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Pressure dependent modulation of renin release in isolated perfused glomeruli

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Pressure dependent modulation of renin release in isolated perfused glomeruli. The isolated perfused glomerulus technique was used to study pressure dependence of renin release in single, microdissected rabbit glomeruli with intact afferent arteriole and intact Bowman's capsule. Renin release from individual afferent-glomerular units was measured in 30 minute intervals while afferent arteriolar pressure was either decreased from 55 to 40 to 25 mm Hg or increased from 25 to 40 to 55 mm Hg. There was a clear, inverse relation of renin release and afferent pressure. Mean renin release rate was 3.2 times higher at 25 than at 55 mm Hg and 1.5 times higher at 40 than at 55 mm Hg. To evaluate the possible role of wall stretch in mediating this response, inner and outer afferent arteriolar diameters were measured by videomicroscopy. Outer afferent diameter remained constant between 25 and 55 mm Hg, whereas inner diameter exhibited a slight increase. Changes of afferent arteriolar wall stretch, however, did not correlate with changes of renin release. These data for the first time directly demonstrate the existence of a renin baroceptor at the level of the renal afferent arteriole. They furthermore suggest that this baroceptor is not a stretch receptor.

Renin is an important determinant of salt/water balance and arterial blood pressure. Of the factors which control renin release [1], the rate of chloride absorption by $Na^+:K^+:2Cl^-$ cotransport at the macula densa in the distal tubule [2, 3] and the level of arterial angiotensin II [4] are among the more prominent. Almost since its discovery, however, the renin-angiotensin system was felt to be regulated by pressure [5], and a number of studies in the 1960's and 70's provided evidence for the existence of a distinct pressure sensitive mechanism which was found to stimulate renin release when transmural pressure in the renal vasculature was decreased [6, 7]. More recently, the operating characteristics of this mechanism were investigated by Kirchheim, Ehmke and Persson, who gradually reduced renal perfusion pressure in chronically instrumented dogs to show that renin release is stable within the GFR autoregulatory range, rises shortly before GFR begins to fall (94 mm Hg) and reaches a high plateau at pressures where RBF autoregulation is lost (67 mm Hg) [8]. Studies by Tobian, Tomboulian and Janecek [9, 10] and Fray [11] put forward the concept that the putative "renin baroceptor mechanism" responds to changes of afferent arteriolar wall stretch ("stretch receptor hypothesis"). More recently, it was hypothesized that pressure dependent modulation of renin release was largely the result of autacoid release from the larger (interlobular and arcuate) renal vessels [12].

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For technical reasons, the "renin baroceptor mechanism" has been difficult to investigate. This was one of the reasons for the recent development of a model which permits to measure renin release in single glomeruli during in vitro perfusion through the afferent arteriole at physiological pressure [13]. The system, in addition, permits a direct measurement of afferent arteriolar wall diameters by videomicroscopy. It is thus ideally suited for studying pressure dependence of renin release in the absence of renal nerves, circulating hormones and fluctuating signals from the macula densa. In addition, the use of a free-flow perfusion system appears to be particularly relevant in view of a recent study which failed to find pressure dependence of renin release with static perfusion of single rabbit glomeruli [14]. The present study was therefore undertaken to investigate the concept that a renin baroceptor mechanism exists at the single nephron level and to clarify the role of afferent arteriolar wall stretch in this mechanism.

Methods

Measurement of renin release in single perfused glomeruli

The method for measuring renin release in isolated perfused rabbit glomeruli has recently been described [13]. In brief, single glomeruli with intact Bowman's capsule and afferent arteriole were microdissected at 4°C from kidneys of New Zealand White rabbits (1.0 to 1.5 kg body wt). No attempt was made to remove the macula densa during dissection, since this maneuver was, in our hands, often associated with either damage to Bowman's capsule or a leak in the terminal part of the afferent arteriole. A suitable glomerulus was then transferred to a thermoregulated (37°C) perfusion chamber mounted on an inverted microscope. The afferent arteriole was cannulated with a system of concentric micropipets consisting of a holding pipet (inner diameter 23 to 25 μm) and a perfusion pipet (outer diameter 10 μm). A third, "pressure" pipet (2 to 3 μm outer diameter) was advanced through the perfusion pipet into the afferent arteriolar lumen after cannulation (Fig. 1). This pressure pipet was filled with 4% FD&C green (in 0.9% NaCl + 4 mM KCl), and permitted to measure afferent arteriolar pressure with the Landis technique.

