73 Introduction to Renal Function, Renal Blood Flow and the Formation of Filtrate

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73.1.1 What If the Kidney Fails?

Our two kidneys do their job silently, and we hardly become aware of their busy work unless something goes wrong. In fact, our awareness only concerns the daily voiding of 1-1.5 l of clear, yellowish urine. Closer inspection and analysis of urine tells us that it contains more than water and some chromophore (urochrome). Table 73.1 summarises the composition of normal antidiuretic urine (urine production < 0.3 ml/min). Urine contains large amounts of urea (ca. 30 g/day, 500 mmol/day), variable amounts of Na⁺ and Cl⁻ (ca. 5-15 g/day, 100-300 mmol/day), variable amounts of K⁺ (50-300 mmol/l), large amounts of phosphates (ca. 20-60 mmol/day), sizeable quantities of creatinine (ca. 900 mg/day, 7 mmol/day), small quantities of urate/uric acid (ca. 5 mmol/day) and variable amounts of Ca²⁺ and Mg²⁺ (ca. 100-300 mg/day or 3-8 mmol/day, and 60-200 mg/day or 2-9 mmol/day, respectively). From the above it can be seen that the composition of urine differs in many respects from that of plasma. Important differences are:

- The high content of nitrogen-containing compounds such as urea, creatinine, NH₃ and uric acid
- The variability of electrolyte content: Na⁺, K⁺, Ca²⁺, Mg²⁺, H₂PO₄⁻, HPO₄²⁻
- The acid pH (5-6) under normal acid-base conditions
- The virtual absence of HCO₃⁻, d-glucose, amino acids and proteins.

As will be shown below, the kidney essentially works by filtering plasma (glomerular filtration) and by reabsorbing constituents of the tubule fluid from and by secreting constituents of plasma into the various tubule segments (cf. Chaps. 74, 75). From the comparison of urine and plasma it becomes clear intuitively that the kidneys must perform important transport work:

- To avoid losses of metabolically valuable filtrate constituents such as d-glucose, amino acids and to a lesser extent small to medium-size proteins
Table 73.1. Composition of antidiuretic urine (cf. also Chap. 126)

<table>
<thead>
<tr>
<th>V (1/day)</th>
<th>Na⁺</th>
<th>Cl⁻</th>
<th>K⁺</th>
<th>Ca²⁺</th>
<th>Mg²⁺</th>
<th>HCO₃⁻</th>
<th>HPO₄²⁻</th>
<th>Urea</th>
<th>Creat.</th>
<th>Urate</th>
<th>NH₄⁺</th>
<th>Osmolality (mosmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ca. 1</td>
<td>30–150</td>
<td>30–150</td>
<td>33–300</td>
<td>3–6</td>
<td>ca. 10</td>
<td>ca. 1</td>
<td>3–20</td>
<td>ca. 300</td>
<td>ca. 10</td>
<td>3</td>
<td>ca. 20</td>
<td>ca. 1000</td>
</tr>
</tbody>
</table>

All values are mmol/day unless otherwise specified

The Na⁺ and Cl⁻ concentrations depend largely on the NaCl metabolism; the concentration of Ca²⁺ is controlled mostly by PTH; the urine is essentially HCO₃⁻ free except in metabolic alkalosis; the urea concentration varies with the N metabolism, and together with NH₄⁺ in metabolic acidosis the creatinine excretion depends on creatine metabolism; urine osmolality can be up to 1500 mosmol/l.

- To prevent losses of the buffer HCO₃⁻.
- To ensure effective excretion of nitrogen compounds and toxic metabolites.

In addition, many xenobiotics (drugs, ξένος = strange, non-genuine) are excreted as such, or after they have been subjected to hepatic metabolism, by the kidneys (cf. Chap. 75).

**Dynamic Range of the Kidneys.** Thus far we have only considered kidney function in the normal steady state. When the body is challenged by large volume or salt loads, the kidney can increase water and salt excretion rapidly. One might call this the dynamic range of the kidneys. For instance if, in the normal hydrated state (Chap. 76), we drink a water load of say 11 within 30 min, the urine flow rate increases abruptly and this extra litre is excreted within 1–2 h. In this way the kidneys prevent the circulation from overfilling, with the possible consequences of damaging heart failure and oedematous states. Similarly, our diet can contain less than 1 and up to 60 g NaCl/day (Chaps. 77, 82), and still we can stay in perfect balance because the kidneys adjust NaCl excretion to uptake [14]. The same holds for K⁺. We can ingest a few to 20 g/day (Chap. 79) without the danger of upsetting the K⁺ balance and without any major change in plasma K⁺ concentration [41]. The kidney also controls mineral metabolism (phosphate, Ca²⁺ and Mg²⁺, cf. Chap. 80) and adjusts renal excretion to the respective needs of the body. Beyond this, the kidney plays a predominant role in acid-base regulation. While the lung can control CO₂ homeostasis by expiring normal or increased amounts, the kidney can increase HCO₃⁻ excretion in metabolic alkalosis and can increase NH₄⁺ excretion in metabolic acidosis (cf. Chap. 78).

**Renal Failure.** When the kidneys fail, the loss of these important functions leads to a life-threatening state: renal failure (for reviews consult, for example, [7]). This failure can occur very rapidly, as a result of excessive blood loss, severe burns, mushroom poisoning, intrinsic renal pathology, acute urinary obstruction etc. Alternatively, it can develop slowly (chronic renal failure) as renal disease progresses. In either case intervention is necessary if renal function, usually quantified as glomerular filtration rate (GFR; a list of abbreviations used frequently in this and the following two chapters is included at the end of this chapter), is reduced to some 20% or less of its normal value. The signs and symptoms of renal failure (insufficiency) can be easily deduced from the above key functions:

- Disturbances of electrolyte balance, e.g., hyperkalaemia
- Metabolic acidosis
- Toxaemia due to the accumulation of so-called uraemic toxins
- Disturbances of mineral metabolism
- Increase in plasma urea and creatinine concentration
- Loss of the ability to deal with volume and salt loading
- Renal anaemia.

In such a state the patient has to reduce oral intake of water to avoid overhydration. Salt and mineral intake must be restricted and be matched closely with residual function. The toxæmia, also called (unduly) uræmia, as well as the disturbed electrolyte metabolism, must be treated by dialysis (or kidney transplantation). In previous pre-dialysis decades toxæmic patients died when they entered terminal renal insufficiency.

As stated above, the word uræmia is a misnomer, inasmuch as it implies that the accumulating urea is the cause for toxæmia. This is not the case unless the urea concentration is excessively high. The relevant toxins belong to a heterogeneous group of small to medium-sized molecules, amongst which parathryoid hormone (PTH), phenols and indols and many more have been incriminated as being responsible for various symptoms [40]. Chronic renal failure, besides the accumulation of these toxins, is also characterised by the failure of the endocrine function of the kidney. Most important are the reductions in the production of erythropoietin and 1,25-(OH)₂-D₃ hormone.

In summary, the kidneys play a pivotal role in several homeostatic processes such as nitrogen, water, electrolyte, mineral and acid-base metabolism. The kidneys are endocrine organs and they are responsible for the excretion of many xenobiotics. This multitude of complex tasks requires a large blood, oxygen and metabolic fuel supply to the kidneys. Acute or chronic failure of kidney function results in complex life-threatening disorders.

