Tubuloglomerular feedback in Dahl rats

FINN M. KARLSEN, PAUL P. LEYSSAC, AND NIELS-HENRIK HOLSTEIN-RATHLOU
Department of Medical Physiology, The Panum Institute, University of Copenhagen,
DK-2200 Copenhagen, Denmark

Karlsen, Finn M., Paul P. Leyssac, and Niels-Henrik Holstein-Rathlou. Tubuloglomerular feedback in Dahl rats. Am. J. Physiol. 274 (Regulatory Integrative Comp. Physiol. 43):R1561–R1569, 1998.—We have previously demonstrated a loss of autoregulation in Dahl salt-sensitive (Dahl-S) rats rendered hypertensive on a high-salt diet. To determine whether this was due to a decreased activity of either the myogenic or the tubuloglomerular feedback (TGF) response, we tested the TGF response in both Dahl-S and salt-resistant Dahl rats on high- and low-salt diets. TGF was investigated in the closed-loop mode with a videometric technique, in which the response in late proximal flow rate to perturbations in Henle flow rate was measured. All Dahl rats showed a similar compensatory response to perturbations around the natural operating point, with a TGF response that was more efficient than in normotensive Sprague-Dawley rats. No evidence of decreased TGF responsiveness in hypertensive Dahl-S rats was found. The results suggest that the loss of autoregulation in hypertensive Dahl-S rats is due to a compromised myogenic response. We also measured the free-flow proximal intratubular pressure in Dahl rats. Perfectly regular oscillations were demonstrated in all Dahl series, including the hypertensive Dahl-S rats. This is the first demonstration of regular oscillations in an experimental rat model of hypertension.

autoregulation; closed-loop mode; oscillations

RENNAL BLOOD FLOW (RBF) and glomerular filtration rate are autoregulated when mean arterial pressure (MAP) is acutely changed within a pressure range from 90 to 180 mmHg. In the kidney two mechanisms contribute to the process of autoregulation (5): the myogenic mechanism and the tubuloglomerular feedback (TGF). The myogenic response is an intrinsic property of the vascular wall and refers to an active constriction of the preglomerular vessels caused by an increase in local transmural pressure. The TGF mechanism constricts the afferent arteriole in response to an increased load of NaCl at the luminal site of the macula densa. The relative contribution of these two mechanisms for the overall regulatory power remains to be established.

A previous study from our laboratory demonstrated a gradual loss of dynamic RBF autoregulation in Dahl salt-sensitive (Dahl-S) rats rendered hypertensive on a high-salt diet. Complete loss of autoregulation was found when high-salt intake for 4 wk was initiated early in life even if it was followed by 2 wk on a low-salt diet before the experiment (11). At that time MAP remained elevated, suggesting that the high blood pressure somehow might be responsible for the autoregulatory impairment in Dahl-S rats.

The exact nature of the impaired autoregulatory capacity in Dahl-S rats is unknown. Loss of autoregulation of RBF may be due to changes in the myogenic response or in the TGF response, or in both. Enhanced TGF response has been demonstrated both in young and adult spontaneously hypertensive rats (SHR) (1, 4, 15), but the TGF activity has not been studied by direct methods in Dahl rats and therefore motivated the present study. Under free-flow conditions, i.e., with the feedback loop in the closed mode, the regulatory efficiency of TGF can be studied by the videometric technique with small perturbations of the dependent variable, late proximal flow rate, around the normal operating point of the intact nephron. A similar approach has not previously been undertaken in hypertensive animals, but was considered advantageous for the present study.

In normotensive, halothane-anesthetized Sprague-Dawley rats, the proximal tubular pressure shows spontaneous, regular oscillations with a frequency of ~30 mHz (9, 14). In SHR and in 2-kidney, 1-clip Goldblatt hypertensive rats, a transition occurs with the development of hypertension from regular to highly irregular pressure fluctuations with a chaotic component (8, 29). Because the statistical measures of the chaotic fluctuations were the same in the two experimental models of hypertension, it was suggested that the underlying system generating the chaotic dynamics in the afferent arteriole might be the same (29). It was therefore a likely possibility that chaotic behavior could be a common characteristic of renal vascular control in hypertension. The present study also tests this hypothesis.

