The Microcirculation of the Renal Medulla

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TRUETA et al. proposed in 1947 that morphological differences between renal cortical and medullary structures reflect a "fundamental difference in the function of the cortical and juxtamedullary vasculo-nephric units." This proposition was reinforced when Wirz et al. first published evidence for the countercurrent mechanism as the basis for urinary concentration in 1951. The countercurrent hypothesis attributes an important role to the medullary microcirculation in the regulation of urinary concentration and water balance as a countercurrent exchanger [e.g., see the mathematical concentration model of Stephenson (1972)] and as the route for removal from the medulla of water reabsorbed from the collecting tubules. Changes in the distribution of blood flow between cortex and medulla have been considered to play a role in salt balance (Stein, 1973), and a reduction in medullary blood flow has been proposed as the basis for several pathophysiological disorders (Thurau, 1964; Fisher et al., 1970; Stein et al., 1973; Karlberg et al., 1983).

In this editorial review, we will focus on recent studies of the physiological role of the medullary microcirculation in the context of the experimental methods used. For earlier work, please see the reviews by Thurau (1964), Pinter (1969), and Aukland (1976, 1980a). The scope of this review will be confined to the normal function of the medullary circulation, since, at present, information about disturbances of medullary circulation in renal disease is limited. We will consider first the architectural organization of the medullary vasculature, then the techniques used to measure medullary blood flow and the results obtained thereby. The next section will be devoted to a discussion of the hematocrit in medullary capillaries. Finally, we will review regulation of medullary blood flow.

Organization of the Renal Medulla

The medulla has two distinct parts, an outer and an inner medulla. The outer medulla has an outer and an inner stripe. It should be noted that lymphatic vessels are very sparse in the outer medulla and have not been found at all in the inner medulla (Kriz and Dieterich, 1970; Jamison and Kriz, 1982). The inner medulla forms from a broad base and tapers toward a narrow tip (the papilla) that in certain rodents, particularly the young, protrudes into the pelvic ureter (Beewkes, 1971). This type of medulla, represented by a single pyramid and papilla, is found in many small animals, as for instance Rodentia, Monotremata, Insectivora. In other mammals, the medulla consists of two or more pyramids (Carnivora, Homo sapiens) (Smith, 1956).

Medullary blood flow is postglomerular in origin. Efferent arterioles of juxtamedullary glomeruli branch into descending vasa recta (DVR) that enter the medulla (Kriz, 1981). These efferent arterioles have a larger diameter, a thicker endothelium, and a more pronounced smooth muscle cell wall than their cortical counterparts (Kriz, 1981). Afferent arterioles of juxtamedullary glomeruli are also distinctive by virtue of having specialized structures at their origin from the interlobular artery. Intraarteriolar "cushions," containing a smooth muscle cell-like structure, protrude into the lumen of the afferent vessel (Moffat and Creasey, 1971) found in rat, cat, and dog, not in rabbit, guinea pig, hamster, pig, sheep, ox, or man (Fourman and Moffat, 1971). Although the function of these cushions is not known, their location makes them ideal candidates for the regulation of blood flow to the medulla. Efferent arterioles deliver blood into the outer medulla, where from one efferent vessel a "horse's tail" of as many as 30 DVR emerge (Moffat, 1975) and descend further into the medulla in "vascular bundles" (Fig. 1). At each level within the medulla, DVR leave the bundles to form a capillary plexus. In the outer stripe of the outer medulla, the plexus is sparse and loosely meshed; in the inner stripe of the outer medulla, it is dense and tightly meshed; in the inner medulla the capillary plexus becomes less dense.
FIGURE 1. Schematic representation of the microvasculature of the mammalian kidney (rat). Arterial vessels, glomeruli, and capillaries are drawn in black and are shown on the left side; venous vessels are white and are demonstrated on the right. The two sides should be imagined superimposed. C = cortex; the dashed line separates the medullary ray from the cortical labyrinth. OS = outer stripe; IS = inner stripe; IM = inner medulla. An arcuate artery (arrow) gives rise to interlobular arteries from which afferent arterioles originate at angles typical for their intracortical location. Efferent arterioles of superficial glomeruli, before splitting off into capillaries, ascend to the renal surface; those of midcortical glomeruli frequently split into capillaries at the border with the medullary rays, and efferent arterioles of juxtamedullary glomeruli divide into descending vasa recta. Note the different patterns of capillary plexuses in the cortical labyrinth, medullary rays, outer stripe, inner stripe, and inner medulla. The interlobular veins are formed in the superficial cortex. Together with arcuate veins, they accept blood from medullary venous vessels. Vascular bundles in the inner stripe contain descending vasa recta and all ascending vasa recta originating from the inner medulla; most ascending vasa recta from the inner stripe ascend separately from the bundles. From Jamison and Kriz (1982), modified from Rollhauser et al. (1964) and Kriz and Lever (1969), by permission.

