Importance of the renal medullary circulation in the control of sodium excretion and blood pressure

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MATTSON, David L. Importance of the renal medullary circulation in the control of sodium excretion and blood pressure. Am J Physiol Regul Integr Comp Physiol 284: R13–R27, 2003; 10.1152/ajpregu.00321.2002.—The control of renal medullary perfusion and the impact of alterations in medullary blood flow on renal function have been topics of research interest for almost four decades. Many studies have examined the vascular architecture of the renal medulla, the factors that regulate renal medullary blood flow, and the influence of medullary perfusion on sodium and water excretion and arterial pressure. Despite these studies, there are still a number of important unanswered questions in regard to the control of medullary perfusion and the influence of medullary blood flow on renal excretory function and blood pressure. This review will first address the vascular architecture of the renal medulla and the potential mechanisms whereby medullary perfusion may be regulated. The known extrarenal and local systems that influence the medullary vasculature will then be summarized. Finally, this review will present an overview of the evidence supporting the concept that selective changes in medullary perfusion can have a potent influence on sodium and water excretion with a long-term influence on arterial blood pressure regulation.

kidney; renal hemodynamics; renal medullary blood flow; hypertension

THE REGULATION OF RENAL MEDULLARY perfusion and the influence of alterations in medullary blood flow on sodium and water excretion have been widely studied. The renal medullary circulation arises from postglomerular branches of the vasculature of juxtamedullary nephrons to provide the blood supply to the structures of the medulla. Despite this vascular arrangement, experimental evidence indicates that medullary perfusion can be regulated independently of renal cortical perfusion. The influence of a number of circulating and local factors on medullary perfusion will then be examined, and the evidence linking changes in renal medullary perfusion with long-term changes in arterial blood pressure regulation will be summarized.

VASCULAR ARCHITECTURE OF THE RENAL MEDULLARY CIRCULATION

The kidney can be grossly divided into four zones: the cortex, the outer stripe of the outer medulla, the inner stripe of the outer medulla, and the inner medulla. The perfusion of these different regions is highly heterogeneous; total tissue blood flow averages 700 ml·min⁻¹·100 g⁻¹ of tissue in the renal cortex, is 300 ml·min⁻¹·100 g⁻¹ near the junction of the cortex and the outer medulla, decreases to 200 ml·min⁻¹·100 g⁻¹ in the inner stripe of the outer medulla, and ranges from 50 to 100 ml·min⁻¹·100 g⁻¹ in the inner medulla.
The blood entering the kidney in the large renal arteries is distributed via the arcuate and interlobular arteries to afferent arterioles and glomerular capillary tufts in the renal cortex. Approximately 90% of the renal blood flow remains in the renal cortex and perfuses the peritubular capillary bed. The remaining 10% of the blood flow perfuses the renal medulla through vessels arising from the postglomerular vasculature (i.e., efferent arterioles) of the inner cortical or juxtamedullary nephrons (19, 56, 144). As depicted in Fig. 1 (56), the efferent arterioles of the juxtamedullary nephrons enter the outer stripe of the outer medulla and divide into vasa recta that descend into the inner stripe of the outer medulla and form vascular bundles. The descending vasa recta (DVR) in the center of the bundles continue into the inner medulla whereas the DVR on the outer margins of the bundles give rise to a capillary plexus between the vascular bundles in the outer medulla. The DVR found in either the outer or inner medulla divide and eventually coalesce into ascending vasa recta that carry reabsorbed solute and water from the medulla back into the venous circulation.

Because the vessels of the medulla are branches of postglomerular vessels of the renal cortex, it is not clear how blood flow can be independently regulated in this region of the kidney. Despite this puzzle, a number of functional studies have demonstrated that blood flow in the renal medullary circulation can indeed be regulated independently of renal cortical blood flow. For example, renal medullary blood flow increases after an elevation in renal perfusion pressure (RPP) despite efficient autoregulation of renal blood flow (RBF), renal cortical blood flow, and glomerular filtration rate (GFR; 15, 78, 114). Furthermore, single nephron GFR of deep (juxtamedullary) nephrons is efficiently autoregulated in vivo (41, 111), and glomerular capillary pressure (12) and blood flow (132) are autoregulated in the in vitro-perfused juxtamedullary nephron preparation. Although the mechanisms that permit modulation of renal medullary blood flow in the absence of changes in renal cortical perfusion are not clear, evidence obtained from both morphological and physiological studies supports the view that the appropriate regulatory components can be found in the medullary circulation, and blood flow can indeed be selectively regulated in this part of the kidney.

As described above, the postglomerular efferent arterioles of the juxtamedullary nephrons descend into the outer medulla and branch into the vasa recta in the outer stripe of the outer medulla. These efferent arterioles contain up to four layers of smooth muscle and a layer of endothelial cells that is continuous as the vessels branch into vasa recta in the outer medulla (56). Although the endothelial cell layer is continuous from the efferent arterioles to the vasa recta, the smooth muscle of the efferent arterioles is gradually replaced by pericytes as the vasa recta divide and branch in the medulla (56). Pericytes are cells with a phenotype similar to that observed in vascular smooth muscle and are found in both the outer and inner medulla (86, 105). It has been demonstrated that pericytes surround the DVR in the renal medulla (86, 96); furthermore, it was demonstrated that the pericytes contain myofibrils similar to those found in vascular smooth muscle cells (44, 95). Because cultured pericytes are capable of contracting both tangentially and circumferentially (91), the pericytes are ideally situated to modulate blood flow in the vasa recta by altering vessel diameter and provide a mechanism by which blood flow within the renal medulla can be altered in response to circulating hormones or locally released paracrine and autocrine factors.