### 73.2 Structure and Morphology of the Kidney

Each kidney weighs ca. 150 g. A frontal section through the human kidney (Fig. 73.1) shows a clearly distinct arrange-
ment of cortex and medulla. Human kidney is multilobular [16,19]. The medulla, on the basis of the contrast caused by variable blood filling, can be subdivided into outer and inner medulla. The former, on the basis of the capillary network, which is sparse in the outer zone and dense in the inner zone, can be further subdivided into an outer and an inner stripe. The medulla points to tips which are called papillae. The border between cortex and medulla is formed by the arcuate arteries. Closer inspection of a section of this kind reveals a complex arrangement of renal vasculature and of the smallest functional units of the kidney, namely the nephrons. Each human kidney possesses some 1.2 million of these nephrons.

73.2.1 The Renal Vasculature: A Portal System

**General Structure.** Figure 73.2B shows the general structure of the vasculature (from Kriz and Kaisling [19]). The renal artery branches into the interlobar arteries, which extend to the border between cortex and medulla. There, the arcuate arteries branch off (and form the border). The arcuate arteries possess perpendicular branches: the interlobular arteries. These branch off to form the afferent arterioles. The afferent arterioles enter the glomeruli and form the glomerular capillaries. The capillaries merge again in efferent arterioles. Then, at the welling points (vasa stellata, superficial nephrons), they branch into another capillary network. These capillary plexus surround the tubules (superficial nephrons). In the deep (juxtamedullary) nephrons the efferent arterioles form descending vasa recta. These vessels merge towards the papilla and end in the inner stripe or in the inner medulla. Together with the ascending vasa recta they form capillary beds which are less dense in the outer stripe of the outer medulla and in the inner medulla and are very dense in the inner stripe of the outer medulla.

**Portal System.** It is important to note that the kidney possesses a portal system with two capillary beds in series. The first supplies the glomeruli, while the second surrounds the tubules and accompanies the long tubule structures of the deep nephrons and of the collecting ducts (cf. also next chapter). The venous effluent is drained by interlobular, arcuate and interlobar veins. The renal vasculature of different species shows some important variations with important functional ramifications [8,23].

73.2.2 The Nephron Consists of Various Tubule Segments of Distinct Appearance and Function

**Proximal Tubule.** Figure 73.2A [19] shows the various tubule segments of a superficial and a deep nephron. The glomerulus (Bowman space) drains into the neck segment of the proximal tubule (PT). On the basis of morphology (cf. also Chap. 74) and functional data, the proximal tubule is subdivided into three segments (S1-S3, or P1-P3). The first part is convoluted (tortuous). The second portion is less convoluted and the third is almost straight. The second half of S2 and S3 are also called pars recta. The pars recta of the superficial tubules is more straight than that of the deep nephrons. All partes rectae end at the border between the outer and the inner stripe of the outer medulla.

**Descending and Ascending Limbs.** The thin descending (DTL or tDL) limbs of the loop of Henle are short in the superficial nephrons. They reach down to the border of the outer and inner medulla. The deep nephrons descend further. However, the length is variable. Only a few reach down into the papilla. In superficial nephrons the thick ascending limb begins immediately at the turn of the loop, whereas thin ascending limbs (ATL or tAL) begin at the turn of the loop of deep nephrons. The thick limbs (of the loop of Henle) begin in the inner stripe of the outer medulla and extend into the cortex. Hence, a medullary portion of the thick ascending limb (mTAL) is distinguished from the cortical thick ascending limb (cTAL).

**Macula Densa.** Each nephron returns to its glomerulus in the cortex and makes close contact with it. This is the macula densa portion of the nephron (MD). The MD segment has a very specific function (cf. below and Chap. 74) inasmuch as it is a "chemoreceptor" of this nephron which
Fig. 73.2. A Superficial and deep nephrons. 1, glomerulus; 2, proximal convoluted tubule (S1); 3, proximal straight tubule (S3); 4, descending thin limb of the loop of Henle (tDL); 5, ascending thin limb of the loop of Henle (tAL); 6, thick ascending limb of the loop of Henle (TAL); 7, macula densa; 8, distal convoluted tubule (DT); 9, connecting tubule; 10, cortical collecting duct (CCD); 11, outer medullary collecting duct (OMD); 12, inner medullary collecting duct (IMD). (With permission from [19]). B Renal vasculature. C, cortex; OS, outer stripe of outer medulla; IS, inner stripe of outer medulla; IM, inner medulla. 1, arcuate artery; 2, interlobular artery; 3, afferent arteriole; 4, glomerulus; 5, efferent arteriole; 6, peritubule capillaries; 7, descending vasa recta; 8, ascending vasa recta; 7 + 8, vascular bundles; 9, interlobular veins; 10, arcuate veins. Not shown are the large vessels: a. renalis, a. interlobaris, v. interlobaris, v. renalis. Note that the efferent arterioles form peritubular capillaries in cortical superficial nephrons, whereas they form descending vasa recta in the juxtamedullary nephrons. Note also that the capillary network is especially dense in the inner stripe of the outer medulla. (Modified from [19])

monitors luminal Cl− concentration and resets the filtration rate accordingly [32]. The thick ascending limb continues a few tens to hundreds μm past the MD.

**Distal Convoluted Tubule.** The nephron continues as the initial distal convoluted (DT) tubule. The last part of the distal tubule is the bright portion. The anatomical nomenclature also subsumes TAL and DT as “distal tubule”.

**Collecting Duct System.** The collecting duct system is ontogenetically of different origin (Wolff’s Gang = Unerierengang). Several nephrons (connecting tubules, CNT) merge into one collecting duct and many collecting ducts merge to form the papillary collecting ducts (ducts of Bellini). The first portion of the collecting duct is the connecting tubule (CNT = DCTc = CCTc), also called the granular distal tubule. The deep nephrons form arcades of connecting tubules which ascend in the cortex before
merging into cortical collecting tubules (CCT), also called light distal tubules. The next portions are the outer and inner medullary collecting ducts (OMD, IMD). Finally the collecting ducts merge to form the papillary collecting ducts (ducts of Bellini).

This brief overview was given here to introduce the single functional unit of the kidney: the nephron. A closer description of the morphology of the various tubule segments and a correlation between appearance and function will be given in Chap. 74.

73.2.3 The Glomerulus: A Filter with High Permeability and Yet Good Selectivity

Hydraulic Conductivity. The 1.2 million glomeruli of each kidney are highly specialised filters with a hydraulic conductivity ($K_v$) exceeding by far that of other capillaries. The normal filtration rate of human kidneys is around 120 ml/min; this corresponds to a filtration coefficient which is ten times or more larger than that of all other capillaries in the body [11]. $K_v$ has been found to be around 0.1 nl/s·mmHg in the Munich Wistar rat, which possesses a large number of glomeruli on the kidney surface [11]. Therefore, for a mean filtration pressure of 8 mmHg, the single nephron filtration rate (SNGFR) would be 0.8 nl/s or 50 nl/min. The 30000 glomeruli of one kidney of this rat would hence produce a GFR of 1.5 ml/min. In man SNGFR is probably similar. The two kidneys, with 2400000 glomeruli, produce a GFR of 120 ml/min.

The high value of $K_v$ is due to the anatomical structure of the glomerulus. A schematic drawing of a glomerulus is shown in Fig. 73.3A [16]. Glomerular capillaries are bulging into the spherical space of the glomerulus (Bowman space). As a result the barrier between blood and Bowman space, the actual filter, has three layers: the fenestrated endothelium, the basement membrane and the podocytes (foot processes) (Fig. 73.3B).