Blood from the capillary plexus is drained by ascending vasa recta (AVR), which ascend within vascular bundles to the arcuate vein.

The architecture of the vascular bundles exhibits two distinct patterns among species. In a simple medulla, the bundles contain only DVR and AVR, with AVR clustered more in the periphery of the bundle. The bundles are surrounded by concentric rings of loops of Henle and collecting ducts in that order, with the long loops of Henle nearest to the bundles. A simple medulla is characteristic of the kidney of man, monkey, dog, cat, guinea pig, and rabbit (Kriz, 1981).

In the complex medulla, descending limbs of short loops of Henle are incorporated along with AVR and DVR into the bundles, primarily near the periphery. The complex medulla is found in the kidney of the rat, mouse, gerbil, and sand rat (Kriz, 1981). The intimacy among AVR, DVR, and Henle’s loops, whether inside or outside the bundle, reinforces the impression that vasa recta are an important part of a countercurrent system that facilitates exchange of water and solute between AVR and DVR and between AVR and Henle’s loops.

The ultrastructure of AVR and DVR differs (Fig. 2). Like arterioles, DVR have a continuous, thick endothelium containing smooth muscle cells proximally and pericytes distally as the vessels descend to the papillary tip (Kriz et al., 1976). In contrast, AVR resemble peritubular capillaries in the renal cortex and ordinary systemic capillaries in that they

FIGURE 2. Descending (D) and ascending (A) vasa recta in the central core of a vascular bundle of the rabbit. The endothelium of descending vasa recta is composed of many endothelial profiles (thin arrows); tight junctions, which connect endothelial profiles, are shallow and situated near the bases of cells. The endothelium is surrounded by pericytes (P). Ascending vasa recta are extensively fenestrated (thick arrows). The interstitium between the vasa recta is sparse. —3100 X. From Jamison and Kriz (1982), by permission.
have a highly fenestrated, thin endothelium. The AVR ultrastructurally are also indistinguishable from the interconnecting capillary plexus (Schwartz et al., 1976; Jamison and Kriz, 1982).

These architectural and ultrastructural findings suggest that DVR deliver blood to the medulla and act as countercurrent exchangers with AVR, while interconnecting capillaries and AVR, with their morphologically much leakier endothelia, serve an additional role as channels to remove reabsorbed fluid and solute from the medulla.

Methods to Measure Medullary Blood Flow

Blood flow in the renal medulla differs from that of most other tissues. As a result of the countercurrent flow, the blood passes a given location twice, entering in DVR and leaving in AVR. Moreover, when considering blood flow in the medulla, it is important to distinguish between inflow and outflow of blood.

Indirect Techniques for Determining Medullary Blood Flow (Table 1)

1. Plasma Transit Time

   *Internal recording of nondiffusible tracers.* Quantitative measurements of medullary blood flow were first performed in dogs by Kramer et al. (1960) using the photoelectric recording of the local transit time of Evans Blue, a dye bound by plasma albumin. From the mean transit time of the injected dye and the blood volume as a fraction of tissue volume, blood flow in the medulla was estimated to be 0.22 ml/min per g tissue in antidiuresis, about 5% of the value for blood flow in the renal cortex. The same principle was used by Wolgast (1968) who inserted detectors sensitive to beta radiation into the medulla to measure the transit time of radiolabeled red cells (³²P) and colloidal tracers (³²P chromic phosphate) as indicators for plasma flow. Medullary blood flow averaged about 1 ml/min per g tissue in antidiuresis.

   Interpretation of values determined with this technique implicitly assumes that the insertion of the detector needle does not injure medullary tissue, and that the tracer does not recirculate during the recording interval. Neither assumption has been validated. Another theoretical problem is how to calculate the true transit time. The mean, median, or mean of the integral of the line described by the recording have each been suggested as the true transit time; the definition used influences the results (Pinter, 1969; Aukland, 1976).

   *External recording of nondiffusible tracers.* External recording in the renal venous blood of the change in concentration ("dilution curve") of albumin-bound dyes has been a popular method to determine

### Table 1

<table>
<thead>
<tr>
<th>Animal</th>
<th>Value</th>
<th>Technique</th>
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<tr>
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* Blood flow.
total renal blood flow. However, the assumption that the dilution curve usually composed of a fast and a slow component reflects blood flow in distinct renal regions has been considerably questioned (Aukland, 1976, 1980b).