The perfusion and bath solutions contained Na 147 mM, K 5 mM, Ca 1.8 mM, Mg 1.0 mM, Cl 141 mM, acetate 10 mM, phosphate 2.0 mM, sulfate 1.0 mM, alanine 5 mM, glucose 8.3 mM and 0.3% bovine serum albumin. Perfused fluid leaving the glomerulus through either the efferent arteriole or the proximal tubule stump issued into the perfusion chamber, which was emptied and washed in 30 minute intervals. FITC-labelled

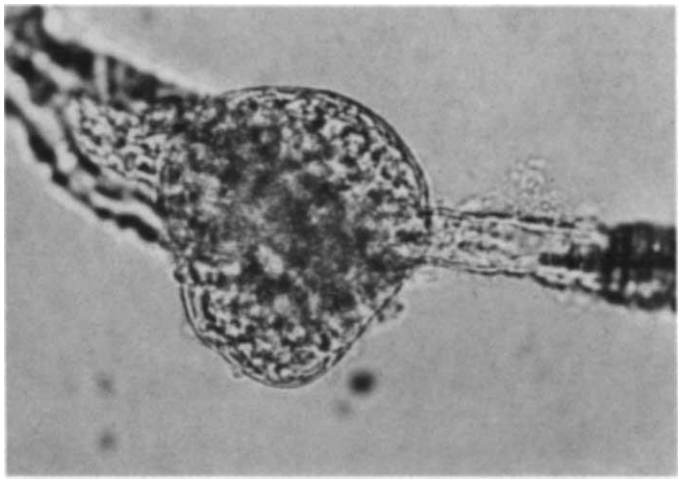

Fig. 1. *An isolated rabbit glomerulus perfused at 40 mm Hg (400× magnification).* Note intact Bowman's capsule and the wide lumen of the afferent arteriole (right side) with the perfusion and pressure pipets. On the left side, the efferent arteriole and part of the distal tubule can be recognized.

dextran (mol wt 150,000) was used to monitor perfusion rate, and the dilution of creatinine (which was added to the bath solution at 1,500 μM) was used to calculate perfusion chamber volume. Renin was measured in 20 μl samples of perfusion chamber fluid after 48 hours of incubation with purified rabbit renin substrate using a sensitive antibody-trapping micro-RIA for angiotensin I. The detection limit of the assay was 2 to 3 nano-Goldblatt units/20 μl. Creatinine was measured on a Beckman Creatinine Analyzer 2. FITC concentrations were measured on a Perkin-Elmer LS-5 fluorescence spectrophotometer using 492 and 520 nm as excitation and emission wavelength, respectively. Osmolality in the perfusion chamber fluid was measured in each period with a Wescor vapor pressure osmometer.

Afferent arteriolar diameter measurements

Experiments were recorded on videotape at 400× microscope magnification using a Visesta camera connected to a Panasonic AG-7330 S-VHS recorder. In suitable recordings, inner and outer afferent diameters were measured on frozen video frames with an ASBA image analysis system (Wild-Leitz AG, Zürich, Switzerland). This was done by manually tracing on the video frame an area delineated by the contour of the afferent arteriole on top and bottom and by two vertical lines at the left and right sides. Mean afferent diameter was calculated as $\frac{\text{traced area}}{\text{horizontal width}}$. All measurements were done in triplicate. For inner diameter, the tracing went along the inner surface of the endothelium.

Protocols

Single glomerular renin release was determined in three consecutive 30-minute perfusion periods, with perfusion pressure decreasing stepwise from 55 to 40 and to 25 mm Hg in six glomeruli (protocol HML) and increasing stepwise from 25 to 40 and 55 mm Hg in five additional glomeruli (protocol LMH). Six glomeruli, in which perfusion pressure was kept constant at 40 mm Hg throughout the experiment, were used as controls. Intact contractility of the afferent arteriole was verified after each experiment by adding norepinephrine 10^{-5} M to the perfusion chamber.