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**Fig. 73.3.** A Section through a glomerulus and the juxtaglomerular apparatus. 1, afferent arteriole; 2, efferent arteriole; 3, Gomorghi cell; 4, macula densa cell; 5, Bowman capsule; 6, glomerular capillaries; 7, proximal tubule (neck segment of S1); 8, mesangial cell; 9, renin producing cells; 10, podocytes (foot processes); 11, basement membrane; 12, endothelium. (Modified from [16]). B Electron micrograph of the filtration barrier in a glomerulus. $E$, endothelium; $BM$, basement membrane; $P$, podocyte. Note the fine slit membranes between foot processes (arrow). (From [16]) $\times 63600$. 

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Filter Selectivity. It is apparent that the endothelium with its large pores will only prevent corpuscular elements from permeation. It cannot account for the fact that the effective pore radius of this filter is around 3 nm. It has long been a matter of debate whether the basement membrane or the podocytes represent the effective barrier. Inspection of Fig. 73.3B might at first glance suggest that the basement, with its complex arrangement of connective tissue fibres, would be the size-selective filter. In fact, this has been put forward on the basis of studies with ferritin [13] and may hold true for neutral and also anionic molecules. Closer inspection of Fig. 73.3B reveals that the foot processes of the podocytes are connected to each other by optically dense slit membranes. Under normal conditions these slit membranes are believed to contribute to the selectivity of the filter, especially for cationic macromolecules [26].

Filtration Coefficients. Figure 73.4 shows the filtration coefficients of various molecules as a function of their size and molecular weight. The filtration coefficient can be determined directly (micro puncture studies) by measurement of the concentration of the molecule under study in circulating plasma and in the Bowman space, or it can be determined from the fractional excretion of this molecule in comparison to a substance known to undergo complete filtration. Such a substance is the polyfructoside inulin (vide infra). One implication in this approach is the assumption that the molecule under study, just like inulin, is neither secreted nor reabsorbed along the nephron and collecting duct system. Inspection of Fig. 73.4 reveals that molecules with a radius of 2 nm or less (corresponding to a molecular weight of approximately 5000Da) are filtered freely. Larger molecules are partially filtered (between 2 and 4 nm): i.e., their concentration in the Bowman space is only a fraction of that in plasma. Molecules with a radius larger than 4 nm are excluded almost completely from filtration. As a consequence large proteins such as albumin, hemoglobin and globulins are filtered very poorly, whereas myoglobin still is filtered to an appreciable extent.

The fractional filtration of large molecules also depends on the dynamics of filtration (cf. below). If renal plasma flow or filtration pressure increases, GFR also increases. The solute filtration, however, does not increase to the same extent. Therefore, the fractional filtration of large molecules is shifted to the left (Fig. 73.5a) [2]. Conversely, a reduction in solvent (water) filtration has the opposite effect.

Effect of Charge on Filtration. It might be expected that the pores of the slit membranes and the serial arrangement of the three barriers have a certain pattern of charges and the charge of the solute interacts with the charges of the filter. This has been proven to be the case [9]. If, for instance, 3.6-nm-radius dextrans with no charges, negative charges or positive charges are compared, the fractional filtration is 1% for the negatively charged species, 15% for the neutral species and 42% for the positively charged species. This is shown in Fig. 73.5b. The basement membrane appears to possess a high density of negative charges. Therefore, negatively charged molecules such as albumin are hindered much more in their permeation than would be predicted on the basis of their molecular radius. A pathological loss or masking of these negative charges of the slit membrane is responsible for the consequent proteinuria [21].
Gibbs-Donnan Formalism. The fact that proteins (due to the size restriction and due to their negative charges) are mostly excluded from glomerular filtration has one consequence, namely the redistribution of small charged molecules (ions) according to the Gibbs-Donnan formalism for large anionic molecules. As a result the equilibrium concentration of positively charged permeable ions is higher on the blood side, and conversely, the concentration of small permeable anions is larger in the Bowman space. Quantitative consideration reveals that these differences are small. For example, the Gibbs-Donnan distribution for Na⁺ results in a tubule (Bowman space) fluid to plasma concentration gradient (TF/Pₜ₉) of >0.95. Conversely, the TF/Pc₉ is <1.05. Because of their very limited quantitative importance, Gibbs-Donnan equilibria will not be considered further in this and the subsequent two chapters.

Binding to Plasma Proteins. Much more relevant is the fact that many small molecules are bound to plasma proteins (triiodothyronine, steroids, very many apolar drugs, and ions such as Ca²⁺). Only the unbound (free) moieties of these molecules will be filtered and the TF/P values can be small, e.g. 0.6 in the case of Ca²⁺ or 0.01 in the case of the diuretic furosemide.

73.3 Glomerular Filtration

Glomerular filtration is a pressure-driven event. Its dynamics will be discussed in Sect. 73.3.3. The magnitude of GFR with normal kidneys is 120 ml/min or 180 l/day. This enormous filtration rate is made possible by the specific properties of the glomerular filter (cf. above). GFR is a good index of renal function. This may be surprising since renal function comprises filtration, tubule transport (reabsorption, secretion) and endocrine processes. However, any marked fall in GFR will produce the related pathophysiological condition (cf. above). Conversely, any tubule damage is paralleled by a fall in GFR. Therefore, the measurement of GFR is of great clinical relevance.

73.3.1 Measurement of Glomerular Filtration Rate

The measurement of GFR is based on simple mass balance. Suitable substances must be:

- Freely filtered at the glomerulus
- Not reabsorbed by the tubule
- Not secreted by the tubule.

These criteria are met, for instance, by inulin, a polyfructoside with a molecular mass of around 5000–6000 Da obtained from a plant root, by iodothalamate and, with some approximations, by creatinine. The latter has the advantage that it need not be administered because it is produced endogenously from creatine (Fig. 73.6). For any of these substances one can write:

\[
\text{filtered amount} = \text{amount excreted in urine} \\
GFR \cdot P_x = \bar{V} \cdot U_x, \tag{73.1a}
\]

where \( P_x \) and \( U_x \) are the concentrations of the substance “x”, and \( \bar{V} \) is the urinary flow rate in ml/min. Equation 73.1a can be solved for GFR:

\[
GFR = \frac{\bar{V} \cdot U_x}{P_x}. \tag{73.1b}
\]

For the endogenously produced creatinine (C) we can assume that, in the steady state, endogenous production must match the amounts excreted and filtered. Hence, for a normal GFR, \( P \), will increase with increasing production. On the other hand, for any given rate of production, \( P \), will be inversely related to GFR. This is apparent from Fig. 73.7. This graph contains the GFR:P relations for three steady state rates of creatinine production. It is apparent that GFR has to fall markedly before the plasma creatinine concentration increases measurably. This part of the curve is called the silent part. Only if GFR falls to fractions of its normal value, will the effect on \( P \, \) be marked. Instead of measuring GFR, which is quantitatively similar to creatinine clearance, plasma creatinine is measured routinely as a simple “kidney function” test (cf. also Chap. 126). This is of limited value unless creatinine production is known. In a given individual monitoring of \( P \, \) may, on the other hand, be sufficient.

Fig. 73.7. Plasma creatinine concentration as a function of the GFR. The correlation is shown for three daily rates of production. Note that the fall in GFR has little effect on creatinine concentration until 30–50 ml/min is reached ("silent" range of curve). Also note that the plasma creatinine concentration itself is a poor indicator of GFR if the daily rate of production is variable.

