

REGULATION OF RENAL HEMODYNAMICS

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Beginning the renal physiology section with a detailed consideration of renal microvascular dynamics allows a smooth transition from cardiovascular-related topics to kidney-related topics. In addition, reductions in renal blood flow (RBF) and glomerular filtration rate (GFR) are often associated with many pathophysiological conditions including hypertension, renal failure, heart failure, and diabetes, and it is essential for the student to obtain a solid foundation regarding the principal mechanisms regulating renal hemodynamics. The following learning objectives provide a clear guide for the student. 1) Be able to define and calculate the renal fraction of the cardiac output and the factors that influence it. 2) Know the average values for RBF and GFR in adult humans. 3) Be able to define and calculate the filtration fraction. 4) Know the major sites of renal vascular resistance and describe the hydrostatic pressure profile along the renal vasculature. 5) Describe the roles of hydrostatic and colloid osmotic pressures in regulating glomerular and peritubular capillary dynamics. 6) Explain in a quantitative manner the determinants of GFR and how these are regulated. 7) Identify the extrinsic, neural, and hormonal systems that regulate renal hemodynamics. 8) Describe the roles of the major paracrine systems that participate in the intrinsic control of renal vascular resistance. 9) Define the phenomenon of renal autoregulation and describe the myogenic mechanism and the tubuloglomerular feedback mechanism in mediating autoregulatory behavior. It is not possible to discuss all these learning objectives in the present article. Consequently, attention has been focused on those aspects that are conceptually more difficult or that cause confusion among the students. In particular, the recent recognition of multiple humoral and paracrine factors regulating renal microvascular dynamics requires a very discriminating selection of specific topics.

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The renal circulation is sometimes briefly described during the cardiovascular section of a physiology course, but this is often not done from the perspective of a renal physiologist. Because of the unique characteristics of the renal microvasculature, it has always seemed more appropriate to me to begin the section of the course dealing with renal, fluid, and electrolyte physiology with a detailed consideration of intrarenal microcirculatory dynamics and the factors regulating the renal circulation. Renal hemodynamics is an integral aspect of renal physiology because the intrarenal

hemodynamic environment determines the formation of the glomerular filtrate, the reabsorption of fluid by the peritubular capillaries, and the maintenance of a hyperosmotic medullary environment (1). These forces are controlled by the vascular smooth muscle cells of the renal vasculature, which respond to a myriad of neural, hormonal, and paracrine stimuli. Because of the close association between renal hemodynamics and renal excretory capability, it is important that the student achieve a clear understanding about the control of renal hemodynamics. Indeed, there are

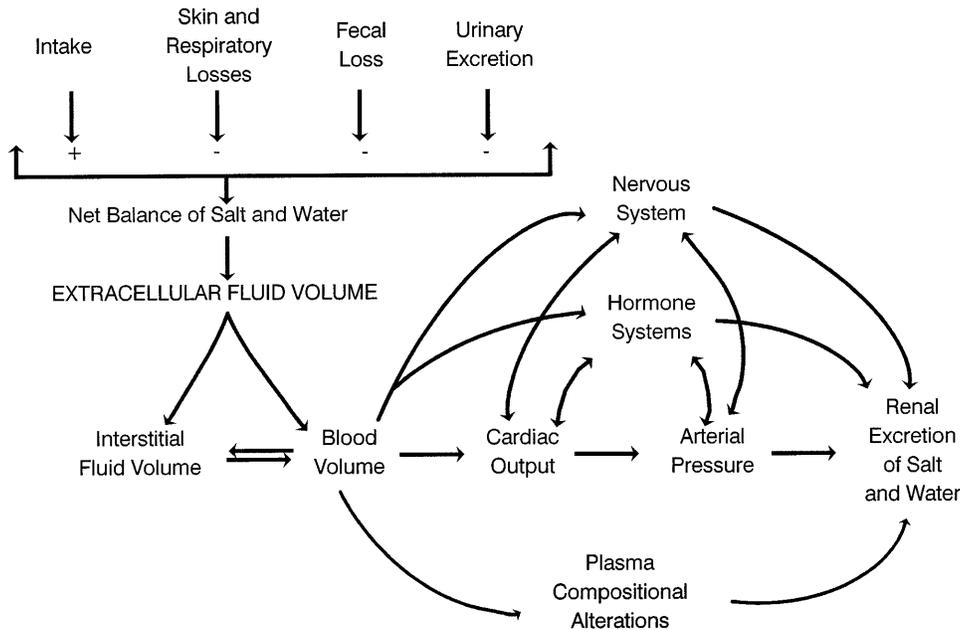


FIG. 1.
Salt and water homeostasis. Interrelationships among salt and water intake, extracellular fluid volume, cardiovascular function, and renal function are shown.

many clinical problems that are linked to derangements in renal hemodynamics, and assessment of glomerular filtration rate (GFR), either directly or indirectly, based on plasma creatinine concentrations, is an important part of most nephrological exams.

Recent developments related to endothelial factors regulating vascular smooth muscle cells and the formation of numerous vasoactive agents by the epithelial cells have revealed the complexity of the various humoral and paracrine systems interacting to control renal hemodynamics (28). It is clearly not possible to cover all of these aspects in the limited time available in the medical physiology course, and thus difficult decisions must be made regarding the appropriate depth necessary to provide students with an adequate understanding of renal hemodynamics.

Starting the section on renal physiology with a discussion of overall cardiovascular dynamics and renal hemodynamics allows a smooth transition from cardiovascular-related topics to kidney-related issues. As an entry point, I start with an overall discussion of salt and water homeostasis, which links the long-term control of blood volume, cardiac output, and arterial pressure with sodium balance and the control of

extracellular fluid volume, using an illustration shown in Fig. 1. This drives home the concept championed by Homer Smith, "In the last analysis, it is the ability of the kidneys to respond rapidly and appropriately to deviations in body fluid volume and composition that enables us to maintain a constant internal environment."

THE MAGNITUDE OF RENAL BLOOD FLOW

Once the more holistic issues are covered, it becomes easier to explain the huge magnitude of renal blood flow (RBF). About 20% of the cardiac output (renal fraction) goes to the kidneys, which means that, expressed per unit of weight, RBF is 10–50 times greater than for most other organs. It is also worthwhile to emphasize that the RBF is far in excess of what is needed to provide the O₂ and metabolic needs of the kidneys. Even though O₂ consumption by the kidneys per unit of organ weight is still very high because of the extensive activity of the sodium-potassium ATPase in the transporting epithelial tissues, the supply is many times greater than needed (1). The exception is the renal medulla. Because of the unique countercurrent arrangement of the vasa recta, there is substantial O₂ shunting from the descending