Two additional glomerular-afferent units were used to demonstrate the development of isometric tension in the arterioles of isolated perfused glomeruli. In these experiments, perfusion pressure was increased from 0 to 70 mm Hg in five minute intervals and the afferent diameter was recorded at the end of each interval. The entire sequence was repeated after adding papaverin [10^{-5} M] to the perfusion chamber.

Calculations and statistical analysis

Renin secretion rates were calculated as pg angiotensin I per hour (of incubation) per hour (of perfusion) (pg · hr^{-1} · hr^{-1}).

The *stretch* components of the afferent arteriolar wall for changing perfusion pressure from 40 to 25 or 55 mm Hg were calculated as follows:

$$\text{Radial stretch } \epsilon_r = \text{change of wall thickness} = \frac{\Delta(r_o - r_i)}{(r_o - r_i)}$$

$$\text{Tangential stretch } \epsilon_\Theta = \text{change of mean circumference}$$

$$= \frac{\Delta 2\pi \frac{r_i + r_o}{2}}{2\pi \frac{r_i + r_o}{2}} = \frac{\Delta(r_i + r_o)}{(r_i + r_o)}$$

Since the terminal part of the afferent arteriole is frequently hidden behind the glomerulus, axial stretch ϵ_Z (= axial elongation of the arteriole segment) was calculated assuming that the volume of the arteriole wall remained constant so that a diminution of the cross-sectional wall area was transmitted into an elongation of the segment under investigation:

$$\text{Volume of arteriole wall} = \pi(r_o^2 - r_i^2)L = \text{const (L = length)}$$

$$\text{hence} \quad \pi(r_{o1}^2 - r_{i1}^2)L_1 = \pi(r_{o2}^2 - r_{i2}^2)L_2,$$

$$\text{and} \quad \frac{L_2}{L_1} = \frac{r_{o1}^2 - r_{i1}^2}{r_{o2}^2 - r_{i2}^2}$$

$$\text{Axial stretch } \epsilon_Z = \frac{\Delta L}{L} = \frac{L_2 - L_1}{L_1} = \frac{L_2}{L_1} - 1 = \frac{r_{o1}^2 - r_{i1}^2}{r_{o2}^2 - r_{i2}^2} - 1$$

The calculation of active and passive wall tension (T_a and T_p) during increasing perfusion pressure (Fig. 6) was based on Laplace's equation:

$$P_{afferent} = \frac{T}{r_i} \Rightarrow T = r_i \cdot P_{afferent},$$

where $T = T_a + T_p$ = overall wall tension, $P_{afferent}$ = afferent arteriolar pressure and r_i = inner vessel diameter. In the presence of papaverin, which abolished active tension, only passive tension is present ($T = T_p$). As suggested by Fray, Lush and Park [15], an exponential regression of T_p ($= r_i \cdot P_{afferent}$) versus r_i was then derived from the papaverin data. The regression equation thus obtained ($r = 0.98$) was applied to the measurements obtained *without* papaverin to calculate T_p from the measured inner radius r_i. Active wall tension T_a was subsequently calculated as the difference between total wall tension (as computed from Laplace's equation) and passive tension ($T_a = T - T_p$).

Shear rate at the afferent arteriolar wall (which is defined as $\frac{4v}{r}$) was calculated as

$$\frac{4 \cdot \text{perfusion rate}}{\pi r_i^2 \cdot r_i}$$

Data were statistically analyzed by two-way analysis of variance. Differences between periods were evaluated with the Least Significant Difference procedure. Renin secretion rate was log transformed for analysis because of considerable baseline variation among glomeruli. P values < 0.05 were considered significant. Data are given as mean ± SEM.