Morphological studies have demonstrated the presence of pericytes on the renal medullary vessels; these contractile cells could potentially serve to modulate blood flow in this portion of the kidney. The best evi-
dence that blood flow can be independently regulated in the medulla, however, has arisen from the work of Pallone and colleagues (98, 103, 109, 123) who have isolated and cannulated DVR for the direct study of vascular constrictor and dilator responses. The changes observed in diameter of isolated DVR that occur in response to various vasoactive agents have unequivocally demonstrated that the vascular diameter of the DVR can be independently altered. More recently, this group demonstrated changes in measurements of intracellular calcium and nitric oxide (NO) in different cell types of the isolated DVR to display not only functional responses to constrictor and dilator agents but also changes in cell signaling pathways in these vessels (103, 109). These elegant studies clearly establish that the regulation of blood flow within the renal medulla can occur independently of changes in vascular resistance in the renal cortex.

The presence of pericytes and the ability of vasoactive agents to alter the diameter of the DVR provide mechanisms that can potentially regulate blood flow to the renal medulla as well as alter the distribution of blood between regions within the medulla. Increased resistance in all of the DVR in the outer medulla would be predicted to decrease total medullary blood flow. In contrast, a preferential decrease in vascular diameter in the descending vasa recta found in the center of the vascular bundles of the outer medulla in the absence of a similar change in resistance in the vessels on the periphery of the bundles could lead to a distribution of blood to the outer medulla while decreasing inner medullary blood flow. Similarly, a selective increase in resistance in the vasa recta found on the periphery of the bundles would tend to redistribute blood toward the center of the vascular bundles and into the inner medulla. This concept is indirectly supported by studies that demonstrated that vasopressin V2 receptor stimulation preferentially increased blood flow in the renal inner medulla but did not significantly alter blood flow in the outer medulla (93), indicating that redistribution within the medulla may occur under different physiological conditions. Despite these data, the regulation of blood flow within the different regions of the medulla remains to be fully explored; circulating hormones, neural input, or paracrine and autocrine agents produced in different cell types of the renal medulla that influence smooth muscle contractility may have a significant impact on the regulation of blood flow within the kidney and also within the renal medulla.

It is important to note that changes in resistance in renal cortical vessels can also have a profound impact on blood flow to the medulla as any change in inflow resistance will be reflected in blood flow in the downstream segments of the renal medulla. Alterations in preglomerular vascular resistance are therefore likely sites that may also control renal medullary perfusion. In addition to the potential role that changes in cortical and medullary vascular diameter may have on the regulation of medullary perfusion, Casellas and Mimran (11) demonstrated the presence of vascular shunts between the afferent and efferent arterioles in ~10% of the juxtamedullary nephrons of the Sprague-Dawley rat (11). These shunt pathways could potentially open and close in response to various stimuli and lead to changes in medullary perfusion. In addition, intraluminal “valves” or “cushions” have been identified at the branching points of the interlobular arteries and the afferent arterioles of the juxtamedullary nephrons (87, 131). These valves are ridgelike structures that anatomically narrow the blood vessels perfusing the juxtamedullary nephrons and may be sites within the renal cortical vasculature where blood can be shunted from the renal medulla to the cortex. Despite the progress to date, the mechanisms by which the renal medullary circulation can be independently regulated are not completely understood, and further work must be performed to clarify this important issue.

REGULATION OF RENAL MEDULLARY BLOOD FLOW

A large number of different methods and techniques have been employed to examine the factors that regulate blood flow in the renal medulla (2, 99, 100, 112). Given the diverse nature of the renal circulation and the profound influence that changes in renal hemodynamics may have on the excretion of water and electrolytes, there has been a tremendous interest in defining the influence of neural, hormonal, paracrine, and autocrine factors on the intrarenal distribution of blood flow. Many techniques have been applied to this problem, including the extraction of indicators secreted by renal tubules, indicator-dilution curves of diffusible substances (H2, 85Kr, 133Xe, heat), and the accumulation of labeled markers (125I-albumin, 51Cr-red blood cells, radiolabeled microspheres) in the renal medulla (2, 99, 100). Intrarenal blood flow distribution has more recently been studied by using laser-Doppler flowmetry (26, 65, 78, 118, 126) and CT-scanning methods (62, 63). Blood flow in vasa recta has also been directly measured in vivo using videomicroscopy in the exposed papilla (13, 19, 50, 93, 100, 143). In addition to the above described in vivo methods, valuable in vitro approaches have been used to directly examine the influence of different vasoactive agents on vascular reactivity; among these are the isolated perfused juxtamedullary nephron preparation (10, 43, 94) and the study of freshly isolated DVR (98, 101, 103, 125). Each of these methods has been thoroughly reviewed, and each is subject to criticisms due to the assumptions required for their use, the invasive nature of some methods, and/or the inability to quantitate absolute levels of blood flow (2, 94, 100, 112). Nonetheless, with the combination of the different approaches that are available, a fairly clear picture of the different factors that can participate in the regulation of blood flow in the renal medulla has emerged.

