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Research Article

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ABSTRACT The present experiments were performed to quantify the effect of changes in distal tubular sodium delivery on glomerular flow dynamics both below and above the normal physiologic range. Glomerular capillary pressure as derived from the tubular stop flow pressure was assessed while the loop of Henle of the same nephron was perfused with varying flow rates. During Ringer perfusion no change of glomerular capillary pressure was observed when flow was increased from 0 to 13 nl/min. Further increasing flow to 27 nl/min was associated with a reduction of glomerular hydrostatic pressure by an average of 7.0 ± 4.4 cm H₂O (\pm SD). During perfusion at a rate of 43 nl/min glomerular pressure was decreased by a mean of 10.5 ± 4.0 cm H₂O. Changing the flow rate in small steps revealed that a significant reduction of capillary pressure was found when increasing the flow rate from 13 to 21 nl/min and that the maximum response was reached at 32 nl/min. No effect of perfusion rate changes on glomerular capillary pressure was observed when 300 mM mannitol was used as perfusion fluid. These results imply that a nonlinear relationship exists between end-proximal flow rate and glomerular capillary pressure. It is suggested that during deviations of distal sodium delivery into a positive direction filtration rate is intrarenally regulated probably by prevalence of afferent arteriolar constriction. During reductions of distal sodium load intrarenal regulation is either abolished or it involves proportionate resistance changes of both afferent and efferent arterioles.

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INTRODUCTION

The mechanisms of regulation of nephron filtration rate (NGFR)¹ in different states of body salt balance and during variations of arterial blood pressure are not understood in detail. Experimental evidence indicates that NGFR is in part intrarenally controlled by a tubulovascular feedback system. Thureau and Schnermann (20) and Schnermann et al. (18) have proposed that variations of sodium delivery to the macula densa region of the nephron initiate a change in vasoconstrictor tone and glomerular capillary pressure (GCP) which leads to inverse variations of NGFR. However, this concept was questioned by reports that the observed load-dependent change of NGFR could not be reproduced (10, 16) and that reduction of distal sodium delivery to zero did not measurably alter GCP (2). Integration of these results into a valid feedback concept may be possible by an assessment of the quantitative relationship between distal sodium delivery and GCP. We therefore determined GCP by using the stop-flow pressure technique of Gertz, Mangos, Braun, and Pagel (8) during variations of loop of Henle perfusion rates both below and above normal. Our results show that GCP falls when loops of Henle are perfused with Ringer's solution at flow rates greater than 13 nl/min, while little or no effect is observed at lower flow rates.

METHODS

Experiments were carried out on male Sprague-Dawley rats (200–300 g body weight) during Inactin anesthesia (110

¹Abbreviations used in this paper: COP, colloid osmotic pressure; COP_e, oncotic pressure of efferent arteriolar blood; GCP, glomerular capillary pressure; NGFR, nephron glomerular filtration rate; SFP, stop-flow pressure; TP, tubular pressure.

mg/kg body weight) (Promonta, Hamburg, West Germany). Saline was infused intravenously at a rate of 0.4–0.5 ml/h·100 g body weight. After tracheostomy the left kidney was exposed for micropuncture, placed in a Lucite cup, and covered with mineral oil of 37°C. Body temperature was regulated with a servo-controlled heating pad and carotid artery pressure was continuously recorded on a compensation recorder via a Statham pressure transducer (Statham Instruments, Inc., Oxnard, Calif.).