Results

The main finding of the present study is that single glomerular renin release was inversely related to perfusion pressure in every experiment. Correspondingly, in each of the HML and LMH protocols, secretion rates at 55 mm Hg were significantly lower than at 25 mm Hg. Secretion rate at 40 mm Hg was significantly lower than at 25 mm Hg in the LMH protocol. Mean values in the HML and LMH protocols were remarkably similar (Fig. 2A). In contrast, perfusion rate exhibited a linear rise with perfusion pressure (Fig. 2B). Overall perfusion resistance significantly changed with perfusion pressure: median values at 25, 40 and 55 mm Hg were 168, 125 and 84 mm Hg/μl/min. No significant change of renin release or perfusion rate was observed in six control glomeruli which were perfused at a constant 40 mm Hg pressure for the same time period (log renin release rates were 0.76 ± 0.27, 0.70 ± 0.27 and 0.88 ± 0.23, corresponding to 5.7, 5.0 and 7.6 pg Al/hr/hr in the three collection periods). Perfusion chamber osmolality did not change (283 ± 4, 281 ± 4, 281 ± 3 in the HML protocol, 280 ± 5, 278 ± 4, 282 ± 3 in the LMH protocol, 286 ± 5, 288 ± 2, 289 ± 2 in the controls).

Changes of renin release correlated equally well with changes in perfusion pressure and perfusion rate (Fig. 3). However, the slope of renin versus perfusion pressure was significantly steeper than of renin versus perfusion rate. Thus, the system behaved as if it were more sensitive to changes in pressure than flow.

Measurements of afferent arteriolar diameter were technically possible in eight experiments of the present study (3 from protocol HML, 5 from protocol LMH). Figure 4 demonstrates that increasing perfusion pressure from 25 to 55 mm Hg failed to alter outer afferent arteriolar diameter (24.6 ± 1.2 vs. 25.1 ± 1.3 μ (SEM), ns). There was, however, a slight increase of inner arteriolar diameter, from 14.6 ± 1.3 to 16.7 ± 1.4 μ ($P < 0.05$). It should be noted that inner arteriolar diameter was measured between the two inner endothelial surfaces and would thus be expected to increase if the endothelial cell layer was flattened or pressed to the muscle layer by increasing perfusion pressure.

Changes of renin release did not correlate with either radial, tangential or axial stretch (Fig. 5). Furthermore, there was no correlation with S, the sum of the three stretch components ($r = 0.15$) and with changes of inner diameter ($r = -0.37$). The correlation between renin release and changes of shear rate, though statistically significant ($r = -0.59$, $P < 0.02$), was inferior to the correlation with perfusion rate or pressure in the same experiments.

Papaverin 10^{-5} M caused a distinct increase in afferent arteriolar diameter between 0 and 70 mm Hg (Fig. 6A), demonstrating the presence of active, isometric muscle tension.

