

Endocrine and Paracrine Regulation of Renal Microcirculations

T Melanson, E Silldorff

Citation

T Melanson, E Silldorff. *Endocrine and Paracrine Regulation of Renal Microcirculations*. The Internet Journal of Nephrology. 2008 Volume 5 Number 1.

Abstract

Perfusion of the renal medulla plays a significant role in the control of salt and water balance. Blood is supplied to the medulla largely by descending vasa recta (DVR), which are derived from the efferent arterioles of the juxtamedullary glomeruli. In addition, some blood is directed to the medulla via periglomerular shunts. Renal microcirculation is modulated by various endocrine and paracrine agents. Through various methods including, in vitro microperfusion and the juxtamedullary nephron preparation, actions of vasoactive agents have been identified. Hormones such as vasopressin and angiotensin II (AngII) regulate salt and water excretion and affect perfusion of the renal medulla. The paracrine agents, nitric oxide (NO), prostaglandins (PG), and arachidonic acid metabolites provide tightly regulated regional control over renal blood flow. Collectively, these endocrine and paracrine agents provide a complex and highly regulated mechanism for the control of renal perfusion.

INTRODUCTION

Approximately 170 liters per day of glomerular filtrate are formed in the human kidney, where the nephrons and collecting ducts are responsible for reabsorbing ~99 percent of the filtrate back into circulation. The renal microcirculation returns this reabsorbed fluid to the systemic circulation through highly specific tubular-vascular relationships in the cortex and medulla. The ability to control regional perfusion within the kidney is highly developed and controlled by vasoactive endocrine and paracrine agents. Numerous suggest that differential blood flow to the cortex and medulla plays an important mechanistic role in the regulation of salt and water excretion. This review discusses the renal microanatomy and the endocrine and paracrine controls that modulate intrarenal blood flow to regulate salt and water excretion.

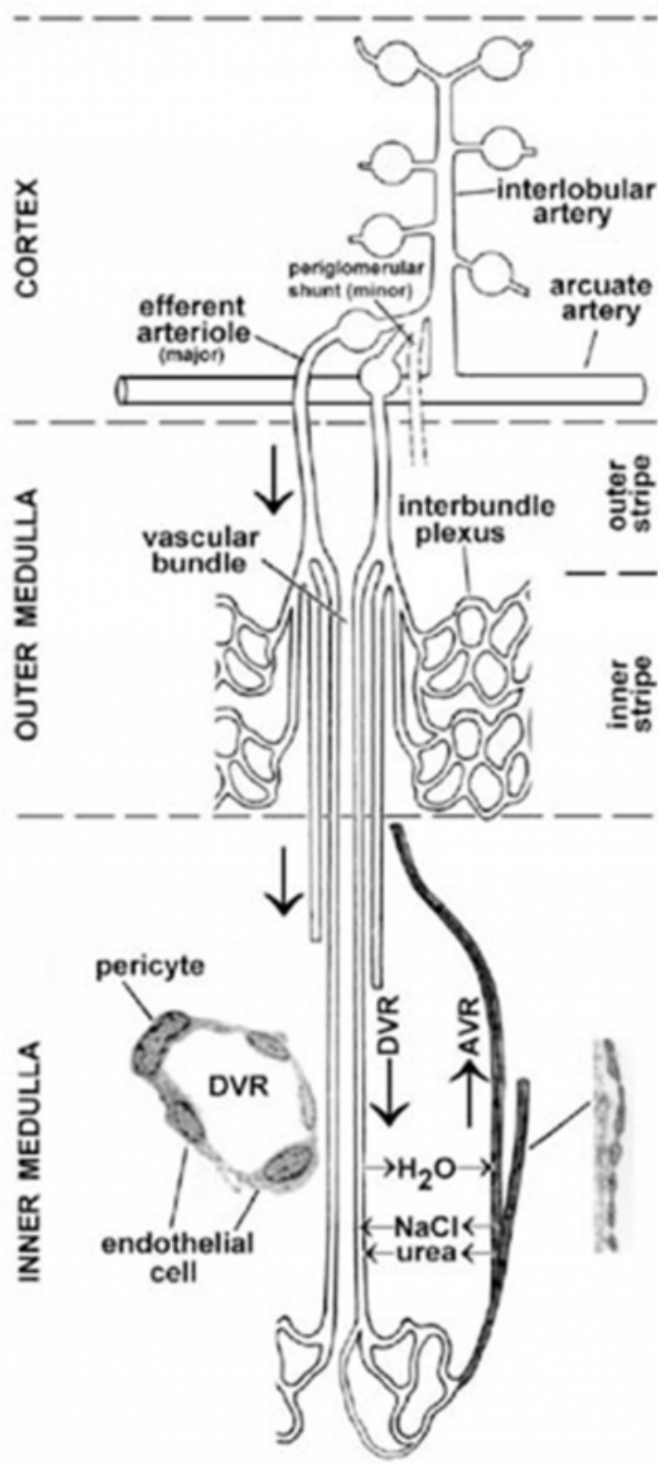
RENAL MICROANATOMY

Blood is supplied to the kidney by the renal artery, which branches into interlobar arteries that travel toward the cortex along the columns of Bertin (multipapillate kidneys), or radiate outward through the renal parenchyma (unipapillate kidneys). These interlobar arteries change direction and become arcuate arteries that travel along the corticomedullary border (Fig. 1). Multiple interlobular arteries branch toward the cortical surface from these arcuate