2. Microspheres

Microspheres with diameters ranging from 10–80 μm are widely used in measurements of tissue perfusion. For studies of renal blood flow, microspheres with a diameter of 15 ± 5 μm are frequently employed. It is assumed that the microspheres are trapped in the glomerular capillaries in an even distribution throughout the cortex (Katz et al., 1971). The juxtamedullary glomerular content of microspheres, moreover, has been used to estimate total medullary blood flow since the efferent arterioles of the juxtamedullary glomeruli exclusively supply blood to the medulla. Bankir et al. (1979), however, showed that the microspheres are not distributed uniformly in glomeruli throughout the cortex. They are trapped disproportionately more in superficial glomeruli than in juxtamedullary glomeruli, which renders the determination of medullary blood flow with microspheres invalid (Aukland, 1980a). In any case, since microspheres are trapped in the glomerular capillaries in the cortex, they cannot be employed to assess differences in blood flow in the various regions of the medulla.

3. Diffusible Tracers—Tissue Analysis

Harsing and Pelley (1965) introduced the use of rubidium to determine renal blood flow. According to the principle outlined by Sapirstein (1956) for potassium, the uptake of 86Rb (or 42K) in tissue is a measure of regional blood flow. Karlberg and colleagues (1982) recently revived this method. From their findings and those of others (Yarger et al., 1978), it is clear that the extraction of 86Rb in the renal cortex is less than 100% and is affected by blood flow. In contrast, Karlberg et al. demonstrated that in the medulla, particularly the inner medulla, extraction of 86Rb is virtually complete and unaffected by variation in blood flow. Thus, the use of 86Rb appears to be a worthy method for determination of renal medullary blood inflow at least under physiological conditions (Aukland, 1980a). Since the tissue must be removed for analysis, it cannot be used only once per experiment, however.

4. Diffusible Tracers—Continuous Recording

Internal recording. As first shown by Kety (1951), tissue perfusion can be calculated from the rate at which a tracer is taken up by or disappears from the tissue. Provided diffusion equilibrium between capillary blood and tissue is reached immediately, the local uptake or washout curve of the tracer can be used as a measure of regional perfusion. This is practical with such tracers as Na2O, H2, 85Kr, 133Xe, and antipyrine (Aukland, 1976, 1980b; Parekh and Veith, 1981), the concentration of which can be measured locally with small detectors inserted into the tissue. Unfortunately, countercurrent exchange causes recycling of these tracers in the medulla; the clearance of these tracers is also influenced by urine flow. For these reasons, regional medullary blood flow, particularly that of the inner medulla, is systematically underestimated by this method.

External recording. External detection of 85Kr and 133Xe has been used for measuring regional renal blood flow (Barger and Herd, 1973; Aukland, 1980b). This technique has the advantages that it can be used repeatedly and does not damage kidney tissue. Calculation of medullary blood flow, however, requires compartmental analysis (see "External recording of nondiffusible tracers" above). The washout curve of the tracer is usually decomposed into three or four exponential curves, with each curve approximating a different renal compartment: I = cortex, II = juxtamedullary, III = inner medulla, and IV = perirenal fat. The assumption that compartment III, for example, always represents inner medullary blood flow has not been convincingly validated (Aukland, 1980b). On the contrary, Ladefoged (1968) has argued that compartment III represents recirculation of the tracer. Neither internal nor external recordings of inert tracers appear to be reliable for determining medullary perfusion.

5. Albumin Accumulation in the Papilla

Since its introduction by Lilienfield et al. (1961), the albumin accumulation technique has become the most popular method used to determine inner medullary (more specifically, papillary) blood inflow. Albumin labeled with radioactive 131I (Lilienfield, 1961) or 125I (Ganguli and Tobin, 1974; Solez et al., 1974) is infused into the renal circulation, and 10–60 seconds later, the blood flow to the kidney is stopped abruptly. Provided that no significant washout of incoming radioactive albumin occurs, the accumulation rate of radioactivity in this region accumulated during this time would be constant and equal to the plasma flow (Lilienfield et al., 1961). This assumption has been repeatedly questioned, however (see Bayle et al., 1982). Short pathways exist in the outer and inner medulla such that tracers disappear from the inner medulla after 10–15 seconds (personal observation). If the tracer has already left the compartment before stopping the blood flow, renal medullary plasma inflow would be underestimated. The technique has been modified by Rasmussen (1978), who used a cross-infusion technique between two rats to obtain a step-function increase in the plasma concentration of radioactive albumin in the medulla. By its nature, the albumin accumulation technique reflects only papillary blood inflow and can be used only once per animal.