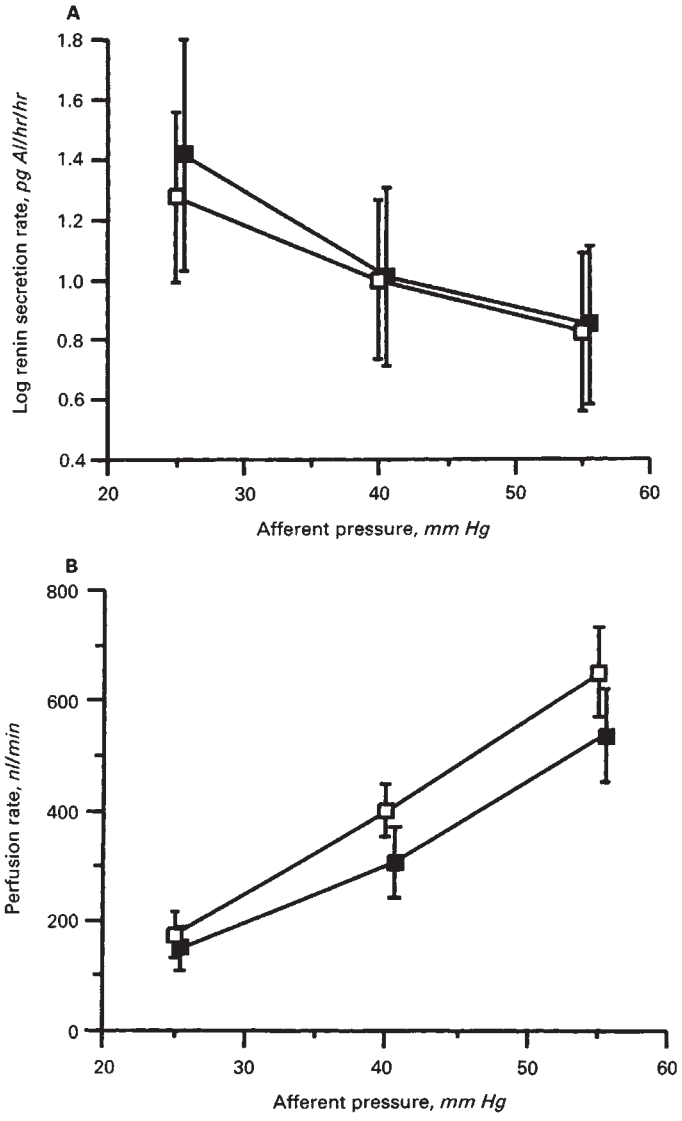

Fig. 2. *Pressure dependence on renin release and perfusion rate in single perfused glomeruli.* Open squares: protocol HML, closed squares: protocol LMH (detailed in **Methods**). **A.** Log renin release vs. perfusion pressure. **B.** Perfusion rate vs. perfusion pressure.

Control diameters in this figure (continuous lines) were conspicuously similar to the ones in Figure 4: from 25 to 55 mm Hg, the inner diameter increased by approximately 2 μ, whereas the outer diameter remained constant. Analysis of active and passive wall tension revealed the active component to prevail in the greater part of the range of the present study (Fig. 6B).

Discussion

Pressure dependence of renin release is a pathophysiological concept of considerable importance. Although the increment in renin release after arterial hypotension or renal artery constriction is in part mediated by the macula densa and neural mechanisms, there is convincing evidence from studies in intact animals [6, 7] and isolated perfused kidneys [16] to support the existence of an intrarenal mechanism which senses either transmural pressure or flow in the renal vasculature. These studies, however, were indirect, had to rely on invasive maneuvers such as renal denervation or hydronephrosis, and did not

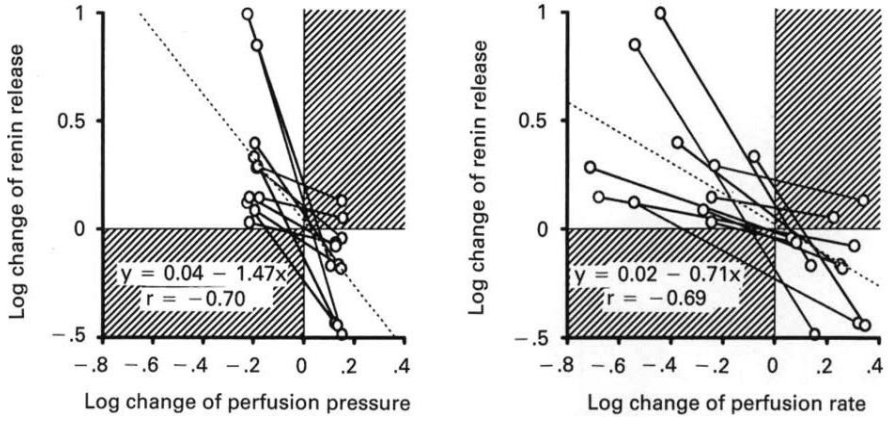

Fig. 3. *Correlation of changes in renin release with changes of perfusion pressure and perfusion rate in groups HML and LMH.* Data are log changes relative to perfusion at 40 mm Hg. Both correlations were highly significant ($P < 0.001$). The slope of renin vs. pressure (-1.47 ± 0.33) was significantly steeper than of renin vs. perfusion rate (-0.71 ± 0.17).