METHODS

Animal Preparation

Male Dahl-S rats, Charles River, Sulzfeld, Germany; Dahl salt-resistant (Dahl-R) rats, Moellegaard Breeding Centre, Lille Skensved, Denmark; and HSDOLA: Sprague-Dawley rats, Harlan, the Netherlands, ~240–360 g body weight, were allowed free access to tap water. The Dahl rats were inbred strains derived from the strains developed by Rapp and Dene (22). The European colonies of Dahl rats have been maintained independently of those in the US. The rats are routinely checked using genetic and biochemical markers, and there has been no evidence for genetic contamination of the Dahl rats in Europe. The experimental protocol had been approved in advance by the institutional animal care committee. The Dahl rats were divided into two series on different diet schemes. Two series were fed a low-salt diet (0.4% NaCl) from the time of weaning at 4 wk of age and for the following 7 wk and were designated S-L for Dahl-S rats and R-L for Dahl-R rats. Two high-salt series were fed a low-salt diet during the first week after weaning, then switched to a high-salt diet (8% NaCl) for the next 4 wk, and finally put on a low-salt diet for the last 2 wk before experiments. These series were designated S-H2L and R-H2L for Dahl-S and -R rats, respectively. The Sprague Dawley rats served as normotensive control rats. All rats were fasted overnight before experiments. The diet was a wet-mash diet based on Altromin.
standard diet flour no. 1314 (Lage, Germany) supplemented with NaCl to a final sodium content of 0.4 or 8%. The Sprague-Dawley rats were fed a standard pellet diet (Altromin, 0.2% NaCl). The rats were fasted overnight before experiments. Anesthesia was induced with 5% halothane delivered in a mixture of 35% oxygen and 65% nitrogen from a Fluotec Mark-3 vaporizer. Polyethylene catheters were inserted into the left jugular vein for infusions and into the right carotid artery for continuous recording of the systemic arterial blood pressure. A tracheostomy was performed, and the rats were placed on a servocontrolled operating table that maintained their body temperature at 37°C. The rats were connected to a small animal respirator that was adjusted to maintain arterial plasma pH between 7.35 and 7.45 with a mixture of 35% oxygen and 65% nitrogen, tidal volume 1.9–2.1 ml, and a frequency of 55–57 breaths/min. The final halothane concentration needed to maintain sufficient anesthesia was ~1%. An intravenous priming dose of 6 mg gallamine triethiodide (Relaxon, A/S GEA) in 0.6 ml of 0.9% saline was given, followed by a continuous intravenous infusion of 12 mg/ml gallamine triethiodide in 0.9% saline at 20 µl/min. An additional infusion of 0.9% saline was given at 10 µl/min. The rats were prepared for micropuncture as previously described in detail (25). In brief, the left kidney was exposed through a midline incision extended to the flank, and the left ureter was cannulated to ensure free flow of urine. The left kidney was immobilized with a Lucite ring and superfused with saline preheated to 37°C. The renal capsule was left intact.

Hydrostatic Pressure Measurements

Systemic arterial pressures were measured by a Statham P23-db pressure transducer (Gould, Oxnard, CA). Intratubular hydrostatic pressures were measured by a servonulling micropressure system, manufactured according to the description of Intaglietta et al. (10) by Reditech, Copenhagen, Denmark, and connected to a Statham P23-db transducer. The sharpened pressure pipettes (1–2 µm OD) were filled with 1 M NaCl solution colored with lissamine green (0.6 g%). The system was calibrated each day in a small pressure chamber. It was linear over the range 0–100 mmHg and had an uncertainty of ±0.2 mmHg. All pressures were recorded on a Goertz Servogor recorder and simultaneously on the audio track of a super VHS videotape with a Panasonic videocassette recorder through a frequency modulator (FM) (Reditech).

