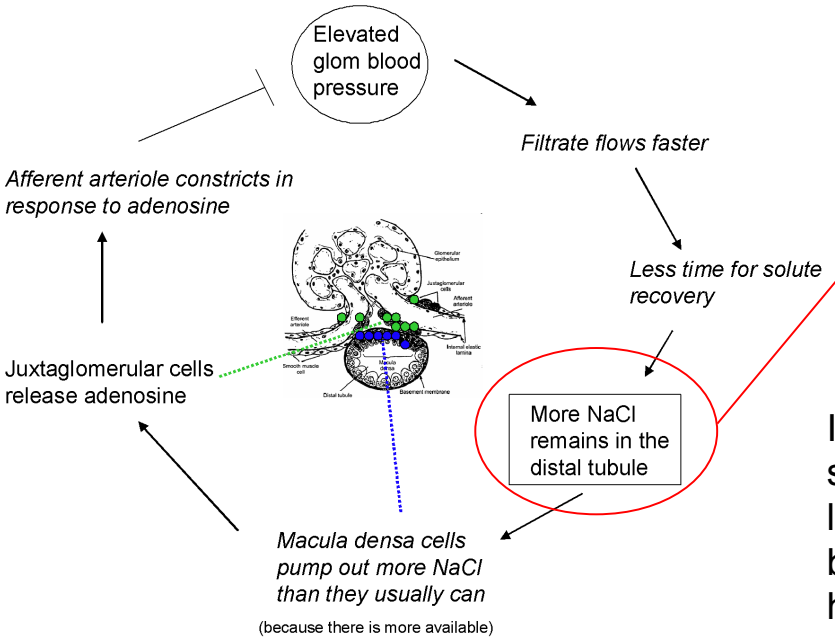
Problem:



Does this mean that glomerular pressure is too high, or that the body suddenly has too much sodium?

If the kidney responds to high sodium at the macula densa by lowering filtration rate, the person becomes even more hypernatraemic.

The kidney can't make decisions on its own – it has to talk to sensors (and effectors) in the rest of the body.

How does the macula densa work?

Elevated glom blood pressure

Filtrate flows faster

Less time for solute recovery

More NaCl remains in the distal tubule

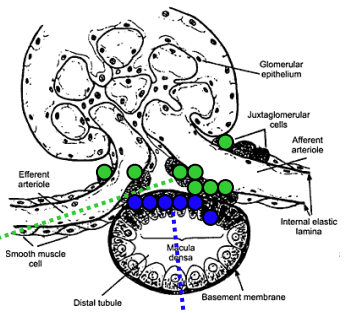
Macula densa cells pump out more NaCl than they usually can

(because there is more available)