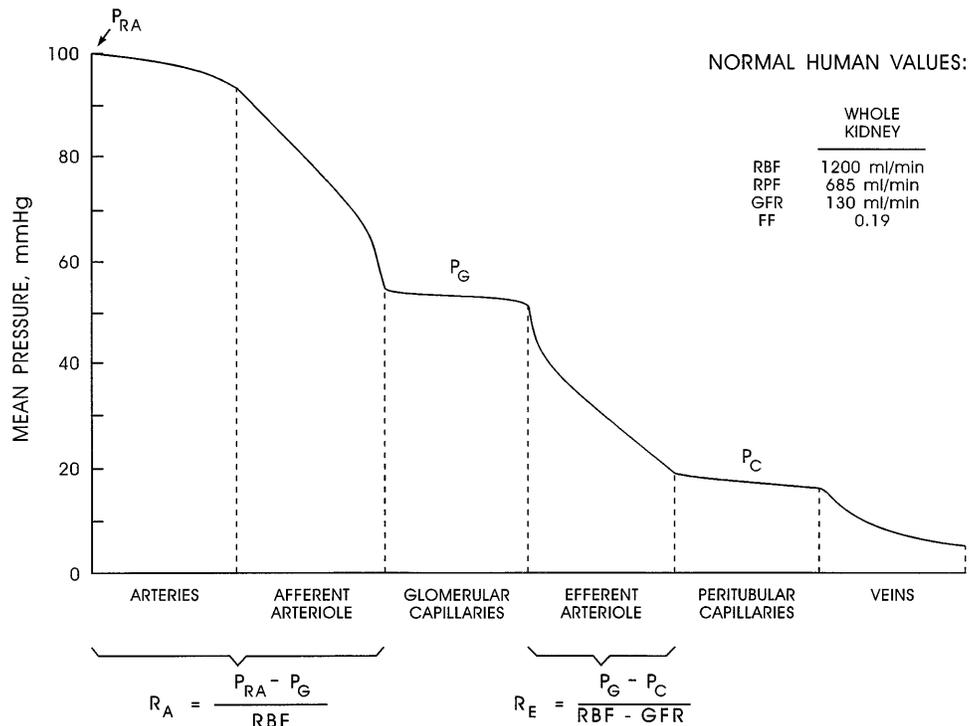


FIG. 2.

Representative hydrostatic pressure profile along nephrovascular unit. Equations for calculating preglomerular (afferent) and efferent resistances and normal values for humans are provided. R_A and R_E , afferent and efferent arteriolar resistances; RBF, renal blood flow; RPF, renal plasma flow; P_{RA} , renal arterial pressure; P_G , glomerular pressure; P_C , peritubular capillary pressure; GFR, glomerular filtration rate; FF, filtration fraction.

vasa recta to the ascending vasa recta, and thus the O_2 supply to the deep medullary structures is rather limited, requiring a greater degree of anaerobic metabolism in this region. Nevertheless, the very high blood flow perfusing renal cortical tissue has led to the conclusion that the mechanisms that regulate RBF are distinct from the metabolically linked mechanisms that regulate blood flow to other tissues.

THE NEPHROVASCULAR UNIT

It is extremely important to go over the characteristics of the nephrovascular unit in detail and emphasize the unique nature of the dual microvascular beds that are in series, namely, the glomerular and postglomerular vascular beds, and also the important differences between the cortical peritubular vasculature and the medullary vasculature (25, 26). A review of the critical morphology is appropriate. The differences in the forces operating within the glomerular and peritubu-

lar capillary systems should also be discussed in detail. A diagram such as that of Fig. 2 describing the hydrostatic pressure profile along the nephrovascular is very useful. The diagram helps the student understand the specific roles of the preglomerular resistance, which is localized primarily to the afferent arterioles, and the postglomerular resistance, which is imposed primarily by the efferent arterioles. The "nesting" of the glomerular capillaries between the afferent and the efferent arterioles allows the maintenance of a high glomerular pressure that can be regulated very precisely. The diagram helps explain that the high glomerular pressure is primarily responsible for formation of filtrate and that the low hydrostatic pressure within the peritubular capillaries allows the elevated plasma colloid osmotic pressure to predominate and thus be responsible for the return of the tubular reabsorbate to the circulation. Once the qualitative considerations are clearly established, it is

then useful to analyze glomerular dynamics quantitatively so that the students obtain a clear understanding of the determinants of effective filtration pressure.

GLOMERULAR DYNAMICS AND GFR

Consideration of glomerular dynamics has been clouded somewhat by the concept of “filtration equilibrium” and its significance (17). The available texts treat this issue very differently, and this topic often causes a great deal of confusion among the students. However, the concepts can be explained reasonably well without going into excessive detail.

The filtration process can operate under one of two conditions. The first condition is the case in which filtration continues throughout the entire length of the glomerular capillaries and in which there remains a finite positive effective filtration pressure at the efferent end of the glomerular capillaries. This pattern of continued filtration throughout the glomerular capillaries is thought to be the norm in humans and is depicted in Fig. 3. Under these conditions, the average

values for the intraglomerular determinants provide a close approximation of the actual integrated values, and the following equation is sufficient

$$GFR = K_f(P_G - P_B - \bar{\Pi}_G)$$

where K_f is the filtration coefficient, P_G is the glomerular hydrostatic pressure, P_B is the counteracting pressure in Bowman’s space, and $\bar{\Pi}_G$ is the average colloid osmotic pressure in the glomerular capillaries. The terms within parentheses define the effective filtration pressure (EFP).

A detailed discussion of the regulation of the filtration coefficient is beyond the scope of the first-year course because there is still no clear consensus on how much physiological regulation there is; nevertheless, the important role of decreases in the filtration coefficient in certain pathophysiological conditions such as hypertension, diabetes, and glomerulosclerosis should be explained. This can occur as a consequence of changes in either the surface area or the hydraulic conductivity.

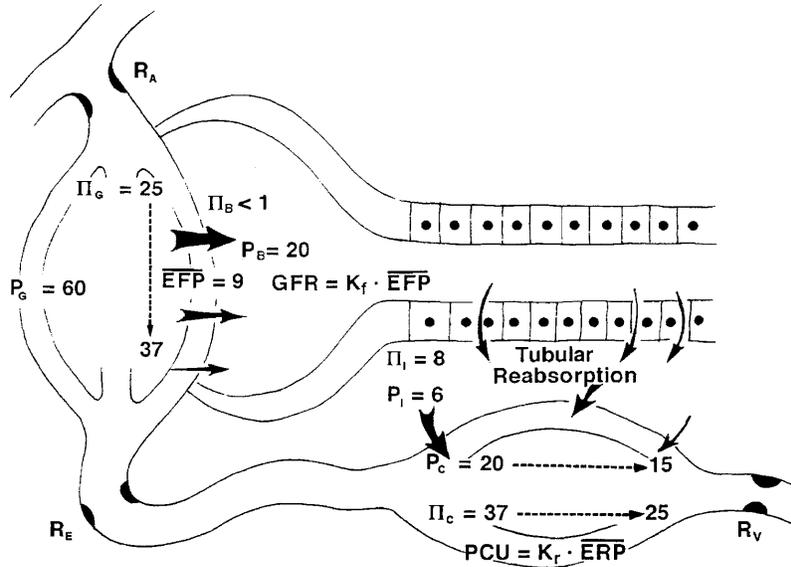


FIG. 3.

Summary of glomerular and peritubular capillary dynamics with representative values for humans. EFP, effective filtration pressure; Π_G , Π_C , and Π_I , plasma colloid osmotic pressure in glomerulus, peritubular capillaries, and renal interstitium, respectively; R_v , vascular resistance of renal venous system; K_f , glomerular filtration coefficient; PCU, peritubular capillary uptake; ERP, effective reabsorptive pressure; K_r , reabsorption coefficient of peritubular capillaries.