Influence of RPP on Renal Medullary Blood Flow

The impact of alterations in perfusion pressure on renal medullary blood flow has been a topic of research interest since the mid 1960s. Although it is well ac-
cepted that total renal blood flow and blood flow in the renal cortex are well autoregulated as RPP is altered over the range of 80–160 mmHg, the literature regarding the relationship between RPP and renal medullary blood flow has been conflicting. It has been reported by a number of different groups using techniques of videomicroscopy (114); laser-Doppler flowmetry in rats, mice, and dogs (36, 78, 114, 128); transit-time measurements of Evans blue dye (135); and CT scanning (63) that renal medullary blood flow is not autoregulated as efficiently as cortical blood flow. This observation is demonstrated in Fig. 2 in which total kidney blood flow and cortical blood flow are shown to be well autoregulated, whereas both outer and inner medullary blood flow exhibit poor autoregulation in anesthetized rats (78). In contrast to those studies, other experiments using videomicroscopy (13), laser-Doppler flowmetry (68, 126), and H₂ gas clearance (32) have indicated that renal medullary blood flow is well autoregulated. The differences in autoregulation of the renal medulla in the different studies appear to be independent of the species studied or the method of measurement. Although this is a subject of some controversy, one potential explanation for the differences observed in autoregulatory behavior of the renal medullary circulation is the volume status of the animal. Roman and colleagues (78, 114) demonstrated using laser-Doppler flowmetry that acute volume expansion in rats severely diminished the autoregulatory capacity of the medullary circulation while having no effect on cortical blood flow autoregulation. Local or circulating agents released in response to changes in the volume-status of the animals under study may therefore have a profound impact on autoregulation of blood flow in the renal medulla.

### Influence of Circulating Factors and Neural Effects on Medullary Perfusion

The renal medullary circulation is under the influence of a number of extrinsic influences, including ANG II, atrial natriuretic peptide, AVP, and renal sympathetic nerves (102, 119). In general, the systems activated in response to a reduction in blood pressure or volume depletion (ANG II, AVP, renal nerves) have overall effects to lower medullary blood flow; the decrease in renal medullary perfusion is therefore consistent with the primary effects of these different regulatory systems to participate in the body’s integrated response to conserve sodium and water. In contrast, atrial natriuretic peptide, an agent released in response to stretch of the atria that causes a natriuresis and diuresis, is a medullary vasodilator. These systems have been extensively reviewed previously (4, 14, 94, 102, 119), and this review will only briefly discuss these different factors.

**ANG II.** In different studies, ANG II has been shown to have a vasoconstrictor effect on the renal medullary circulation (25, 98), no influence on the medullary circulation (80, 81), or even an increase in medullary blood flow when high doses of ANG II are administered (97). In general, the vasoconstrictor action of ANG II in the medullary circulation is attenuated by prostaglandins (19, 81, 98), NO (129, 148), and kinins (97), which lead to variable responses depending on the experimental preparation. The net effect of ANG II on blood flow in the renal medulla in vivo appears to be due to increased resistance in the efferent arterioles of the juxtamedullary nephrons (9) and/or due to direct effects of ANG II on the DVR (98). Although ANG II is a potent vasoconstrictor, the net effect of changes in circulating ANG II in the physiological range on medullary blood flow in conscious rats is minimal (35), presumably due to the counteracting effects of different vasodilatory factors.

**AVP.** Another potent circulating vasoconstrictor agent is AVP, which has been demonstrated to have renal medullary vasoconstrictor effects in vivo (29, 30, 93, 143). This circulating peptide, which is released from the posterior pituitary in response to elevated plasma osmolality or decreased blood volume, alters renal medullary perfusion in addition to its antidiuretic effects in the distal portions of the nephron. The overall effect of AVP on medullary perfusion is a balance of vasodilatory effects mediated by stimulation of the vasopressin V₂ receptor and vasoconstriction mediated by the vasopressin V₁ receptor. Increases in medullary blood flow were measured after selective V₂ receptor stimulation, whereas decreased flow followed selective V₁ receptor stimulation (30, 93). The net effect of AVP to decrease medullary blood flow in vivo may be mediated by changes in resistance in the efferent arterioles of the juxtamedullary nephrons (43) and/or due to direct effects of vasopressin on the DVR (137). Although this peptide’s tubular antidiuretic effects are well recognized, the decrease in renal medullary blood flow during stimulation of AVP may aid in...
the maintenance of the osmotic gradient in the renal medulla to permit efficient and maximal concentration of the excreted urine.

ANP. One additional circulating factor that influences blood flow in the renal medulla is ANP. This peptide, which is released from the heart in response to stretch, has been demonstrated to increase perfusion of the medulla (50, 133). This effect may be mediated by direct effects of ANP to dilate the DVR as well as effects in the renal cortical vasculature. ANP has been demonstrated to dilate the preglomerular cortical vascularization (72, 138) and has a minimal influence on the efferent arteriole (138) or even constricts the efferent arteriole at high concentrations (72). Despite the observation that ANP has a dilatory effect in the renal medullary vasculature, the functional importance of this hemodynamic response is unclear because the diuretic and natriuretic effects of this peptide occur at doses below those that influence medullary hemodynamics (50, 133).

Renal nerves. Renal sympathetic nerve stimulation, activated in response to a decrease in central venous or arterial blood pressure, has also been demonstrated to influence blood flow in the renal medulla. In addition to the multiple effects of sympathetic nerve stimulation on kidney function (21), renal nerve stimulation decreases blood flow in the renal cortex and medulla (61, 121). Pharmacological studies have demonstrated that norepinephrine, a sympathetic neurotransmitter, decreases renal medullary perfusion by stimulating α-receptors (145). Interestingly, blood flow in the renal cortex is more sensitive than medullary perfusion to renal nerve stimulation (61, 121); this may be due to the influence of α2-receptor stimulation by norepinephrine in the medulla to increase the release of NO, which opposes the vasoconstrictor effects of norepinephrine (145). The mechanism of the decrease in medullary blood flow appears to be due to a combination of a reduction in renal cortical blood flow (61) as well as direct effects of norepinephrine to vasoconstrict the DVR (141).