Fig. 73.6. Creatinine is produced from creatine. The turnover is largely dependent on muscle mass and muscular activity.
One limitation of creatinine clearance as a measure of GFR derives from the fact that creatinine can be secreted to some extent (for review: [6]). This generates systematic errors, especially in patients with reduced GFR and hence increased P_c. As an alternative, more accurate markers for GFR such as inulin and iodothalamate can be used [6]. Even with these markers, clearance measurements are sometimes inaccurate because of errors in the determination of urinary flow rate. It is customary to collect the urine for a longer period to reduce this error or to increase the urinary flow rate, e.g., by water diuresis.

Glomerular filtration rate and renal blood flow (RBF) vary with a circadian rhythm. GFR is highest during the daytime and lowest during the night. The differences are on the order of 20%. Also GFR is acutely increased by meals if they have a high protein content [11]. This protein (amino acid)-induced hyperfiltration may be pathophysiologically relevant.

### 73.3.2 The Clearance Concept Describes the Clearing Function of the Kidney

In the preceding section GFR was introduced as the clearance of inulin, creatinine or iodothalamate. This is based on the finding that, for these substances, the filtered amount appears in the urine. A creatinine clearance of 120 ml/min therefore indicates that 120 ml of plasma is cleared of creatinine every minute. It was also stated above that in the case of creatinine, the basic assumption may not be entirely correct inasmuch as under certain circumstances creatinine also can be secreted by the tubule. Then, the clearance of creatinine will exceed the GFR because an extra volume of plasma is cleared of creatinine by secretion.

For some substances the secretion can be very relevant. One example is para-aminohippurate (PAH, Fig. 73.8). This is an organic acid which is not formed in the body. At low plasma concentrations this substance is secreted so efficiently by the proximal tubule that the venous effluent from the kidney is PAH free. Then we can write, according to mass balance, that the amount entering the kidney (by renal plasma flow = RPF) is equal to that leaving the kidney via urine:

$$ \text{RPF} \cdot \frac{P_{\text{PAH}}}{P_{\text{PAH}}} = \dot{V} \cdot U_{\text{PAH}}. $$

(73.1c)

The clearance of PAH is then identical to RPF and amounts to some 600 ml/min. With increasing plasma concentrations of PAH the secretion becomes less complete. As a consequence renal venous blood is not PAH free. If this concentration (\(P_{\text{PAH}}^*\)) is known, RPF can still be determined as:

$$ \text{RPF} (P_{\text{PAH}}^* - P_{\text{PAH}}) = \dot{V} \cdot U_{\text{PAH}}, $$

(73.1d)

where \(P_{\text{PAH}}^*\) stands for the PAH concentration in the arterial plasma.

In a more general way the clearance concept can be formulated for any substance:

$$ C_x = \dot{V} \cdot U_x / P_x. $$

(73.2)

The clearance of substance \(x\) then describes the plasma volume per minute which is cleared of this substance. For example, as will be discussed explicitly in Chaps. 74 and 75, the clearance for Na⁺ is only a few ml/min, because most of the Na⁺ is reabsorbed along the nephron.

Instead of absolute values, the clearance of \(x\) is often given as a fraction of that for inulin or creatinine (or GFR). This term is called fractional excretion (FE):

$$ \text{FE}_x = C_x / \text{GFR} = U_x \cdot P_x / P_x \cdot U_x. $$

(73.3)

Equation 73.3 has been obtained from Eqs. 73.1 and 73.2. FE is without dimension.

### 73.3.3 The Dynamics of Glomerular Filtration

The process of glomerular filtration can be written according to Ohm’s law as:

$$ \text{SNGFR} = \Delta P \cdot K_f. $$

(73.4)

SNGFR and \(K_f\) have been introduced above; \(\Delta P\) is the mean pressure gradient across the filtration barrier. Figure 73.9 denotes mean values as they have been obtained from direct measurements in the Munich Wistar rat [2]. The hydrostatic pressure at the beginning and at the end of the glomerular capillaries is around 45–50 and 44–49 mmHg, respectively. When compared to the systemic circulation, these values may appear surprisingly high. However, it has to be remembered that glomerular capillaries are the first capillary network of a portal system (cf. above). Also, it is worth noting that the pressure drop along the glomerular capillaries is very small. Therefore, the filtration process is not controlled by the alterations in axial pressure along the glomerular capillaries.
identical to that at the welling point of peritubule capillaries. The increase in onotic pressure along the glomerular capillary is a direct consequence of the filtration process. Since the filtrate is essentially protein free, the onotic pressure on the blood side will increase due to water removal (cf. also Chap. 125). The effective filtration pressure ($\Delta P$) at any one point of a glomerular capillary can be written as:

$$\Delta P = P_c - P_b - \pi_c + \pi_b.$$  \hspace{1cm} (73.5)

$P_c$ and $P_b$ denote the hydrostatic pressures in the capillary (cf. above) and in the Bowman space. The latter value has been determined in micropuncture studies [2,3] and was found to be 10–12 mmHg. $\pi_c$ and $\pi_b$ are the onotic pressures in capillaries and the Bowman space. That for the Bowman space is close to zero (no quantitatively relevant protein filtration), while that for glomerular capillaries increases along the capillary from 20 to 35 mmHg.

Therefore, the effective filtration pressure at the beginning of the glomerular capillary may be: $\Delta P_0 = 46 - 20 - 12 = 14$ mmHg, and that at the end of the capillary: $\Delta P_F = 45 - 33 - 12 = 0$ mmHg. This latter state, with no net driving force for filtration, is called *filtration equilibrium*.

As shown in Fig. 73.9a, the point at which filtration equilibrium is achieved is determined exclusively by the shape of the curve of the increase in $\pi_c$. The mean net filtration pressure ($\Delta P$) can be determined from the mean height of the area under the curve. In the example of Fig. 73.9a the mean $\Delta P$ is 5 mmHg.

Now consider Fig. 73.9b, in which the assumption is made that the blood capillary flow has doubled from 200 to 400 nl/min (plasma flow 100–200 nl/min). It is evident that now filtration equilibrium will no longer be achieved since the increase in onotic pressure is less marked when the value is 70 nmHg and $\pi_b$ is 12 mmHg. This latter state, with no net driving force for filtration, is called *filtration equilibrium*. As a result the mean filtration pressure and hence SNGFR increase.

Changes in RPF therefore have a large impact on GFR. As will be shown in the next section, the regulation of RBF by various factors - hormones, transmitters and local factors - is one of the determinants of glomerular filtration rate (cf. next section).

Equation 73.4 suggests that $K_i$ and $\Delta P$ are independent parameters. The concept of filtration equilibrium, however, generates a complex interrelationship between $\Delta P$ and $K_i$. The latter term contains two components: the filtration area ($A$) and the hydraulic conductance of the filter ($K$):

$$K_i = K \cdot A.$$  \hspace{1cm} (73.6)

In filtration equilibrium a sizeable fraction of $A$ may not be used because the equilibrium may be reached before the end of the capillary. If now the plasma flow rate is enhanced and a positive filtration pressure prevails towards
the very end of the capillary, the area, and hence $K_r$, is increased. Therefore, strictly speaking GFR increases due to both an enhanced $\Delta P$ and an enhanced $K_r$. Most of the factors to be discussed below change $K_r$ by changing $A$. However, for some of the factors a direct effect on $K$ has been discussed (summarised in: [11]). The concept of filtration equilibrium has thus far been proven only for a very few species, and it is by no means certain that it applies to, for example, dog and man. However, the concept appears very attractive because it can explain why GFR is so exquisitely dependent on variations in renal blood flow, $\pi_c$ and $P_c$.