Microperfusion

For perfusion of late proximal tubular segments, we used artificial tubular fluid (ATF) with the following composition (in mM): 132 NaCl, 4 NaHCO₃, 4 KCl, 2 CaCl₂, 1 MgCl₂, 7.5 urea, and lissamine green (0.6 g%). The microperfusion pipette was mounted in a microperfusion pump (Fa. Hampel, Frankfurt, Germany).

Tubular Flow Measurements

Late proximal tubular flow rate was measured optically by a modification of the method of Chou and Marsh (2, 9). The experimental setup has been described in detail in a previous publication from this laboratory (16). In brief, small boluses (10–15 pl) of rhodamine-labeled dextran (molecular wt 17,200; Sigma, St. Louis, MO) in 0.9% saline were injected into a late proximal convolution by a pneumatic picopump (model PV280; World Precision Instruments, New Haven, CT), one pulse every 2 s. A green He-Ne laser (1 mW, 543 nm; Melles Griot) directed at the field of observation excited the dye. The fluorescent image was observed at ×80 magnification and passed through a red filter to an image intensifier (GEN II SYS; Dage-MTI, Michigan City, IN) connected to a charge-coupled device camera (model C72, Dage-MTI). The output from the camera was displayed on a 14-in. video monitor and recorded on super VHS videotape with a Panasonic videocassette recorder for later offline analysis. The tubular pressure and the blood pressure were recorded onto the audio track of the videotape after frequency modulation.

The composite video signal was routed to an imaging board (Matrox IP-8) mounted in a computer, which allowed two sample windows of variable size to be placed independently on the video image at two points along the nephron just distal to the injection pipette. Two digital signals were returned, each of them proportional to the light intensity of the image defined by the sampling window. The time delay for the passage of the dye bolus between the two windows was calculated for each individual pulse. On-screen measurements of the tubular length and diameter allowed for calculation of the tubular fluid flow rate.

The pressure signal recorded on the audio track was sampled at 50 Hz by an analog-to-digital converter (DT-2801A, Data Translation) through an FM demodulator (Reditech), and the mean value of each 2-s interval was used for further analysis.

Experimental Procedure

Free-flow proximal tubular pressure. Proximal tubular pressure (Pprox) was measured in free-flowing nephrons. A proximal convolution was impaled, and the proximal pressure was measured for 5–15 min.

Late proximal flow rate. Pprox and late proximal flow rate were measured. After localization of the surface proximal convolutions, the pressure pipette was inserted in a midproximal convolution and the dye containing pipette connected to the picopump was inserted in the very beginning of the last accessible proximal convolution. A nephron was selected for study only if the last convolution had a length permitting the video sampling windows to be positioned at some distance from each other. With the pump set at 0 nl/min, the microperefusion pipette containing ATF was inserted at the end of the last proximal convolution. The flow rate was measured immediately upstream from the microperefusion pipette by velocimetric flow velocimetry as flow was perturbed by addition or subtraction of fluid. Proximal intratubular pressure was measured continuously throughout the experiments. A control period (2 min) was obtained with zero microperefusion. Then the microperefusion was started, and the following perfusion rates were applied: –12, –8, –4, +4, +8, +12 nl/min. Each perturbation was sustained for a period of 2 min, and each level of perturbation was separated by a 1-min period at 0 nl/min perfusion in which the system was allowed to return to the control value before another perturbation was applied. After the last perfusion period, the pump was set at 0 nl/min, and a final control period lasting 2 min was obtained. The perturbations were applied in a random order, but usually the suction periods preceded the perfusion periods to assure that most of the perfusate delivered to the proximal tubule was native tubular fluid.

After steady state was reached following a perturbation, the tubular flow rate and the pressure were obtained by averaging over an interval of ≥1 min. The mean fluid flow rate without perturbation was calculated by averaging the zero perfusion periods before and after the perturbation. The decrease or increase in tubular fluid flow rate during perturbation was then calculated by subtracting the zero fluid flow rate from the perturbation value. The mean free-flow tubular...
fluid flow rate was estimated by averaging all zero flow rates from the entire experiment. The proximal tubular pressure values were processed in a similar manner.