arteries. Interlobular arteries give rise to afferent arterioles that supply blood to the glomeruli for filtration. Afferent arterioles that branch toward the cortical surface give rise to superficial glomeruli while those that supply juxtamedullary glomeruli leave the interlobular artery at a recurrent angle. Afferent arteriolar muscle and elastic tissue diminish near the glomerulus and, in the juxtaglomerular apparatus, are replaced by granular cells. Glomeruli in the superficial cortex give rise to efferent arterioles that branch to form a dense cortical peritubular capillary plexus. Conversely, the efferent arterioles of the juxtamedullary glomeruli regularly cross the corticomedullary border into the outer stripe of the outer medulla where they form descending vasa recta (DVR). Also, a small amount of blood bypasses the juxtamedullary glomeruli to perfuse the medulla via shunt vessels [12] (dashed line, Fig. 1).

Figure 1

Figure 1: Microanatomy of renal microcirculation. DVR: Descending vasa recta, AVR: Ascending vasa recta. Arrows indicate blood flow direction [1].

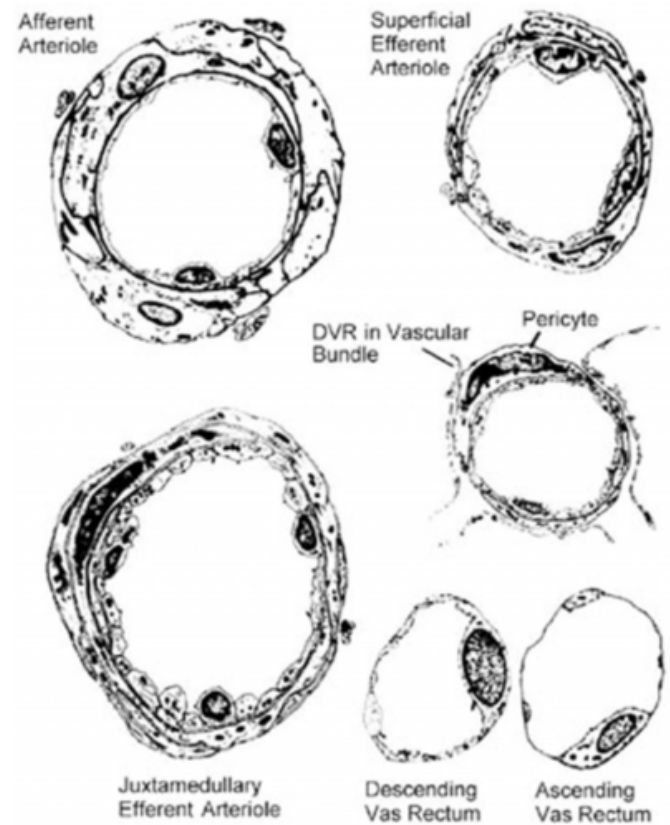


Renal medullary blood flow is supplied mainly by DVR branching from the juxtamedullary efferent arterioles. Contractile cells, called pericytes gradually replace the smooth muscle of the efferent arteriole and encircle the endothelium of DVR (Fig. 2) [34]. The abundance of

pericytes decreases with medullary depth yet they are maintained well into the inner medulla [5].

Figure 2

Figure 2: Renal microvessels cross-sections [1].



The efferent arterioles and the periglomerular shunts descend from the cortex through the outer stripe of the outer medulla. In the inner stripe of the outer medulla, these vessels give rise to dense vascular bundles of DVR and subsequently, ascending vasa recta (AVR) (Fig. 1). DVR located peripherally within vascular bundles branch off to form the interbundle capillary plexus, which supplies nephron segments in the inner stripe [6]. The largest DVR in the bundle center penetrate into the inner medulla and give rise to a sparse capillary plexus. This plexus develops into highly fenestrated AVR forming a countercurrent exchanger with DVR [7]. This arrangement dictates that blood supplied to the inner medulla must return to the cortex via AVR in vascular bundles, while blood in the interbundle plexus returns to the cortex without rejoining the bundles. Thus, nephron-derived vasoactive agents may control regional medullary blood flow in a paracrine fashion. Constriction of vessels on the bundle periphery should favor perfusion of the inner medulla, while constriction of DVR in the bundle center should favor perfusion of the outer medullary interbundle region. Regulation of this sort has been

hypothesized to maintain critical medullary PO₂ values. However, it may also be employed to alter vasa recta counter-current exchanger efficiency and thus concentrating ability.

Collecting duct (CD) clusters become the prominent structure in the inner medulla as vascular bundles disappear. These CD clusters are composed of a CD symmetrically surrounded by AVR and ascending thin limbs [8]. Outside of the CD clusters, DVR run countercurrent to AVR. These specific arrangements are most likely important for the creation and maintenance of the inner medullary osmotic gradient. Interstitial columns appear between collecting ducts, AVR and ascending thin limbs of Henle in a highly consistent fashion [8]. In the rat, these columns are broken into vertical segments by renal medullary interstitial cells (RMIC) that are tethered horizontally between thin limbs of Henle and vasa recta [9]. RMIC are contractile and, by limiting diffusion along the corticomedullary axis, may help to preserve corticomedullary solute gradients [10].