Influence of Local Paracrine and Autocrine Agents on Medullary Hemodynamics

As described in a number of recent reviews (94, 102, 119) there are many autocrine and paracrine agents released from blood vessels, renal tubules, and renal interstitial cells that can alter perfusion of the renal medulla. Among these factors are prostaglandins, NO, kinins, adenosine, endothelins, and superoxide. These and other local or circulating agents have been demonstrated to exhibit a profound impact on renal medullary blood flow. Moreover, the interaction between the different vasoconstrictor and dilator agents are subjects of intense current research investigation that should reveal important insight into the long-term regulation of arterial blood pressure. Each of these autocrine or paracrine factors, its effect on the medullary circulation, and the potential sources of each factor will be briefly described below.

Prostaglandins. The renal medulla is capable of producing large amounts of prostaglandins (58). Cyclooxygenase 1 and 2, the enzymes that metabolize arachidonic acid into prostaglandins E2, Fα, and Dα, are found in tubular, vascular, and interstitial cells of the renal medulla (42, 58, 142). The vasodilatory effect of prostaglandins in the renal medulla is well-recognized because administration of cyclooxygenase inhibitors leads to a profound decrease in blood flow in the renal medulla (60, 104, 117). It has been demonstrated in a number of different preparations that prostaglandins blunt the vasoconstrictor effects of ANG II (81, 98, 104), norepinephrine (104), and endothelin (125) in the renal medulla and the renal cortex (22, 43). In addition, it has been proposed that prostaglandins are released locally in the kidney in response to elevated perfusion pressure and participate in the accompanying natriuresis (120). Although it is clear that these cyclooxygenase products have potent effects on renal medullary function, the precise role and regulation of prostaglandin release in the renal medulla remains to be fully understood.

Kinin. All of the components necessary for the synthesis, cellular action, and degradation of kinins are present in the tubular, vascular, and/or interstitial cells of the renal medulla (37, 139). The kallikrein-kinin system is therefore well localized to influence renal medullary tubular and vascular function. A large amount of experimental evidence indicates that kinins have a potent vasodilatory effect in the renal medulla. Administration of bradykinin or kininase inhibitors led to an increase in renal medullary perfusion (75, 81, 116), whereas administration of a bradykinin B2 receptor antagonist led to a decrease in blood flow in the medulla (28). Moreover, bradykinin vasodilates isolated outer medullary DVR (101). The kallikrein-kinin system could potentially play an extremely important role in the control of medullary perfusion. Despite the evidence indicating that stimulation of kinin levels can influence renal medullary perfusion, the conditions and mechanisms that lead to physiological modulation of the kallikrein-kinin system are not clearly understood and remain a subject for further study.

NO. In recent years the role of NO in the regulation of renal tubular and vascular function has generated a large amount of interest (54). Blockade of NO synthase (NOS) leads to a reduction in blood flow in the renal cortex as well as the renal medulla (27, 54, 76, 82, 92). Inhibition of NO in vitro leads to constriction of the renal cortical vasculature (45, 47) and addition of L-arginine stimulates NO production in isolated DVR (109). Because NOS isoforms have been demonstrated to be present in both the tubules and blood vessels of the medulla (83, 140), local production of NO may have a potent influence on the regulation of medullary perfusion. Recent work with NOS isoform-specific inhibitors has indicated that NO derived from NOS1 and/or NOS2 has a minimal effect on blood flow in the renal medulla (48, 73, 79); although NOS3-selective inhibitors are not yet available, the current data indicate that NO derived from NOS3 is primarily involved in
the regulation of medullary perfusion (48). The physiological mediators that stimulate NO production in the medulla are not fully understood, but it is currently clear that vasoconstrictors, such as ANG II, AVP, and norepinephrine, all stimulate NO production in the medulla, and the physiological effects of these agents can be modulated by the release of NO (106, 129, 130, 145). The release and regulation of NO in the medulla is, therefore, an important and potent local modulator of blood flow in this region of the kidney, although the mechanisms that regulate NO release remain to be determined.

Free radicals. Oxygen free radicals are generated by reduction of O₂ to generate superoxide (O₂⁻), hydrogen peroxide (H₂O₂), hypochlorous acid, and hydroxyl radical. Collectively, these reactive oxygen species (ROS) favor vasoconstriction at least in part due to the reaction of NO with O₂⁻ to form peroxynitrite (ONOO⁻). Virtually all cell types in the vasculature are capable of producing ROS (33) from a large number of oxidation reactions, although O₂⁻ levels are normally converted to O₂ and H₂O₂ by superoxide dismutase (SOD). Recent evidence indicates that ROS may favor renal vasoconstriction and contribute to the development of hypertension (52). In studies with the isolated outer medullary DVR, administration of the SOD mimetic tempol enhanced NO levels and blunted ANG II-induced vasoconstriction (109). In anesthetized rats, administration of the SOD mimetic tempol increased medullary blood flow, whereas the SOD inhibitor diethyldithiocarbamic acid (DETC) decreased medullary blood flow (146). Moreover, long-term administration of DETC directly into the renal medullary interstitial space of conscious rats led to a sustained decrease in renal medullary blood flow and the development of hypertension (70). The level of oxygen free radicals therefore appears to be an important modulator of flow and function in the renal medulla.