### 73.3.4 Mesangial Cells: Regulators of Filtration Area?

Several hormones have been shown to act on mesangial cells in culture and on $K_r$, in vivo. Amongst these hormones are norepinephrine, angiotensin II, antidiuretic hormone (AVP), parathyroid hormone, bradykinin and many more [31]. The general effect is a decrease in $K_r$ and a contraction of mesangial cells in culture. On the one hand, anatomical studies do not support the view that mesangial cells modulate the perfusion pressure [16]. On the other hand, it cannot be excluded that contraction of mesangial cells turns off some capillaries and reduces $A$ without any significant effect on $P_c$ [24,25].

The contraction of mesangial cells is mediated by Ca$^{2+}$, as has been shown for vasopressin (antidiuretic hormone), bradykinin and angiotensin II [22]. The effect of other agonists may be mediated indirectly by renin release and angiotensin II production, e.g., parathyroid hormone, insulin and norepinephrine. The fact that mesangial cells in culture possess renin has been interpreted as evidence that these cells have their own renin-angiotensin system. This is unlikely since the expression of renin synthesis may be an artefact of mesangial cell culture. In general, the results obtained from mesangial cell cultures cannot naively be translated into in vivo conditions since mesangial cells in culture change their biological properties easily and rapidly. Still, it appears feasible that several of the above hormones modulate mesangial cell tone by local renin release and angiotensin II production.

### 73.4 Renal Blood Flow Control: A System Constructed to Optimise Control of SNGFR

Renal blood flow (RBF) amounts to approximately 25% of cardiac output, i.e., 1.2 l/min. This is very impressive given the low kidney weight of 150 g/organ. The renal blood supply is therefore calculated as 4 ml/g-min. This is the highest perfusion rate in the body. Moreover this disregards the fact that the blood supply is very high to the cortex and very low to the medulla. Consequently, the perfusion of renal cortex is even considerably higher. Unlike that of brain, heart or skeletal muscle, the venous outflow of the kidney is still well saturated with oxygen. This finding has led to the interpretation that the kidney has a “luxury” perfusion. As will be shown in the next two chapters, this interpretation is wrong inasmuch as a fall in kidney perfusion is poorly tolerated and may cause acute renal failure with the loss of the organ. High renal perfusion is required for two main reasons:

- To warrant a constant and high filtration rate
- To supply sufficient substrate and oxygen to the tubule in order to sustain the tubule transport work

Given this pivotal role of adequate renal perfusion, it is not surprising that renal perfusion, like, for instance, that of the brain, is well regulated and kept constant under conditions of altered systemic blood pressure.

#### 73.4.1 Three Resistors Control RBF and GFR

Figure 73.10 depicts the portal system of the renal vasculature. On the afferent side all resistor vessels are lumped together into one afferent resistor ($R_A$) and on the efferent side all resistor vessels are lumped into one efferent resistor ($R_E$). Between the two resistors filtration takes place across the glomerular capillaries ($R_c = 1/K_r$). The numerical values of $R_A$, $R_E$ and $R_c$ are such that $R_c$ is bigger than the other two. Hence, changes in $K_r$ have little effect.

![Fig. 73.10. The effect of variation in afferent resistance ($R_A$), efferent resistance ($R_E$) and resistance of the filtration barrier ($K_r$) on renal blood flow (RBF) and glomerular filtration rate (GFR). RBF (black line) and GFR (blue line) as well as the resistances are given as relative values. Note that an increase in $R_A$ has a comparable effect on RBF and GFR, whereas an increase in $R_E$ enhances GFR (increased filtration pressure) but reduces RBF. Changes in $R_c$ have little effect on RBF but marked effects on GFR (not shown), because $R_c >> R_A$ or $R_E$.](image-url)
3.4.2 Control of Glomerular Blood Flow

Figure 73.11 summarises data obtained in the above in situ and in vivo preparation with noradrenaline. Two types of experiments were performed. In the first systemic pressure increases overlay local effects, while in the second approach the renal artery was equipped with an adjustable ligature such that renal perfusion pressure was kept constant. In the first approach vasoconstriction was observed for pre- and postglomerular vessels. When perfusion pressure was controlled, noradrenaline had very little effect on preglomerular vessels, but there was a strong constriction of the postglomerular vasculature.

A comparable study with another important vasoconstrictor, angiotensin II (AII), is depicted in Fig. 73.12. It is evident that AII constricts the efferent but also the afferent vasculature. As a result RBF falls strongly. In addition AII reduces $K_f$ (cf. above). Hence GFR tends to fall and FF increases slightly after AII.

Effects of other potent agonists on renal vasculature are summarised in Table 73.2. Adenosine is a potent vasoconstrictor which results in a reduction of GFR (summarised in: [11]; also cf. below). Adenosine [38] is a potent vasoconstrictor of afferent and even more so of efferent arterioles. This explains the strong fall in RBF. The concomitant fall in SNGFR is due to a marked fall in $K_f$.

Many other substances produce increases in RBF (vasodilators): acetylcholine, bradykinin, histamine, dopamine and others belong to this group of substances. The increases in RBF are paralleled by smaller increments in SNGFR. It appears likely that these agonists act via endothelial-derived relaxing factor (EDRF). EDRF has been found recently to be identical with NO [1]. (cf. also Chaps. 5 and 6). The aforementioned substances, after binding to endothelial receptors, activate the production of NO from arginine and the release of NO.

The changes in the respective resistors can be gradual: therefore, the outcome is a fine tuning of the GFR.

The filtration fraction (FF) is the ratio of GFR and RPF. Under normal circumstances this value is $120/600 = 0.20$. It may be enhanced if $R_a$ and $R_e$ increase simultaneously or when $R_e$ increases alone.

Thus far we have simplified the analysis by ascribing all the afferent and efferent resistors to $R_a$ and $R_e$. In fact, it was tacitly assumed that these resistors are localised just before and after the capillaries. This appears the more likely since the small diameter of the arterioles renders them resistor vessels and changes in their diameter would have a large impact on pressure drops. In in vitro perfused renal vasculature [12] and in one in vivo model [36], the hydropenicotic split kidney preparation, these assumptions have been examined experimentally. Although the findings obtained in both preparations do not match for all experimental manoeuvres, the general conclusion is that changes in diameter occur not only in afferent and efferent arterioles but also in adjacent vascular beds.
activates the guanylate cyclase of smooth muscle cells, which leads to increases in cGMP. This second messenger, probably via protein kinase G, relaxes smooth muscle cells. This mechanism now seems proven for ATP, bradykinin, thrombin, platelet activated factor (PAF) and others (cf. Chap. 98).

Other factors, such as the atriopeptides [atrial natriuretic factor (ANF)], appear to act via cGMP directly and to dilate the afferent renal vasculature [36]. ANF increases SNGFR with little change in RBF. This seems to be caused by an afferent vasodilatation and an efferent vasoconstriction [36]. Hence total resistance stays constant but FF and GFR increase.

Little is known of the physiological effects of the various factors summarised in Table 73.2. AllI obviously plays a key role in the renin-II system (cf. below), and NE has a clear function as the transmitter of sympathetic innervation. At this stage the detailed mechanisms involved in autoregulation and in tubuloglomerular feedback are still not known (cf. next section).

### 73.4.3 RBF and GFR Are Autoregulated

When blood pressure changes from its normal mean value of, say, 100 mmHg (13.3 kPa) to higher or lower values, corresponding changes in RBF would be predicted on the basis of Ohm's law. This, however, is not what is observed. As is shown in Fig. 73.13, RBF and GFR are maintained almost constant within a pressure range of 60–160 mmHg; only below and above this range is some sort of Ohmic behaviour observed. These data have been obtained in the non-anaesthetised dog [18].