6. Other Indirect Techniques

The use of the laser-Doppler technique for measurement of renal blood flow was first described by Stern et al. (1979). The kidney of a rat was illuminated with a helium-neon laser, and the light re-
flected from the renal surface was analyzed. The magnitude of the shift in the Doppler frequency of the reflected light is a measure of the change in blood velocity, and the relative intensity of the reflected light signal is related to the volume of perfusion. The primary advantage of this method is that it is noninvasive and can be used repeatedly in the same kidney, but the determination of inner medullary blood flow is unfortunately hampered by the physical size of the device. Moreover, until absolute values of blood flow can be deduced from the analysis of Doppler signals, the technique is useful only to detect relative changes in perfusion.

Direct Determination of Medullary Blood Flow (Table 2)

The direct observation of the deepest part of the inner medulla—the papilla—is possible in a few species. The golden hamster and the rat (Munich-Wistar and Wistar Furth strains), for example, have been studied because of their long extrarenal papilla, representing about 30-40% of the total axial length of the inner medulla in young animals. After the animal is anesthetized and the kidney is uncovered, the papilla is exposed by severing the ureter as close to the kidney as possible. Blood flow in individual vasa recta of the exposed papilla is then observed by microscopic techniques.

1. Light Microscopy

Direct observations of medullary blood flow were first published by Steinhausen (1964), who recorded movement of the dye Lissamine green in the vasa recta of the exposed papilla of hamsters photographically. Attempts to quantify flow velocities in vasa recta of the hamster were made by Marsh and Segel (1971). The renal papilla was exposed, and the animal was placed on a movable stage beneath a microscope. The red cell velocity in a selected vas rectum was determined by moving the stage in a direction opposite to that of the blood flow at a rate to maintain the red cells stationary in the field of view. The velocity of the stage was equal to the velocity of red cells in the capillary observed. Determined by this approach, red cell velocities averaged 0.49 mm/sec in DVR and 0.19 mm/sec in AVR. From the measured red cell velocity and the measured vasa recta diameter, blood flow in vasa recta was calculated.

Böttcher and Steinhausen (1976) employed microkymography for the measurement of red cell velocity, a technique originally introduced by Basler (1918) and subsequently modified by Castenholz (1973). With this technique, the flow of erythrocytes in a capillary is recorded as lines on a film strip oriented perpendicularly to the axis of capillary flow. The velocity of red blood cells is calculated from the speed of the moving film and the angle of the lines on the film. Erythrocyte velocities in DVR and AVR in antidiuretic rats were 0.64 mm/sec and 0.47 mm/sec, respectively. The blood flow of single vasa recta, calculated from the red cell velocity and capillary diameter, averaged 8.3 nl/min in DVR and 5.8 nl/min in AVR.

2. Videomicroscopy

Intaglietta et al. (1975) introduced the television camera as a means to study regional capillary blood flows. The movement of erythrocytes in capillaries viewed through the light microscope was recorded on videotape for off-line analysis. This permitted the determination of flow in several capillaries during the same real time by replaying the video tape. Gussis et al. (1979a) adapted this technique to young rats in which the renal papilla is exposed and viewed under epi-illumination, since the papilla is too thick for transillumination. The loss in light intensity due to the use of incident light illumination rather than transillumination was compensated by the incorporation of a high sensitivity silicon-intensified target camera, instead of the standard vidicon tube. Red cell velocities were measured with an electronic dual slit technique (Wayland and Johnson, 1967) that was adapted earlier for television techniques by

<table>
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<th>Diameter (μm)</th>
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<th>Blood flow (nl/min)</th>
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<td>DVR</td>
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</tr>
<tr>
<td>18.8</td>
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* OLM = ordinary light microscopy; FLM = fluorescent light microscopy.
† Not corrected for Fahraeus effect.
Intaglietta et al. (1975). Gussis et al. (1977a) found the mean erythrocyte velocity in vasa recta in antidiuresis of 0.36 mm/sec, but were unable to demonstrate a significant difference in erythrocyte velocity between AVR and DVR.