Using a Leitz double-headed stereomicroscope (E. Leitz, Inc., Rockleigh, N. J.) micropuncture experiments were performed by two operators according to the following protocol. An 8 μ m pipette connected to the microperfusion pump was first inserted into a proximal tubular segment. When the downstream movement of the injected colored fluid indicated an early proximal puncture site, the cannula was withdrawn and introduced into the last superficial segment, the perfusion rate being 13 nl/min. A 15 μ m pipette containing silicone oil with a viscosity of 30,000 cSt (Kebo, AB, Stockholm, Sweden) was then inserted at the puncture site used previously for identification and an oil block was injected. Care was taken to cover the injection site and keep the proximal end of the oil column in a clearly visible position. Due to the high viscosity of the oil and the sluggish downstream movement only little oil had to be replaced to keep this oil meniscus constant; therefore, tubules could be studied for periods up to 20 min. The experiment was terminated when the oil had reached the perfusion cannula. Increasing the perfusion rate up to 50 nl/min did not lead to upstream movement of the oil block. After oil block insertion a pressure recording pipette of 3–5 μ m was introduced into the upstream portion of the segment containing the proximal oil meniscus or into another upstream segment which could be identified by the widened diameter. The pressure recording system was a servo-nulling system of the type described by Wiederhielm, Woodbury, Kirk, and Rushmer (22) and other authors (2, 3, 7) as manufactured by Instrumentation for Physiology and Medicine, San Diego, Calif. The micropuncture pipettes used for pressure recording were filled with a 0.5 M NaCl solution stained with Evans blue. Zero pressure was set with the pipette tip in the thin layer of fluid on the kidney surface.

Three different perfusion solutions were used: (a) Ringer consisting of 136 mM NaCl, 4 mM NaHCO₃, 4 mM KCl, 2 mM CaCl₂, 1 mM MgCl₂, 7 mM urea, and 0.1 g/100 ml lissamine green; (b) 300 mM mannitol, and 0.1 g/100 ml lissamine green; (c) 70 mM Na₂SO₄, 2 mM K₂SO₄, 80 mM mannitol, and 0.1 g/100 ml lissamine green. The sequence of flow rate change was usually: 13 nl/min, 43 nl/min, 13 nl/min, 27 nl/min, 13 nl/min, 0 nl/min. In several experiments the effect of zero distal perfusion on stop-flow pressure (SFP) was studied before introducing the perfusion pipette. Perfusion rate was not changed before a constant pressure level was reached. A feedback regulated microperfusion pump of high precision was used for the microperfusion. The reproducibility of the pump system was verified by repeated calibration both in vivo and in vitro.

RESULTS

In five experiments intratubular pressure was simultaneously measured in identical tubular segments with both the servo-nulling system and the Landis technique. The following differences were noted (“Landis pressure” minus “servo-null pressure” in centimeters H₂O):

–0.3, –0.1, +0.5, ± 0 , ± 0 . Mean tubular pressure equalled 18.3 cm H₂O ± 1.17 SD using the Landis technique and 18.28 cm H₂O ± 1.29 SD using the servo-null technique.

To study the effect of changes in oil block position on SFP the oil was deliberately shifted into an upstream direction with maximal manual force applied to the syringe barrel. The displacement of the oil thus produced was about 10–20 times the normally occurring fluctuations. However, the high viscosity of the oil permitted only a rather slow motion so that SFP never increased by more than 1 cm H₂O, a pressure which rapidly fell to the original value when the block was kept at its new position.

The changes in SFP during perfusion with Ringer's solution at varying flow rates are listed in Table I. During zero distal perfusion SFP averaged 53.3 \pm 5.2 cm H₂O (\pm SD). When perfusion was increased to 13 nl/min—corresponding roughly to the normal end-proximal flow rate—no significant change of GCP was noted.² However, during perfusion at a rate of 27 nl/min GCP was diminished by an average of 7.0 \pm 4.4 cm H₂O ($P < 0.001$). A further, but relatively smaller fall in GCP by 10.5 \pm 4.0 cm H₂O was observed when perfusion rate was elevated to 43 nl/min. The sequence of perfusion rate changes did not influence the effect of GCP. GCP decrease was observed in every single tubule at both 27 and 43 nl/min although the magnitude of the pressure change varied considerably. A representative recording is demonstrated in Fig. 1. Shortly after increasing the flow rate SFP falls rapidly to the new level. The time lag between the change of perfusion rate and the reaction onset corresponds approximately to the loop passage time (17). Usually the return to the original SFP occurred slower than the pressure fall. In some experiments where perfusion rate was kept constant at a high level for periods up to 10 min no indication of an adaptation of the GCP response was noted. During zero or low flow rates SFP appeared to change parallel to spontaneous fluctuations of arterial blood pressure while at higher flows such pressure changes did not affect SFP.