Considering the mixed elastic and compliant nature of renal vessels one would predict that any increase in

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Table 73.2. Hormonal effects on RBF and GFR (modified from [11])

<table>
<thead>
<tr>
<th>Agonist</th>
<th>RBF</th>
<th>SNGFR</th>
<th>$K_t$</th>
<th>Glom rec.</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>AlI</td>
<td>−</td>
<td>NC</td>
<td>−</td>
<td>+</td>
<td>SNGFR – when PG synthesis is blocked</td>
</tr>
<tr>
<td>NE</td>
<td>−</td>
<td>NC</td>
<td>−</td>
<td>+</td>
<td>AII independent</td>
</tr>
<tr>
<td>ISO</td>
<td>−</td>
<td>NC</td>
<td>−</td>
<td>+</td>
<td>Effects reversed by AII</td>
</tr>
<tr>
<td>ADH</td>
<td>−</td>
<td>NC</td>
<td>−</td>
<td>+</td>
<td>Effects reversed by AII</td>
</tr>
<tr>
<td>PTH</td>
<td>(+)</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>Effects reversed after Throm A2 blockade</td>
</tr>
<tr>
<td>PGE2</td>
<td>(+)</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>Effects reversed after Throm A2 blockade</td>
</tr>
<tr>
<td>ADE</td>
<td>−</td>
<td>−</td>
<td>NC</td>
<td>+</td>
<td>H2 receptors</td>
</tr>
<tr>
<td>Throm</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>Not blocked by AII blockade</td>
</tr>
<tr>
<td>PAF</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

Glom. rec., glomerular receptors; AII, angiotensin II; NE, norepinephrine; ISO, isoproterenol; ADH, antidiuretic hormone; PTH, parathyroid hormone; PGE2, prostaglandin E2; ADE, adenosine; Throm, thromboxane; PAF, platelet activating factor; EGF, epidermal growth factor; ACH, acetylcholine; BRA, bradykinin; HIS, histamine; ANF, atrial natriuretic factor (peptide); −, decreased; +, increased; NC, no change; ?, unclear
perfusion pressure would cause an increase in radius (compliance), and this increase in radius would reduce resistance markedly (4th power of radius in Hagen-Poiseuille's law). Hence, an over-proportional increase in perfusion would be the result. To explain the observation not only constancy but even a pressure-dependent constriction of the vessels has to be postulated. If RBF is perfectly autoregulated, the autoregulation of GFR can be explained as a consequence of this.

73.4.4 Autoregulation: Bayliss Effect or Tubuloglomerular Feedback?

Current evidence favours the view that both components, the Bayliss effect and tubuloglomerular feedback (TGF), are involved in normal autoregulation. However, it is evident at the same time that autoregulation can be shown in the absence of TGF and also without changes in renin.

The Bayliss effect implies that an arteriole put under luminal pressure (stretch) responds with constriction. Such an effect could be produced by a paracrine factor (cf. Chap. 98), or it may simply be caused by stretch activation of, for example, a non-selective cation channel. Ca\(^{2+}\) would enter through this channel and this might mediate constriction. The principal components of such a mechanism have been identified by patch clamp techniques and fura-2 Ca\(^{2+}\) measurements in various cells. However, the final proof that such a mechanism operates in afferent arterioles is still missing.

The TGF is a complex mechanism which consists of several functional components (Fig. 73.3a):

- Macula densa (MD) cells, which sense the luminal Cl\(^{-}\) concentration via the Na\(^{+}\)2Cl\(^{-}\)-K\(^{+}\) cotransporter present in the luminal membrane of these cells (cf. also Chap. 75). This "chemoreceptor" responds to an increase in luminal Cl\(^{-}\) with a depolarisation of the voltage.
- Goormaghtigh cells (extraglomerular mesangium) which somehow have to process the MD signal.
- Smooth muscle cells of the afferent arteriole of the same nephron.
- Renin-producing cells in the afferent arteriole.

Pertinent experimental observations [5] are summarised in Fig. 73.14. A fall in SNGFR is observed when the loop is perfused at high flow rates with NaCl-containing Ringer's solution. This is especially pronounced if the loop is perfused retrogradely. Instead of SNGFR, early proximal tubule flow rate is monitored in these experiments. The fall in early proximal flow rate is most marked for small anions such as Cl\(^{-}\) and small cations such as Na\(^{+}\). The TGF response consists in: (1) vasoconstriction whenever the Cl\(^{-}\) concentration in the MD segment increases above a certain value, and (2) a reduction in renin secretion. A fall in Cl\(^{-}\) concentration or an inhibition of the sensor (Na\(^{+}\)2Cl\(^{-}\)-cotransporter) by loop diuretics [29,30] has the opposite effect.

If we consider an inappropriately high SNGFR, say due to imperfect autoregulation, the capacity of the thick ascending limb to cope with this enhanced NaCl load may be compromised. This will lead to an increase in luminal Na\(^{+}\) and Cl\(^{-}\) concentrations. The MD, put strategically at the end of this nephron segment and in close vicinity to the vasculature serving this nephron, senses this increment in Cl\(^{-}\) and conveys a message to the afferent arteriole to constrict. This negative feedback between tubule and glomerulus (hence the name TGF) reduces RBF and SNGFR.

It is still not clear how this feedback is processed from the MD to the smooth muscle cells [32]. Originally it was suggested that the renin system and AII were the mediators (cf. below). This appeared especially attractive since the renin-producing cells are part of this functional unit and because AII is a potent vasoconstrictor on renal arterioles. On the other hand, it is now clear that the observed vasoconstriction cannot be explained by reference to AII since renin secretion is reduced rather than enhanced with high loop perfusion. Other possible mediators are prostaglandins, CAMP, Ca\(^{2+}\) and adenosine [32]. Especially adenosine is a likely candidate because it might be produced at increased metabolism by the MD cells. In addition, vasoconstriction of afferent arterioles by adenosine has been demonstrated. Furthermore, inhibitors of A1 receptors suppress the TGF response.

The second component of TGF is a reduction in renin release. Direct vasoconstriction, e.g., by adenosine, and the attenuation of this response by a fall in AII counterbalance each other to some extent. The function of this second and attenuating loop in TGF is unclear. It might serve for fast resetting and fine tuning. The systemic effects of renin and AII are discussed elsewhere (cf. Chap. 94). In summary, autoregulation of RBF and SNGFR are due to the concerted action of vascular response and TGF.

73.5 Deep Versus Superficial Nephrons

As shown in Fig. 73.2, the nephrons can be classified by the location of their glomeruli in the cortex and by the depth which the loops reach in the outer medulla, in the inner medulla or in the papillae. These classifications are different for various species. Even in very early studies (reviewed in [28]) it was clear that in the human kidney the majority of nephrons are short looped (superficial), with only about one-seventh having long loops (deep nephrons). It was also evident from a large number of comparative studies in different species that the size of the glomeruli is larger for the deep nephrons than for the superficial ones. This also applies to the kidneys of children, but not to those of adults. As outlined in a previous section, the vasculature and tubule segments of deep and superficial nephrons have distinct differences [8,23].

