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Tubuglomerular feedback control in long-looped nephrons

Topical Minireview

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ABSTRACT

The tubuloglomerular feedback mechanism is highly activated in juxtamedullary nephrons and considered to play a major role in intrarenal regulation of glomerular filtration rate. The vasculature of juxtamedullary nephrons is highly vasoreactive with a high ability for vasodilation. This vasoreactivity is a prerequisite for an important influence of the tubuloglomerular feedback mechanism on the medullary blood flow and its regulation.

The renal medulla is of particular interest since the processes which regulate the osmolar concentration of the extracellular fluid by forming a dilute or concentrated urine primarily occur in this region. The nephrons, which constitute the functional units of the kidney, are not a homogenous group of structures. Instead, those nephrons which originate closer to the cortico-medullary border (juxtamedullary nephrons), as opposed to those which originate closer to the renal surface (superficial nephrons), are the nephrons which primarily are involved in the processes giving rise to a dilute or concentrated urine. The underlying reason for this is that only juxtamedullary nephrons have long loops of Henle that protrude all the way down into the inner medulla and, furthermore, give rise to vessels (vasa recta) which perfuse the medulla. These structures produce and preserve the progressive axial osmotic concentration gradient from the cortico-medullary border to the tip of the papilla. The present paper evaluates some special features of the juxtamedullary nephrons and points out some differences in functional aspects between the two nephron sub-populations.

We (8) have found that the interlobular arteries in rat kidneys behave as resistance vessels. According to calculations made by other authors (9), this is also true for dog kidneys. The blood pressure drop along an interlobular artery amounts in normotensive, normohydrated adult rats to 40-45 mm Hg. This pressure drop is a prerequisite for different haemodynamic

conditions for the outermost (superficial) and innermost (juxtamedullary) nephrons within the cortex. There are indications that the glomerular capillary hydrostatic pressure is about the same in both superficial and juxtamedullary glomeruli (1), which means that the pressure-drop in afferent arterioles of superficial glomeruli is smaller than in those of juxtamedullary glomeruli. In fact, we propose (3) that the superficial afferent arterioles are nearly maximally dilated, while the juxtamedullary afferent arterioles are significantly constricted in normotensive, normohydrated rats. We have also discovered that the tubuloglomerular feedback mechanism (TGF) is normally strongly activated in juxtamedullary nephrons (3).

In young Sprague-Dawley rats the papilla was exposed by excising the ureter and prepared for micropuncture procedures. The single nephron glomerular filtration rate (SNGFR) was measured by quantitative sampling of urine in a loop of Henle with an oil blockade distal to the sampling site. In this situation the urine flow to the macula densa is blocked, resulting in a stop-flow condition. In rats prepared in the same manner the SNGFR was also measured with a modified Hanssen technique (12) where a free-flow condition exists at the macula densa. During stop-flow conditions the SNGFR of juxtamedullary glomeruli amounted to 84.1 ± 8.5 nl·min^{-1} (n=15, mean ± 1SEM) and during free-flow conditions it amounted to 27.7 ± 2.9 nl·min^{-1} (n=7).

In other experiments (3) on the same animal model free-flow and stop-flow pressures were measured in proximal and distal tubules on the renal surface and in the loop of Henle in the papilla. From the values obtained, it was possible to estimate the net driving force for glomerular filtration at the beginning of glomerular capillaries of juxtamedullary nephrons. The results indicate a much higher net driving force during stop-flow (47 mm Hg) than during free-flow conditions (19 mm Hg).

In a third series of experiments (11) it was possible to calculate the urine flow rate during free-flow conditions by measuring the linear velocity of small dye boli injected into the loops of Henle of juxtamedullary nephrons. The passage of the boli and the diameter of the loop lumen were recorded with a video-technique. According to the calculations the urine flow rate during free-flow conditions, 3.9 ± 0.37 nl·min^{-1} (n=8), differs markedly from that during stop-flow conditions, 8.0 ± 0.54 nl·min^{-1} (n=8). All the previously given results firmly support our proposal of a strongly activated TGF in intact juxtamedullary nephrons under normal physiological conditions.