The alternative filtration process occurs when the increase in colloid osmotic pressure within the glomerular capillaries is so rapid that the forces opposing filtration become equal to the forces favoring filtration at some point within the capillary system. This condition is termed *filtration equilibrium* (17). Under equilibrium conditions, the latter part of the available filtering surface area is not utilized and becomes a *functional reserve*. Under conditions of filtration equilibrium, an increase in plasma flow minimizes the increase in colloid osmotic pressure along the length of the glomerular capillaries. Thus effective filtration pressure is not dissipated as quickly, and the point of equilibration of hydrostatic and colloid osmotic forces is moved toward more terminal sites, which, in effect, results in recruitment of additional filtering surface area and an increase in the functional K_f . Consequently, increases in plasma flow will increase the GFR proportionately even when glomerular capillary pressure is unchanged. In the case of filtration disequilibrium, increases in plasma flow increase GFR only modestly as a consequence of a reduced colloid osmotic pressure profile, and there is no net recruitment of previously unused surface area. Thus the magnitude of the effects of selective increases in plasma flow is greater during filtration pressure equilibrium than during nonequilibrium conditions. In either case, however, the hydrostatic pressure gradient is still the most significant determinant of GFR (1). It is sometimes suggested erroneously that glomerular pressure is not the main determinant of GFR when the system is in filtration equilibrium. In humans, the low filtration fraction and the relative lack of plasma flow dependence of GFR indicate that the filtration process continues throughout the entire length of the glomerular capillaries. If time is very limited, it is not really necessary to discuss the concept of filtration equilibrium, and filtration dynamics can be explained adequately by considering the average forces operating across the glomerular capillary. Every student should clearly understand and be able to work problems based on average values for the intraglomerular forces.

Another aspect of glomerular dynamics that often causes a great deal of confusion is related to the relative effects of selective changes in afferent and efferent arteriolar resistances on GFR and RBF. The ratio of GFR to renal plasma flow is the filtration

fraction, and many students, teachers, and clinicians make the serious mistake of using the changes in filtration fraction to estimate the relative changes in the pre- and postglomerular resistances in response to a specific stimulus or drug. It is often stated that renal vasoconstriction associated with an increase in filtration fraction and renal vasodilation associated with decreases in filtration fraction indicate that the resistance changes occurred predominately at efferent arterioles. However, this conclusion fails to recognize that disproportionate changes in GFR and RBF also occur when both resistances are altered (1). The confusion can be clarified by consideration of the effects of increases or decreases in afferent or efferent arteriolar resistances on glomerular dynamics and GFR. A selective increase in afferent resistance reduces both plasma flow and glomerular hydrostatic pressure; however, GFR decreases more than plasma flow, and thus the filtration fraction falls. In contrast, an increase in efferent arteriolar resistance reduces plasma flow but increases glomerular pressure. GFR initially increases slightly but eventually decreases because of the counteracting effects of the increases in glomerular colloid osmotic pressure. Thus RBF falls more than GFR, and the filtration fraction increases. However, combined increases in afferent and efferent resistances also reduce the plasma flow more than the GFR, and the filtration fraction increases. Likewise, when a drug such as an angiotensin converting-enzyme (ACE) inhibitor increases RBF without increasing GFR, this can be explained best by combined decreases in both afferent and efferent arteriolar resistances and not by a selective decrease in efferent arteriolar resistance as is often concluded. It can be readily appreciated that a selective decrease in efferent arteriolar resistance would increase blood flow and markedly lower GFR, because the associated decreases in glomerular pressure would cause disproportionately much greater relative decreases in effective filtration pressure and, thus, GFR (10). Actually, this problem can be expanded in laboratory sessions, and there are several good mathematical models that can be used to explain the effects of various combinations of changes in afferent and efferent arteriolar resistances on glomerular pressure and GFR (10). If the students can obtain a clear understanding of the fundamental aspects of these difficult issues, they are less likely to be confused in future discussion.

REGULATION OF RENAL VASCULAR RESISTANCE AND THE AUTOREGULATORY MECHANISM

Once the basic forces operating across the glomerular and peritubular capillary membranes are appreciated, the students then can readily recognize the importance of the mechanisms that regulate vascular smooth muscle tone in the renal microcirculation. The major challenge in teaching this section is how to limit discussion to the most critical control factors. If the teacher attempts to discuss every humoral, paracrine, endothelial, and neural factor that has been identified to date (23, 28), the litany will be quite confusing to the students and they likely will not remember the key fundamentals.

The regulatory systems can be categorized as those originating outside the kidney (such as circulating vasoactive agents or renal sympathetic nerve activity) and those intrinsic to the kidney. The autoregulatory intrinsic mechanism is responsible for maintaining RBF and GFR within narrow limits in the face of a variety of external perturbations including alterations in arterial pressure. This autoregulatory mechanism is important in stabilization of the glomerular pressure

and filtered volume to the tubules under conditions of moderate variations in cardiovascular function. For example, mean arterial pressure may decrease as much as 15–20 mmHg during deep sleep. Without an autoregulatory response, this would lead to decreases in glomerular pressure and GFR. In addition, the kidney is protected from the effects of variations in arterial pressure due to normal daily activities. Even small increases in arterial pressure can cause marked increases in filtered load and sodium excretion in the absence of normal autoregulatory capability. Thus autoregulation is a continuously operating negative feedback servocontrol system that maintains an optimum filtered load in the face of varying external influences. Autoregulation also contributes to the kidney's reserve capability that can be utilized in response to a variety of injurious processes that could otherwise lead to diminished renal function.

As illustrated in Fig. 4, autoregulatory responses are mediated by active adjustments of smooth muscle tone, primarily in the afferent arterioles. This explains the highly efficient autoregulation of both RBF and GFR in response to changes in perfusion pressure. In addition, the intrarenal pressure in the glomerular and

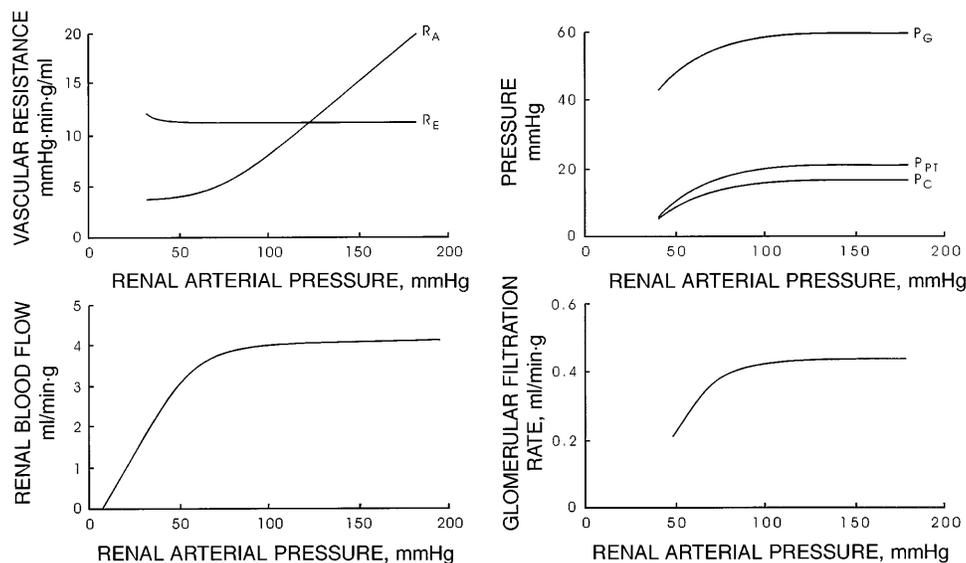


FIG. 4.

