128. Blood flow in the kidney, its regulation

Kidney- blood supply

• Blood flow to the kidney is about 20-25% of the cardiac output at rest (1-1.25 L/min). • Considering the fact that both kidneys weigh about 300-400 gr and constitute less than 1% of the body weight, we can see that the kidneys receive an extremely high blood flow, greatly exceeding its own metabolic needs. • The blood supply of the kidney forms a portal system, a unique vascular arrangement found only in 3 locations in the body (liver, kidneys, hypophysis). • Renal portal system (2 capillary beds in series): afferent arteriole -> glomerular capillaries -> efferent arteriole -> peritubular capillaries -> vasa recta -> interlobular veins.

Renal blood flow (RBF)

• Blood flow through the kidney serves several important functions: 1. Indirectly determines GFR (glomerular filtration rate). 2. Delivers oxygen, nutrients, hormones to the kidneys tissues, and returns CO2, reabsorbed fluid and solutes back to the general circulation. 3. Modifies the rate of solute and water reabsorption by the proximal tubule. 4. Participates in concentration and dilution of urine. 5. Delivers substrates for excretion in urine.

• The afferent arterioles, efferent arterioles and interlobular arteries are the major resistance vessels in the kidneys, thus they determine the renal vascular resistance. • By adjusting the renal vascular resistance, the kidneys regulate the renal blood flow in response to changes in arterial pressure. • These adjustments are so precise that the RBF and GFR remain relatively constant between arterial pressures of 90-180 mmHg. The same mechanisms regulate both GFR and RBF. • RBF and RPF: because the plasma is what actually gets filtered in the glomerulus, Renal plasma flow (RPF) is an important

value as well. • RPF = RBF X (1 – hematocrit) • RPF = about 600-700 ml/min

Measurement of RPF and RBF

• For RPF (renal plasma flow) to be estimated, there should be an indicator substance that is completely cleared from the plasma. In that case, the clearance = RPF. • Because GFR is about 20% of RPF, the indicator must be excreted by secretion as well. • The only known substance known for this is the organic acid, para-aminohippuric acid (PAH). • PAH characteristics as an indicator- it is not synthesized or metabolized by the kidney. It is both filtered and secreted into the urine. About 90% of it is cleared from the plasma by the kidney (the best we got). • If you take into account the PAH plasma concentration, PAH urine concentration and diuresis (urine excretion rate) you can get an approximate calculation of the RPF. • From the RPF value, RBF can be calculated using hematocrit value.

Autoregulation of RBF and GFR

• 2 mechanisms are responsible for RBF and GFR autoregulation: myogenic mechanism (faster) and tubuloglomerular feedback (slower). • The myogenic mechanism responds to changes in the arterial pressure, while the tubuloglomerular feedback responds to changes in the tubular fluid. • Importance of these mechanisms: without those mechanisms even a small change in the arterial pressure would of change the amount of urine excretion (diuresis) dramatically. • Example: normal GFR is 180 L/day, 178.5 L are reabsorbed and 1.5 L excreted, a change of arterial pressure from 100 to 125 mmHg would of changed the GFR to 225 L/day. If still only 178.5 L are reabsorbed the urine flow would have been 46.5 L/day (more than the whole plasma). Myogenic mechanism • Increased arterial pressure stretches the smooth muscle in the afferent arterioles. • This stretching induces opening of stretch-activated calcium channels in the smooth muscle, leading to depolarization (Ca influx) and contraction. • The smooth muscle contraction increases afferent arteriolar resistance, thus decreasing the GFR to normal. • In contrast, decreasing arterial pressure leads to relaxation and decreased afferent arteriolar resistance.

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Tubuloglomerular feedback

• This feedback mechanism depends on the special anatomical arrangement of the juxtaglomerular apparatus. The juxtaglomerular apparatus contains: 1. Macula densa cells in the junction between the straight and convoluted distal tubules. 2. Juxtaglomerular cells (also granular cells) in the walls of afferent and efferent arterioles. cells.

• The macula densa cells are able to sense Na and Cl concentrations in the distal tubule fluid.