Our present view on the relationship between the SNGFR and the urine flow rate at the macula densa is summarized in Fig. 1. In this figure, points A and D represent the SNGFR values obtained with the micropuncture techniques and points B and E are yielded from the modified Hanssen technique. Point C is derived from values given by Schnermann et al. (10). The value

of F is uncertain, as we have no experimental values available. The points B and E thus represents the operation points for the flow characteristics of normohydrated, normotensive rats. We have thus found a great influence of TGF on the glomerular filtration rate in juxtamedullary nephrons. The question then arises as to whether the blood flow to these nephrons is simultaneously influenced by the TGF. Up to date we have not been able to find a reliable method to determine the blood flow in single juxtamedullary nephrons so it has not been possible to directly study the relation between the TGF and blood flow in these nephrons. We have therefore chosen to examine the medullary blood flow which mirrors the blood flow in the juxtamedullary nephrons since only these nephrons give rise to vessels (vasa recta) which perfuse the medulla.

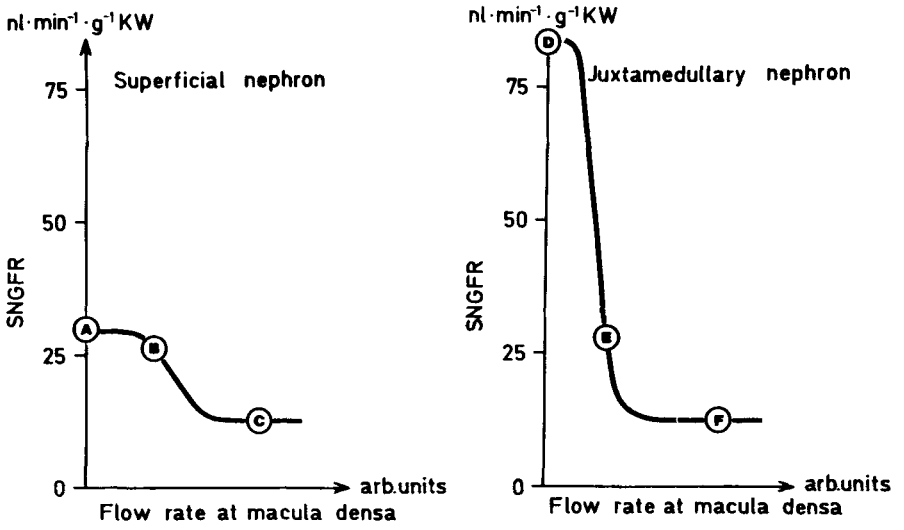

Fig. 1. Schematic influence of urine flow rate at the macula densa on the single nephron glomerular filtration rate (SNGFR). Points A and D represent the values obtained with a blocked urine flow at the macula densa and B and E those with a normal flow. Thus B and E constitute the operation points for the two nephron populations during normal conditions. Points C and F are expected values for high urine flow rates. KW = kidney weight (from Acta Physiol Scand 14: 203-209, 1982).

In one series of experiments in adult Sprague-Dawley rats we estimated the plasma flow in the inner and outer medulla by the extraction of radioactively labelled rubidium (^{86}RbCl). The method has previously been described by Karlberg et al. (7). Simultaneously, we also estimated the SNGFR with a modified Hanssen technique (described by Sjöquist et al. (12)) in three layers of the cortex, namely the outer, the middle and the inner cortex. In order to study the vasoreactivity of the vessels in the juxtamedullary vasculature, we continuously, intravenously infused the calcium entry blocker verapamil (Isoptin, Knoll AG, Germany) or the angiotensin converting enzyme inhibitor captopril (SQ14225, Squibb & Sons, NJ, USA). The results from these experiments are depicted in the left panel of Fig. 2. Neither verapamil (0.6 $mg \cdot h^{-1} \cdot kg^{-1}$ body weight) nor captopril (3 $mg \cdot h^{-1} \cdot kg^{-1}$ body weight) caused any change in the SNGFR of the different nephron populations. Thus no change in the distribution of glomerular filtration rate between different nephron populations were indicated. A redistributing effect of the drugs might, however, have been camouflaged by the drop in arterial blood pressure which for verapamil was from 127 ± 3 mm Hg to 113 ± 4 mm Hg and for captopril from 120 ± 3 mm Hg to 102 ± 5 mm Hg (4). The right panel of Fig. 2 gives the plasma flows in the outer and inner medulla. In both medullary regions verapamil and captopril markedly increased the plasma flow. Captopril-treatment caused an increase of about 90 % in the inner medullary plasma flow, which is in agreement with earlier findings by Eloy et al. (2). An estimation of the cortical plasma flow showed that captopril increased the flow by only 10-20 %. The results thus strongly indicate that the vasculature of the juxtamedullary nephrons is highly vasoreactive and has a high potential to dilate, which must be a prerequisite for the TGF to potently influence the medullary plasma flow.