Renal autoregulation. In response to alterations in renal arterial pressure, P_G , proximal tubular pressure (P_{PT}), and P_C all exhibit autoregulatory behavior in association with RBF and GFR. These parallel responses indicate that the predominant site of the vascular resistance changes is preglomerular (R_A). R_E does not change very much during the autoregulatory response.

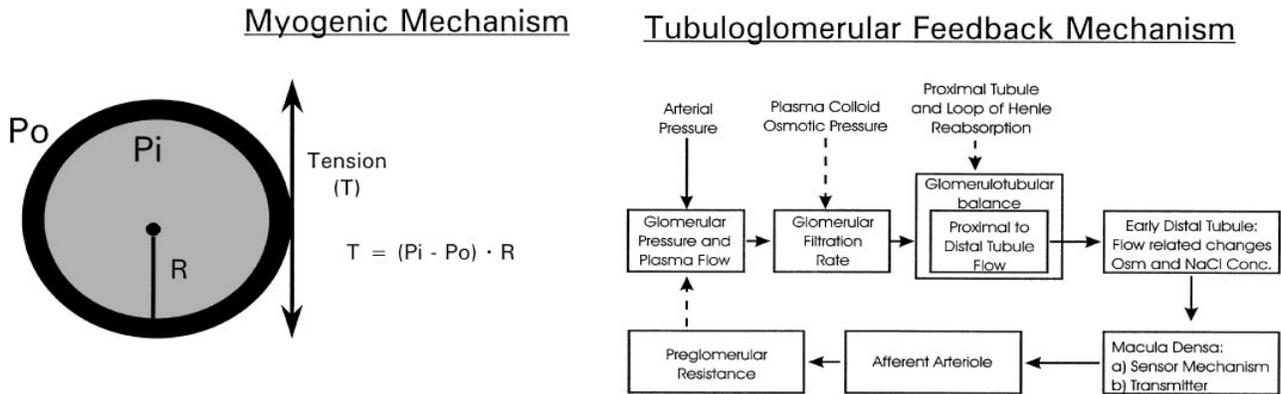


FIG. 5.

Myogenic (left) and tubuloglomerular feedback (TGF) mechanisms (right) mediating renal autoregulatory responses. Myogenic mechanism is intrinsic to arterial tree and regulates blood flow by regulating transmural wall tension (T). Tension is determined by the pressures inside (Pi) and outside (Po) and by the radius (R). TGF mechanism primarily regulates tubular fluid composition (osmolality, NaCl concentration) at level of macula densa and adjusts filtered load by regulating afferent arteriolar tone. Direct lines indicate direct effects, and dashed lines indicate inverse effects. [TGF diagram adapted from Braam et al. (6).]

peritubular capillaries and in the proximal tubules exhibit autoregulatory behavior, again indicating that the major site for autoregulatory resistance adjustments is preglomerular. As shown in Fig. 5, there are two mechanisms mediating renal autoregulation: the macula densa tubuloglomerular feedback (TGF) mechanism and the myogenic mechanism. The myogenic mechanism allows preglomerular arterioles to sense changes in vessel wall tension and respond with appropriate adjustments in vascular tone. An increase in wall tension, occurring as a passive response to an elevation in arterial pressure, stimulates a sensor element and initiates vascular smooth muscle contraction. Interlobular arteries and afferent arterioles exhibit myogenic responses to changes in wall tension. The macula densa-TGF mechanism responds to disturbances in distal tubular fluid flow past the macula densa. Increases in flow elicit vasoconstriction, whereas decreases in flow cause vasodilation. Micropuncture experiments have shown that increases in distal volume delivery in a single nephron elicit reductions in single-nephron GFR (SNGFR), glomerular capillary hydrostatic pressure, and glomerular plasma flow. Furthermore, interruption of fluid delivery to the distal nephron increases SNGFR above values obtained under conditions of maintained distal flow. This manipulation, depicted in Fig. 6, opens the feedback loop and impairs autoregulation of SNGFR and glomerular pressure, indicating that an intact TGF mechanism is required for complete and efficient

autoregulation. Autoregulatory responses seen at the level of the whole kidney thereby represent one manifestation of this homeostatic mechanism, which maintains a balance between filtered load and the reabsorptive capabilities of each nephron.

Several recent experiments have demonstrated that a residual autoregulatory capacity, although with substantially diminished efficiency, occurs during blockade of the TGF mechanism. Thus both the myogenic mechanism and the TGF mechanism participate in the autoregulatory response of the renal vasculature, but the TGF mechanism is responsible for the extremely high autoregulatory efficiency characteristic of the renal microvasculature. Autoregulatory behavior has been demonstrated in all regions of the kidney, and deep nephrons autoregulate as efficiently as superficial nephrons. Thus the autoregulatory mechanism provides a critical mechanism for stabilizing the microcirculatory environment throughout the kidney.

The TGF mechanism contributes significantly to the overall regulation of GFR and, ultimately, to the long-term control of sodium balance and extracellular fluid volume. By operating in concert with glomerulotubular balance, the TGF mechanism stabilizes delivery of volume and solute to the distal nephron. Under normal conditions, flow-related changes in the tubular fluid composition at the macula densa are sensed and