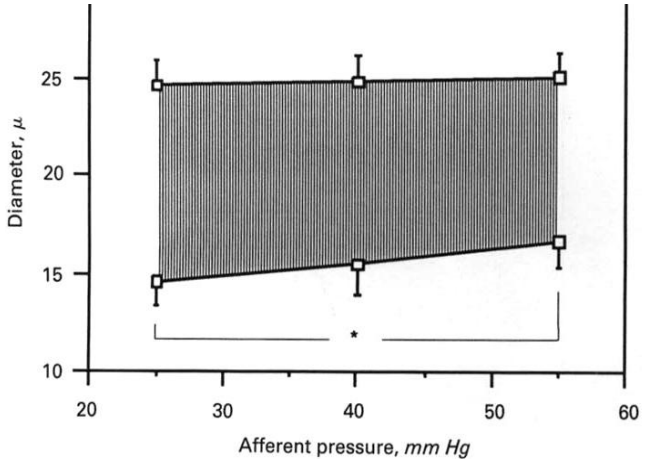

Fig. 4. *Pressure dependence of inner and outer afferent arteriolar diameter in 8 glomeruli of the HML* (N = 3) *and LMH* (N = 5) *protocols (mean ± SEM).* The increase of inner arteriolar diameter was statistically significant ($P < 0.05$).

permit to exactly identify the location of the putative "baroceptor" in the renal vasculature. The present data demonstrate for the first time an inverse relation of renin release and perfusion pressure in individual afferent-glomerular units. This is direct evidence for a pressure sensitive mechanism, that is, a "renin baroceptor" at the single nephron level.

The most likely location of the baroceptor is the terminal part of the afferent arteriole, site of the synthesis and storage of renin. In theory, the receptor could also be contained within the glomerulus or the efferent arteriole, but upstream signal transduction from these sites would be difficult to conceive. Within the afferent arteriole, either the endothelial or the vascular smooth muscle/renin secreting layer could be the site of the sensor element.

Unfortunately, the physiological stimulus of this mechanism can not be determined from the present experiments. Either pressure or flow could be the stimulus, since the experimental design did not permit one to vary independently from the other. Relatively smaller changes of pressure than of flow were associated with the observed changes in renin release, which could indicate a preferential sensitivity of the mechanism to pressure changes (Fig. 3). However, changes of both parameters correlated equally well with changes in renin release.

The sensor element in a flow sensing baroceptor would most likely be the endothelial cells of the afferent arteriole. Cultured endothelial cells are known to release EDRF (nitric oxide) [17], when exposed to shear stress, and some recent studies suggest that EDRF is capable of inhibiting renin release [18]. This concept has the theoretical advantage of distinguishing separate sensor and effector cells. A flow sensing baroceptor would also explain why Salomonsson, Skøtt and Persson [14] failed to find pressure dependence of renin release from rabbit arterioles in a static perfusion system (in these experiments, the glomerulus was sucked into a holding pipette to stop the flow).

In a pressure sensing baroceptor, either the endothelial or the smooth muscle cells would be candidates for the sensor. Since stretch-activated cation channels have been demonstrated in cultured endothelial cells [19], stretching of the endothelial cells could, theoretically, stimulate them to release a renin-inhibiting autacoid. However, despite the pressure associated increase of mean inner diameter in the present experiments, changes of inner diameter did not correlate with changes in renin release.

A pressure sensing baroceptor, in which both sensor and effector cells are assumed to reside in the arteriolar smooth muscle layer has been the previously dominant concept. How pressure would act upon the renin secreting cells has, however, been a matter of discussion. In 1976, Fray presented an elaborate concept termed "stretch receptor mechanism for renin release" [11]. The present data clearly disprove both the basic assumption and the consequences of this "stretch receptor" hypothesis.

Fray tried to determine whether the pressure induced alterations in renin release could be explained by alterations of the stretch state of the renin releasing smooth muscle cells. Stretch is defined as a relative change of length, $\epsilon = \frac{\Delta L}{L}$. Stretch in the wall of the afferent arteriole can occur in radial, tangential and axial direction. Fray, therefore, used a composite stretch term, "volume strain", which was defined as the sum of these three stretch components: $S = \epsilon_r + \epsilon_\Theta + \epsilon_Z$. Since these components could not be measured at the time, Fray assumed that the cells of the afferent arteriolar wall passively obeyed Hooke's law which states that the stretch (ϵ) of an object is proportional to