Adenosine. Adenosine is another locally produced factor that has been demonstrated to influence blood flow in the renal medulla. In contrast to the effects of adenosine to decrease total RBF (94), infusion of adenosine has been demonstrated to increase renal medullary blood flow (85, 147) through stimulation of adenosine A₂ receptors (123, 147). Adenosine is ideally situated to modulate renal medullary blood flow because adenosine is produced by cells under conditions of hypoxia, the adenosine A₁ and A₂ receptors are present on the DVR (55), renal interstitial adenosine levels are approximately fourfold higher in the renal medulla than in the renal cortex (147), and adenosine dilates isolated DVR (123, 124). Local production of adenosine therefore appears to be an important factor that helps prevent ischemia in the renal medulla.

Endothelins. A final category of autocrine or paracrine factors that may influence blood flow in the renal medulla are the endothelins that are produced in the inner medulla (51). Endothelin-1, endothelin-2, and endothelin-3 constrict freshly isolated outer medullary DVR in a process that is blunted by prostaglandins (125). In contrast, in vivo studies in anesthetized rats indicate that endothelin-1 administration leads to a transient renal medullary vasodilation, which is mediated by endothelin ET₃ receptors and may involve NO and/or prostaglandins (39). The role of endothelins in the regulation of medullary blood flow remains to be further examined.

Renal medullary oxygen consumption and PO₂. In addition to the large number of locally produced factors that may influence medullary perfusion, local oxygen consumption is also a likely determinant of blood flow in the renal medulla. There is a steep decrease in the partial pressure of oxygen (PO₂) from the renal cortex to the medulla (3, 7, 8, 59), with the PO₂ in the renal cortex averaging 50–70 mmHg and the PO₂ in the medulla averaging less than 20 mmHg (7, 8). Because active tubular transport in different regions of the medulla, particularly in the outer medulla, is important for integrated function of the kidney, the oxygen supply to these segments can be a critical factor. Evidence for local metabolic control of medullary perfusion was provided in studies by Brezis et al. (7, 8). It was observed that furosemide and other loop diuretics, which block transport in the thick ascending limb and therefore decrease tubular oxygen consumption, led to an increase in renal medullary PO₂ and a decrease in medullary blood flow (7). These experiments raised the possibility that local metabolic needs may be matched by perfusion in the medulla. A number of different locally produced mediators, including adenosine, may be included in this response. Recent studies by Zou et al. (149) indicated that hypoxia inducible factor-1α, a transcription factor that regulates the oxygen-dependent expression of a number of genes, is modulated in the renal medulla by changes in PO₂. Changes in local oxygen consumption and PO₂ are therefore important factors in the regulation of renal medullary perfusion.

There are clearly a large number of factors capable of influencing perfusion of the renal medulla. Although a fairly extensive understanding of the effects of the different circulating and local systems currently exists, a complete understanding of the factors that lead to the stimulation or inhibition of the different systems in health and disease is currently lacking. This is particularly true in the case of the different autocrine and paracrine agents, the regulation of which is just beginning to be elucidated. In addition, a number of different local or circulating factors, including different metabolites of arachidonic acid, various fibrinolytic factors, and other paracrine and autocrine factors that affect vascular tone, capillary permeability, and/or blood coagulation all have the potential to affect hemodynamics in the renal medullary circulation and, through the mechanisms reviewed below, influence fluid and electrolyte homeostasis and arterial blood pressure.

**IMPORTANCE OF THE KIDNEY IN BLOOD PRESSURE CONTROL**

To appreciate the importance of renal medullary blood flow in the control of arterial blood pressure, one must first accept the important role of the kidney in the
The theoretical importance of the kidney in the control of arterial blood pressure and the concept that alterations in renal function lead to adjustments in arterial blood pressure was first introduced by Guyton and colleagues (40) and has been reviewed extensively (14). Although arterial blood pressure is controlled by many regulatory systems, it is proposed that the kidney, through its ability to regulate extracellular fluid volume, is the dominant long-term controller of arterial pressure.

The most convincing data that demonstrate the importance of the kidney in the development and maintenance of hypertension have been obtained from renal transplant studies in patients and experimental animals (108, 122). Renal transplant studies performed between hypertensive and normotensive strains of rats have demonstrated that the long-term level of arterial pressure in the recipient is dependent on the genetic background of the donor kidney. Transplantation of the kidney from the Dahl salt-sensitive rat, the Milan hypertensive rat, the spontaneously hypertensive rat (SHR), the stroke-prone SHR, and the Prague hypertensive rat to the appropriate normotensive recipients results in hypertension in the recipient (14, 74). The opposite experiments have also been successfully performed; kidney transplantation from a normotensive donor to a genetically hypertensive recipient normalizes arterial blood pressure in the recipient. These convincing results have been obtained in the absence of any signs of immunological rejection of the renal graft and indicate that the level of blood pressure in the recipient is critically dependent on the donor kidney.

Similar data have been obtained from clinical studies. It was first demonstrated that mean arterial pressure was significantly higher in patients who received a renal transplant from a donor with a family history of hypertension than in patients whose donor family had a normotensive history (38). Second, patients who received a transplant from a hypertensive donor had higher blood pressures compared with patients who received kidneys from normotensive donors (127). Finally, transplantation of a kidney from a normotensive donor produced a sustained normalization of arterial pressure in hypertensive patients who had demonstrated long-standing essential hypertension (20). These clinical data emphasize the importance of the kidney in the development and maintenance of hypertension in humans and experimental animals.