Table II summarizes 12 experiments where the Ringer perfusion rate was altered in small steps to permit determination of the reaction threshold. Related to an average SFP of 54.4 \pm 6.8 cm H₂O GCP fell by 0.46 \pm 1.08 at a rate of 13 nl/min, and by 2.7 \pm 2.3 cm H₂O at a

² Since GCP equals the sum of SFP and colloid osmotic pressure (COP) and since glomerular capillary COP is unchanged during application of the stop-flow technique, any change in SFP directly reflects changes in GCP. To obtain GCP in absolute terms one has to augment SFP by the oncotic pressure of 6.4 g/100 ml of protein which is the protein concentration in the pooled plasma of 21 rats as determined by the Lowry method.

TABLE I
Change of Glomerular Capillary Pressure during Perfusions of
Loops of Henle with Ringer Solution

Exp. no.	Tubule no.	SFP, 0 nl/min <i>cm H₂O</i> †	Δ SFP		
			13 nl/min	27 nl/min	43 nl/min*
1	1	51.5	±0	-11.0	-13.0
	2	53.5	-0.5	-15.0	-19.0
	3	44.5	±0	—	-12.0
	4	53.0	-1.0	-13.5	-8.5
	5	60.0	±0	—	-5.0
2	1	54.5	-0.5	-6.5	-7.0
	2	57.5	±0	-4.0	-7.0
	3	49.0	+0.5	—	-9.5
	4	61.0	+0.5	-6.5	-8.5
	5	48.0	±0	—	-8.0
	6	57.0‡	±0	-8.0	-13.0
	7	55.0‡	±0	-3.5	-8.0
	8	49.0‡	±0	-15.5	-19.5
3	1	50.0	+0.5	-9.5	-11.5
	2	52.0	±0	-1.5	-10.5
	3	43.5	-0.5	-10.0	-11.0
	4	55.5	±0	-0.5	-7.0
	5	58.0	-0.5	-6.0	-7.5
	6	54.0	±0	-1.0	-8.0
	7	56.5	-0.5	-6.5	-12.0
	8	48.0	+0.5	-5.0	-12.0
4	1	56.0	±0	-6.0	-16.0
	2	45.5	-2.0	-10.5	-8.0
	3	64.5	+0.5	-1.0	-5.0
	4	56.0‡	±0	-7.0	-15.5
Mean		53.3	-0.1	-7.0	-10.5
±1 SD		5.2	0.5	4.4	4.0
				(<i>P</i> < 0.001)§	(<i>P</i> < 0.001)§

* The actual sequence of perfusion rate changes is given in the text.

† SFP tended to increase during the observation period; ΔSFP is related to the actual SFP immediately before elevating the perfusion rate.

§ The reference for the significance test is the ΔSFP at a perfusion rate of 13 nl/min.

rate of 21 nl/min. The difference in pressure fall between these groups of perfusions is significant at $p < 0.01$. Virtually the full response of about 10 cm H₂O was obtained when raising the perfusion rate to 32 nl/min. At higher rates of perfusion only small additional effects were noted. The obvious nonlinearity between end-proximal flow rates and GCP change is diagrammatically presented in Fig. 2.

In 13 tubules perfused with the 300 mM mannitol solution no measurable changes of GCP were observed when perfusion rates were increased to 13, 27, and 43 nl/min. SFP in this group averaged 56.3 ± 11.5 cm H₂O, a value not significantly different from those measured in the other groups. A typical example is shown in Fig. 3.

A series of perfusions with the sulfate solution is summarized in Table III. Average SFP was 51 ± 4.7 cm

H₂O. Mean reductions of GCP at perfusion rates of 13, 27, and 43 nl/min were 0.7 ± 0.4 , 1.7 ± 2.3 , and 3.8 ± 2.8 cm H₂O.