Because AVR are larger and more numerous than DVR, single vessel perfusion velocity falls as the overall microvessel cross-sectional area increases along the medullary microvasculature [11]. This increase in vascular space accommodates the fluid volume reabsorbed from the loop of Henle and collecting duct and may serve to maintain RBC transit times and oxygen delivery.

In small blood vessels, RBCs migrate to and flow at the center, while the plasma flows at the periphery. The plasma flowing at the periphery of the interlobular arteries is “skimmed” from the red cell free layer of blood into the afferent vessels of the deep glomeruli, thus keeping cortical hematocrit higher than that of the medulla [12,13]. In addition, blood flow rate and hematocrit are reduced with medullary depth [14]. This may be due to increased vascular space (flow) and RBC dehydration (hematocrit) as blood perfuses the hypertonic inner medulla. Some species (rat, cat, dog, and gerbil) contain muscular cushions at the junction between the interlobular artery and the juxtamedullary afferent arterioles which may aid in this plasma “skimming” [15]. Constriction of these cushions could limit juxtamedullary perfusion leading to enhanced superficial cortical blood flow.

METHODS FOR MEASURING RENAL BLOOD FLOW AND MICROVESSEL REACTIVITY

Measurements of regional renal blood flow were originally attempted using tracers and demonstrated that inner

medullary blood flow is less than cortical blood flow [11]. Because these methods give a wide range of estimates, more reliable methods have been developed. Single vessel flow rates can be calculated using videomicroscopy to measure microvessel diameter and RBC velocity with a pencil lens camera [16]. Enhancement of video images can be achieved by the injection of fluorescein isothiocyanate labeled gamma globulin and use of a silicon intensified target camera to increase the contrast between RBC's and the capillary wall [17]. While data obtained using this technique is reliable, its use is limited to the surface of the cortex or the exposed papilla [17]. Laser Doppler flowmetry is the preferred method for measuring regional tissue blood flow rates deeper in the parenchyma. In this method, light from an inserted optical fiber is scattered by flowing RBC's and detected by the same optic probe [18]. The amount of light scattering is measured and converted into tissue blood flow rates, however, quantification of the units is generally not possible.

Methods are also available for the direct measurement of vasoactive agent effects on microvessels. These methods aid in the localization of vasoactive agent action. Additionally, they can provide data on the concentrations required for a response. Finally, information can be obtained about the activity of vasoactive agents on selective receptor subtypes. The *in vitro* microperfusion method used to study transport in renal tubules can be used to measure effects of vasoactive agents on microvessels [19]. However, this method may not always give an accurate assessment of *in vivo* conditions. For example, the actions of nitric oxide (NO) may be enhanced *in vitro* by the absence of the NO scavenger hemoglobin [20]. This limitation can be overcome by use of the juxtamedullary nephron preparation method, which enables direct observation of RBC flow and microvessel diameters. The method involves surgical isolation and hemisection of the kidney to expose the vessels of the juxtamedullary region. This allows measurement of vasoactive agent effects under controlled conditions while preserving the tubular-vascular relationship [21]. Another preparation for visualizing intact microvessels is the split hydronephrotic kidney. Hydronephrosis is induced by surgical ligation of the ureter. This destroys the renal tubular network while preserving renal vascular structure. Three weeks after surgery, the hydronephrotic kidney becomes thin and can be split along its curvature. This allows for visualization of the glomerular vascular network under a microscope. Vasoactive agents can be directly applied to the preparation and changes in blood flow and vessel diameter are then measured by videomicroscopy [22].

REGULATION OF RENAL MICROCIRCULATION

Renal microanatomy provides numerous points for the control of regional perfusion of the cortex and medulla (Fig. 1). Changes in medullary blood flow may aid in the control of urine concentration by altering the efficiency of the countercurrent exchange system via alteration of the NaCl and urea corticomedullary gradients [11]. For example, decreased blood flow to the medulla leads to an increase in urine concentration. The endocrine and paracrine agents that control renal vasoactivity may have opposing effects in different regions of tissue allowing for simultaneous constriction of one region and dilation of another. This differential regulation could be the result of regional receptor subtype heterogeneity or regulation of local vasoactive agent production.

VASOPRESSIN

Vasopressin is a neurohormone that has important vasoactive effects in the control of renal perfusion. Studies indicate that vasopressin decreases blood flow in the inner medulla without affecting flow in the outer medulla or the cortex [23]. Vasopressin V_1 receptor agonists have been found to constrict juxtamedullary arterioles [24] and outer medullary DVR [25] favoring cortical perfusion and reducing medullary perfusion. Water deprived rats with increased plasma vasopressin show a reduction of inner medullary blood flow that was reversed in the presence of a V_1 receptor antagonist [26]. Infusion of a selective V_1 receptor agonist also demonstrated a reduction in inner medullary blood flow without affecting the outer medulla or the cortex [27]. Furthermore, decerebrate rats infused with physiological concentrations of vasopressin demonstrated reduced medullary blood flow and increased urine concentration [28]. These data support the claim that vasopressin reduces inner medullary blood flow and favors antidiuresis through constriction of juxtamedullary arterioles and DVR.

Vasopressin may also initiate nitric oxide (NO) mediated vasodilation by acting on V_2 receptors [29]. Infusion of selective V_2 agonists dilates precontracted afferent arterioles [30] and outer medullary DVR [25], while chronic infusion increases medullary blood flow [31]. V_2 mediated vasodilation may serve to protect the outer medulla from ischemia during hypertension caused by prolonged vasopressin induced constriction [32].