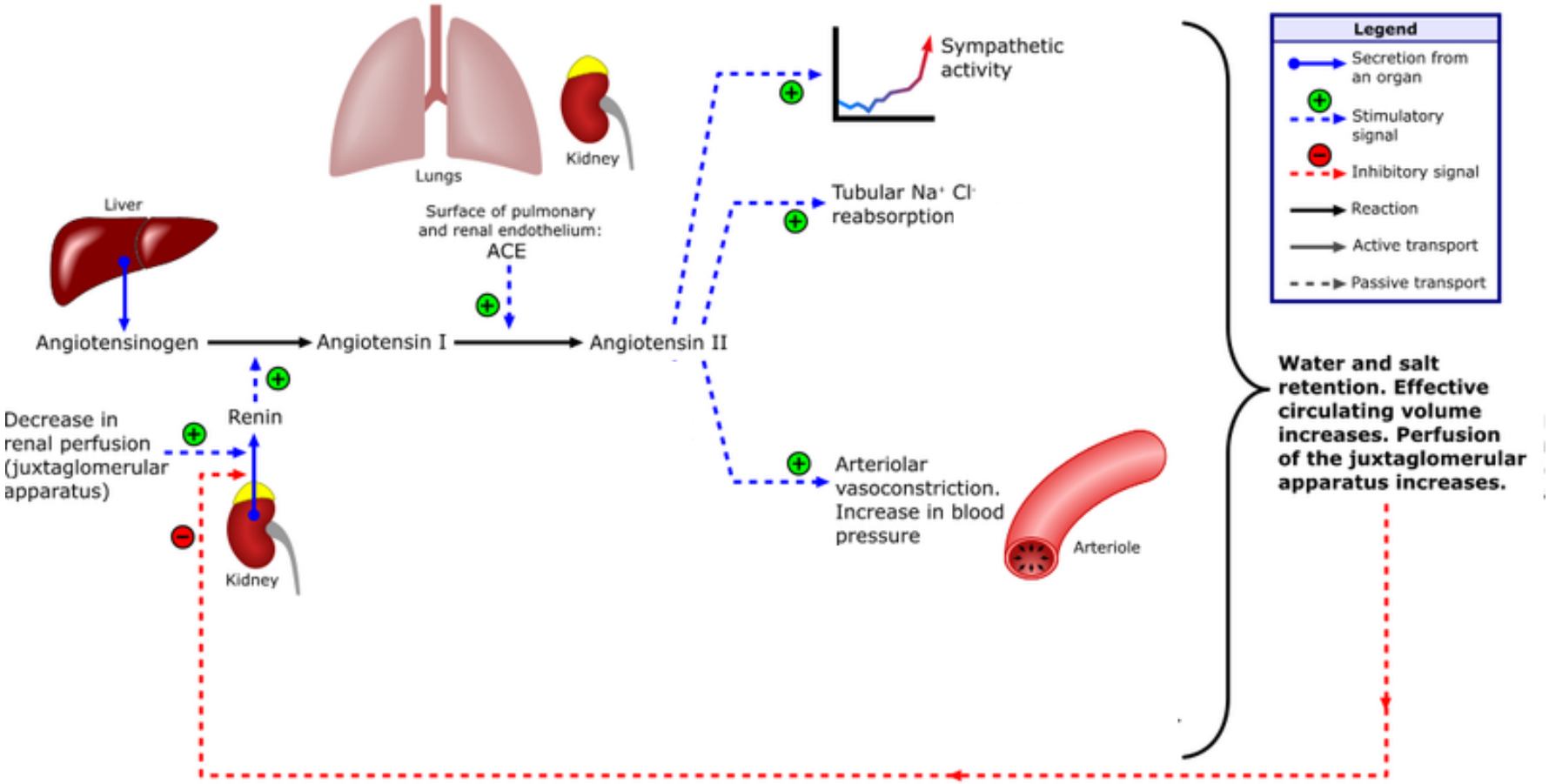
Juxtaglomerular cells release renin

Afferent arteriole constricts in response to adenosine