DISCUSSION

Earlier studies suggested that NGFR varies inversely with distal tubular sodium load (18, 20). It was proposed that this result was evoked by either afferent or efferent vasomotor activity with subsequent changes of GCP. Recently, however, Blantz, Israelit, Rector, and Seldin (2) published results suggesting that any change in NGFR during acute reductions of distal sodium delivery must be a consequence of an altered glomerular plasma flow at unchanged GCP. The present experiments were designed to quantitatively evaluate flow dependency

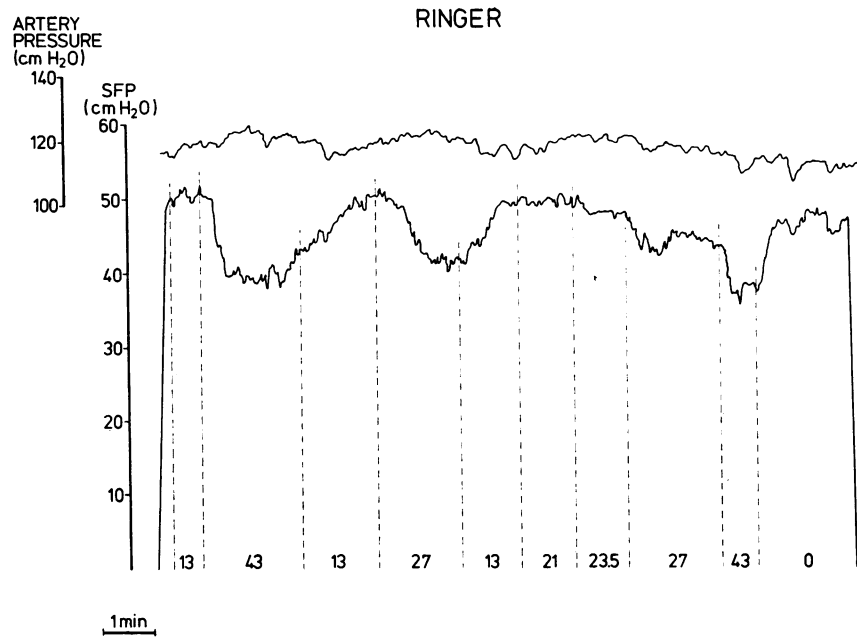


FIGURE 1 Effect of Ringer perfusion of the loop of Henle on SFP in the same nephron. Perfusion rates (nanoliters per minute) are given by bottom numbers. The upper tracing is the mean arterial blood pressure.

of GCP during both reduction and elevation of distal sodium delivery.

GCP has been indirectly determined by Gertz et al. (8) from early proximal tubular SFP and systemic COP. That this method is in principle sound was re-

cently demonstrated by comparison with GCP's measured by direct micropuncture of single glomerular loops (1, 2). It is to be noted that our SFP's of 51-54.4 cm H₂O are somewhat higher than some values previously reported. Andreucci, Herrera-Acosta, Rector, and Seldin

TABLE II
Change of Glomerular Capillary Pressure following Stepwise Changes of Ringer Perfusion Rate

Tubule no.	SFP, 0 nl/min <i>cm H₂O</i>	Δ SFP					
		13 nl/min	21 nl/min	27 nl/min	32 nl/min	36 nl/min	43 nl/min*
1	52.5	-0.5	—	-2.0	-7.5	-9.0	-11.0
2	42.5	+0.5	-2.5	-9.5	—	-11.5	-11.5
3	57.5	-1.0	-3.5	-6.5	—	-6.5	-8.5
4	48.5	± 0	-1.5	-5.0	—	-12.0	-12.0
5	59.0	-1.0	-1.0	-11.5	—	-11.5	-11.5
6	46.0	± 0	-6.5	-9.0	—	—	-8.5
7	57.0	-0.5	-6.0	-9.5	-8.5	-8.0	-7.5
8	50.0	± 0	± 0	-8.0	—	-11.5	-12.5
9	56.5	± 0.5	-1.0	-9.0	-11.5	-16.0	-17.0
10	67.0	± 0	± 0	-8.0	-10.0	-10.0	-10.0
11	60.0	± 0	-2.5	-4.5	-9.0	-9.0	-9.0
12	56.5	-3.5	-5.0	-5.5	-8.0	-9.0	-9.0
Mean	54.4	-0.46	-2.7	-7.3	-9.1	-10.4	-10.7
± 1 SD	6.8	1.08	2.3	2.7	1.5	2.5	2.6
			($P < 0.01$) \ddagger		($P < 0.001$) \ddagger		