ANGIOTENSIN II

The role of angiotensin II (AngII) to modulate regional

perfusion in the kidney has also been investigated [33,22,24].

AngII affects perfusion in the kidney via type 1 ($AT1_A$ and $AT1_B$) and type 2 ($AT2$) receptors, which are expressed in both vascular and tubular components of the kidney [34]. Specifically, all three receptor subtypes have been found in muscular juxtamedullary efferent arterioles that perfuse the medulla. $AT1_A$ and $AT2$ receptors are also expressed in the efferent arterioles that give rise to the juxtamedullary capillary plexus in the cortex [35]. AngII mainly acts on $AT1$ receptors for vasoconstriction, but may also vasodilate via compensatory $AT2$ receptor activation during prolonged AngII induced vasoconstriction.

AngII activated $AT1$ receptors cause vasoconstriction of renal vessels [36]. As with vasopressin, studies have shown that AngII constricts superficial arterioles, juxtamedullary arterioles [37], and DVR [24,33,22]. Additionally, $AT1_A$ null mice showed a reduced response to AngII at the afferent arteriole and no response at the efferent arteriole [38]. Efferent arterioles and DVR have been found to be the most sensitive to AngII mediated constriction ($EC_{50} \sim 0.5$ nM) [39].

$AT2$ receptor activation favors vasodilation via the generation of vasodilators including NO [40], CYP450 epoxygenase products (EETs) [41], and other endothelium derived vasodilators [42]. $AT2$ activation may also cause vasodilation by inhibiting constrictive reactive oxygen species (ROS) formation in the efferent arterioles and DVR [43]. These responses may serve to self-attenuate AngII induced vasoconstriction. NITRIC OXIDE

As previously stated, one of the major roles of NO is to serve in a compensatory manner to limit the effects of endocrine and paracrine vasoconstrictors. NO is a vasodilatory paracrine agent that is produced by nitric oxide synthase (NOS) isoforms which are greatly expressed in the inner medullary collecting duct and vasa recta, but can be found throughout the kidney [44]. During vasoconstriction caused by various endocrine and paracrine agents, NO is produced to avoid medullary ischemia by attenuating their effects. As previously mentioned, vasopressin stimulates V_2 receptors and in turn increases NO production leading to dilation [29]. Blockade of NO production during vasopressin elevation leads to hypertension signifying that V_2 mediated NO production may serve to protect the outer medulla from ischemia as well as to prevent hypertension [32]. Also, AngII stimulation of both $AT1$ and $AT2$ receptor subtypes has been shown to increase NO generation to compensate for constriction at the afferent arterioles and DVR [41].

Studies with NOS inhibitors have suggested ubiquitous functions of NO in control of the renal microcirculation. The NO synthase inhibitor N^w-nitro-L-arginine methyl ester (L-NAME) increases renal vascular resistance and decreases pressure natriuresis [45]. Furthermore, chronic infusion causes hypertension and decreased medullary blood flow in rats [46]. In addition, preglomerular microcirculation of the juxtamedullary nephron was constricted in the presence of a NOS inhibitor [47]. Studies also indicate that NO generated by increased pressure in DVR may inhibit salt reabsorption by adjacent nephrons thus aiding in pressure natriuresis [48]. All together, these data suggest that NO not only serves to attenuate the actions of vasoconstrictors, but also plays important roles in pressure natriuresis and vascular-tubular communication.

REACTIVE OXYGEN SPECIES

The effects of NO may be diminished by reactive oxygen species (ROS), such as superoxide ($O_2^{\cdot -}$). ROS are oxygen derived free radicals that are produced by numerous natural cell processes and may play a role in the renal microcirculation. For example, studies indicate that ROS are produced during AngII stimulation of DVR [42]. By reacting with NO to form peroxynitrite ($ONOO^{\cdot -}$), $O_2^{\cdot -}$ decreases renal levels of NO thereby reducing its ability to act as a vasodilator. Under normal conditions, ROS levels are controlled by the conversion of $O_2^{\cdot -}$ to H_2O_2 and then to water by superoxide dismutase (SOD) and catalase, respectively. Left unchecked, ROS may terminate the compensatory vasodilatory effects of NO [42]. Studies suggest that hypertension can be caused by either the elevation of ROS or the inhibition of SOD [45], indicating the importance of SOD in controlling ROS levels to prevent medullary ischemia and hypertension.

PROSTAGLANDINS

In addition to the hormones vasopressin and AngII, locally produced vasoactive agents are also responsible for regional microcirculatory control. Among these vasoactive agents are the arachidonic acid metabolites derived from cell membrane lipids liberated by phospholipases. They include the renal paracrine and autocrine agents, prostaglandins (PG) and cytochrome P450 molecules. Prostaglandins are produced by renal cyclooxygenases (COX-1 and COX-2) where they exert a wide range of effects, which are mainly vasodilatory. Studies indicate that PGs generally enhance renal blood flow. For example, prostaglandin E₂ (PGE₂) relaxes AngII induced constriction of DVR [49]. Studies in

vitro demonstrate that both PGE₂ and prostacyclin (PGI₂) dilate afferent arterioles, while PGI₂ dilates efferent arterioles as well [50]. Conflicting studies report that hormonal constriction of the afferent arteriole is enhanced by PGE₂ and reversed by PGI₂ [51]. This discrepancy may be attributed to the differential actions of PGE₂ on varying receptor subtypes. For example, stimulation of the prostaglandin E₂ receptor (EP2) and E₄ receptors (EP4) favor vasodilation, while stimulation of the prostaglandin E₃ receptor (EP3) favors vasoconstriction [52].