3. Fluorescence Videomicroscopy

Further improvement in the determination of vasa recta blood flow was made by combining fluorescence illumination with the videomicroscopy technique (Wayland, 1982). Holliger and coworkers (1983) used fluorescein isothiocyanate (FITC)-labeled γ-globulin for visualization of papillary vasa recta. This tracer remains inside the capillaries and facilitates the measurement of the diameter of vasa recta. With this technique, erythrocyte velocities averaged 1.04 mm/sec in DVR and 0.38 mm/sec in AVR. To calculate mean blood flow from erythrocyte velocity and vasa recta diameter, the authors were the first to correct the calculation of vasa recta blood flow velocity for the Fahraeus effect (Fahraeus, 1928; Cokelet, 1976); a characteristic non-Newtonian behavior of blood in tubes with diameters less than 200 μm. Erythrocytes are forced to flow in the center of the capillary, the flow region with the highest velocities, whereas plasma is not restricted from any capillary region and flows disproportionately in the periphery where it is retarded by friction with the capillary wall. As a consequence, the velocity of the red cells exceeds that of plasma. Holliger et al. (1983) used a function derived from in vitro perfusion of quartz capillaries. Mean blood velocity was about 30% less than the measured erythrocyte velocity (Holliger et al., 1983; Zimmerhackl et al., 1985c). Blood flow in vasa recta, calculated from the mean blood velocity and capillary diameter, averaged 8.83 nl/min in DVR and 4.82 nl/min in AVR, quite similar to the earlier findings of Böttcher and Steinhausen (1976). Using fluorescently labeled red cells as markers for erythrocyte flow and FITC-labeled dextrans to facilitate measurement of capillary diameter, Zimmerhackl et al. (1983a, 1983b) found that mean erythrocyte velocity in antidiuresis was 1.39 mm/sec in DVR and 0.47 mm/sec in AVR. Calculated values of volume flow uncorrected for the Fahraeus effect averaged 13.8 nl/min in DVR and 6.2 nl/min in AVR, respectively.

To convert blood flow in individual vasa recta to total papillary blood flow, Holliger et al. (1983) counted the total number of DVR and AVR in the exposed renal papilla. From histological sections of the papilla obtained at the same site where the microscopic observations were made, AVR and DVR were identified from electron micrographs according to ultrastructural criteria (Schwartz et al., 1976) and counted. Total papillary inflow in antidiuresis, calculated by multiplying the total number of DVR times the mean blood flow in DVR was 5.2 μl/min, or 2.9 ml/min per g tissue (range 1.3–5.9 ml/min per g). Total papillary outflow, calculated similarly from the number of AVR and the mean blood flow in AVR, was 11.3 μl/min and 6.3 ml/min per g tissue, respectively. These values are higher than estimates obtained using the albumin infusion technique, but the values for DVR inflow are similar to those determined by ⁸⁶Rb uptake (Balint et al., 1969; Yarger et al., 1978; Bartha and Hably, 1982).

Comments

Despite the importance of medullary blood flow, no ideal technique for its measurement has as yet been developed. Most indirect techniques provide estimates of medullary blood inflow only, not outflow. Furthermore, with many techniques, only one determination per animal is possible. One important advantage of direct methods is that they can be repeated during an experiment in the same animal. A second advantage is that blood inflow and outflow can be determined separately. The disadvantages of direct methods are that they require anesthesia and laparotomy, and excision of the ureter, which may change papillary blood flow (Chuang et al., 1978).

No completely satisfactory method is available to measure blood flow in the outer medulla; the ⁸⁶Rb uptake technique appears to offer some promise. Perhaps the laser-Doppler technique will be adapted to monitor microcirculatory changes in medullary blood flow.