* Perfusion rates were changed in a random sequence.

\ddagger The reference for the significance test is the Δ SFP at a perfusion rate of 13 nl/min.

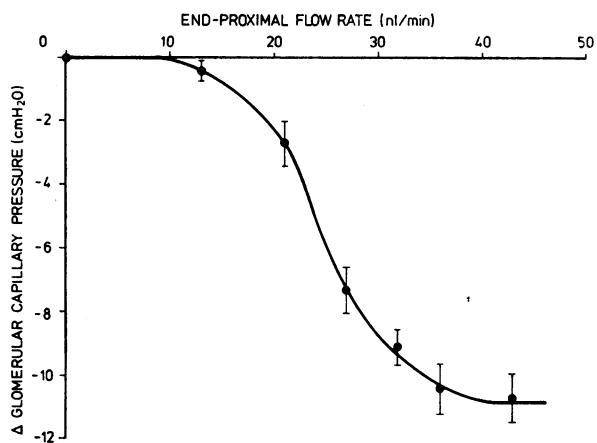


FIGURE 2 Relationship between the change of glomerular capillary pressure (± 1 SE) and loop of Henle perfusion rate—graphical presentation of the data summarized in Table II.

(1) found SFP's of between 42.6 and 44.8 cm H₂O, Blantz et al. of between 41 and 47 cm H₂O (2), Brenner, Troy, and Daugharty of about 41 cm H₂O (3) and Hayslett, Domoto, Kashgarian, and Epstein (11) of 39.5 cm H₂O. On the other hand, Gertz, Brandis, Braunschubert, and Boylan (9) reported SFP's of between 61.5 and 74.5 cm H₂O, and Koch, Dume, Krause, and Ochwad (13) and Krause et al. (14) of around 72 cm H₂O. These higher values have been ascribed (1) to the use of the Landis technique (15) where leakage of fluid into the blocked segment may occur during color front compensation. As a sole explanation this argument seems unsatisfactory in view of the fact that careful application of the Landis technique provides data comparable to those obtained with other methods (1). A systematic er-

ror of servo-null pressure recording in our experiments is virtually excluded by the identity of "servo-null" and "Landis" pressures in identical tubular segments. Thus, it appears more likely that GCP may indeed vary by 10 cm H₂O or more in different rat strains or as a consequence of differences in experimental and/or preexperimental treatment. One should not forget that the directly measured GCP's of Brenner et al. (3) and Blantz et al. (2) are based on measurements in a mutant Wistar strain (the so-called Munich strain) which in our hands appears to behave especially delicately under surgical stress. It is suggestive that Brenner et al. (3) measured a NGFR of 27.5 nl/min in these rats whereas in Sprague-Dawley rats NGFR's from this laboratory are usually around or above 40 nl/min (4, 5, 7). In general, it would not be surprising if variations of GCP were related in some way to the considerable variations of NGFR (for reference see 23). It has been demonstrated (3) that filtration equilibrium, i.e., equality of GCP and the sum of oncotic pressure of efferent arteriolar blood (COP_e) and tubular pressure (TP), is reached within the glomerular capillary bed. With our GCP of about 80 cm H₂O and a TP of 18 cm H₂O equilibrium would be achieved by a COP_e of 62 cm H₂O. This corresponds to a protein concentration of 10 g/100 ml or a filtration fraction of 0.36 (3-5). Thus, no forcible argument appears to invalidate the magnitude of SFP's found in the present experiments. In addition, identity of SFP-derived GCP with true intraglomerular pressure is not a necessary requirement in our studies since all conclusions are based on relative pressure changes.