Distribution of the COX isoforms may also contribute to the control of PG activities. COX-1 is widely expressed in the kidney, while COX-2 is mainly expressed in the macula densa [53]. COX-2 expression in the macula densa is stimulated by increased medullary electrolyte tonicity [54] and results in the formation of PGE₂ [53,55]. Antagonism of both COX-1 and COX-2 with nonselective inhibitors decreases medullary blood flow by favoring constriction [56]. This indicates that COX mediated PGs are primarily vasodilatory agents in the medulla. Selective inhibition of COX-2 diminishes tubuloglomerular feedback [36] and increases sensitivity to vasoconstriction [55]. As with NO, PG may help protect the renal medulla from hypoxia by reversing the prolonged activity of vasoconstrictors. For example, it has been reported that PGE₂ dilates AngII constricted juxtamedullary arterioles [57]. Furthermore, interstitial cells in the medulla that express receptors for vasoconstrictors also express both COX-1 and COX-2, which generate vasodilatory PGE₂ in response to prolonged constriction [53].

CYTOCHROME P450 METABOLITES

In the kidney, cytochrome P450 (CYP) isoforms CYP2C and CYC2J synthesize vasoactive epoxyeicosatrienoic acids (EETs), while the CYP4A isoform synthesizes vasoactive hydroxyeicosatetraenoic acids (HETEs) [58]. The 20 ω -hydroxylation product, 20-HETE, is a powerful vasoconstrictor that mediates autoregulation of the renal microcirculation in response to the presence of molecular oxygen [58,59]. 20-HETE exerts its effects by depolarizing smooth muscle [60], through inhibition of K_{Ca} channel activity [59], enhancing constriction by AngII [41] and endothelin-1 [61]. Studies indicate that 20-HETE regulates blood pressure. The inhibition of 20-HETE synthesis has been linked to salt sensitive hypertension in the rat [62] and to essential hypertension in humans [63]. As with other vasoconstrictors, 20-HETE activity may be attenuated by

NO. In this case, NO inhibits CYP4A activity thus lowering 20-HETE synthesis [64].

In contrast, EETs are mainly vasodilatory [52]. EET synthesis is stimulated by activation of the A2 adenosine receptor [65] and the AT2 AngII receptor [41] and enhances the vasodilatory properties of adenosine and AngII, respectively. EETs may vasodilate due to their ability to activate K_{Ca} channels [66] and act as endothelium dependent hyperpolarizing factors (EDHF) [67]. EDHFs relax vessels by causing hyperpolarization of endothelium and smooth muscle. EETs may act as EDHFs by opening endothelial K_{Ca} channels to release K^+ ions into the myoendothelial intercellular space resulting in hyperpolarization and vasodilation [67]. Studies indicate that hypertension caused by enhanced afferent arteriole constriction can be reversed by EET enhancement [68].

ADDITIONAL VASOACTIVE AGENTS

Other endocrine and paracrine agents have been found to aid in the regulation of regional renal microcirculations. Their local release and differential actions on receptor subtypes allows for tight regulation of perfusion in specific regions of the kidney. For example, recent research has shown that the hormone aldosterone, not only stimulates the transcription of renin for salt reabsorption, but also is vasoactive. Specifically, aldosterone constricts smooth muscle, while also stimulating compensatory release of the vasodilator, NO [69]. Adrenomedullin is a powerful vasodilator that is synthesized by many tissues including vascular smooth muscle and endothelium. In the kidney, production of adrenomedullin is stimulated by hypoxia to increase overall renal blood flow [70]. Similarly, adenosine, which is produced by the medullary thick ascending limb of Henle, increases medullary blood flow during hypoxia [71]. In the kidney, adenosine acts on the P1-purinoceptor A1 to cause constriction and A2 to cause vasodilation and is considered to be the primary mediator of tubuloglomerular feedback [72]. ATP also acts as a renal vasoactive agent. Micromolar concentrations of ATP cause constriction of preglomerular vessels via the P2-purinoceptor P2X and dilation via P2Y in the presence of NO [73]. Endothelins (ETs) are autocrine and paracrine agents that act in a similar fashion to ATP and adenosine. ET1 is produced by the medullary collecting duct [74] and causes potent renal vasoconstriction. Receptor expression largely determines ET1 effects such that stimulating cortical ETA receptors causes vasoconstriction while ETB receptor activation results in vasodilation via NO

production in the medulla [75]. Finally, atrial natriuretic peptides vasodilate preglomerular vessels leading to increased renal blood flow, glomerular filtration rate, papillary plasma flow, and sodium excretion [76].

CONCLUSION

Renal vascular anatomy suggests that regulation of vasoactivity is responsible for variations in regional perfusion. Constriction of superficial arterioles should favor redistribution of blood flow toward juxtamedullary glomeruli and the medulla. Alternatively, constriction of the intra-arterial cushions or juxtamedullary arterioles would favor cortical perfusion. Within the medulla, constriction of DVR that perfuse the inner medulla should direct blood flow to the outer medullary interbundle capillary plexus, while constriction of DVR on the bundle periphery would result in enhanced papillary flow. A complex interaction of endocrine and paracrine agents serves to coordinate regional microperfusion for the purpose of regulating sodium excretion, urinary concentration, countercurrent exchanger efficiency, as well as to provide compensatory effects to prevent renal ischemia.