**Data Analysis**

The data set was described by a third-order polynomial

\[
y = ax^3 + bx^2 + cx + d
\]

The polynomial described the change in measured late proximal flow rate (\(\Delta Q_{\text{LM}}\)) as a function of the microperfusion rate (I), i.e., \(x = I\), and \(y = \Delta Q_{\text{LM}}\). Curve fitting was performed with use of a modified least-squares method (17). The loss function, \(L\), was defined by the equation

\[
L = (\text{observed value} - \text{predicted value})^2 + \exp(-1,000\cdot a)
\]

This modification of the curve-fitting procedure assured that the compensation achieved a maximum value within the range of perturbations.

The effectiveness of the regulation was quantified by calculation of the compensation (23). If \(dI\) is defined as the change in the microperfusion rate, and \(dQ_{\text{M}}\) is defined as the change in flow rate measured just proximal to the microperfusion pipette, the compensation \(C\) is given by

\[
C = -\frac{dQ_{\text{M}}}{dI} \cdot 100\%
\]

The compensation expresses the response of the regulatory system as a fraction of the perturbation. If the system perfectly counterbalances all external perturbations, the flow change measured just proximal to the perfusion pipette should equal the size of the perturbation, and the compensation is 100%. If there were no regulation at all, no flow changes would occur in response to the perturbation, and the compensation would be zero.

**Statistics**

Data were analyzed using a two-way ANOVA and least-significant difference test as a post hoc test. In the cases where no significant differences were found between the different groups of Dahl rats, all data were pooled and compared with the data from the Sprague-Dawley rats by an unpaired Student’s t-test. A P value <0.05 was considered statistically significant. All values are given as means \(\pm SE\). All statistical analysis and curve fitting were done using the software package Statistica for Windows (5.1) (StatSoft, Tulsa, OK).

**RESULTS**

**Free-Flow \(P_{\text{prox}}\)**

A total of 52 tubules was studied in 50 rats. Mean values for free-flow \(P_{\text{prox}}\), peak-to-peak pressure measurements, number of oscillations per minute, arterial blood pressure, and body weight are listed in Table 1. The Dahl-S rats gained more weight during the period up to the experiments than the Dahl-R rats. Dahl-S rats on a high-salt diet showed a significant rise in blood pressure compared with the S-L rats. In the salt-resistant rats, the high-salt diet also increased the arterial blood pressure, although only to a level comparable to S-L rats.

Free-flow proximal intratubular pressure did not depend on the strain of the Dahl rats; also, no effect could be detected of the salt content of the diet. All \(P_{\text{prox}}\) data from Dahl rats were thus pooled, and the mean value was \(12.8 \pm 0.2\) mmHg, which did not differ from \(P_{\text{prox}}\) in Sprague-Dawley rats. All tubules, independent of rat strain or salt content of the diet, demonstrated regular pressure oscillations. The average peak-to-peak amplitude did not differ between the four Dahl rat series and all data were pooled. The peak-to-peak value was \(4.2 \pm 0.2\) mmHg in Dahl rats, which was significantly higher than in Sprague-Dawley rats (2.6 \pm 0.3). The frequency of the oscillations was \(\sim 1.8\) oscillations/min in all series except R-H2L, which showed a moderately, although significantly, higher value of 2.0.

Representative experiments demonstrating free-flow \(P_{\text{prox}}\) measurements are shown in Fig. 1. Data from an S-H2L rat are shown in Fig. 1A, and \(P_{\text{prox}}\) measured in a normotensive Sprague-Dawley rat is shown in Fig. 1B.