ROLE OF RENAL MEDULLARY HEMODYNAMICS IN THE CONTROL OF SODIUM EXCRETION

Transplant studies established the role of the kidney in arterial blood pressure regulation, but the intrinsic renal mechanisms that regulate arterial pressure are not revealed by these experiments. The kidney could influence blood pressure regulation by altering renal afferent nerve activity (21), releasing vasoactive factors into the circulation (5), or by altering extracellular fluid volume through a number of different mechanisms (17). Although these and other influences of the kidney may be important in the regulation of arterial blood pressure, the remaining portion of this review will focus on the role of renal medullary perfusion in the regulation of fluid and electrolyte excretion and arterial blood pressure.

Some of the initial data implicating changes in blood flow in the renal medulla as an important mechanism in the regulation of sodium and water excretion arose from observations made during the infusion of different pharmacological agents into the kidney. It was demonstrated that intrarenal arterial infusion of the vasodilators secretin, acetylcholine, and bradykinin all led to an equivalent increase in renal blood flow, yet only during the administration of bradykinin and acetylcholine was an increase in renal interstitial hydrostatic pressure and sodium excretion observed (23, 57, 71). Of the three vasodilators, only acetylcholine and bradykinin increased blood flow in the inner medulla, whereas secretin (which increased total renal blood flow) did not affect renal medullary blood flow (23, 57). These pharmacological data have been interpreted to indicate that dilation of the renal medullary circulation can have a natriuretic and/or diuretic effect.

Further evidence supporting the importance of the renal medullary circulation arose from work performed to discern the mechanism of the pressure natriuretic response. A direct increase in RPP leads to increased sodium and water excretion in the isolated perfused kidney (1, 136) as well as kidneys studied in vivo (67–69, 80, 111, 113, 114) in the absence of measurable changes in whole kidney RBF or GFR. In addition, it has been clearly demonstrated that the hydrostatic pressure in the postglomerular capillaries in the renal cortex, the peritubular capillaries, is also constant as RPP is increased (113, 114). In vivo experiments using laser-Doppler flowmetry, videomicroscopy, servo-null micropressure measurements, and micropuncture were used to examine the intrarenal mechanisms that mediate the increase in excretion after an increase in RPP (111, 114). Despite the autoregulation of GFR and RBF, blood flow in the vasa recta capillaries of the renal medulla was demonstrated to increase directly with RPP in normal mice, rats, and dogs (5, 24, 36, 46, 78, 114, 128). The increase in flow in this capillary bed in the renal medulla is coincident with an increase in vasa recta hydrostatic pressure (114), increased renal interstitial hydrostatic fluid pressure (31, 107, 114), decreased reabsorption of sodium and water from the proximal segments of deep nephrons (41, 111), and increased excretion of sodium and water (113, 114). Together with the results of the pharmacological studies described above, the results of these experiments implicate the medullary circulation in the control of renal fluid and electrolyte excretion, although a direct relationship between a primary change in medullary perfusion and the resultant effects on excretion was not established.
Influence of Selective Alterations in Renal Medullary Perfusion on Sodium and Water Excretion

To test the hypothesis that the medullary circulation is important in the regulation of sodium excretion and blood pressure, experimental techniques were developed to selectively manipulate blood flow in the renal medulla. Polyethylene catheters with a 100-μm diameter tip were inserted directly into the medullary interstitial space, and experimental solutions were delivered at a rate of ~8.3 μl/min (66, 75). Autoradiographic and functional studies demonstrated that this infusion method localizes infused compounds in the renal medullary interstitial space. In addition, to monitor changes in blood flow that occurred during interstitial infusion of different agents, optical fibers for laser-Doppler flowmetry were implanted into the renal cortical and medullary tissue. This technique was demonstrated to provide a reproducible value for periods of 2–3 wk with reproducible changes to an ANG II bolus injection (65). Moreover, it was demonstrated that the chronic implantation of optical fibers and infusion into the medullary interstitial catheter did not significantly alter renal hemodynamics, urine flow, sodium excretion, or the maximal ability of the kidney to concentrate urine (65, 77).

Experiments in anesthetized rats demonstrated that renal medullary interstitial infusion of bradykinin, diltiazem, or the SOD mimetic tempol led to a selective increase in renal medullary blood flow (66, 75, 146). In contrast, infusion of vasoconstrictors such as the NOS inhibitor Nω-nitro-L-arginine methyl ester (L-NAME) or the SOD inhibitor DETC resulted in a selective reduction in medullary blood flow (82, 146). Furthermore, clearance studies performed during acute administration of these compounds confirmed the concept that selective changes in renal medullary blood flow lead to changes in sodium excretion. As summarized in Fig. 3, renal medullary interstitial infusion of L-NAME (120 μg/h) to anesthetized Sprague-Dawley rats decreased renal medullary blood flow by 29% and led to a decrease of sodium and water excretion by ~35%. The selective change in medullary hemodynamics significantly decreased renal interstitial hydrostatic pressure by 23% without altering GFR or superficial cortical blood flow in the infused kidney. Mean arterial pressure and contralateral kidney hemodynamic and excretory function were also unchanged, indicating minimal recirculation of the infused L-NAME in this acute study (82). Similar results were observed when the SOD inhibitor DETC was administered into the medullary interstitial space of anesthetized rats (146).

In contrast to the effects of selective renal medullary constriction, infusion of the vasodilators bradykinin and diltiazem or the SOD mimetic tempol led to a selective increase in medullary blood flow that was accompanied by a natriuresis and diuresis (66, 74, 75, 146). As an example, renal medullary interstitial infusion of bradykinin increased medullary blood flow by 17% and doubled sodium and water excretion without altering GFR or RBF (75). Together, these studies demonstrated that acute increases or decreases in renal medullary blood flow are associated with selective changes in renal medullary blood flow and parallel alterations in sodium and water excretion.