References

1. Casellas D, Mimran A. Shunting in renal microvasculature of the rat: a scanning electron microscopic study of corrosion casts. *Anat Rec* 1981;201:237-248
2. Pallone TL, Turner MR, Edwards A, Jamison RL. Countercurrent exchange in the renal medulla. *Am J Physiol Regul Integr Comp Physiol* 2003;284:R1153-R1175
3. Jamison RL, Kriz W. Urinary Concentrating Mechanism: Structure and Function. 1982
4. Shepro D, Morel NM. Pericyte physiology. *FASEB J* 1993;7:1031-1038
5. Park F, Mattson DL, Roberts LA, Cowley AW, Jr. Evidence for the presence of smooth muscle alpha-actin within pericytes of the renal medulla. *Am J Physiol* 1997;273:R1742-R1748
6. Lemley KV, Kriz W. Cycles and separations: the histotopography of the urinary concentrating process. *Kidney Int* 1987;31:538-548
7. Mink D, Schiller A, Kriz W, Taugner R. Interendothelial junctions in kidney vessels. *Cell Tissue Res* 1984;236:567-576
8. Pannabecker TL and Dantzler WH. Three-dimensional architecture of inner medullary vasa recta. *Am J Physiol Renal Physiol* 2006;290:F1355-F1366
9. Lemley KV, Kriz W. Anatomy of the renal interstitium. *Kidney Int* 1991;39:370-381
10. Takahashi-Iwanaga H. The three-dimensional cytoarchitecture of the interstitial tissue in the rat kidney. *Cell Tissue Res* 1991;264:269-281
11. Pallone TL, Robertson CR, Jamison RL. Renal medullary microcirculation. *Physiol Rev* 1990;70:885-920
12. Fahraeus R. The suspension stability of blood. *Physiol Rev* 1929;9:241-274
13. Pappenheimer JR, Kinter WB. Hematocrit ratio of blood within mammalian kidney and its significance for renal hemodynamics. *Am J Physiol* 1956;185:377-390