In another series of experiments we studied the influence of verapamil and captopril on the medullary red cell flux with a video-technique (5, 6) . In young Munich-Wistar rats the papilla was exposed and with a highly sensitive TV-camera we followed the number of fluorescently labeled (FITC) red cells passing vas rectum per minute. The same vessels were investigated before and during infusion of drugs. Figure 3 shows the results thereby obtained. Two different doses of verapamil were used and in both cases the red cell flux increased in the vasa recta; with the lower dose (0.6 $mg \cdot h^{-1} \cdot kg^{-1}$ body weight) the increase was 30 ± 6 % ($p<0.01$) and with the higher dose (2.4 $mg \cdot h^{-1} \cdot kg^{-1}$ body weight) the corresponding value was 39 ± 7 % ($p<0.01$). In the animals treated with captopril (3 $mg \cdot h^{-1} \cdot kg^{-1}$ body weight) the red cell flux increased by 40 ± 4 % ($p>0.01$). These results confirm our theory of a high vasoreactivity in the juxtamedullary vasculature.

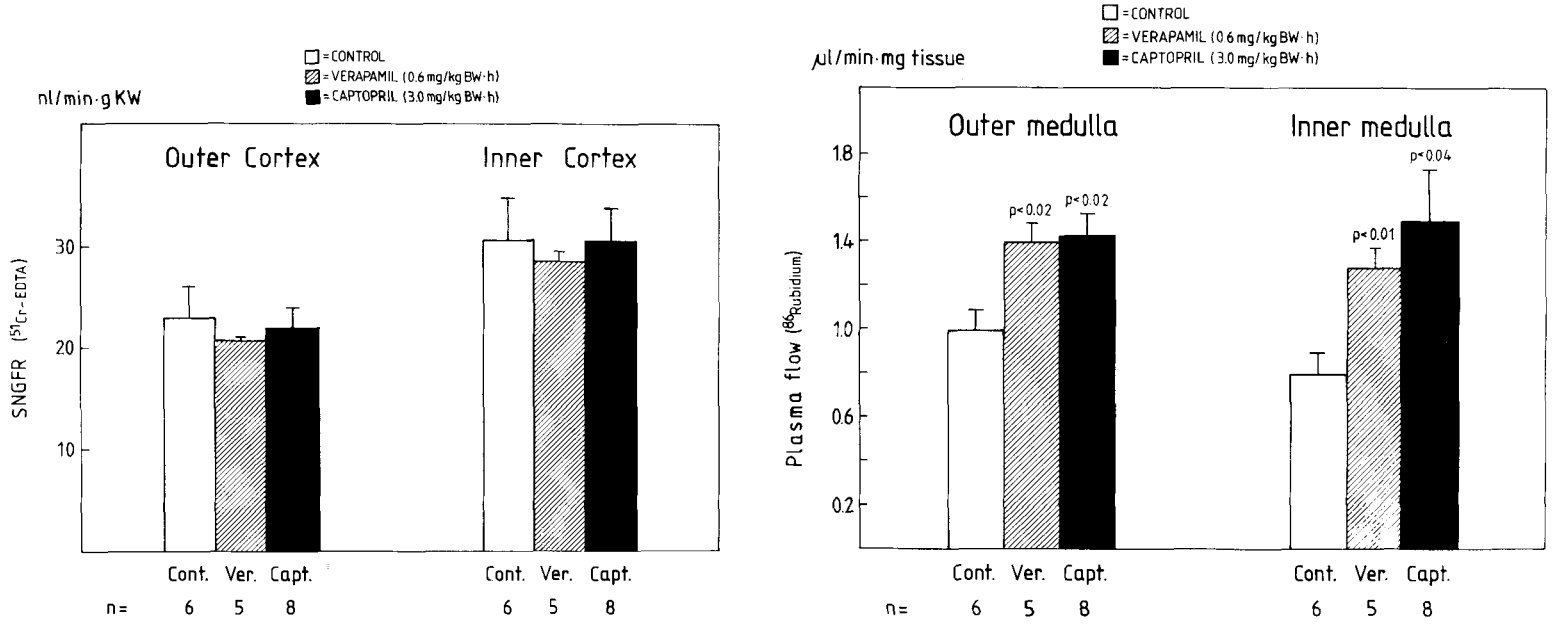

Fig. 2. The SNGFR in the inner and outer cortex (left panel) and plasma flow rates in outer and inner medulla (right panel) during control conditions and during continuous infusions of verapamil and captopril. KW = kidney weight.

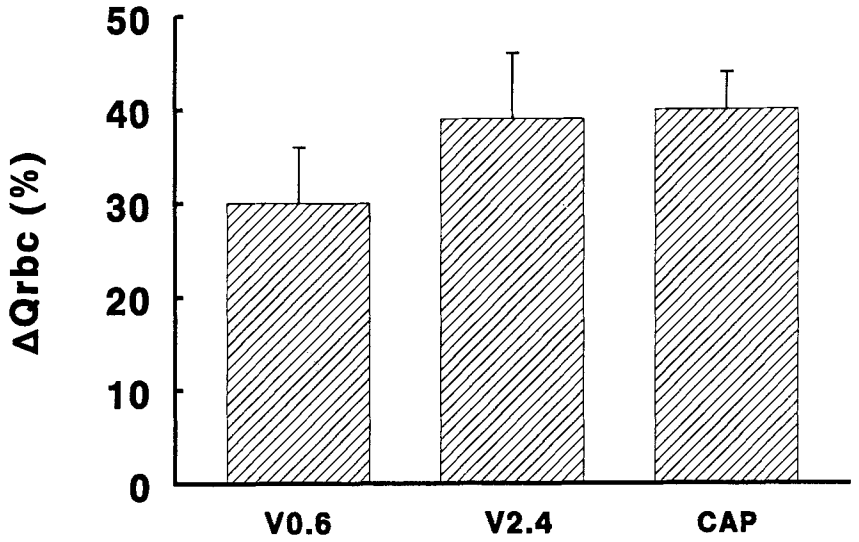

