoregulation of RBF occurs (3, 13). Compared with the RBF autoregulation curve obtained when RAP is stepwise reduced from its basal value to $\sim 50$ mmHg, the RBF autoregulation curve obtained when RAP is increased from $50$ mmHg back to its basal value exhibits marked hysteresis with a substantial reduction in basal RBF when RAP is restored to its basal value. Furthermore, there is a decrease in the autoregulatory threshold, i.e., the RAP at which RBF autoregulation becomes impaired. After angiotensin II-converting enzyme inhibition, the descending RBF autoregulation curve was unaffected while the ascending RBF autoregulation curve was restored to normal with elimination of the hysteresis and the shift in the autoregulatory threshold. Thus angiotensin II is necessary for RBF autoregulation to operate at a lower RAP. This involves angiotensin II facilitation of both the TGF (3) and myogenic components (17) of autoregulation. The findings herein that, in the control state before losartan administration, the rank order of transfer function gain at the TGF frequency was LNa (increased angiotensin II) < NNa (normal angiotensin II) < HNa (decreased angiotensin II) suggest a relationship between the amount of endogenous angiotensin II and the degree of facilitation of the TGF component. Although there are interpretative complications related to the losartan-induced decrease in AP, the angiotensin II-related facilitation of the TGF component was significantly diminished by losartan in the groups where endogenous angiotensin was normal (NNa) or increased (LNa) but not in the group where endogenous angiotensin II was decreased (HNa).

In the control state (i.e., before losartan administration), an effect of alterations in the level of activity of the renin-angiotensin system as produced by differences in dietary sodium intake was seen in the dynamic autoregulation of RBF but not in the renal vascular frequency response. It is possible that this difference relates to the differences in the nature of the input signal. In the case of dynamic autoregulation of RBF, the input signal is the AP waveform wherein the duration of each pulse varies with the heart rate (125 ms at 8 Hz to 200 ms at 5 Hz), each pulse has both a rise and decay pattern that are different from each other and the pulse height varies (sinus arrhythmia). In the frequency domain (frequency range of twice heart rate frequency), the power spectrum is not flat and is characterized by higher power at low frequencies than at higher frequencies with notable power at the frequency of heart rate (5–8 Hz) and respiration (1.0–1.4 Hz). In the case of the PRBS input signal, this is an investigator-determined standard regular pulse with an unvarying short duration (2 ms), pulse height, and identical rise and decay patterns. In the frequency domain, the power spectrum is flat over the investigator-determined frequency range of interest.

In summary, physiological alterations in the activity of the endogenous renin-angiotensin system, as produced by changes in dietary sodium intake, affect two important aspects of the dynamic regulation of RBF. Both increased and normal levels of activity of the renin-angiotensin system enhance the contribution of the TGF mechanism (but not that of the myogenic mechanism) to dynamic autoregulation of RBF. Increased levels of activity of the renin-angiotensin system affect the frequency response of the renal vasculature, resulting in less attenuation of neural input across the entire frequency range. These effects are mediated by the angiotensin II AT1 receptor as they are reversed by treatment with losartan, an angiotensin II AT1-receptor antagonist.

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