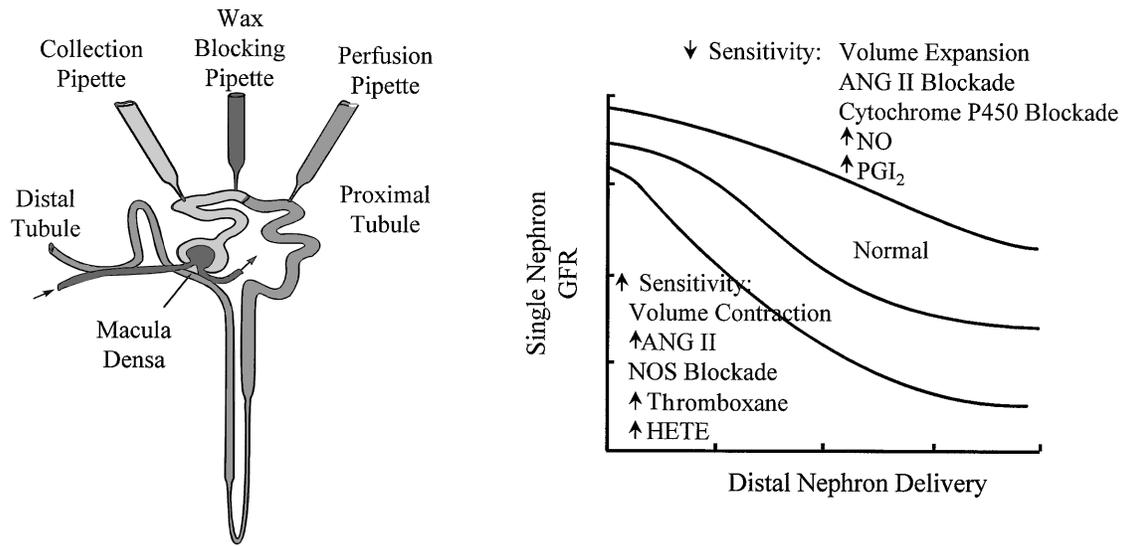


FIG. 6. Schematic of micropuncture procedures used to assess TGF responses (*left*) and representative relationships between distal nephron volume delivery and single-nephron GFR TGF responses. Effects of some agents that decrease (↓) sensitivity of TGF responses and agents that increase (↑) sensitivity of TGF responses are indicated. NOS, nitric oxide synthase; HETE, 20-hydroxyeicosatetraenoic acid; PGI₂, prostacyclin. [Nephron illustration courtesy of Dr. Pamela Carmines.]

signals are transmitted to the afferent arterioles to regulate the filtered load. Early distal tubular fluid is hypotonic (~100 mosmol/kg H₂O), and its composition is closely coupled to fluid flow along the ascending loop of Henle such that increases in flow cause increases in tubular fluid osmolality and NaCl concentration at the macula densa. The specific intraluminal constituent and the intracellular transduction mechanisms responsible for mediation of feedback signals remain unresolved, and it is best not to get into too much detail in explaining these issues to the students. However, the inquisitive students will be curious about the mechanisms and mediators involved. At the cellular level, it has been postulated that increases in tubular fluid osmolality elicit increases in cytosolic Ca²⁺ concentration in macula densa cells, which result in the release of a vasoconstrictive factor from these cells. Suggested mediators of TGF include purinergic compounds, such as adenosine or ATP, and one or more of the eicosanoids, such as 20-hydroxyeicosatetraenoic acid. The factor mediating TGF responses vasoconstricts afferent arteriolar vessels through the opening of voltage-gated Ca²⁺ channels in vascular smooth muscle cells.

The sensitivity of the TGF mechanism can be modulated by many agents and circumstances, some of which are associated with changes in extracellular fluid volume. TGF sensitivity is diminished during volume expansion, thus allowing a greater delivery of fluid and electrolytes to the distal nephron for any given level of GFR. By allowing GFR to be maintained or even augmented at elevated distal nephron volume delivery rates, reductions in TGF sensitivity allow correction of the volume expansion. In contrast, contraction of extracellular fluid and blood volume is associated with an enhanced sensitivity of the TGF mechanism, which, together with an augmented proximal reabsorption, helps to conserve fluid and electrolytes. One major regulator of TGF sensitivity is angiotensin II (ANG II). In states of low ANG II activity (i.e., extracellular volume expansion, salt loading) the TGF mechanism is less responsive, whereas feedback sensitivity is enhanced during conditions of high ANG II activity such as that occurring during dehydration, hypotension, or hypovolemia. As shown in Fig. 6, several other hormones that are responsive to the status of extracellular fluid volume also participate in modulating TGF sensitivity (23).

CONTRASTING THE TGF MECHANISM AND MACULA Densa MECHANISM FOR RENIN RELEASE

In discussing the TGF mechanism, a particularly difficult dilemma that is often raised by the inquisitive students relates to the role of the macula densa in the control of renin release and its role in mediating changes in afferent arteriolar vascular tone. Upon initial analysis, these two mechanisms seem diametrically opposed to each other. As explained, the TGF mechanism responds to increases in flow, which leads to flow-dependent increases in NaCl concentration and osmolality at the level of the macula densa. In turn, this elicits afferent arteriolar vasoconstriction. There is also a macula densa mechanism for the control of renin release. Overall, the control of renin release involves multiple mechanisms and is best discussed in a separate session specifically focused on the renin-angiotensin system (see Ref. 30). Nevertheless, it is difficult to ignore the apparent dilemma raised by the macula densa-mediated control of renin release. In essence, reduced flow to the macula densa such as that occurring with reduced perfusion pressure, reduced filtered load, or augmented proximal tubular fluid reabsorption rate leads to decreased distal sodium delivery and NaCl concentration at the level of the macula densa. Although the initial consequence would be afferent arteriolar vasodilation mediated through the TGF mechanism, a parallel macula densa mechanism responds to sustained reductions in NaCl concentration and elicits signals to the juxtaglomerular cells of the afferent arterioles to increase renin release. Renin catalyzes formation of ANG I, which is then converted to ANG II by ACE. Because ANG II constricts the afferent and efferent arterioles, this system thus seems to be operating directly opposite to the tubuloglomerular feedback mechanism. Whereas the actual interrelationships between these two mechanisms are quite complex (7, 8, 20), they can be explained satisfactorily along the following lines. The TGF mechanism is a rapidly acting mechanism that responds within a few seconds and adjusts afferent arteriolar resistance to maintain filtered load. It is particularly powerful in response to increases in distal volume delivery, eliciting afferent arteriolar vasoconstriction to protect against overloading of the limited transport capability of distal nephron segments. In contrast, the macula densa mechanism for

renin release responds to sustained decreases in distal NaCl concentration, which occur with decreases in arterial pressure and with decreases in extracellular volume (8, 20). It is important to emphasize that this is only one of several mechanisms regulating renin release and that increased renal sympathetic nerve activity is probably a more powerful regulator of renin release. Indeed, increases in renal nerve sympathetic activity stimulate renin release at lower levels of activity than are required to elicit renal vasoconstriction. Regardless of the initiating signals, the stimulation of renin release leads to increases in intrarenal renin content, which lead to augmented intrarenal levels of ANG II. These elevated ANG II levels then influence the TGF mechanism indirectly by modulating the sensitivity of the vascular smooth muscle to signals from the macula densa cells. In essence, although these two distinct macula densa mechanisms share a common transmission station (7), they are temporally dissociated and have their major influence over different operating ranges. Furthermore, it is important to emphasize strongly that angiotensin II is *not* the mediator of the TGF response but does serve a very important function, which is to modulate the sensitivity of this mechanism (20, 28).

CONTROL OF RENAL HEMODYNAMICS BY THE RENIN-ANGIOTENSIN SYSTEM

The renin-angiotensin system is best treated as a separate topic because of the multiple actions of angiotensin II on vascular and epithelial tissues (20, 22, 30). Nevertheless, its importance in regulating renal vascular function cannot be neglected, so it also must be discussed when mechanisms regulating renal microvascular function are being considered. Also, because of the widespread clinical use of drugs that antagonize or block the renin-angiotensin system, this topic has a very high degree of clinical relevance. Renin is an aspartyl proteinase that cleaves the decapeptide ANG I from angiotensinogen, an α_2 -globulin formed primarily by the liver but also in the kidneys and other tissues. The major site of renin formation in the kidneys is the juxtaglomerular epithelioid cells of the afferent arteriole. Renin release is stimulated by decreases in sodium intake, reduced extracellular fluid and blood volume, decreases in arterial pressure, and increased sympathetic activity. ANG I generation is determined by renin activity because substrate availability is usually ample. The decapeptide is subsequently

cleaved to the octapeptide, ANG II, by ACE. ACE is abundant in the lungs, bound to endothelial cells, but is also found in many other organs including the kidney. The major renal sites of ACE localization are on the luminal surfaces of endothelial cells lining afferent and efferent arterioles and glomerular capillaries and on the proximal tubular cells bound to the brush border. Functional data also indicate the presence of ACE in the renal interstitium. ANG II can be formed from angiotensinogen extrarenally and delivered in the circulation, or it may be formed locally.