Fig. 3. Percentage increase in red cell flux (ΔQrbc) in the vasa recta after continuous intravenous infusions of verapamil at two different doses (V0.6, 0.6 $mg \cdot h^{-1} \cdot kg^{-1}$; V2.4, 2.4 $mg \cdot h^{-1} \cdot kg^{-1}$) and captopril (CAP, 3.0 $mg \cdot h^{-1} \cdot kg^{-1}$) (values from Am J Physiol 254: F492-F499, 1988 and Acta Physiol Scand 134: 9-15, 1988).

Finally, Table 1 shows the urinary excretion of sodium and potassium and of osmotically active particles during control conditions and during infusions of verapamil and captopril. Both drugs increased the excretion of sodium, potassium and osmotically active particles. A slight increase in urine flow and a distinct rise in the urine osmolality was evident. According to a theoretical concept by Thurau et al (13) the increase in medullary plasma flow induced by the two drugs might have been expected to give a so-called "washing-out" effect of the concentration gradient in the renal medulla and thus decrease the concentrating ability of the kidney. The expected relationship between medullary blood flow and concentrating ability was thus not evident in this study, instead the increase in plasma flow was accompanied by an increase in ion-excretion and in concentrating ability which may be due to a direct effect of the drugs on ion transport in tubular structures. The inhibition of transport mechanisms may counteract and overcome the washing-out effect.

Table 1. Renal excretion data during control conditions and during continuous intravenous infusion of verapamil and captopril.