Juxtaglomerular cells release adenosine



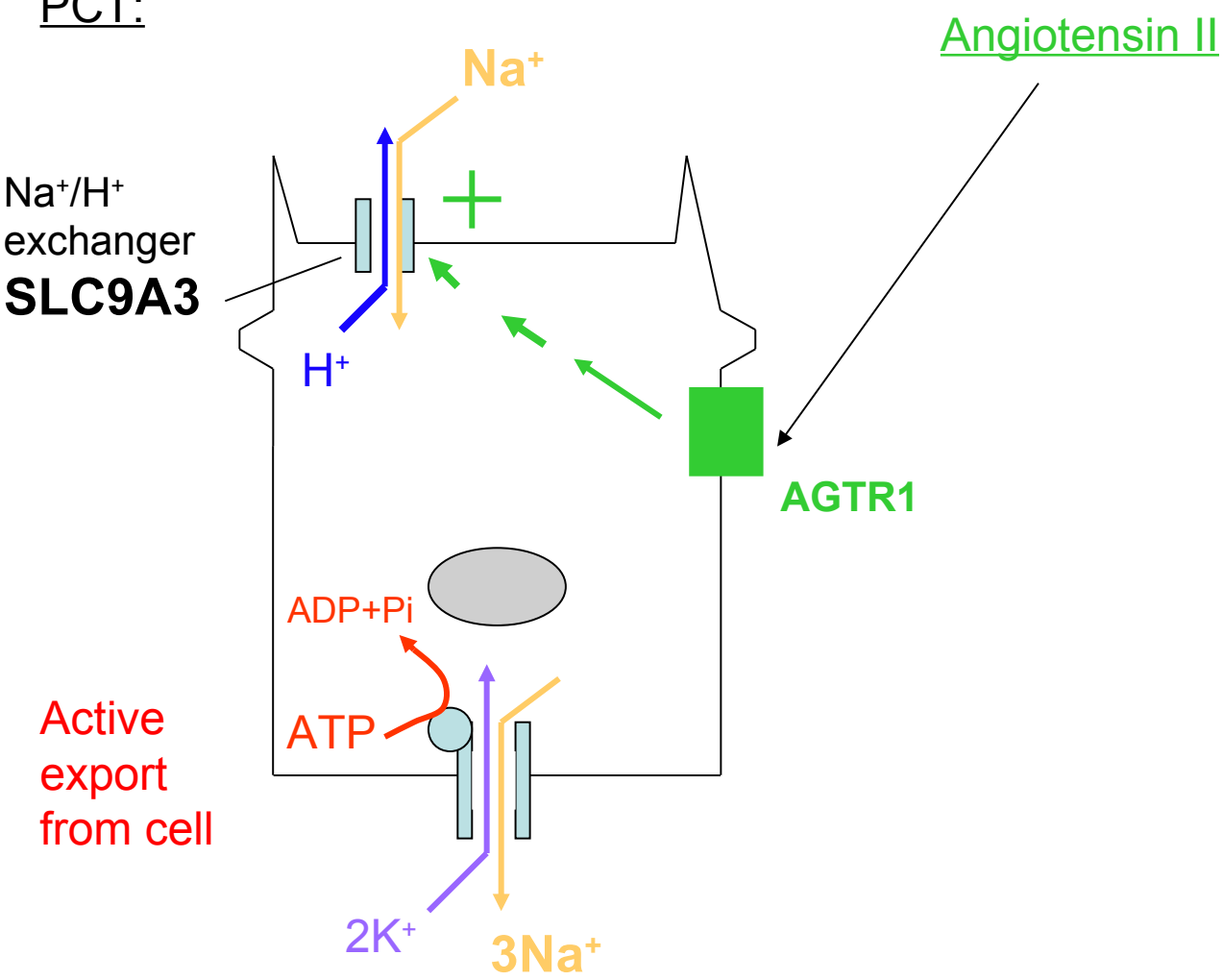
Renin-angiotensin-aldosterone system