Hematocrit in Medullary Vessels

Almost 30 years ago, Pappenheimer and Kinter (1956) proposed that the acute angle between the interlobular artery and the afferent arterioles supplying juxtaglomerular glomeruli could cause the capillary hematocrit in the medulla to be considerably lower than that in the renal cortex. Since the red blood cells are primarily in the center of the vessels, they would continue to flow in the interlobular artery toward the superficial cortex, while the plasma in the periphery of the capillary would be captured by the juxtaglomerular afferent arterioles—so-called plasma skimming. Using micropuncture techniques, Ullrich et al. (1961) obtained blood samples from vasa recta and found that the number of red cells and the hemoglobin concentration in vasa recta capillaries were indeed less than half their values, respectively, in the systemic circulation. The finding of a lower hematocrit in vasa recta in the inner medulla was confirmed by Wolgast (1973), Rasmussen (1974), and Zimmerhackl et al. (1983b). Aside from plasma skimming, however, several other explanations could account for the low hematocrit in the inner medulla: (1) short-circuiting of red cells in postglomerular vessels (afferent arteriole, descending vasa recta) of the outer medulla with a higher fraction of red cells than that of red cells in AVR originating deeper in the medulla; (2) the hyperosmotic interstitium of the inner medulla, which causes erythrocytes to shrink, thus lowering the hematocrit; (3) the Fahraeus effect (Fahraeus, 1928; Cokelet, 1976) (see above) according to which, at
any given moment, the fraction of red cells present in any segment of the capillary is less than the fraction of red cells in the blood of the systemic circulation. Although the Fahraeus effect decreases the capillary hematocrit in vivo (apparent hematocrit), methods using micropuncture techniques or the counting of tissue-containing labeled erythrocytes reflect the so-called discharge hematocrit, which is the actual fractional volume of erythrocyte present in a specific region. With either method, the hematocrit of vasa recta blood was found to be low (Ullrich et al., 1961; Wol gast, 1973; Rasmussen, 1974). Similarly, while a hyperosmotic milieu would reduce the hematocrit, it does not lower the number of erythrocytes per unit volume of blood or the hemoglobin concentration. As noted above, hemoglobin concentration and the number of red cells per unit volume were reduced in vasa recta relative to systemic blood (Ullrich et al., 1961; Zimmerhackl et al., 1983b). If the lowered hematocrit is due to short circuiting of erythrocytes in postglomerular vessels, the hematocrit in vessels in the outer medulla should be higher than either the hematocrit in vessels in the inner medulla or in the systemic circulation. Since the fraction of blood distributed to the papilla is small compared to the total renal blood flow, however, this skimming effect might not be detectable. Furthermore, skimming of red cells, i.e., a higher hematocrit in superficial arterioles than in the systemic circulation, was reported by Jensen et al. (1984). Consequently, at the present time, the most likely explanation for the true reduction in red cells in the vasa recta would seem to be plasma skimming in vessels upstream to juxtapamedullary glomeruli, that is, in the cortex rather than the medulla.

**Regulation of Medullary Blood Flow**

**Autoregulation of the Medullary Microcirculation**

While it is generally accepted that renal blood flow as a whole is virtually constant over a mean arterial perfusion pressure ranging from 80–150 mm Hg, the behavior of medullary blood flow over the same range is uncertain. Thurau et al. (1960) studied autoregulatory behavior in the medulla by measuring the transit time of Evans Blue. As blood pressure increased, transit time decreased, indicating a rise in medullary blood flow with pressure. These findings are frequently cited as evidence that medullary blood flow is not autoregulated. Later studies using the H$_2$ washout technique (Aukland, 1968), the transit time of labeled red cells (Graensgoe and Wol gast, 1972), or the laser-Doppler technique (Stern et al., 1979), however, did not entirely support the initial findings of Thurau et al. Cohen et al. (1983) demonstrated autoregulation in the medulla up to a mean arterial pressure of 120 mm Hg; at higher pressures medullary flow increased, although total renal blood flow continued to be autoregulated until the blood pressure averaged 140 mm Hg. Cohen and coworkers (1983) concluded that in the inner medulla the autoregulatory range of blood flow is narrower in the inner medulla than in the renal cortex.

In summary, medullary blood flow appears to be autoregulated between 80 and 120 mm Hg.

**Fluid Uptake by the Medullary Microvasculature**

Under steady state conditions, mass balance for fluid in the renal medulla requires that fluid reabsorbed from medullary tubule segments be removed from the medulla at the same rate it is reabsorbed. Since lymphatics are thought to be absent in the inner medulla, the only structures which would serve as channels for fluid removal are the interconnecting capillaries and AVR. As noted before, the ultrastructure of capillary endothelia points to the interconnecting capillaries and AVR as the site of fluid uptake. This is supported by experiments in which the plasma protein concentration in AVR was found to be significantly less than that in the DVR (Gottschalk et al., 1962; Sanjana et al., 1975, 1976; Zimmerhackl et al., 1985a). Direct estimates of fluid uptake by vasa recta were made by Hølliger et al. (1983), who determined blood flow in individual DVR and AVR by fluorescence video-microscopy and the total number of DVR and AVR (see above). The capacity of vasa recta to remove fluid from the papilla under antidiuretic conditions was estimated to range between 1.3 and 6.2 µl/min, enough to account for the volume of fluid reabsorbed from tubules in antidiuresis (Hølliger et al., 1983; Zimmerhackl et al., 1985a). The implication of these findings is that total medullary blood flow is influenced by the volume of water reabsorbed from the renal tubule in the medulla. In water diuresis, fluid removal from the inner medulla is paradoxically greater than in antidiuresis (Jamison et al., 1971), which is one reason that inner medullary blood flow is higher during water diuresis than in antidiuresis.