Long-Term Influence of Renal Medullary Hemodynamics on Fluid and Electrolyte Balance and Blood Pressure

Renal medullary vasoconstriction in normotensive rats. The above experiments described the relationship between acute changes in renal medullary perfusion and renal sodium excretion; but the influence of sustained changes in renal medullary blood flow on the long-term regulation of fluid and electrolyte excretion and arterial blood pressure remained to be determined. Experiments were then performed to determine the influence of continuous renal medullary interstitial infusion of vasoconstrictors or vasodilators on sodium balance and blood pressure. The results of long-term blockade of NOS in the renal medulla of normotensive Sprague-Dawley rats are summarized in Fig. 4 (77). Chronic interstitial L-NAME (8.6 mg·kg⁻¹·day⁻¹) significantly decreased renal medullary blood flow by 30% throughout the 5 days of infusion. The decrease in medullary blood flow was accompanied by a significant retention of sodium, an increase in body weight (data not shown), and the development of hypertension. When the interstitial L-NAME infusion was discontinued, renal medullary blood flow returned to control levels, the rats went into a negative sodium balance, and blood pressure returned to levels not different from control. Results of this experiment indicate that a selective, sustained decrease in medullary perfusion can lead to retention of sodium and development of hypertension. This concept was recently confirmed in a study by Makino et al. (70) in which Sprague-Dawley rats were administered the SOD inhibitor DETC into the renal medullary interstitial space for 5 days. It was observed that continuous infusion of DETC led to a
sustained decrease in renal medullary blood flow that was accompanied by an increase in mean arterial pressure in the absence of any changes in renal cortical blood flow. Together, these two studies support the concept that the medullary circulation is important in the long-term regulation of fluid and electrolyte balance and blood pressure.

Renal medullary vasodilation in hypertensive rats. Because chronic vasoconstriction of the renal medullary vasculature led to sodium retention and hypertension in normal rats, experiments were performed to determine if a sustained increase in renal medullary perfusion would normalize arterial blood pressure in hypertensive rats. The SHR has a blunted pressure natriuretic-diuretic response (110) and a reduced level of renal inner medullary blood flow (115) compared with its normotensive Wistar-Kyoto control rat. The angiotensin-converting enzyme inhibitor captopril was therefore delivered directly into the medullary interstitium of SHR rats at a dose that had no effect when infused intravenously (64). Angiotensin-converting enzyme inhibitors are thought to increase medullary blood flow in the rat by decreasing ANG II formation and/or decreasing kinin degradation (81, 116). A 5-day continuous renal medullary interstitial infusion of captopril increased medullary blood flow in conscious SHR by 40%, did not alter renal cortical blood flow, and led to a 20-mmHg fall in arterial pressure. Accompanying this decrease in arterial pressure was an unloading of sodium as indicated by negative daily sodium balance. Combined, the data in which l-NAME or DETC was administered to normal rats and captopril was given to SHR indicate that direct alterations in renal medullary blood flow can lead to changes in sodium and water excretion. These long-term changes in fluid and electrolyte balance translate into sustained alterations in sodium balance and a new level of arterial blood pressure.

Postulated Mechanisms through Which Changes in Renal Medullary Hemodynamics May Alter Sodium Excretion

Changes in Renal Interstitial Hydrostatic Pressure and Washout of the Medullary Gradient

As described above, there is a fair amount of data demonstrating that changes in renal medullary perfusion are associated with alterations in sodium excretion. Despite these observations, the mechanistic link between changes in hemodynamics in this portion of the kidney and the observed alterations in sodium and water excretion are not clear. Work by Roman and colleagues (114) indicated that renal medullary blood flow and vasa recta capillary hydrostatic pressure in the anesthetized rat increased directly with elevations in RPP in volume-expanded rats. Further studies demonstrated that this alteration in medullary blood flow was associated with increased renal interstitial hydrostatic pressure and decreased reabsorption of sodium and water in the proximal tubule and/or thin descending limb of deep nephrons (111). From these data, it has been theorized that the increased hydrostatic pressure in vasa recta alters Starling forces for reabsorption in the medulla, which results in an elevation of renal interstitial pressure. An elevated renal interstitial hydrostatic pressure is then postulated to lead to an inhibition of tubular reabsorption by increasing backleak in the proximal tubule or thin descending limb of Henle (16, 17, 74, 119). Alternatively, the increase in medullary blood flow has been postulated to lead to a dissipation or “washout” of the medullary interstitial osmotic gradient and thereby lead to alterations in tubular sodium and water reabsorption by changing the osmotic forces surrounding the tubules (100). A mechanistic link between changes in medullary perfusion and tubular sodium handling has not, however, been established and is an important challenge facing investigators in this field.