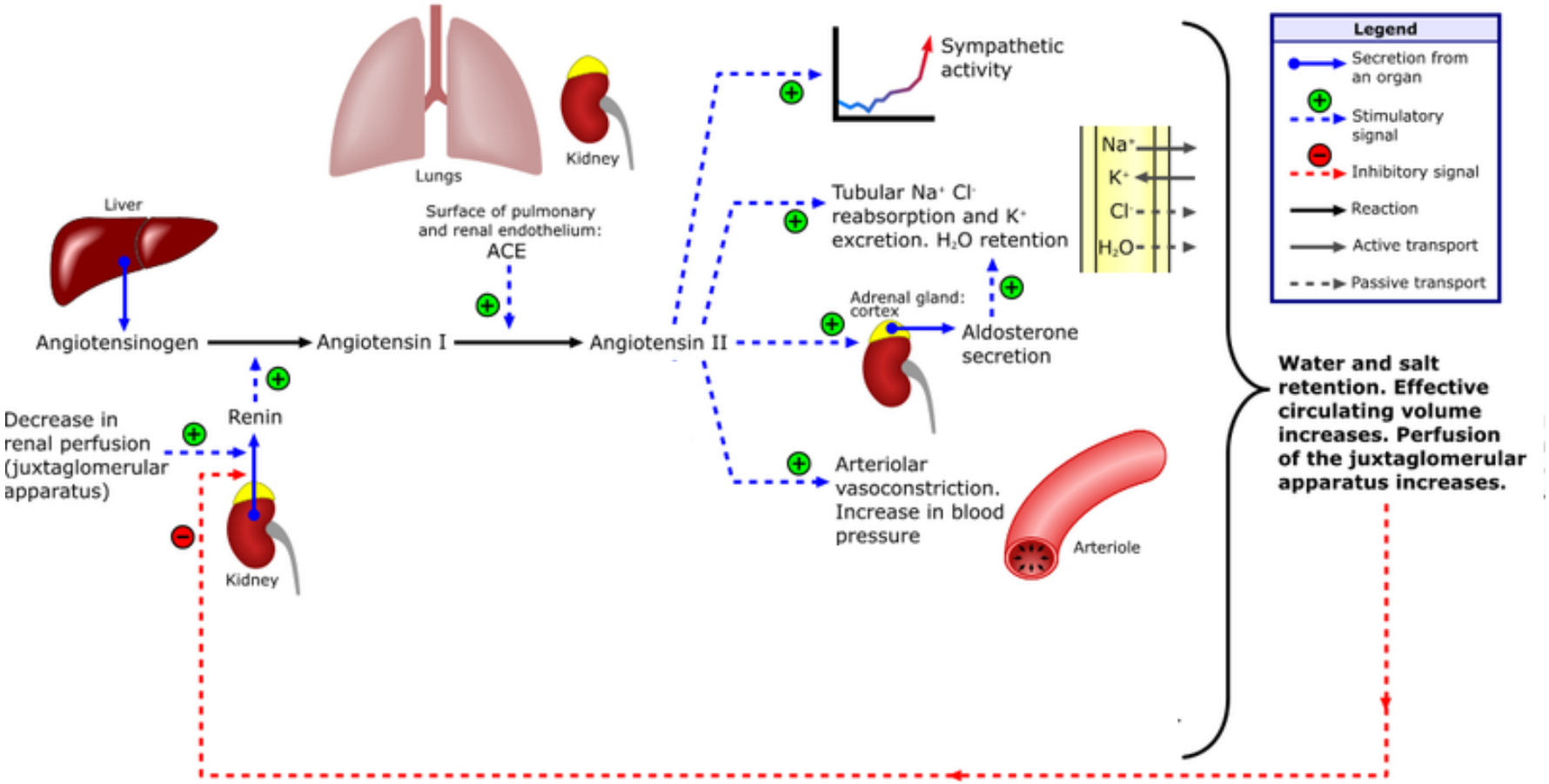
Wikipedia commons

Action of Angiotensin II on kidney cells:

PCT:

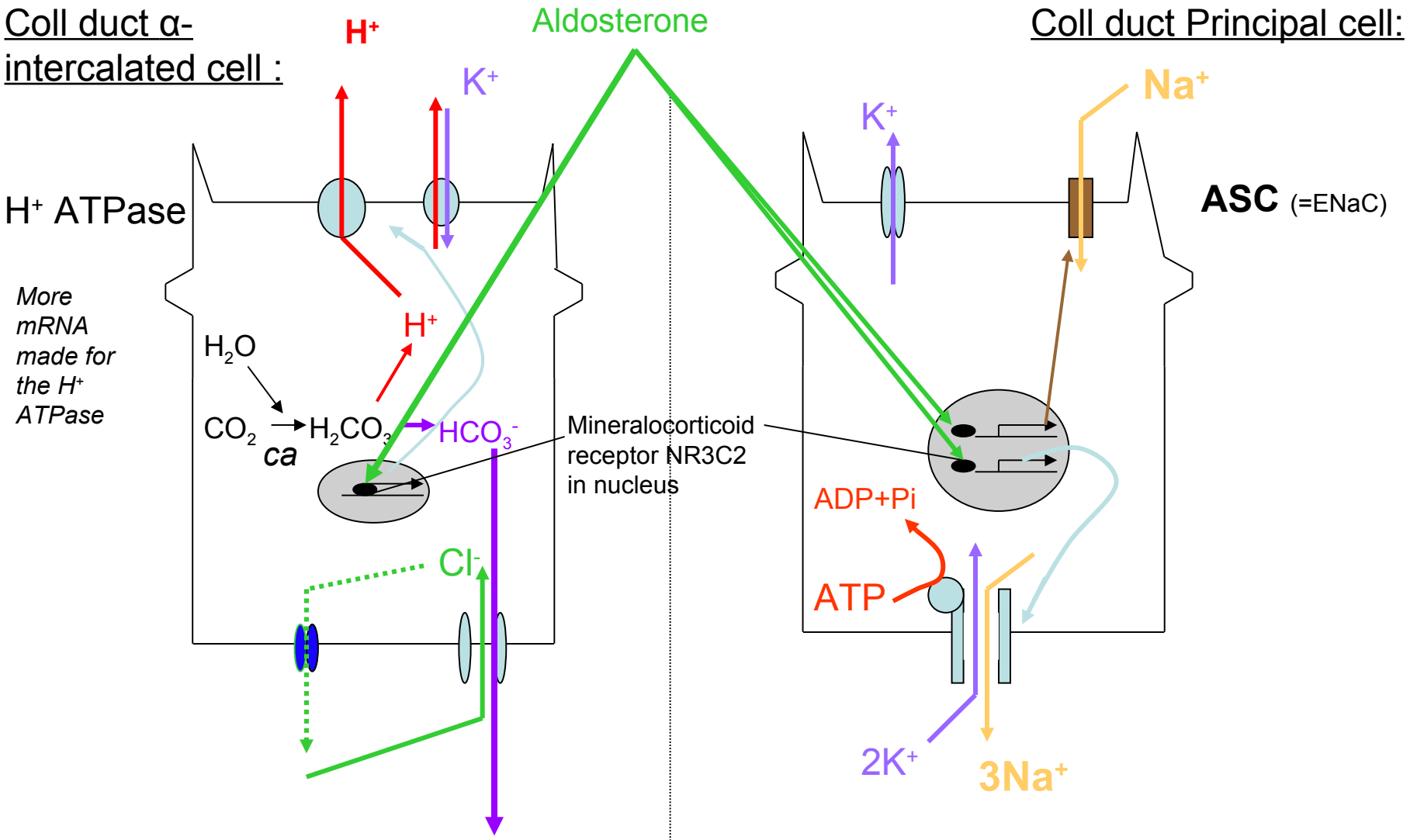


Renin-angiotensin-aldosterone system



Wikipedia commons

Action of Aldosterone on kidney cells:

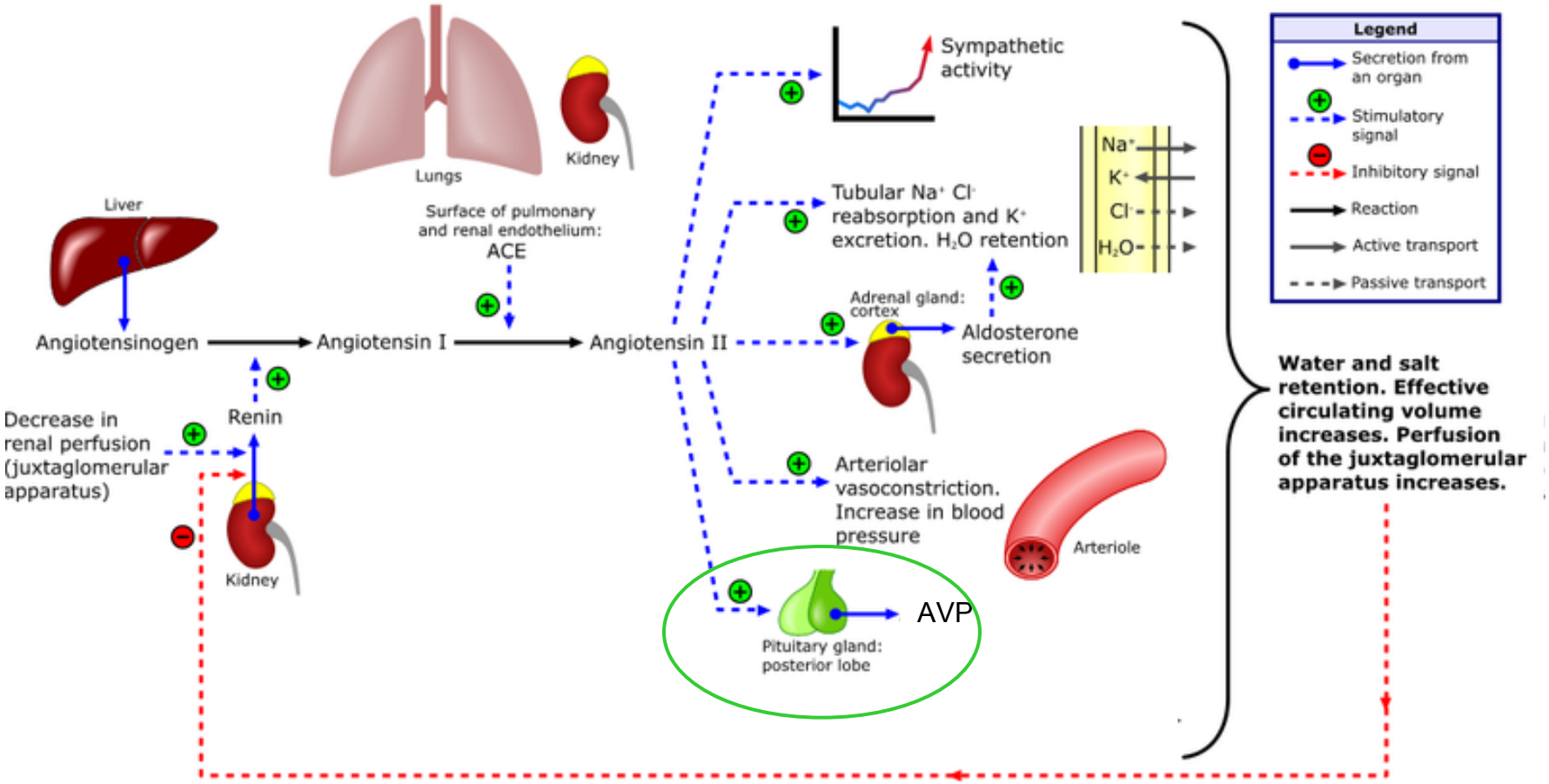


These type A cells throw H^+ out of the body -> body gets less acid

-> and more Na recovery and K secretion

Roy A, Al-bataineh MM, Pastor-Soler NM. Collecting duct intercalated cell function and regulation. Clin J Am Soc Nephrol. 2015 Feb 6;10(2):305-24.