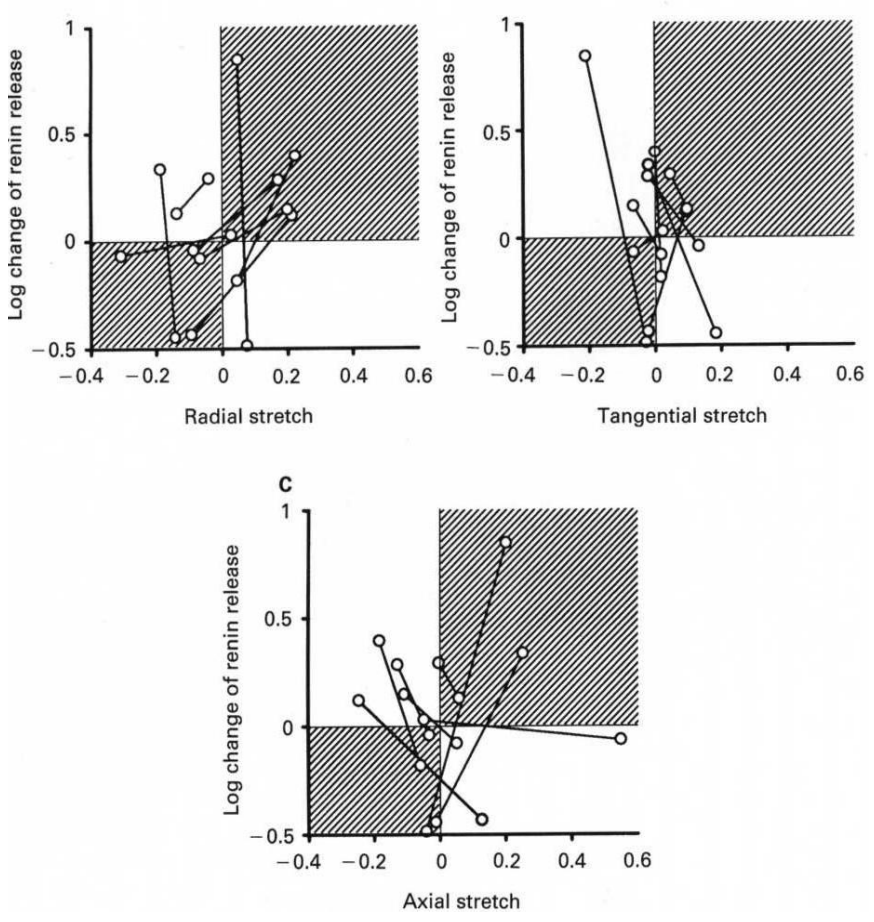

Fig. 5. *Missing correlation of renin release with afferent arteriolar stretch.* Data are from the same 8 experiments as Figure 4. The "stretch" receptor hypothesis would predict that increased stretch was associated with decreased renin release, that is, all points should be in the non-hatched areas (cf. Fig. 3). This is clearly not the case.

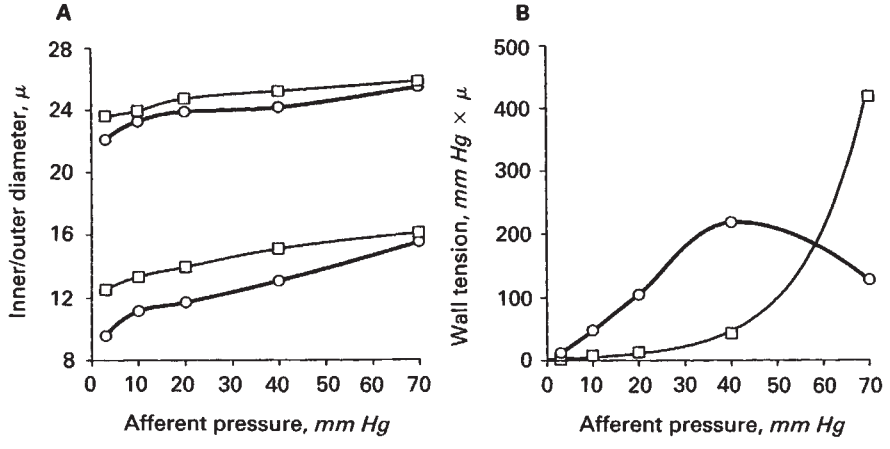

Fig. 6. *Development of isometric tension in the arteriole of isolated glomeruli perfused at increasing pressure, in the presence and absence of papaverin 10^{-5} M.* **A.** Mean inner and outer diameter of two afferent arterioles perfused at increasing pressure (**Methods**). Compared to control (○) papaverin causes a distinct dilatation (□) at pressures below 70 mm Hg. **B.** Calculated mean active (○) and passive (□) components of wall tension in the same two experiments (**Methods**).