• If GFR decreases -> more Na and Cl are reabsorbed in the tubules -> low levels of Na/Cl at the macula densa.

• If GFR increases -> less Na and Cl are reabsorbed in the tubules -> high levels of Na/Cl at the macula densa.

• When the macula densa cells sense high Na/Cl levels they release adenosine in a paracrine mechanism. The adenosine causes vasoconstriction in the afferent arteriole -> higher afferent arteriolar resistance- ->GFR down. The adenosine also inhibits renin secretion (from juxtaglomerular cells). • When the macula densa cells sense low Na/Cl levels they release the vasodilator NO (nitric oxide) dilating the afferent arterioles ->lower resistance -> GFR up. In addition, the paracrine signaling also leads to renin secretion from the juxtaglomerular cells. • Effect of high protein diet on tubuloglomerular feedback: the high protein diet increases the amino acid levels in the plasma. Meaning more amino acids are reabsorbed in the proximal tubule. Because amino acid reabsorption is accompanied with Na reabsorption, it leads to lower Na levels in the macula densa. Which in turn cause GFR to increase. • GFR and RBF autoregulation enables relatively constant GFR between 90-180 mmHg and when the extracellular fluid volume is normal. • But when the arterial pressure is below 90 mmHg or when the extracellular fluid volume is low, external regulatory mechanisms act on the GFR and RBF.

External regulation of GFR and RBF

Vasoconstrictors (GFR down) Sympathetic nervous system • The kidney's arteries are sympathetically innervated. When, arterial blood pressure decreases below 90 mmHg, norepinephrine released from the sympathetic nerves as well as circulating epinephrine from the adrenal gland. • This leads to stimulation of α-1 adrenoceptors -> vasoconstriction especially of afferent arterioles (highest number of receptors) -> afferent arteriolar resistance up -> GFR down.

Angiotensin II

• Angiotensin II is a vasoconstrictor that is considered a circulating hormone and a locally produced autacoid (vasoactive substance produced in the kidney and acts locally). • There are receptors for angiotensinogen in all the kidney vessels, but the efferent arterioles have the highest sensitivity (the effect on afferent arterioles is reduced by prostaglandins and NO). • Small increase in angiotensin II levels leads to -> higher efferent arteriolar resistance -> preventing decrease in hydrostatic pressure in glomerulus -> GFR remains normal. • This also leads to decreased blood flow in peritubular capillaries -> higher reabsorption of Na, Cl. • Large increase in angiotensin II levels leads to -> RBF down -> GFR down.

Endothelin

• Secreted by endothelial cells in the renal vessels, mesangial cells, and in the distal tubules in response to angiotensin II, epinephrine and shear stress. • Endothelin is a vasoconstrictor, it decreases GFR and RBF. • Usually it doesn't have an effect on resting individuals, but it is of importance in renal pathologies.

Vasodilators (GFR up)

NO (nitric oxide)

• Derived from endothelial cells, it is an important vasodilator (GFR/ RBF up). • It counteracts the effect of angiotensin II and catecholamines. • It seems like there are basal constant levels of NO, needed for normal excretion of urine. When NO production is stimulated -> GFR up, when NO production is inhibited -> GFR down. Prostaglandins and bradykinins • Can be produced locally in the kidney and cause vasodilation of the afferent and efferent arterioles. These vasodilators doesn't appear to have a major regulatory importance normally. • But when the sympathetic system is activated, secretion of prostaglandins and bradykinin reduces the vasoconstrictive effect of epinephrine/norepinephrine, preventing an excessive decrease in the GFR.

Atrial Natriuretic peptide (ANP) and Brain Natriuretic peptide (BNP)

• ANP is secreted by atrial cardiomyocytes and BNP is secreted by ventricular cardiomyocytes, in response to increases in extracellular fluid volume in these tissues, leading to higher tension on the heart chamber walls. • ANP and BNP cause vasodilation in the afferent arteriole and vasoconstriction in the efferent arteriole, leading to increase in GFR. Dopamine • Can be produced in the proximal tubules. Low doses of Dopamine are vasodilators in the cerebral, coronary, splanchnic and renal circulations (RBF/GFR up). Also it inhibits renin secretion.