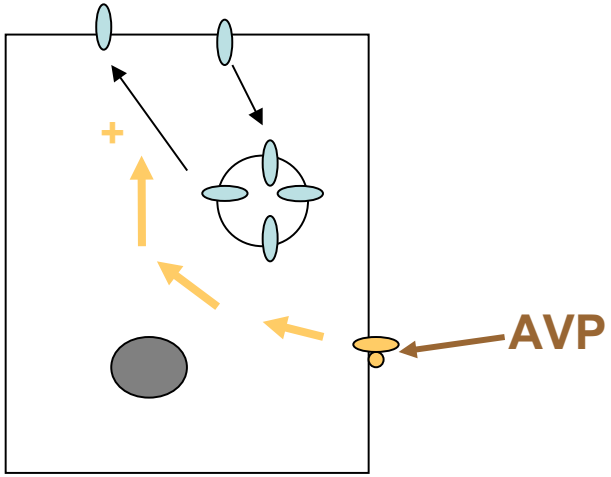
Renin-angiotensin-aldosterone system



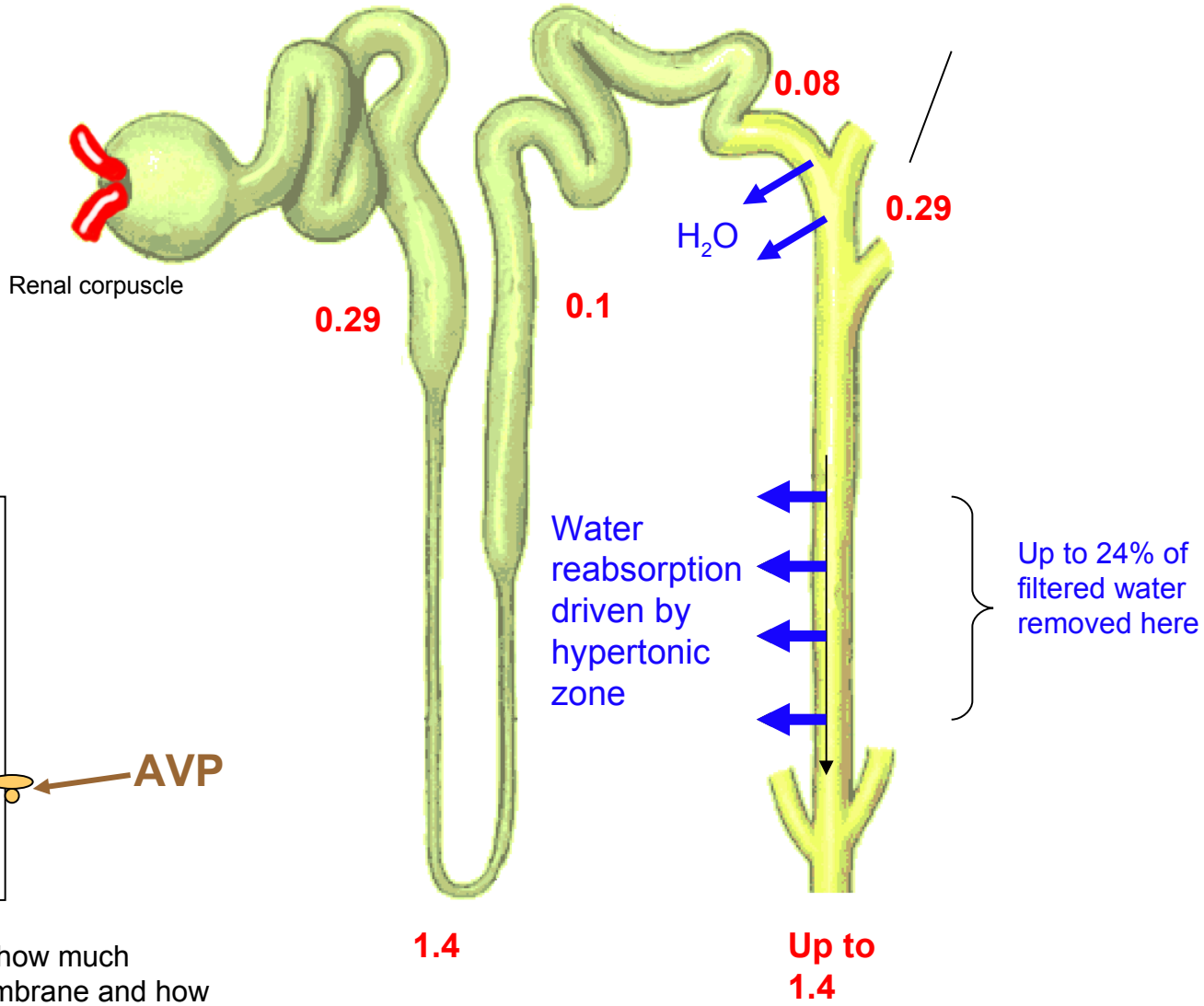
Wikipedia commons

Effect of Arginine Vasopressin (AVP) on kidney cells

(AVP = ADH = Vasopressin = argipressin = antidiuretic hormone, in old money)



Coll duct cells can choose how much aquaporin to put in the membrane and how much to store on vacuoles. Regulated by vasopressin (see lecture 4)