**Late Proximal Flow Rate**

A total of 39 tubules was studied in 33 rats. A typical experiment is shown in Fig. 2, which shows late proximal flow rate and proximal pressure during an entire perturbation protocol. The tubule is from a series S-L rat. Each perturbation step led to immediate regulatory responses. A decrease in late proximal flow rate measured immediately upstream to the perfusion pipette was visible just after the onset of microperfusion, whereas suction of tubular fluid led to an increase in measured flow rate. As expected, the compen-

---

**Table 1. Free-flow values of \(P_{\text{prox}}\), peak-to-peak pressure values, number of oscillations per minute, arterial blood pressure, and body weight**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(P_{\text{prox}},) mmHg</td>
<td>13.4 ± 0.3</td>
<td>12.3 ± 0.4</td>
<td>13.0 ± 0.3</td>
<td>12.9 ± 0.4</td>
<td>13.1 ± 0.3</td>
</tr>
<tr>
<td>Peak-to-peak, mmHg</td>
<td>3.5 ± 0.3</td>
<td>4.6 ± 0.5</td>
<td>4.2 ± 0.3</td>
<td>4.2 ± 0.7</td>
<td>2.6 ± 0.3</td>
</tr>
<tr>
<td>Oscillations/min</td>
<td>1.84 ± 0.04</td>
<td>1.78 ± 0.04</td>
<td>1.84 ± 0.04</td>
<td>2.00 ± 0.06</td>
<td>1.82 ± 0.05</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>129 ± 28(c)</td>
<td>149 ± 29(cd)</td>
<td>118 ± 3</td>
<td>126 ± 28(c)</td>
<td>112 ± 3</td>
</tr>
<tr>
<td>Body weight, g</td>
<td>320 ± 58(c)</td>
<td>331 ± 68(c)</td>
<td>280 ± 4</td>
<td>273 ± 6</td>
<td>283 ± 12</td>
</tr>
</tbody>
</table>

Values are means ± SE; numbers in parentheses = no. of experiments/no. of animals. \(P_{\text{prox}}\), proximal intratubular pressure; MAP, mean arterial pressure; S-L, salt-sensitive rats fed low-salt diet; S-H2L, salt-sensitive rats fed a high-salt diet followed by 2 wk of low-salt diet; R-L, salt-resistant rats fed a low-salt diet; R-H2L, salt-resistant rats fed a high-salt diet followed by 2 wk of low-salt diet; SPD-N, Sprague-Dawley normotensive rats. \(\dagger P < 0.05\) vs. S-L; \(\ddagger P < 0.05\) vs. S-H2L; \(\dagger \ddagger P < 0.05\) vs. SPD-N; \(\dagger \ddagger \ddagger P < 0.05\) vs. S-L; \(\dagger P < 0.05\) vs. S-H2L; \(\dagger P < 0.05\) vs. Dahl rats (all series pooled).
A third-order polynomial (Eq. 1) was fitted to the data from each experiment to obtain estimates for the compensation at a given tubular flow rate. The data in the individual experiments were well fitted by the polynomial equation, with mean values for $r^2$ of 0.93 (range 0.76–1.00), 0.97 (range 0.92–0.99), 0.95 (range 0.90–0.99), 0.94 (range 0.88–0.99), and 0.95 (range 0.89–0.99) for series S-L, S-H2L, R-L, R-H2L, and Sprague-Dawley normotensive controls, respectively. The derivative with respect to $I$ of the polynomial is