When it comes to function of the two major populations of nephrons, several aspects, though challenged by some studies, deserve mention. The autoregulation of RBF of the
Fig. 73.14. Feedback responses in rat nephron. Fall in early proximal tubule flow rate ($\Delta V_{TP}$) with retrograde perfusion of solutions containing various cations and anions. Retrograde perfusion was chosen in order to control the ion composition at the macula densa site. It is shown that a maximal TGF is obtained with high concentrations of Na$^+$ and Cl$^-$. Several small cations can substitute for Na$^+$, but only Br$^-$ for Cl$^-$. This suggests that TGF is mediated mostly by a Cl$^-$ sensing mechanism. Meanwhile it has been shown that this sensing occurs via the Na$^+$-2Cl$^-$K$^+$ cotransporter [30]. (From [5])

deep nephrons appears less perfect than that of RBF of the superficial nephrons. As a consequence, increases in blood pressure increase medullary blood flow proportionally more than superficial blood flow. This has certain consequences: the interstitium of the renal medulla is "washed out" (cf. Chap. 74) and the kidney loses some of its concentrating ability, resulting in a "pressure diuresis" [39].

The deep nephrons, due to their long loops, are suited for salt and water conservation (cf. Chap. 74). Some manoeuvres such as acute or chronic salt loading appear to induce a redistribution of RBF and even more so of SNGFR. The SNGFR of the superficial nephrons tends to increase and that of the deep nephrons to fall. Concomitantly the filtration fraction is almost constant for the superficial nephrons but falls in the deep ones. Therefore, simplistically speaking, the filtrate is now shifted from the "salt-saving" to the "salt-losing" nephrons. Furthermore, the relative increase in medullary blood flow (fall in filtration fraction of deep nephrons) leads to a "medullary wash out" with the above consequences.

As yet there is little direct support for these considerations as far as the human kidney is concerned, simply because we rely entirely on anatomical studies and have very few functional data. In other species (rat, dog, rabbit) an enormous amount of data is available. Nonetheless it should be kept in mind that we have no direct means of measuring glomerular dynamics in deep nephrons. Comparative data on kidney anatomy and function of various mammals adapted to extreme environmental conditions have been pivotal in the understanding of the renal concentrating mechanism [8].

73.6 The Kidney: An Endocrine Organ

The kidney produces several hormones and local factors such as renin, erythropoietin, 1,25-dihydroxycholec-
alciiferol, prostaglandins, adenosine, NO, endothelin, kinins and probably many others. In this section the first three of these hormones will be briefly discussed; the others are mentioned in other sections of this chapter.

### 73.6.1 The Renin-Angiotensin System

The renin-angiotensin system has already been mentioned in previous sections. Here we shall briefly outline its components and its function, because this knowledge will be required for several of the following chapters.

**Renin: A Neutral Aspartyl Protease Not Unique for the Kidney.** Renin (prorenin) is produced in isofoms in a variety of organs such as the liver, several areas of the brain, the kidney and some glands [37]. It is species specific and made from a large 1.2-kb gene. The processed renin in the cisternae of the endoplasmic reticulum of the renin-producing cells contains the polypeptide (317AA, MW 42kDa) which consists of two chains connected by a single disulphide bridge. The release and the transcription of renin are regulated locally (vide infra).

Once released (mostly to the perivascular side) and taken up (mostly into the capillary network), renin, as an aspartyl protease, cleaves systemically circulating angiotensinogen (Fig. 73.15).

**The Angiotensin Cascade.** Angiotensinogen is a 53- to 57-kDa peptide, produced in impressive amounts (circulating concentration is in the μmol/l range), essentially by the liver. Angiotensinogen is cleaved on its amino terminus between two leucins to form the decapeptide angiotensin I (AI). AI has little biological activity and is cleaved further by angiotensin-converting enzyme (ACE).

ACE (EC 3.4.15.1) is a peptidyl-dipeptide-carboxylhydrolase which cleaves off Leu-His at the carboxy end of AI and thus forms angiotensin II (AII), an octapeptide. ACE is present mostly in the luminal membrane of the vasculature. It is a 200-kDa protein. The name may, in fact, be misleading because ACE is indistinguishable from kininases, which cleave kinins such as bradykinin.

In this context it is likely that the high immunological ACE activity found in microvilli (proximal tubule, choroid plexus, intestine, placenta etc.) reflects the ability of these structures to cleave bradykinin, rather than implying that they play a role in the formation of AII. This multiple function of ACE should also be considered when examining the beneficial effects in ACE inhibitor treatment. Some of these effects can be clearly ascribed to an increase in bradykinin.

AII is a potent vasoconstrictor, but besides this it also enhances renal tubule NaCl reabsorption, it releases aldosterone from the zona glomerulosa of the cortex of the adrenal gland, it releases antidiuretic hormone (ADH) from the posterior lobe of the pituitary gland, and it produces thirst in the hypothalamus (cf. Chap. 82). The CNS effects of AII appear to be possible since the blood-brain barrier is “incompetent” (permeable) in this hypothalamic area. AII is a labile hormone and it is cleaved or degraded by angiotensinases. One substrate formed is the heptapeptide angiotensin III (AIII), which has much less biological activity than AII.

**Intrarenal Renin-Angiotensin System (RAS).** Figure 73.3A shows the specialised cells which are the main production sites of renin within the kidney. These cells, mostly located in the most distal part of the afferent arteriole, have intimate contact to their neighbours in the juxtaglomerular apparatus (JGA). These are (a) the Goormaghthigh cells (on a section such as that in Fig. 73.3A, these cells lie within a triangle formed by the base of the macula densa cells and the afferent and efferent arterioles entering the glomerulus) and (b) the macula densa cells. Since the early studies, e.g., by Goormaghthigh [15], the function of the JGA has largely remained a mystery. Some of the regulatory aspects of this machinery have been discussed above (see Sect. 73.3.4); here the regulation of renin release will be summarised. The key stimuli for renin release are:

- Fall in systemic blood pressure
- Sympathetic discharge to the kidney
- Fall in NaCl concentration delivered to the macula densa

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![Fig. 73.15. The regulation of AII production. For further details consult text](Image)
- Prostaglandins such as PGE$_2$ and PGI$_2$
- Kinins.

Drugs can also increase renin release. Amongst these several important ones are:

- β-Agonists
- Loop diuretics
- ACE inhibitors
- Ca$^{2+}$ antagonists
- α$_1$-antagonists
- Saralasin.

Conversely, renin secretion can be inhibited by increased blood pressure, diminished sympathetic discharge and increased NaCl delivery to the macula densa. In addition renin release is diminished by AII, α$_1$-agonists, vasopressin, endothelin, adenosine, NO, β-blockers etc.

**How is Renin Released.** It is difficult, at this stage, to define a general concept of how renin is released. It has been claimed that the effects of some of the above-mentioned regulators can be explained by their ability to increase (stimulate) or diminish (inhibit) cAMP in the granulated renin-producing cells. Such factors comprise β-agonists, PGE$_2$, etc. Renin secretion may also be inhibited by agonists increasing cGMP; such agonists include, for example, ANP and NO [20].