Thus ANG II can function as a hormone and as a paracrine factor. Recent studies have shown that intrarenal ANG II levels in certain compartments within the kidney, including the proximal tubules and the interstitium, are much higher than plasma levels, thus supporting the premise that much of the intrarenal ANG II is formed endogenously (27).

The multiple actions of ANG II, some of which are shown in Fig. 7, act in concert to minimize renal fluid and sodium losses and to maintain arterial blood

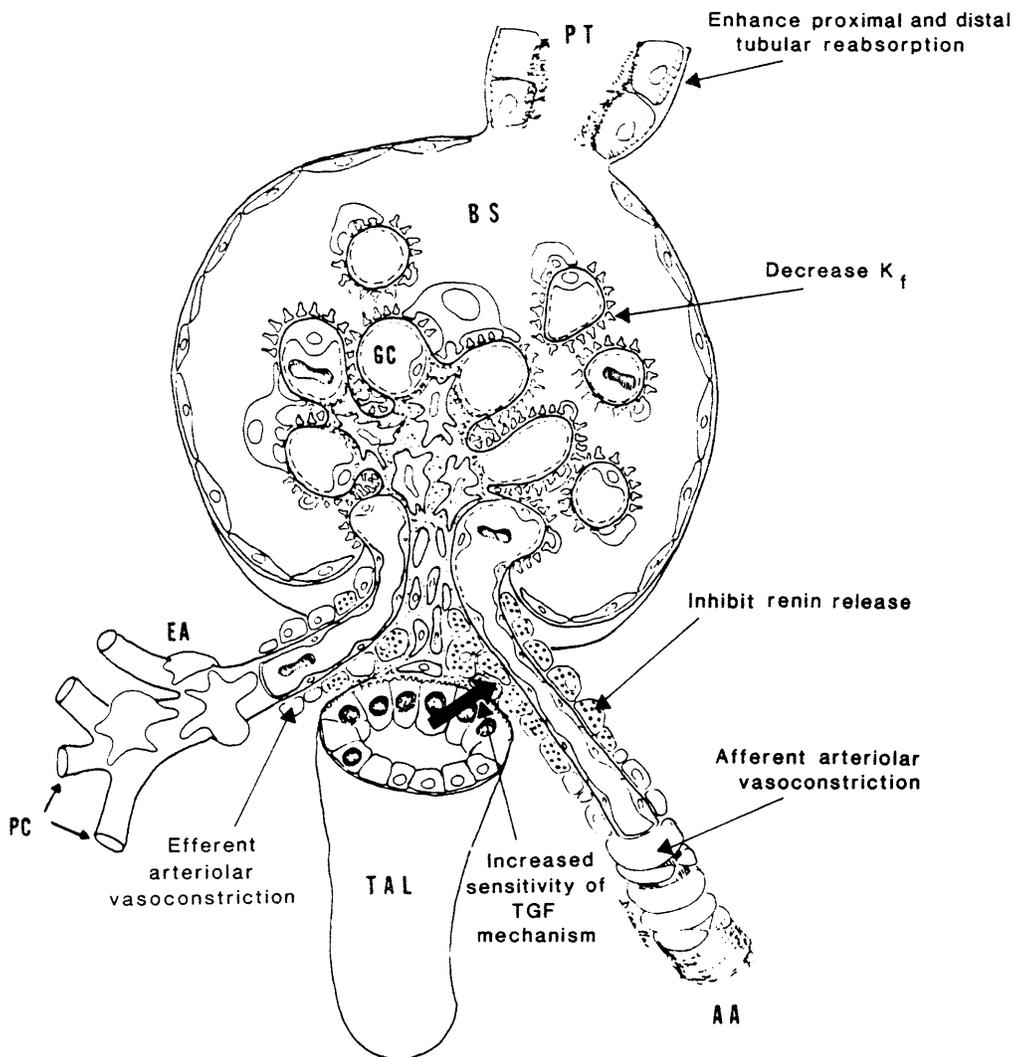


FIG. 7.

Multiple actions of ANG II on renal function. PT, proximal tubule; BS, Bowman's space; GC, glomerular capillaries; EA, efferent arteriole; PC, peritubular capillaries; TAL, thick ascending limb; AA, afferent arteriole. [Original drawn by Dr. Daniel Casellas.]

pressure (20, 22). In addition to its renal vascular effects, ANG II stimulates aldosterone release, enhances proximal tubular reabsorption rate, stimulates thirst, and enhances sympathetic nerve activity. ANG II exerts powerful vascular effects that elicit decreases in RBF and, to a lesser extent, in GFR; thus there is usually an increase in filtration fraction. Although it is sometimes stated that ANG II primarily constricts the efferent arterioles, many studies have demonstrated clearly that ANG II vasoconstricts both preglomerular as well as postglomerular arterioles (9, 20, 28). The preglomerular effects of ANG II include direct vasoconstrictive actions as well as indirect effects caused by increased sensitivity of the TGF mechanism, as previously described. ANG II can also decrease the glomerular filtration coefficient by reducing hydraulic conductivity of glomerular capillaries. ANG II may also influence medullary hemodynamics at concentrations lower than those required to elicit cortical vasoconstriction, which may be related to the greater ANG II-receptor density in the outer medulla (1, 4, 17, 24, 25, 28).

ANG II-receptor antagonists and ACE inhibitors are frequently utilized clinically to block the effects of endogenous ANG II in various conditions such as hypertension, congestive heart failure, and diabetes. Thus there are many patient-oriented problems that can be used to discuss the actions of ANG II. During conditions associated with an enhanced ANG II activity, inhibition of the renin-angiotensin system increases RBF, whereas GFR either increases or does not change. However, GFR may sometimes decrease in association with decreases in arterial pressure or when there is severe arteriolar sclerosis or stenoses. Under most conditions, however, blockade of the renin-angiotensin system causes decreases in both preglomerular and postglomerular resistances.

At the cellular level, ANG II increases cytosolic Ca^{2+} concentration by enhancing Ca^{2+} entry through voltage-dependent Ca^{2+} channels as well as by mobilization of the ion from intracellular storage sites. ANG II-induced depolarization of preglomerular vascular smooth muscle cells elicits opening of voltage-gated Ca^{2+} channels and subsequent vasoconstriction. Accordingly, the preglomerular vasoconstrictor response to ANG II is blocked by Ca^{2+} -channel blockers. Interestingly, efferent arterioles respond to ANG II

even in the presence of Ca^{2+} -channel blockers, indicating that there are separate vasoconstrictive mechanisms for ANG II-induced afferent and efferent constriction (9, 21, 23, 28).