Release of Anti hypertensive Factors from the Renal Medulla

An alternative mechanism that may also have an important impact on blood pressure during long-term alterations in renal medullary blood flow is the release of an antihypertensive depressor substance from the interstitial cells of the renal medulla (88). Evidence for
the release of an antihypertensive substance from the kidneys arose from studies by Grollman and colleagues (34). They observed that hypertension occurs after bilateral nephrectomy (renoprival hypertension) or ureteral ligation but hypertension did not occur in dogs in which the ureters were anastomosed to the vena cava. From these and other experiments it was proposed that the kidney releases an antihypertensive substance important in the long-term control of arterial blood pressure (134). Subsequent studies by Muirhead et al. (90) demonstrated the reversal of renoprival hypertension when explants of the renal medulla, but not the renal cortex, were implanted in different parts of the body. Moreover, the effects of the renal medullary explants were mimicked by subcutaneous implantation of renal medullary interstitial cells in Goldblatt hypertensive rats (89). From these and a number of other experiments it was concluded that a renal medullary antihypertensive lipid, termed medullipin I, is secreted from the renomedullary interstitial cells and converted to medullipin II by cytochrome P-450 enzymes in the liver. Medullipin II is hypothesized to be the active substance that leads to vasodilation and suppression of sympathetic tone (88, 134). Further studies in the isolated, cross-perfused kidney preparation have indicated that the level of RPP may regulate the release of this antihypertensive substance (49). Because an elevation of RPP has been demonstrated to increase blood flow in the renal medulla, changes in renal medullary blood flow may very well alter the release of medullipin I, which could participate in the long-term regulation of arterial blood pressure. To date, the structure of medullipin is not known, although experimental data indicate that medullipin is not a prostaglandin, platelet activating factor, or NO. A great deal of experimental work remains to elucidate the role and regulation of this intriguing system.

The potential role of changes in interstitial hydrostatic pressure, the medullary concentrating gradient, and/or the release of antihypertensive substances from the renal medulla during increases in medullary perfusion is illustrated in Fig. 5. It is clear that increased vasodilatory agents, decreased vasoconstrictor factors, and/or increases in RPP can all lead to an elevation of medullary perfusion. The increase in medullary perfusion is then proposed to result in an increase in medullary interstitial hydrostatic pressure and a loss of the medullary concentrating gradient resulting in decreased tubular sodium reabsorption. The decrease in tubular sodium reabsorption translates into natriuresis and diuresis, a decrease in extracellular fluid volume, and a reduction in arterial blood pressure. Alternatively, the increase in medullary perfusion may lead to the release of medullipin I, which is converted to medullipin II in the liver. The active medullipin II could then exert vasodepressor effects on the vasculature, leading to a decrease in total peripheral resistance and a fall in mean arterial pressure. Although
the exact mechanisms linking changes in medullary perfusion to alterations in arterial blood pressure are not known, this schematic represents a possible integration of these two important systems for the long-term regulation of arterial blood pressure.

**Perspectives**

This review presented a large amount of evidence indicating that the renal medullary circulation is important not only in the supply of nutrients to the renal medulla and the uptake of reabsorbed solute and water but also in the regulation of fluid and electrolyte excretion and in the long-term maintenance of arterial blood pressure. Despite these data, there is still an enormous amount of work to be done to fully understand the regulation of blood flow in this part of the kidney and the mechanisms whereby changes in blood flow can translate into alterations in arterial blood pressure.

First, the means through which blood flow in the renal medullary circulation can be selectively altered in the face of undetectable changes in renal cortical blood flow are not clearly defined. Although pericytes on the DVR may contract and dilate in response to various agents and lead to an alteration of the distribution of blood flow within the renal medulla, it is unclear how such a mechanism can lead to active recruitment of blood flow from the renal cortex or shunting of blood flow away from the medulla in the absence of changes in cortical perfusion. Similarly, the glomerular shunts and the intra-arterial cushions observed in the vasculature of the deep glomeruli may provide a mechanism to transfer blood from the renal cortex to medulla, but the regulation and importance of these structures is not clearly defined. The mechanisms that permit blood flow in the renal medulla to be selectively altered remain to be fully elucidated.

Second, although a large amount of information exists regarding different circulating and paracrine factors that regulate medullary blood flow, the stimuli that activate and inactivate many of these systems are largely unknown. For example, although many of the stimuli that regulate circulating levels of AVP, the renin-angiotensin system, and renal sympathetic nerve activity have been well described, the sources and mechanisms of regulation of NO, ROS, prostaglandins, kinins, and other locally produced factors are not well understood. Studies aimed toward a more complete understanding of the regulation of the release and actions of these different factors as well as the potential interactions between the different systems should provide a large amount of work for researchers in this field.

Third, the data in this review emphasized the influence of different agents infused into the renal medullary interstitial space that led to selective increases or decreases in medullary blood flow with corresponding changes in sodium and water excretion and blood pressure. Although these data support the concept that the rate of blood flow in the renal medulla is important in the regulation of renal fluid and electrolyte handling, it is important to note that these agents could also have directly influenced tubular sodium and water handling or led to the release of a factor or factors that led to an alteration in tubular sodium handling. The reviewed experiments do not therefore prove that changes in medullary blood flow lead to changes in sodium and water excretion; they simply demonstrate that a correlation exists between changes in blood flow and sodium and water excretion. Until specific tools are developed, perhaps using transgenic or knockout mouse technology, it will be difficult to demonstrate unequivocally that changes in medullary blood flow alter sodium and water excretion. Moreover, the mechanisms that transduce changes in medullary flow into changes in tubular sodium handling also remain to be elucidated.

In conclusion, the integrated actions of a large number of circulating and local agents act to regulate vascular and tubular function in the renal medulla. Experimental evidence indicates that alterations in perfusion in this part of the body can have a marked impact on urinary concentrating ability, tissue oxygenation, fluid and electrolyte handling, and blood pressure regulation. Alterations in blood flow in the renal medullary circulation can therefore have a significant impact on function at the level of the renal medulla, the whole kidney, and the entire body.

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**REFERENCES**


55. Krebs MS, Sildorff EP, and Pallone TL. Localization of adenosine-receptor subtype mRNA in rat outer medullary de-