14. Rasmussen SN. Red cell and plasma volume flows to the inner medulla of the rat kidney: determinations by means of a step function input indicator technique. *Pflugers Arch* 1978;373:153-159
15. Fourman J, Moffat DB. The effect of intra-arterial cushions on plasma skimming in small arteries. *J Physiol* 1961;158:374-380
16. Yamamoto T, Tada T, Brodsky SV, Tanaka H, Noiri E, Kajiya F, Goligorsky MS. Intravital videomicroscopy of peritubular capillaries in renal ischemia. *Am J Physiol Renal Physiol* 2002;282:F1150-F1155
17. Zimmerhackl B, Tinsman J, Jamison RL, Robertson CR. Use of digital cross-correlation for on-line determination of single-vessel blood flow in the mammalian kidney. *Microvasc Res* 1985;30:63-74
18. Stern MD, Bowen PD, Parma R, Osgood RW, Bowman RL, Stein JH. Measurement of renal cortical and medullary blood flow by laser-Doppler spectroscopy in the rat. *Am J Physiol* 1979;236:F80-F87
19. Pallone TL. Microdissected perfused vessels. *Methods Mol Med* 2003;86:443-456
20. Martin W, Villani GM, Jothianandan D, Furchgott RF. Selective blockade of endothelium-dependent and glyceryl trinitrate-induced relaxation by hemoglobin and by methylene blue in the rabbit aorta. *J Pharmacol Exp Ther* 1985;232:708-716
21. Casellas D, Navar LG. In vitro perfusion of juxtamedullary nephrons in rats. *Am J Physiol* 1984;246:F349-F358
22. Steinhausen M, Kucherer H, Parekh N, Weis S, Wiegman DL, Wilhelm KR. Angiotensin II control of the renal microcirculation: effect of blockade by saralasin. *Kidney Int* 1986;30:56-61
23. Zimmerhackl B, Robertson CR, Jamison RL. Effect of arginine vasopressin on renal medullary blood flow. A videomicroscopic study in the rat. *J Clin Invest* 1985;76:770-778
24. Weihprecht H, Lorenz JN, Briggs JP, Schnermann J. Vasoconstrictor effect of angiotensin and vasopressin in isolated rabbit afferent arterioles. *Am J Physiol* 1991;261:F273-F282
25. Turner MR, Pallone TL. Vasopressin constricts outer medullary descending vasa recta isolated from rat kidneys. *Am J Physiol* 1997;272:F147-F151
26. Franchini KG, Cowley AW, Jr. Renal cortical and medullary blood flow responses during water restriction: role of vasopressin. *Am J Physiol* 1996;270:R1257-R1264
27. Nakanishi K, Mattson DL, Gross V, Roman RJ, Cowley AW, Jr. Control of renal medullary blood flow by vasopressin V1 and V2 receptors. *Am J Physiol* 1995;269:R193-R200
28. Franchini KG, Cowley AW, Jr. Sensitivity of the renal medullary circulation to plasma vasopressin. *Am J Physiol* 1996;271:R647-R653
29. Aki Y, Tamaki T, Kiyomoto H, He H, Yoshida H, Iwao H, Abe Y. Nitric oxide may participate in V2 vasopressin-receptor-mediated renal vasodilation. *J Cardiovasc Pharmacol* 1994;23:331-336
30. Tamaki T, Kiyomoto K, He H, Tomohiro A, Nishiyama A, Aki Y, Kimura S, Abe Y. Vasodilation induced by vasopressin V2 receptor stimulation in afferent arterioles. *Kidney Int* 1996;49:722-729
31. Park F, Zou AP, Cowley AW, Jr. Arginine vasopressin-mediated stimulation of nitric oxide within the rat renal medulla. *Hypertension* 1998;32:896-901
32. Evans RG, Madden AC, Denton KM. Diversity of responses of renal cortical and medullary blood flow to vasoconstrictors in conscious rabbits. *Acta Physiol Scand* 2000;169:297-308
33. Harrison-Bernard LM, Carmines PK. Impact of cyclo-oxygenase blockade on juxtamedullary microvascular responses to angiotensin II in rat kidney. *Clin Exp Pharmacol Physiol* 1995;22:732-738
34. Miyata N, Park F, Li XF, Cowley AW, Jr. Distribution of angiotensin AT1 and AT2 receptor subtypes in the rat kidney. *Am J Physiol* 1999;277:F437-F446
35. Helou CM, Imbert-Teboul M, Doucet A, Rajerison R, Chollet C, Alhenc-Gelas F, Marchetti J. Angiotensin receptor subtypes in thin and muscular juxtamedullary efferent arterioles of rat kidney. *Am J Physiol Renal Physiol* 2003;285:F507-F514
36. Deng A, Wead LM, Blantz RC. Temporal adaptation of tubuloglomerular feedback: effects of COX-2. *Kidney Int* 2004;66:2348-2353
37. Goransson A, Sjoquist M, Ulfendahl HR. Superficial and juxtamedullary nephron function during converting enzyme inhibition. *Am J Physiol* 1986;251:F25-F33
38. Harrison-Bernard LM, Cook AK, Oliverio MI, Coffman TM. Renal segmental microvascular responses to ANG II in AT1A receptor null mice. *Am J Physiol Renal Physiol* 2003;284:F538-F545
39. Nishiyama A, Seth DM, Navar LG. Angiotensin II type 1 receptor-mediated augmentation of renal interstitial fluid angiotensin II in angiotensin II-induced hypertension. *J Hypertens* 2003;21:1897-1903
40. Carey RM. Update on the role of the AT2 receptor. *Curr Opin Nephrol Hypertens* 2005;14:67-71
41. Kohagura K, Arima S, Endo Y, Chiba Y, Ito O, Abe M, Omata K, Ito S. Involvement of cytochrome P450 metabolites in the vascular action of angiotensin II on the afferent arterioles. *Hypertens Res* 2001;24:551-557
42. Zhang Z, Rhinehart K, Kwon W, Weinman E, Pallone TL. ANG II signaling in vasa recta pericytes by PKC and reactive oxygen species. *Am J Physiol Heart Circ Physiol* 2004;287:H773-H781
43. Endo Y, Arima S, Yaoita H, Omata K, Tsunoda K, Takeuchi K, Abe K, Ito S. Function of angiotensin II type 2 receptor in the postglomerular efferent arteriole. *Kidney Int Suppl* 1997;63:S205-S207
44. Mattson DL, Wu F. Nitric oxide synthase activity and isoforms in rat renal vasculature. *Hypertension* 2000;35:337-341
45. Majid DS, Williams A, Navar LG. Inhibition of nitric oxide synthesis attenuates pressure-induced natriuretic responses in anesthetized dogs. *Am J Physiol* 1993;264:F79-F87
46. Nakanishi K, Mattson DL, Cowley AW, Jr. Role of renal medullary blood flow in the development of L-NAME hypertension in rats. *Am J Physiol* 1995;268:R317-R323
47. Imig JD, Roman RJ. Nitric oxide modulates vascular tone in preglomerular arterioles. *Hypertension* 1992;19:770-774
48. Zhang Z, Pallone TL. Response of descending vasa recta to luminal pressure. *Am J Physiol Renal Physiol* 2004;287:F535-F542
49. Silldorff EP, Yang S, Pallone TL. Prostaglandin E2 abrogates endothelin-induced vasoconstriction in renal outer medullary descending vasa recta of the rat. *J Clin Invest* 1995;95:2734-2740
50. Edwards RM. Effects of prostaglandins on vasoconstrictor action in isolated renal arterioles. *Am J Physiol* 1985;248:F779-F784
51. Inscho EW, Carmines PK, Navar LG. Prostaglandin influences on afferent arteriolar responses to vasoconstrictor agonists. *Am J Physiol* 1990;259:F157-F163
52. Imig JD. Eicosanoid regulation of the renal vasculature.