ENDOTHELIAL AND OTHER PARACRINE FACTORS

As mentioned earlier, there are many paracrine agents that influence the renal microvasculature, and it is impossible to cover all of them. However, it is important to discuss several that are clinically very important. One particularly intriguing and growing area of interest is related to the formation and release of paracrine agents by adjoining endothelial cells.

From studies in many organ systems, it has been determined that the endothelial cells respond to various physical stimuli (e.g., shear stress) and hormonal agents (e.g., thrombin, bradykinin) to release vasoactive factors. Some of these are shown in Fig. 8. The substance that has received the most intense investigation recently is nitric oxide (NO), which is now known to be endothelium-derived relaxing factor (12, 16, 28). NO is formed intracellularly by NO synthases (NOS), which cleave NO from L-arginine. In endothelial cells, NO is formed constitutively and diffuses out of the cell into adjoining cells. Through stimulation of soluble guanylate cyclase and increased cGMP levels in smooth muscle cells, NO exerts powerful vasodilator actions. Substantial interest has been focused recently on the role of NO in regulating renal vascular function in normal and pathophysiological conditions. Because NO is derived from arginine, several nonmetabolizable analogs of arginine have been used to block the formation of NO. Administration of these arginine analogs causes a 25–40% increase in renal vascular resistance. In general, the decreases in RBF are greater than the decreases in GFR (3, 19, 28, 31). Some of this increase in renal vascular resistance is thought to be mediated by an enhanced activity of the renin-angiotensin system during NO blockade. There are also important interactions between intrarenal ANG II and intrarenal NO such that increased intrarenal NO partially buffers the vascular actions of increased ANG II. Both preglomerular and postglomerular arterioles are responsive to NO, thus explaining why NO blockade decreases GFR less than RBF (13, 28, 29).

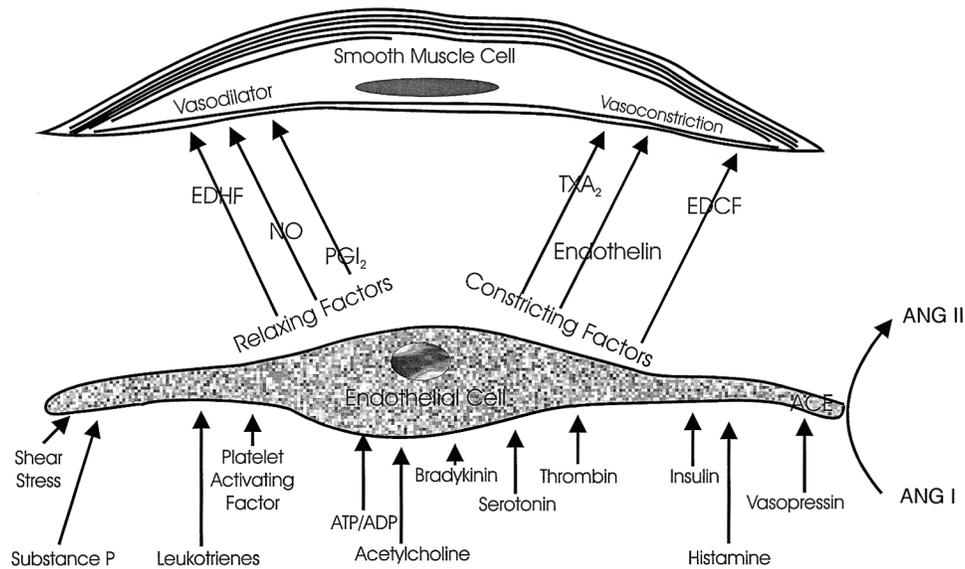


FIG. 8. Multiplicity of endothelium-vascular smooth muscle interactions with release of vasoactive agents. Examples of constricting and relaxing factors are indicated. EDHF, endothelium-derived hyperpolarizing factor; NO, nitric oxide; TXA₂, thromboxane A₂; EDCF, endothelium-derived constricting factor, ACE, angiotensin-converting enzyme.

Whereas it is generally recognized that NO is formed by NOS in endothelial cells, there is also growing interest in the specific role of the neuronal isoform of NOS that has been localized in macula densa cells (2, 33). Several recent studies indicate that the NO produced by the macula densa cells exerts an important modulating influence on the TGF mechanism that counteracts the vasoconstrictor response (5, 32, 34). In particular, during sustained increases in distal nephron volume and NaCl delivery, there is an increased activation of vasodilatory influences exerted by neuronal NOS-mediated NO (14). These recent studies have established important roles for NO in the overall regulation of renal hemodynamics. It should also be mentioned that intrarenal NO also has important effects on sodium excretion and is thought to serve as the mediator of pressure natriuresis (18). However, the topic of pressure natriuresis is best covered within the context of an overall integrative discussion on the control of arterial pressure and the pathophysiology of hypertension (22).

Renal prostaglandins or eicosanoids constitute another very significant paracrine family that also influences renal vascular resistance, arterial pressure, so-

dium and water excretion, and renin release. Prostaglandins are synthesized from arachidonic acid at several sites within the kidney and can influence a variety of cellular processes. Although this is a very complex topic, it is another highly clinically relevant area because there are so many pharmacological agents that target some aspect of this system. Thus some mention of the roles of these substances in the control of renal hemodynamics should be included. As shown in Fig. 9, endoperoxides (PGE₂, PGF₂, PGI₂, and thromboxane A₂) are synthesized by the cyclooxygenase enzymatic pathway while the leukotrienes and lipoxins are formed by lipoxygenases. Administration of PGE₂ or PGI₂ (prostacyclin) into the renal artery causes vasodilation; thromboxane A₂ and leukotrienes constrict the renal vasculature. A rapidly growing field is related to the eicosanoids formed through the cytochrome P450 monooxygenase enzyme system. Several of the resultant epoxides and their derivatives exert actions on both the renal vasculature and the tubules (15, 23, 28). In teaching this subject, it is worthwhile to provide the student with an overall schematic of the arachidonic acid family similar to that shown in Fig. 9 (28). In terms of understanding mechanisms, however, it is important to focus on only