$$d(\Delta Q_M)/dl = dQ_M/dl = -C = 3aI^2 + 2bl + c \quad (4)$$

thus the first-order derivative of the third-order polynomial is a measure of the compensation at a given infusion rate. The system shows the highest degree of regulation where the compensation is at a maximum. The point where the compensation is maximal is found by taking the second derivative of the third-order polynomial, setting it equal to 0, and solving for $I$. In terms of the coefficients of the original polynomial, the microperfusion rate at which the maximal compensation is obtained is given by $I = -2b/6a$ and is designated Perf(max). The compensation at this microperfusion rate is termed Comp(max) and designates the maximal regulatory capacity. The compensation in the unperturbed tubule, i.e., at a microperfusion equal to 0 nl/min, is designated Comp(0), and equals the coefficient $-c$. The values for Perf(max), Comp(max), and Comp(0) are given in Table 2. The maximal compensation occurred at microperfusion rates that were not statistically different from zero. As also is evident from the Perf(max) values, the compensation reached its maximum at a tubular flow rate close to the free-flow value, and it decreased as the tubular flow rate was either increased or decreased. The point of maximal compensation is equivalent to the inflection (turning) point of the TGF curve and corresponds to the point where the system has its maximal sensitivity, or gain. Therefore, the regulatory efficiency of the system reached its maximum close to the normal tubular flow rate.

The compensation values all exceeded 100% for Dahl rats, indicating that the TGF system in this genetic hypertensive strain of rats not only was able to compensate fully for a given perturbation, the system actually overcompensated; i.e., the change in late proximal flow rate measured just proximal to the perfusion pipette superseded the size of the perturbation step. A two-way ANOVA demonstrated that the effect of strain (Dahl-S and -R), salt content of the diet (low salt vs. a period of high salt), or the combined effect did not have any influence on the compensation, neither for Comp(max)
nor Comp(0). The data from the Dahl rats were therefore pooled and subsequently compared with the Sprague-Dawley rat data. The maximal compensation in Sprague-Dawley rats was 93 ± 8%, significantly lower than the mean value of all Dahl rats, 139 ± 8%. Similarly, the compensation at the operating point, Comp(0), was 89 ± 9% in Sprague-Dawley rats, which should be compared with 136 ± 8% in Dahl rats (P < 0.05).

DISCUSSION

Dahl-S rats show a complete loss of autoregulatory control of RBF when put on a high-salt diet early in life (11). Because two mechanisms, the myogenic response and the TGF mechanism, have been shown to contribute to autoregulation in the kidney, the decreased dynamic autoregulation could be due to abnormalities in either of the two mechanisms, or in both. The current study was undertaken to investigate the TGF system. The results demonstrate that the TGF mechanism is fully operational in Dahl-S rats on both a high- and a low-salt diet. This suggests that the loss of autoregulatory efficiency seen in Dahl-S rats on a high-salt diet is due to a compromised myogenic activity. In addition, there were no significant differences in the closed-loop TGF responses between Dahl-S and -R rats. Compensation in Dahl rats ranged from 123 to 148%, significantly higher than that seen in normotensive Sprague-Dawley rats. The results indicate an enhanced TGF efficiency in Dahl rats, irrespective of the presence of hypertension, compared with Sprague-Dawley rats. This is consistent with our previous study (11), in which a strong peak was present in the transfer function between arterial pressure and RBF at the operating frequency of the TGF response in the Dahl rats.

All Dahl rats compensated more than 100% when challenged with an external perturbation of the late proximal flow rate. The reason for this overcompensation is not easily explained. Flow-dependent changes in the rate of fluid reabsorption in the tubular segment between the perfusion and measurement site could contribute to an overestimation of the regulatory efficiency. Because the measurement site is upstream to the site of perturbation, a flow-dependent change in the rate of fluid reabsorption between the two sites would result in an overestimation of the size of the compensation at the site of infusion. For example, if a certain decrease in flow rate is observed at the measurement site, and there is a decrease in the rate of tubular reabsorption between the measurement and the infusion site, the effective decrease in the flow rate at the infusion site will be smaller. It is the change at this site that is the relevant parameter. However, at present it is not technically feasible to measure tubular flow at exactly the site of infusion. Although this mechanism may play a role, it is probably insufficient to explain the data. The distance is quite short between the two sites (<150 µm), and the rate of fluid reabsorption in this segment is not large enough to fully account for the observed overcompensation.