**Medullary Blood Flow and Urinary Concentration—Influence of Antidiuretic Hormone**

That medullary blood flow influences urinary concentration is implicit in the principle of countercurrent exchange. Experiments by Thurau and coworkers in 1960 showed an inverse relationship between urine-to-plasma osmolality (U/P$_{osm}$) and the transit time of Evans Blue. High urinary osmolality was accompanied by low medullary perfusion; in water diuretic states, medullary blood flow was high. Above a U/P$_{osm}$ of 2, however, transit time did not decrease further. More than 20 years later, Bayle et al. (1982) reinvestigated this phenomenon in Brattleboro rats, a strain that has a hereditary lack of antidiuretic hormone (ADH) and so is in a perpetual state of water diuresis. Using the albumin accumulation technique, Bayle et al. confirmed that after administration of ADH, urinary concentration is inversely correlated with medullary blood inflow.
They also observed, however, that above a urinary osmolality of 1000 mOsm/kg H2O (U/Posm approximately equal to 3.5), medullary plasma flow did not continue to decline.

Antidiuretic hormone decreases urinary flow and enhances urinary osmolality in several ways (Jamison and Kriz, 1982). It increases the osmotic water permeability of the entire collecting tubule in cortex and medulla and the urea permeability of the medullary collecting duct. It stimulates NaCl reabsorption in the medullary thick ascending limb. The net effect is to enhance the medullary hypertonicity at the same time that water is reabsorbed from the collecting duct. The basic pattern appears to be conservation of dilute fluid in the cortical collecting tubule (reduction of free water clearance to zero) and concentration of the remaining fluid in the medullary collecting duct (free water reabsorption). Exogenous antidiuretic hormone administered in a dose much greater than that necessary to mimic the endogenous hormonal effect on urinary flow and concentration causes generalized vasoconstriction (as one of its common synonyms “vasopressin” implies) and it is tempting to postulate that ADH might enhance urinary concentration by reducing medullary blood flow.

The effect of ADH in physiological doses on medullary blood flow, however, is controversial. A slight increase in medullary blood flow was observed by Persson et al. (1974) and Johnson et al. (1977), whereas others reported either no change (Gussis et al., 1979b) or a slight decrease (Thurau et al., 1960; Davis and Schnermann, 1971; Cross et al., 1974; Bayle et al., 1982; Holt et al., 1983). The inverse correlation between urinary concentration and medullary blood flow might not necessarily be the result of a direct vasoconstrictive action of ADH. Instead, it might simply reflect the influence of medullary fluid uptake since less water is reabsorbed in the inner medulla in antidiuresis than in water diuresis (Jamison et al., 1971). Recently, Zimmerhackl and his colleagues (in press) employed the synthetic selective antagonist of the vascular action of ADH (Sawyer and Manning, 1984) to determine if ADH reduces medullary blood flow directly by vasoconstriction in the medullary microcirculation. They found that administration of arginine vasopressin (AVP, the mammalian antidiuretic hormone) in physiological doses reduced both DVR and AVR blood flow, and that the decrease could be prevented by infusing a vascular antagonist of AVP along with the hormone. These findings indicate that AVP reduces medullary blood flow directly by vasoconstriction. It is highly likely that AVP also reduces medullary blood flow indirectly by decreasing the volume to be removed from the papilla in antidiuresis.

Other Factors Affecting Medullary Blood Flow

1. Prostaglandins

Prostaglandins are synthesized intensively by cells located in the interstitium of the renal medulla and by medullary collecting duct cells (Beck and Dunn, 1981). Prostaglandins E2 and F2α, are increased by a variety of stimuli (angiotensin II, bradykinin, furosemide) (Gerber and Nies, 1981; Beck and Dunn, 1981), and concentrating ability is enhanced when the production of prostaglandins is inhibited (Anderson et al., 1975). Since PGE2 and PGF2α are both vasodilators, it has been speculated that prostaglandins sustain medullary blood flow by counteracting vasoconstrictive agents (Baer and McGiff, 1980; Beck and Dunn, 1981). However, studies of the effects of prostaglandins on medullary blood flow have yielded conflicting results. In a study by Solez et al. (1974), indomethacin (5 mg/kg) administered to rats inhibited prostaglandin synthesis by 27% and decreased papillary flow from 33–21 ml/min per 100 g papilla, as determined by the albumin accumulation technique. Ganguli et al. (1977) infused rats with indomethacin, 10 mg/kg, a dose which completely abolished prostaglandin synthesis. Thirty minutes after the injection of indomethacin, papillary plasma flow decreased by 13%. However, slow infusion of the same amount of indomethacin over 5 minutes had no effect on papillary plasma flow. Bartha and Hably (1982) found no change in medullary plasma flow, measured with the 86Rb technique, after administration of indomethacin (4 mg/kg) to nondiuretic rats. Fejes-Toth et al. (1977) reported an increase in the flow to the inner renal cortex, measured by microsphere technique, after the simultaneous infusion of ADH and indomethacin. In contrast to these variable effects of prostaglandin inhibitors on medullary blood flow, as assessed by indirect methods, observation of the papillary microcirculation by direct microscopy revealed a significant decrease (−24%) in vasa recta erythrocyte velocity after inhibition of prostaglandin synthesis with either indomethacin (5 mg/kg) or meclofenamate (5 mg/kg) in antidiuresis (Jamison et al., 1981; Lemley et al., 1984).