- Am J Physiol Renal Physiol 2000;279:F965-F981
53. Campean V, Theilig F, Paliege A, Breyer M, Bachmann S. Key enzymes for renal prostaglandin synthesis: site-specific expression in rodent kidney (rat, mouse). *Am J Physiol Renal Physiol* 2003;285:F19-F32
54. Zhang MZ, Sanchez LP, McKanna JA, Harris RC. Regulation of cyclooxygenase expression by vasopressin in rat renal medulla. *Endocrinology* 2004;145:1402-1409
55. Lopez R, Llinas MT, Roig F, Salazar FJ. Role of nitric oxide and cyclooxygenase-2 in regulating the renal hemodynamic response to norepinephrine. *Am J Physiol Regul Integr Comp Physiol* 2003;284:R488-R493
56. Lemley KV, Schmitt SL, Holliger C, Dunn MJ, Robertson CR, Jamison RL. Prostaglandin synthesis inhibitors and vasa recta erythrocyte velocities in the rat. *Am J Physiol* 1984;247:F562-F567
57. Matsuda H, Hayashi K, Arakawa K, Kubota E, Honda M, Tokuyama H, Suzuki H, Yamamoto T, Kajiya F, Saruta T. Distinct modulation of superficial and juxtamedullary arterioles by prostaglandin in vivo. *Hypertens Res* 2002;25:901-910
58. Harder DR, Narayanan J, Birks EK, Liard JF, Imig JD, Lombard JH, Lange AR, Roman RJ. Identification of a putative microvascular oxygen sensor. *Circ Res* 1996;79:54-61
59. Imig JD, Zou AP, Stec DE, Harder DR, Falck JR, Roman RJ. Formation and actions of 20-hydroxyeicosatetraenoic acid in rat renal arterioles. *Am J Physiol* 1996;270:R217-R227
60. Ma YH, Gebremedhin D, Schwartzman ML, Falck JR, Clark JE, Masters BS, Harder DR, Roman RJ. 20-Hydroxyeicosatetraenoic acid is an endogenous vasoconstrictor of canine renal arcuate arteries. *Circ Res* 1993;72:126-136
61. Imig JD, Pham BT, LeBlanc EA, Reddy KM, Falck JR, Inscho EW. Cytochrome P450 and cyclooxygenase metabolites contribute to the endothelin-1 afferent arteriolar vasoconstrictor and calcium responses. *Hypertension* 2000;35:307-312
62. Hoagland KM, Flasch AK, Roman RJ. Inhibitors of 20-HETE formation promote salt-sensitive hypertension in rats. *Hypertension* 2003;42:669-673
63. Gainer JV, Bellamine A, Dawson EP, Womble KE, Grant SW, Wang Y, Cupples LA, Guo CY, Demissie S, O'Donnell CJ, Brown NJ, Waterman MR, Capdevila JH. Functional variant of CYP4A11 20-hydroxyeicosatetraenoic acid synthase is associated with essential hypertension. *Circulation* 2005;111:63-69
64. Alonso-Galicia M, Sun CW, Falck JR, Harder DR, Roman RJ. Contribution of 20-HETE to the vasodilator actions of nitric oxide in renal arteries. *Am J Physiol* 1998;275:F370-F378
65. Cheng MK, Doumad AB, Jiang H, Falck JR, McGiff JC, Carroll MA. Epoxyeicosatrienoic acids mediate adenosine-induced vasodilation in rat preglomerular microvessels (PGMV) via A2A receptors. *Br J Pharmacol* 2004;141:441-448
66. Fukao M, Mason HS, Kenyon JL, Horowitz B, Keef KD. Regulation of BK(Ca) channels expressed in human embryonic kidney 293 cells by epoxyeicosatrienoic acid. *Mol Pharmacol* 2001;59:16-23
67. Fleming I. Cytochrome P450 epoxigenases as EDHF synthase(s). *Pharmacol Res* 2004;49:525-533
68. Imig JD, Zhao X, Falck JR, Wei S, Capdevila JH. Enhanced renal microvascular reactivity to angiotensin II in hypertension is ameliorated by the sulfonimide analog of 11,12-epoxyeicosatrienoic acid. *J Hypertens* 2001;19:983-992
69. Schmidt BM, Oehmer S, Delles C, Bratke R, Schneider MP, Klingbeil A, Fleischmann EH, Schmieder RE. Rapid nongenomic effects of aldosterone on human forearm vasculature. *Hypertension* 2003;42:156-160
70. Majid DS, Kadowitz PJ, Coy DH, Navar LG. Renal responses to intra-arterial administration of adrenomedullin in dogs. *Am J Physiol* 1996;270:F200-F205
71. Sildorff EP, Pallone TL. Adenosine signaling in outer medullary descending vasa recta. *Am J Physiol Regul Integr Comp Physiol* 2001;280:R854-R861
72. Nishiyama A, Inscho EW, Navar LG. Interactions of adenosine A1 and A2a receptors on renal microvascular reactivity. *Am J Physiol Renal Physiol* 2001;280:F406-F414
73. Churchill PC, Ellis VR. Pharmacological characterization of the renovascular P2 purinergic receptors. *J Pharmacol Exp Ther* 1993;265:334-338
74. Abassi ZA, Ellahham S, Winaver J, Hoffman A. The intrarenal endothelin system and hypertension. *News Physiol Sci* 2001;16:152-156
75. Just A, Olson AJ, Arendshorst WJ. Dual constrictor and dilator actions of ET(B) receptors in the rat renal microcirculation: interactions with ET(A) receptors. *Am J Physiol Renal Physiol* 2004;286:F660-F668
76. Kiberd BA, Larson TS, Robertson CR, Jamison RL. Effect of atrial natriuretic peptide on vasa recta blood flow in the rat. *Am J Physiol* 1987;252:F1112-F1117

Author Information

Thomas S. Melanson, M.S.

Department of Biological Sciences, Towson University

Erik P. Sillardorff, Ph.D.

Department of Biological Sciences, Towson University