Dietary salt loading is associated with volume expansion and leads to a blunting of the TGF response (e.g., Refs. 3, 6, 13, 20). This is an adequate response, because it allows an increase of the single-nephron glomerular filtration rate (SNGFR) and the late proximal flow rate, factors that contribute to an increased renal sodium excretion (19). Salt loading and volume expansion are not likely as confounding factors in the present experiments. The rats that were maintained on a high-salt diet for 4 wk were shifted to a low-salt diet 2

---

**Fig. 2.** Response of late proximal flow rate (A) and tubular pressure (B) to microperfusion or suction. Shaded areas represent periods of perfusion or suction. Figures given at top are microperfusion/suction rates. Experiment is from Dahl salt-sensitive rats on a low-salt diet (S-L).
wk before experiments. Therefore, any possible effect of the dietary salt loading probably would have disappeared by the time of the experimental procedure.

Differences in the dietary protocol may, however, explain the apparent discrepancies between the present study and a prior study of the TGF response in salt-sensitive Dahl rats by Wilcox and Welch (28). The feedback response was studied in the open-loop mode, and salt loading was associated with a modest, albeit significant attenuation of the maximal TGF response (28). The discrepancy is probably explained by the different diet regimens. In the study of Wilcox and

Table 2. Mean flow rates at zero microperfusion and perfusion rate at maximal compensation, maximal compensation, and compensation at zero microperfusion

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>QM(0), nl/min</td>
<td>26.3 ± 1.9</td>
<td>28.3 ± 3.0</td>
<td>21.1 ± 2.0</td>
<td>18.4 ± 1.5</td>
<td>22.9 ± 1.0</td>
</tr>
<tr>
<td>Perf(max), nl/min</td>
<td>1.5 ± 1.4</td>
<td>-0.6 ± 1.9</td>
<td>-0.8 ± 0.5</td>
<td>-0.4 ± 0.8</td>
<td>-1.2 ± 1.9</td>
</tr>
<tr>
<td>Comp(max), %</td>
<td>148 ± 23</td>
<td>154 ± 23</td>
<td>134 ± 10</td>
<td>125 ± 7</td>
<td>93 ± 8†</td>
</tr>
<tr>
<td>Comp(0), %</td>
<td>144 ± 23</td>
<td>148 ± 23</td>
<td>132 ± 10</td>
<td>123 ± 8</td>
<td>89 ± 9†</td>
</tr>
</tbody>
</table>

Values are means ± SE; nos. in parentheses = no. of experiments/no. of animals. QM(0), flow rate at zero microperfusion; Perf(max), microperfusion rate at maximal compensation; Comp(max), compensation at a microperfusion rate equal to Perf(max); Comp(0), compensation at zero perfusion rate. *P < 0.05 vs. R-H2L; †P < 0.05 vs. Dahl rats (all series pooled).
Welch, the rats were kept on the high-salt diet up to the time of the experiments, whereas in our study a 2-wk period of low-salt intake preceded the experiments, thereby minimizing the effects of the volume expansion associated with the high-salt diet.

The compensatory response of the TGF system in the closed-loop mode has not previously been investigated in hypertensive animals. To compare the results obtained in our laboratory with results from other laboratories, we performed measurements in normotensive Sprague-Dawley rats. In these animals the compensation at the operating point was 89%, which should be compared with 56% (18) and 76% reported in previous studies (7). In normotensive Munich-Wistar rats, TGF compensation was reported to be 50–85% in closed-loop experiments (26, 27). To allow for a comparison with the previous studies, the Sprague-Dawley rats were maintained on a standard rat diet. This had a salt content that was slightly lower than the low-salt diet for the Dahl rats. However, the low-salt diet should result in a stronger TGF response in the Sprague-Dawley rats and therefore cannot explain the present findings of a significantly weaker TGF response compared with the Dahl rats.

Hypertension is known to influence the feedback system. Compared with Wistar-Kyoto rats, both young and adult SHR show an increased activity of the TGF (1, 4, 15). An exaggerated TGF is, however, not an ubiquitous finding in hypertensive states. In the unclipped kidney of 2-kidney, 1-clip Goldblatt hypertensive rats, the efficiency of the feedback system was severely reduced (21). The attenuation of the feedback response was proportional to the duration of renal artery stenosis. The magnitude of the TGF response is
therefore not directly predictable from the presence of hypertension, but varies from one hypertensive animal model to another. The present results confirm this conclusion, because all Dahl rats showed a uniform TGF response, independent of the level of the blood pressure.