2. Renin-Angiotensin System

After infusion of exogeneous angiotensin II in high doses, or in states of high plasma renin concentration, renal blood flow is decreased (Levens et al., 1981). Angiotensin II acts as a vasoconstrictor of efferent arterioles, thereby decreasing glomerular blood flow, as observed in superficial glomeruli (Myers et al., 1975; Ichikawa et al., 1979; Levens et al., 1981; Steinhausen et al., 1983; Zimmerhackl et al., 1985b). Angiotensin II also constricts afferent arterioles of juxtamedullary glomeruli as reported in preliminary form by Casellas et al. (1984) and Casellas and Navar (1984). Since medullary flow may be regulated by changes in blood flow to juxtamedullary arterioles, it seems likely that medullary flow is also reduced by angiotensin II. The influence of angiotensin on the intrarenal distribution of blood flow, however, is controversial. Tyssenbotn and Kirkebo (1975) found that blood flow to the outer and inner cortex in dogs was reduced proportionately; Aukland (1968) reported a decrease in total renal...
blood flow and outer medullary blood flow to the same extent. Faubert et al. (1983) reported that medullary blood flow in dogs, measured with the Lilienfeld technique, was selectively decreased after infusion of angiotensin (0.5 ng/min per kg), whereas there was no detectable effect on total renal blood flow.

3. Acetylcholine, Bradykinin, and Secretin

The effect of acetylcholine has been studied in rats (Lameire et al., 1980) and dogs (Fadem et al., 1982). In both species, renal papillary perfusion increased concomitantly with total renal plasma flow. A similar effect was observed after the administration of bradykinin; blood flow in the renal papilla increased, in proportion to total renal blood flow (Fadem et al., 1982). In contrast, after the infusion of secretin, total renal blood flow increased but papillary blood flow either remained unchanged (Fadem et al., 1982) or increased only slightly (Lameire et al., 1980).

Conclusions

The renal microcirculation is truly a unique regional capillary circulation. Like other regional circulations, it supplies oxygen to the interstitium and removes carbon dioxide and other waste products. It also removes water and solutes reabsorbed from the renal tubule, and at the same time acts as an efficient countercurrent exchanger. Despite the importance of medullary blood flow to renal function, attempts to study it have been hampered by technical problems. The greater the accuracy of the technique employed to measure medullary blood flow, the more invasive are the procedures required and the greater the risk of disturbing that which is being studied. The most promising techniques are the uptake of $^{86}$Rb, the accumulation of radioactive albumin, and fluorescence videomicroscopy. Studies using indirect techniques ($^{86}$Rb and radioactive albumin) have shown that, compared to blood flow to the renal cortex (4–5 ml/min per g), blood inflow to the outer medulla (2–3.5 ml/min per g) and inner medulla (0.3–0.8 ml/min per g) is lower. There is, however, considerable variability among the values for blood flow to the renal papilla determined by indirect techniques (0.2–2.4 ml/min per g) and a discrepancy between these values and those determined directly (1.3–5.9 ml/min per g), which is a less than completely satisfactory state of affairs. Despite these limitations, several facts seem reasonably well established. The hematocrit in vasa recta blood is approximately half that of systemic blood for several reasons, including plasma skimming, the Fahraeus effect, and the hyperosmotic interstitium. The medullary microcirculation is subject to autoregulation over a range of pressures from 80–120 mm Hg. In accord with its role as a countercurrent exchanger, medullary blood flow is highest when urinary osmolality is very low and urinary flow is high (water diuresis), and declines as urinary osmolality rises and urinary flow falls. The decline in medullary blood flow probably reflects both direct and indirect actions of ADH. Prostaglandins, at least the vasodilatory species, appear to play a role in sustaining medullary blood flow. The role of other hormones such as angiotensin, acetylcholine, bradykinin, and secretin, however, remains to be elucidated.

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