As regards most of the other regulators, it has been claimed that they increase renin release by a reduction of cytosolic Ca$^{2+}$ ([Ca$^{2+}$]). Hence Ca$^{2+}$ antagonists, or α$_1$-antagonists, enhance renin release and Ca$^{2+}$ mobilising agents such as α$_1$-agonists, AII, vasopressin, endothelin, pressure-induced stretch etc. inhibit renin release. This concept of direct control of renin release by [Ca$^{2+}$], appears attractive, but it may not be applicable. First, it stands in contrast to most if not all exocytotic secretion processes, where increases in [Ca$^{2+}$], are required for exocytosis; second, this concept is not unchallenged by contradictory results. It is clear, at any rate, that renin release occurs from vesicles which, upon stimulation, fuse with the plasma membrane. It may turn out that [Ca$^{2+}$] has a dual effect on renin secretion, and that the local Ca$^{2+}$ activity close to the respective vesicles differs from that of the bulk phase of the cells. It has also been claimed that the renal RAS works as a self-supporting independent regulatory system, very much like the RAS of the brain. Such a system would require that angiotensinogen is present locally and need not be delivered from the circulation. In fact, the co-secretion of renin and AII from renin-producing cells has been claimed. The as yet open question is whether renally produced angiotensinogen suffices to explain normal function [27]. Hence this entire concept has to be questioned, and it appears safe to conclude that local and systemic renin concentrations stand in close relation under most conditions.

73.6.2 Erythropoietin Is Mostly Produced in the Kidney

Erythropoietin is a glycosylated peptide hormone with 137 amino acids. Most of the hormone in adults comes from the kidney; a minor fraction is produced in the liver. The half-life of erythropoietin is 5–9h. The main target of erythropoietin is the bone marrow, where it increases the formation of red blood cells (erythropoiesis). A fall in arterial O$_2$ pressure and/or a fall in hemoglobin serves as an adequate stimulus for erythropoietin secretion by the kidney. Both signals have in common the fact that they define the delivery of O$_2$ to the kidney [35] (cf. Chap. 84).

It may appear surprising that the O$_2$ delivery is monitored in the kidney, where blood supply is as high as 4 ml/min·g and O$_2$ supply is 1 ml/min·g. This is the more surprising
since the erythropoietin-producing cells seem to be present exclusively in the cortex, where blood supply is especially high. This puzzle is as yet unresolved. It may be that tube transport in the cortex generates a fall in local pO₂ when oxygen supply does not match the needs. The erythropoietin-producing cells appear not to be vascular, endothelial or tubular. They seem to be specialised cells most probably located in the peritubular space, although a definite answer as to the precise localisation is still missing [17].

In severe chronic renal failure the lack of erythropoietin is believed to be the main cause of anaemia. Consequently, with the advent of recombinant human erythropoietin, replacement therapy is now used clinically [42].

73.6.3 The Production of the Hormone 1,25-(OH)₂-Cholecalciferol Requires an Intact Kidney

Figure 73.16 summarises the metabolism of 1,25-(OH)₂-cholecalciferol [1,25-(OH)₂-D₃]. In the presence of UV light, calciferol can be formed from cholesterol in the skin. Calciferol is then hydroxylated in the liver to form 25-OH-D₃. This is then delivered to the kidney to form 1,25-(OH)₂-D₃. This latter reaction is controlled by PTH [10]. Only in the presence of PTH are sufficient amounts of 1,25-(OH)₂-D₃ synthesised. Besides 1,25-(OH)₂-D₃, 24,25-(OH)₂-D₃ is formed. This compound has much less, if any, biological activity compared with 1,25-(OH)₂-D₃. The effects of 1,25-(OH)₂-D₃ are discussed in Chap. 80. It may suffice to state here that this hormone increases Ca²⁺ absorption from the intestine and increases osteoclast activity. Because, at the same time, plasma Ca²⁺ is increased, this leads to the formation of new bone. The direct effects of this hormone on the kidney are probably minor. Deficiency of this hormone leads to the clinical pictures of rickets in children and osteomalacia in adults.

Appendix. Glossary and Abbreviations for Chaps. 73, 74 and 75

The abbreviations used in renal physiology have been standardized recently. However, the cited literature uses many synonyms. Therefore, both the recommended (italics) and frequently used abbreviations are given below.

**AI = angiotensin I**
**AII = angiotensin II**
**ACE = angiotensin-converting enzyme, catalyses AI → AII**
**ADH = antidiuretic hormone, also referred to as AVP**
**ANP = atrial natriuretic factor = ANP**
**ANP = atrial natriuretic peptide = ANF**
**Antiparal = transport coupling into opposite directions by a carrier**

**ARF = acute renal failure**
**ALT = thin ascending limb of the loop of Henle = tAL**
**Autoregulation = constancy of renal blood flow and glomerular filtration rate, despite changes in renal perfusion pressure**
**Baylis effect = one component of autoregulation of RBF**
**Bowman space = intraglomerular compartment into which filtration proceeds**
**CCT = cortical collecting tubule = CCD = cortical collecting duct**
**CNT = connecting tubule = first portion of collecting tubule**
**Cotransport = transport coupling into the same direction by a carrier**
**Countercurrent concentrating mechanism = specific countercurrent arrangement of tubule and vascular structures in renal medulla and papilla which makes it possible to concentrate urine**
**CRF = chronic renal failure**
**Creatinine = usual (endogenously produced) marker for measurement of GFR**
**CTAL = cortical thick ascending limb of the loop of Henle**
**DT = distal tubule**
**DTL = thin descending limb of the loop of Henle = tDL**
**Ducts of Bellini = papillary collecting tubule**
**Electrogenic = transporting an electric charge = rheogenic**
**Feedback = usually more specifically referred to as tubuloglomerular feedback**
**Filtration fraction = GFR/RPF**
**GFR = glomerular filtration rate**
**Glomerulotubular balance = readjustment of proximal tube transport rate according to variations in SNGFR. High SNGFR enhances, for example, HCO₃⁻ absorption. Low SNGFR has the opposite effect.**
**GTB = glomerulotubular balance**
**IMCD = inner medullary collecting duct = IMD**
**IMD = inner medullary collecting duct = IMCD**
**Intercalated cells = acid/bicarbonate secreting cells of the collecting tubule = A/B cells**
**Inulin = polyfructoside, a marker for measurement of GFR**
**Kᵣ = hydraulic conductivity of glomerular filter**
**Loop diuretics = diuretic and saluretic substances acting in the thick ascending limb of the loop of Henle**
**Macula densa mechanism = sensing of tubule fluid at this nephron site. High luminal Cl⁻ leads to a reduction in SNGFR (tubuloglomerular feedback) and to a reduction in renin secretion**
**MCD = medullary collecting duct**
**MD = macula densa segment**
**MTAL = medullary thick ascending limb of the loop of Henle**
**OMCD = outer medullary collecting duct = OMD**
**OMD = outer medullary collecting duct = OMD**
**PAH = para-aminohippurate, a marker for the measurement of RPF**
**Pars recta = straight portion of proximal tubule, usually corresponding to S₁ and S₂**
**PCD = papillary collecting duct**

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PG = prostaglandin
PT = proximal tubule
PTH = parathyroid hormone, parathyrin
RBF = renal blood flow
Rheogenic = transporting an electric charge = electrogenic
RFP = renal plasma flow
Principal cells = Na⁺- and water-absorbing and K⁺-secreting cells of the collecting tubule
S₁ = convoluted part (first part) of proximal tubule
S₂ = second (intermediate) part of proximal tubule
S₃ = third (last) part of proximal tubule
SGF = single nephron filtration rate
TAL = thick ascending limb of the loop of Henle
tAL = thin ascending limb of the loop of Henle = ATL
tDL = thin descending limb of the loop of Henle = DTL
TGF = tubuloglomerular feedback
Tubuloglomerular feedback = readjustment of SGF by early distal tubule (macula densa) ion composition. High Cl⁻ at this nephron site reduces SGF. Low Cl⁻ has the opposite effect.
Vasa recta = straight vascular structures of renal medulla and papilla, part of the countercurrent concentrating system.

References