The main technical problem arises from the possibility that increased flow rates may affect SFP by an increased back pressure or by mechanical compression of the glo-

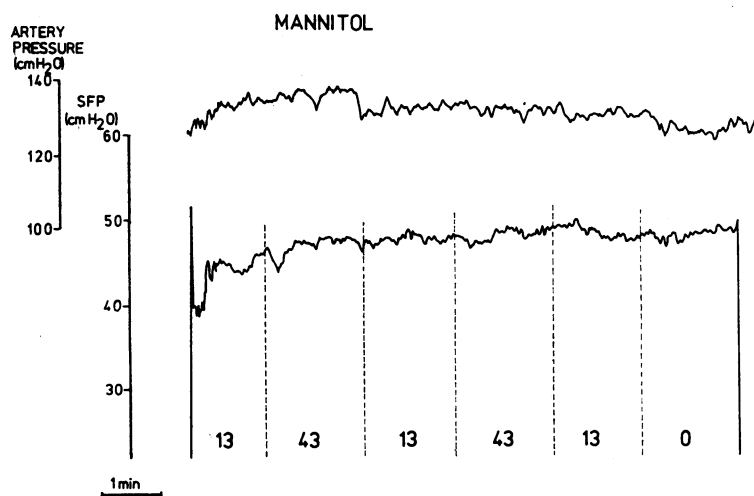


FIGURE 3 Effect of mannitol perfusion of the loop of Henle on SFP in the same nephron. Perfusion rates (nanoliters per minute) are given by bottom numbers. The upper tracing is a recording of mean arterial blood pressure.

TABLE III

Effect of Na₂SO₄ Perfusions on Glomerular Capillary Pressures

Exp. no.	Tubule no.	SFP, 0 nl/min	ΔSFP		
			13 nl/min	27 nl/min	43 nl/min*
		<i>cm H₂O</i>	<i>cm H₂O</i>		
1	1	52.0	±0	-6.0	-7.0
	2	44.0	+0.5	—	-5.5
	3	45.0	±0	—	-4.0
	4	60.0	±0	—	±0
2	1	53.5	+0.5	±0	-2.5
	2	52.5	-0.5	-1.0	-4.0
	3	59.5	-1.0	-1.0	-2.5
	4	52.0	±0	±0	-0.5
	5	46.5	-0.5	—	-4.0
	6	50.0	±0	±0	-0.5
3	1	48.0	-0.5	—	-4.0
	2	48.5	±0	-5.0	-7.5
	3	52.0	±0	±0	-2.0
	4	51.0	+0.5	-2.0	-9.5
Mean		51.0	-0.3	-1.7	-3.8
±1 SD		4.7	0.3	2.3	2.8
				(<i>P</i> < 0.02)‡	(<i>P</i> < 0.001)‡

* The actual sequence of perfusion rate changes is given in the text.

‡ The difference to the ΔSFP at a perfusion rate of 13 nl/min was tested.

merular vessels. Transmission of pressure across the high viscosity oil was excluded by the very small and transient SFP changes after deliberate shifts in oil block position which were more than 10 times the normally occurring fluctuations. It is to be stressed that these fluctuations in the standard experiment were kept minimal by continuous visual control and careful adjustment of the rate of oil injection and that it is our notion that any pressure changes exerted to the distal end of the block do not affect the SFP if they do not induce shifts of the proximal end of the oil block in either direction. Furthermore, increased flow rates during Ringer perfusions which are known to create increased back pressure (17) were associated with decreased SFP. Mechanical effects on the glomerular vessels can be rejected because of the absence of any reaction during mannitol perfusions performed according to an identical protocol. In this situation, a given perfusion rate is associated with even higher rates of loop and distal tubular flow due to net water addition (18), as compared with Ringer-perfused tubules.