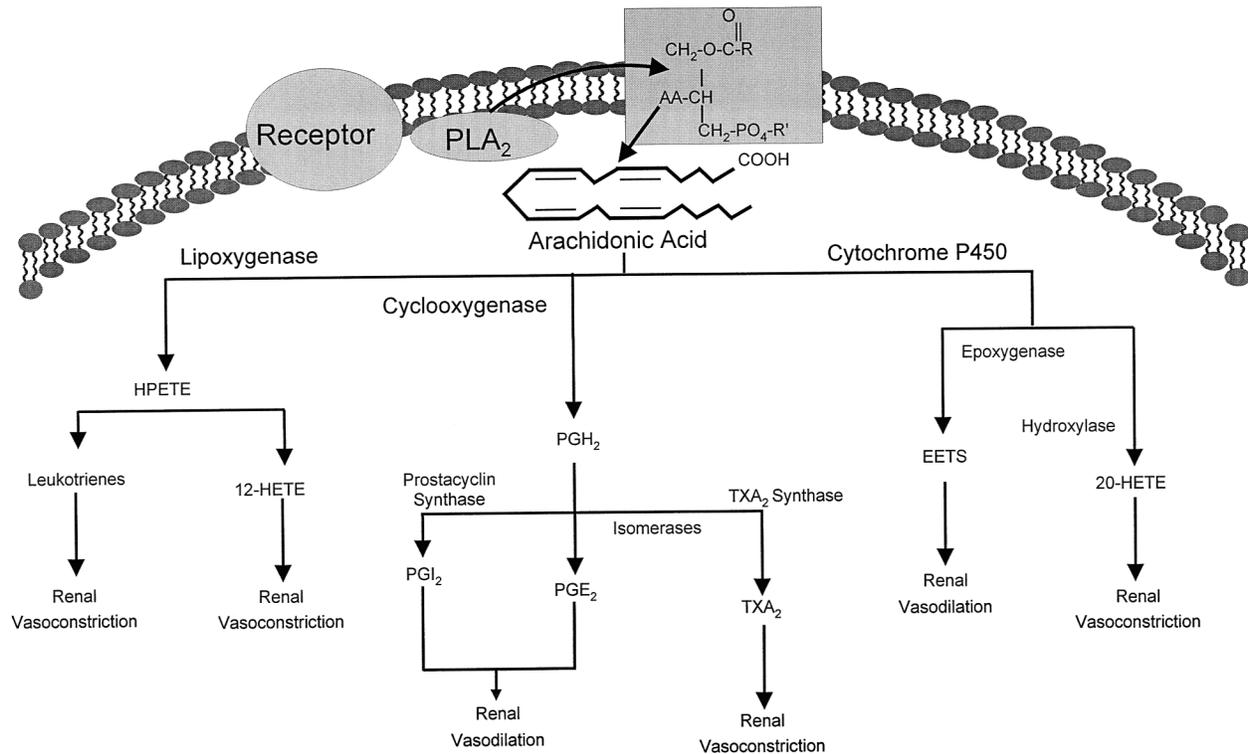


FIG. 9.

Arachidonic acid cascade showing metabolism by 3 major enzymatic pathways: cyclooxygenases, lipoxygenases, and cytochrome P-450 monooxygenases. Cascade has been simplified to show only a few of the metabolites that have been shown to exert vasoactive actions. PLA₂, phospholipase A₂; HPETE, hydroperoxyeicosatetraenoic acid; EETS, epoxyeicosatrienoic acids.

a few select issues that are particularly relevant. In essence, it is currently thought that prostaglandins are not major determinants of resting renal vascular tone under normal states of hydration and sodium balance. In conscious animals, prostaglandin metabolites are formed at low rates and cyclooxygenase inhibitors do not appreciably alter RBF or GFR. Rather, there is a general consensus that prostaglandins exert protective effects in response to vasoconstrictor stimuli, hypovolemic states, or hypotensive episodes. When the kidney is under the sustained influence of vasoconstrictor stimuli such as elevated catecholamine levels, increased renal nerve activation and increased activity of the renin-angiotensin system, activation of prostaglandin production helps counteract the vasoconstrictor effects of these stimuli. When prostaglandin production is blocked with cyclooxygenase inhibitors, the unopposed actions of the coexisting vasoconstrictor agents are manifested by greater reductions in RBF and renal function (1). Thus prostaglandins may take

on a greater regulatory role in pathophysiological conditions that compromise renal hemodynamics. In such conditions, the blockade of prostaglandins with nonsteroidal antiinflammatory drugs (which block cyclooxygenase activity) may leave unopposed the vasoconstrictor influence of elevated levels of ANG II and catecholamines and decrease RBF, GFR, and sodium excretion. This is probably the most important clinically relevant information related to prostaglandins that should be remembered by the students. Additional exposure to the arachidonic acid family and the drugs that are used to block selective pathways of formation is best left for the pharmacology course.

Many other vasoactive agents are produced by the kidney. Some of these agents may be released under normal physiological conditions, whereas others may reach effective concentrations only under adverse circumstances such as prolonged ischemia, decreases

in extracellular volume, or during inflammatory responses. The list of such vasoactive systems is potentially endless and includes the kallikrein-kinin system, purinergic agents such as adenosine and ATP, and other peptide hormones including endothelin and atrial natriuretic peptide (1, 28). Time constraints prevent detailed consideration of this large assortment of vasoactive agents, and it is sufficient to list them and to point out the general effects of vasodilators and vasoconstrictors and their consequences without going into too much detail.

NEURAL CONTROL OF RENAL CIRCULATION

It is important not to neglect the influence of renal nerves on the renal circulation (11). RBF is markedly influenced by extrinsic stimuli such as stress, trauma, hemorrhage, pain, and exercise. These conditions elicit increases in sympathetic nervous activity to the kidney that directly increase renal vascular resistance. Strong activation of the renal sympathetic nerves results in marked renal vasoconstriction mediated by α -adrenoreceptors, leading to decreases in both RBF and GFR, increases in renin release, and increases in proximal tubular sodium and water reabsorption. Increases in renal sympathetic nerve activity can be a part of an overall sympathetic response or may be more selective. Decreases in renal nerve activity can be elicited reflexively through cardiopulmonary receptors and renorenal reflexes.

As previously mentioned, low-level renal nerve stimulation may elicit increases in renin release mediated by a direct action on juxtaglomerular apparatus cells via β -adrenergic receptor activation along with increases in tubular sodium reabsorption even in the absence of perceptible renal vasoconstriction. Moderate levels of renal nerve stimulation elicit parallel increases in afferent and efferent arteriolar resistance, leading to slightly greater decreases in RBF than in GFR. With higher stimulation frequency, a powerful preglomerular vasoconstrictor response predominates and K_f is decreased, causing major decreases in GFR. The increase in renal vascular resistance induced by α -adrenoreceptors also represents a pathway for α -adrenoreceptor influence over renin secretion through the baroreceptor mechanism. The influence of neural activity on the medullary circulation may also be of importance, because outer medullary descending vasa recta receive sympathetic innervation. It should be empha-

sized, however, that the tonic influence of the sympathetic nervous system on renal hemodynamics under unstressed conditions is thought to be relatively low.

In addition to control by sympathetic nerves, the renal circulation is subject to influences by the adrenal medulla, which releases epinephrine systemically in response to many stress conditions. Smooth muscle-containing vessels of all sizes, from the main renal arteries to afferent and efferent arterioles, respond to exogenous norepinephrine and epinephrine. Afferent arterioles appear to be more sensitive than efferent arterioles to the vasoconstrictive effect of norepinephrine. GFR is maintained at near-normal levels during infusion of relatively small doses of catecholamines; however, larger doses of norepinephrine are capable of inducing marked renal vasoconstriction, leading to major decreases in GFR.

In summary, a serious consideration of the control of renal hemodynamics is a critical aspect of teaching renal physiology and should not be neglected or shifted over to the cardiovascular segment. The maintenance of optimum renal excretory function depends critically on the contribution of many different systems that interact to establish and maintain an appropriate intrarenal hemodynamic environment. Because of the growing complexity of the area, it is important to focus on the most critical issues needed to provide a solid foundation requisite for further understanding of renal physiology, pharmacology, and pathophysiology.

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