Excretion parameter	CONTROL	VERAPAMIL	CAPTOPRIL
V (μl/min)	2.12 ± 0.30	2.72 ± 0.86	2.91 ± 0.26*
U_{Na} (mM)	62 ± 11	74 ± 7	88 ± 12
U_K (mM)	134 ± 30	272 ± 29*	231 ± 42*
$U_{Na}V$ (μmol/min)	0.14 ± 0.03	0.21 ± 0.04*	0.24 ± 0.04*
U_KV (μmol/min)	0.31 ± 0.09	0.75 ± 0.14*	0.66 ± 0.15*
Uosm (mOsm)	1316 ± 120	1743 ± 160*	1603 ± 157*
UosmV (μosm/min)	2.72 ± 0.45	4.53 ± 0.65*	4.50 ± 0.56*

Urine flow rate (V), urinary concentration of sodium (U_{Na}) and potassium (U_K), sodium and potassium excretion ($U_{Na}V$, U_KV), urine osmolality (Uosm) and excretion of osmotically active particles (UosmV). * $p<0.05$ vs control.

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REFERENCES

1. Aukland, K., Tonder-Heyeraas, K. & Naess, G.: Capillary pressure in the deep and superficial glomeruli of the rat kidney. Acta Physiol Scand 101: 418-427, 1977.

2. Eloy, L., Grünfeld, J., Bayle, F., Bankir, L., Ramos-Frendo, B. & Trinh-Trang-Tan, M.: Papillary plasma flow in rats. II. Hormonal control. Pflügers Arch 398: 253-258, 1983.

3. Ericson, A.-C., Sjöquist, M. & Ulfendahl, H.R.: Heterogeneity in regulation of glomerular function. Acta Physiol Scand 114: 203-209, 1982.

4. Göransson, A. & Sjöquist, M.: The effect of a converting enzyme inhibitor on autoregulation and intrarenal distribution of glomerular filtration in the rat. Acta Physiol Scand 124: 515-523, 1985.

5. Hansell, P., Sjöquist, M. & Ulfendahl, H.R.: The calcium entry blocker verapamil increases red cell flux in the vasa recta of the exposed renal papilla. Acta Physiol Scand 134: 9-15, 1988.

6. Hansell, P., Sjöquist, M. & Ulfendahl, H.R.: Effect of a converting enzyme inhibitor on vasa recta blood flow in rat kidney. Am J Physiol 254: F492-F499, 1988.

7. Karlberg, L., Källskog, Ö., Öjteg, G. & Wolgast, M.: Renal medullary blood flow studied with the 86-Rb extraction method. Acta Physiol Scand 115: 11-18, 1982.

8. Källskog, Ö., Lindbom, L.O., Ulfendahl, H.R. & Wolgast, M.: Hydrostatic pressures within the vascular structures of the rat kidney. Pflügers Arch 363: 205-210, 1976.

9. Ofstad, J., Mörkrid, L. & Willassen, Y.: Diameter of the afferent arteriole in the dog kidney estimated by the microsphere method. Scand J Clin Lab Invest 35: 767-774, 1975.

10. Schnerman, J., Persson, A.E.G. & Ågerup, B.: Tubuloglomerular feedback. Non-linear relation between glomerular hydrostatic pressure and loop of Henle perfusion rate. J Clin Invest 52: 862-869, 1973.

11. Sjöquist, M. & Ulfendahl, H.R.: The tubuloglomerular feedback mechanism in juxtamedullary nephrons. In: The Juxtaglomerular apparatus (ed. A.E.G Persson & U. Boberg), pp. 201-210. Elsevier Science Publishers (Biomedical Division), Amsterdam , 1988.

12. Sjöquist, M., Göransson, A., Källskog, Ö. & Ulfendahl, H.R. 1984. The influence of tubuloglomerular feedback on the autoregulation of filtration rate in superficial and deep glomeruli. Acta Physiol Scand 122: 235-242, 1984.

13. Thurau, K., Deetjen, P. & Kramer, K.: Hämodynamik des Nierenmarks. II. Wechselbezieung zwischen vasculären und tubulären Gegenstromsystem bei arterillen Druchsteigerungen, Wasserdiurese und osmotischer Diurese. Pflügers Arch 270: 270-275, 1960.

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