The results thus permit to draw several conclusions concerning existence and operation of tubuloglomerular feedback in the single nephron unit. It appears to be beyond doubt that when elevating Ringer perfusion rate from normal to supranormal, a flow-dependent signal is sensed at distal tubular sites which elicits changes in glomerular arteriolar tone. The fall of GCP under these

conditions provides one hemodynamic explanation for our earlier observations (18) that increased distal sodium delivery leads to a reduction of NGFR. That GCP and NGFR are interrelated is also supported by the absence of an effect of mannitol perfusions on both GCP and NGFR (18). This does not preclude the possibility that a reduction of plasma flow might at the same time affect the rate of ultrafiltration if indeed the hemodynamic alterations are accompanied by diminished glomerular plasma flow. Our studies do not contribute to clarifying the exact nature of the input signal and of the mediating mechanism, but support the concept that the amount of sodium delivered to the macula densa site initiates a regulatory process which induces changes in vasomotor tone by mediation of the renin-angiotensin system (19).

The most striking result of this study is the finding that nonlinearity of GCP and loop perfusion rate is a characteristic of tubuloglomerular feedback (Fig. 2). A similar nonlinearity exists when GCP is related to distal sodium load or sodium concentration as previously determined (18). A significant change in GCP was discovered when the flow rate was elevated from 13 to 21 nl/min. Although free flow end-proximal flow rates were not assessed in these rats it is clear that this range corresponds closely to the normal end-proximal flow rates during hydropenia as measured in numerous studies (for reference see 23). Thus, a perceptible response

of GCP is established when end-proximal flow rates just tend to exceed physiological values. The maximum fall in GCP was reached at a perfusion rate of 32 nl/min. In accordance with the result of Blantz et al. (2) no change of GCP was discovered when flow rates were decreased below normal. Identical results were recently reported by Hierholzer, Butz, Mueller-Suur, and Lichtenstein (12). The reasons for the asymmetric behavior of GCP are not clear and need further investigative effort. It appears that the mechanisms of regulation of GCP are different for positive or negative deviations from normal of the sensed parameter. During flow elevation a predominant vasomotion of either afferent or efferent arterioles induces a reduction of GCP. Afferent vasoconstriction seems more plausible because the concomitant fall in glomerular plasma flow would potentiate the effect of the fall in GCP. If the renin-angiotensin system is a constituent of the mediating mechanism, an afferent site of action is indeed suggested by the result of Thurau and co-workers (21) that injection of isotonic NaCl solutions into single distal tubular segments leads to an activation of renin within the juxtaglomerular complex of the same nephron unit. During flow reduction, on the other hand, glomerular arteriolar tone is either unchanged or afferent and efferent resistance decreases proportionately with a concomitant increase of plasma flow. Determination of NGFR within the low perfusion range would permit to differentiate between these two possible effects. In the former case, NGFR should remain constant, while in the latter NGFR should increase as a consequence of increased glomerular plasma flow without change of GCP as recently suggested (2, 6). The dependency of NGFR upon perfusion rate as reported by Schnermann et al (18) does not discriminate between these possibilities since in the group of rats on a comparable diet flow rates were seldom varied below 15 nl/min, i.e., below the physiological range.

Until this question is solved we tend to believe that arteriolar tone as governed by tubular signals is set closely to the minimal resistance at normal flow rates. At subnormal flows glomerular filtration dynamics appear to escape intrarenal regulation and systemic influences may be dominant. It is consistent with this concept that during zero or low distal flow rates GCP was observed to change parallel to spontaneous changes in arterial blood pressure. Our results suggest that in a state of normal salt balance GFR is intrarenally controlled whenever systemic influences such as increased blood pressure cause a deviation into positive direction. In contrast, GFR may not be maintained when it tends to fall, as for example during circulatory hypovolemia.

The significance of such biphasic characteristics of intrarenal regulation for salt homeostasis is teleologically immediately apparent. One may anticipate that the sensitivity of GCP to changes in distal sodium delivery varies during different states of body salt balance.

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