the acting stress, that is to pressure. Based on this assumption, he calculated volume strain (= stretch) as a function of radii and pressures in the afferent arteriole [11, 15]:

$$S = K\left[\frac{r_i^2P_i - r_o^2P_o}{r_o^2 - r_i^2}\right] = \left[\frac{(r_i/r_o)^2P_i - P_o}{1 - (r_i/r_o)^2}\right]$$

where r_i and r_o are the inner and outer arteriolar radii, P_i and P_o the internal and external pressure, respectively, and K is a constant.

Assuming, furthermore, that renin release was reciprocal to volume strain S and using physiological values for radii and pressures, Fray derived the following equation [11]:

$$\Delta \text{ renin release} = -0.0003\,\Delta P_i + 0.00054\,\Delta P_o - 0.10086\,\Delta(r_i/r_o)$$

which implied that renin release was over 300 times more sensitive to changes in the (r_i/r_o) ratio than to pressure.

However, the assumption that afferent arteriolar stretch obeys Hooke's law is clearly invalid for smooth muscle cells of viable afferent arterioles. Figure 6 demonstrates that an isolated afferent arteriole perfused with increasing pressure develops

active, isometric tension and thereby changes the proportionality between stretch and stress.

Still, the present data would, at first glance, appear consistent with Fray's formula for renin release: Since r_i increased with pressure and r_o remained constant, r_i/r_o increased as well. However, direct measurements of the individual stretch components (Fig. 5) in the present experiments did not reveal any association between changes in renin release and stretch. The same was true for the sum of the three stretch components. Thus the concept of the renin baroceptor as a passive sensor of wall stretch appears quite unlikely.

However, other possibilities to sense pressure clearly exist. Figure 6 demonstrates that the afferent arteriolar wall develops active, isometric tension with increasing perfusion pressure. Similar observations have previously been reported from studies with both isolated rabbit and rat arterioles [20, 21]. It is reasonable to assume that this myogenic, isometric contraction might be associated with an increase of intracellular calcium concentration, which is known to inhibit renin release. In a more recent analysis, Fray, Lush and Park [15] pointed out that arteriolar stretching could be a transient phenomenon due to an increase of intravascular pressure, since the opening of stretch-dependent calcium channels would ultimately reverse the stretch via vascular contraction. The present data are not inconsistent with such a concept. The existence of stretch-dependent calcium channels in juxtaglomerular cells, however, remains to be demonstrated.

It may be appropriate to question whether the terminal segment of the afferent arteriole is physiologically suited to perceive changes in renal perfusion pressure. Data obtained with the in vivo perfused hydronephrotic rat kidney [22] or the in vitro blood-perfused juxtamedullary nephron preparation [23] would indicate that myogenic autoregulation upstream from the afferent arteriole is so effective that pressure changes hardly get transmitted to this segment, as long as systemic pressure is within a normal range. However, once renal perfusion pressure drops below 80 to 90 mm Hg, glomerular (and terminal afferent) pressure clearly starts to decrease [24]. This is in fair agreement with baroceptor data obtained in intact animals which demonstrate stable renin secretion from 90 to 160 mm Hg [8]. The parameter regulated by the renin baroceptor mechanism, would then appear to be glomerular entrance pressure. In other words, the renin baroceptor is a mechanism which begins to operate once the autoregulation of glomerular filtration pressure begins to fail.

In summary, we have demonstrated that a renin baroceptor mechanism exists at the single nephron level, in the terminal afferent arteriole. As changes in renin release were not associated with changes in arteriolar wall stretch, this baroceptor does not appear to be a stretch receptor. The data at this point are not complete enough to distinguish between a baroceptor which senses flow, for example, via shear stress receptors in the endothelium, or pressure, such as, via coupling to the myogenic pressure response of the afferent arteriole. These questions remain open to further investigation.

Acknowledgments

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