In addition to the alterations in the open-loop feedback response, hypertension is also associated with changes in the TGF-mediated oscillations seen in the tubular pressure and flow (8, 29). Sustained regular oscillations are present in the proximal tubular pressure of halothane-anesthetized Sprague-Dawley and Wistar rats (14). The characteristic frequency of the oscillations is ~30–35 mHz, i.e., 1.8–2.1 oscillations/min (9, 14). Although there were small differences in the oscillatory frequency between the groups in the present study, the values in all the groups fall within the range of frequencies reported previously (9, 14). In SHR and in the undipped kidney of 2-kidney, 1-clip Goldblatt hypertensive rats, the oscillations appear as highly irregular fluctuations with several peaks in the power density spectrum (8, 29). The irregular fluctuations have chaotic components, and it was speculated that chaotic behavior was a generic feature of renal vascular control in hypertension (29). The present data are the first to show regular oscillations in proximal intratubular pressure in a chronically hypertensive rat model. This demonstrates that chaotic pressure fluctuations are not just a simple secondary effect of the high blood pressure, but that other factors need to be present. In agreement with the stronger feedback response in the Dahl rats, the amplitude of the oscillations were significantly increased in the Dahl rats compared with the Sprague-Dawley rats.

Even in the absence of a TGF response, microperfusion in the proximal tubule elicits an increase in $P_{\text{prox}}$, which lowers the net ultrafiltration pressure and thereby partially compensates for the perturbation. It could therefore be argued that the observed closed-loop responses represented a pressure effect and not the response of the feedback system. This possibility has been evaluated in previous studies, where it was shown that around the operating point the pressure effect accounts for only a few percent of the total response (7, 12). Thus, under the present conditions, TGF plays a major role in the regulation of SNGFR and late proximal flow rate.

In conclusion, Dahl rats have an efficient TGF response, as evidenced both from the perturbation analysis and from the presence of perfectly regular oscillations in proximal tubular pressure. The efficiency of the TGF response was independent of the salt diet and the presence of hypertension.

**Perspectives**

In a previous study from this laboratory (11), we have shown a loss of autoregulation in Dahl-S rats that were challenged with a high-salt diet early in life. In the present study TGF was shown to be operational in these hypertensive animals. The results seem to support the suggestion that a reduced myogenic responsiveness is responsible for the impaired autoregulation. This is also in accordance with the results of Takenaka et al. (24) obtained in the isolated, perfused hydronephrotic kidney preparation. Although several studies point in the same direction, a final confirmation awaits direct studies of the myogenic response in isolated vessels. Further studies are also necessary to enlighten the putative relationship between renal vascular injuries and decrease in myogenic responsiveness in hypertensive Dahl rats.

Previous studies have shown an association between hypertension and chaotic vascular control and hence irregular tubular pressure fluctuations. The present study demonstrates that chaotic vascular control is not a generic finding in hypertension. Rather, it may play a specific role in the pathogenesis of hypertension in certain animal models. One might speculate that the presence of irregular pressure fluctuations in hypertensive states depends on an intact myogenic response.

The excellent technical assistance of Ian Godfrey, Anni Salomonsen, and Eva Christensen Heins is gratefully appreciated.

This work was supported by grants from The Danish Heart Association, the Danish Medical Research Council, and the Novo-Nordisk Foundation.

Address for reprint requests: F. M. Karlsen, Univ. of Copenhagen, Dept. of Medical Physiology, The Panum Institute, Bldg. 10.5, 3 Blegdamsvej, DK-2200 Copenhagen, Denmark.

Received 19 September 1997; accepted in final form 17 February 1998.

**REFERENCES**