(You have seen this slide in lecture 3)

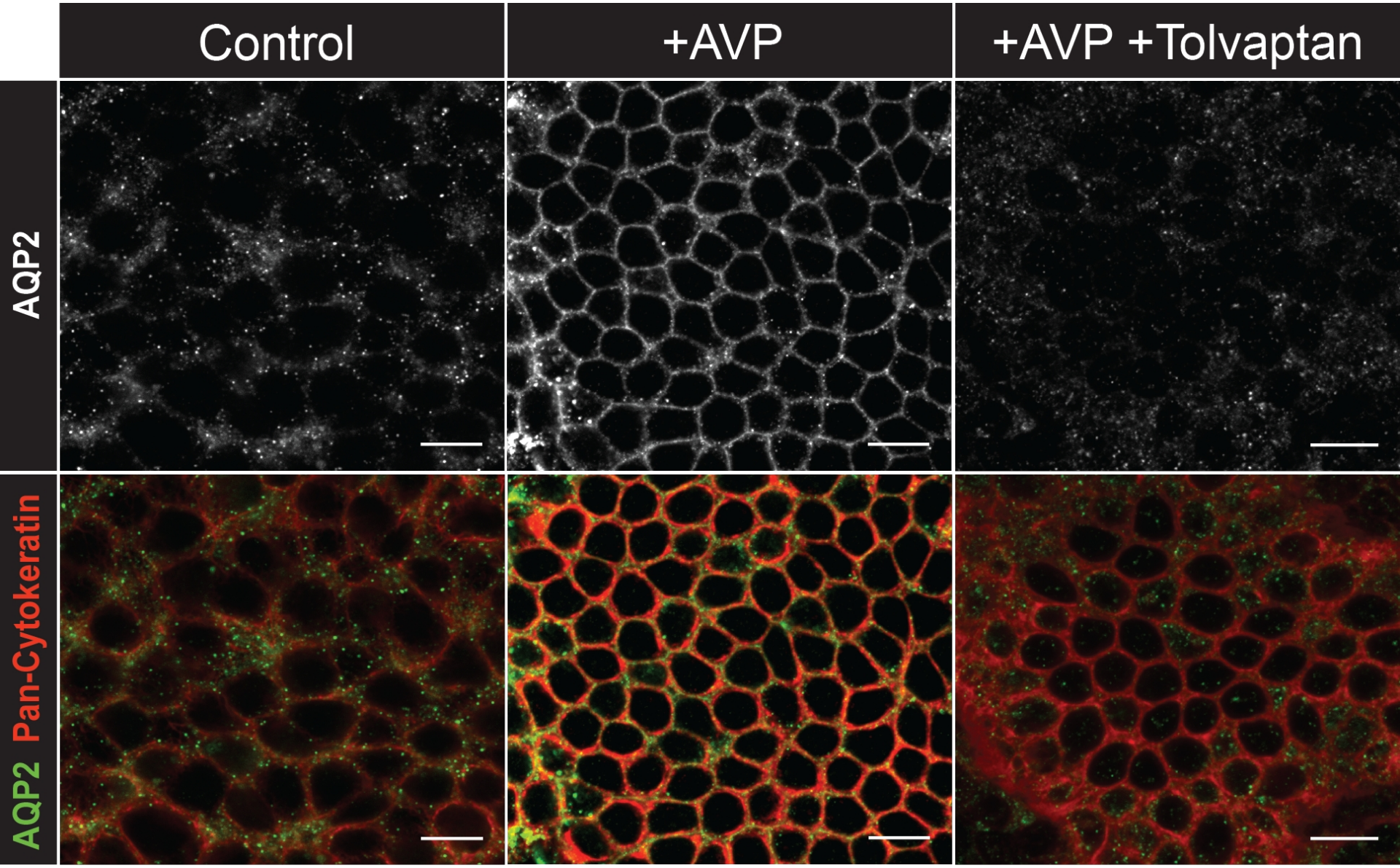
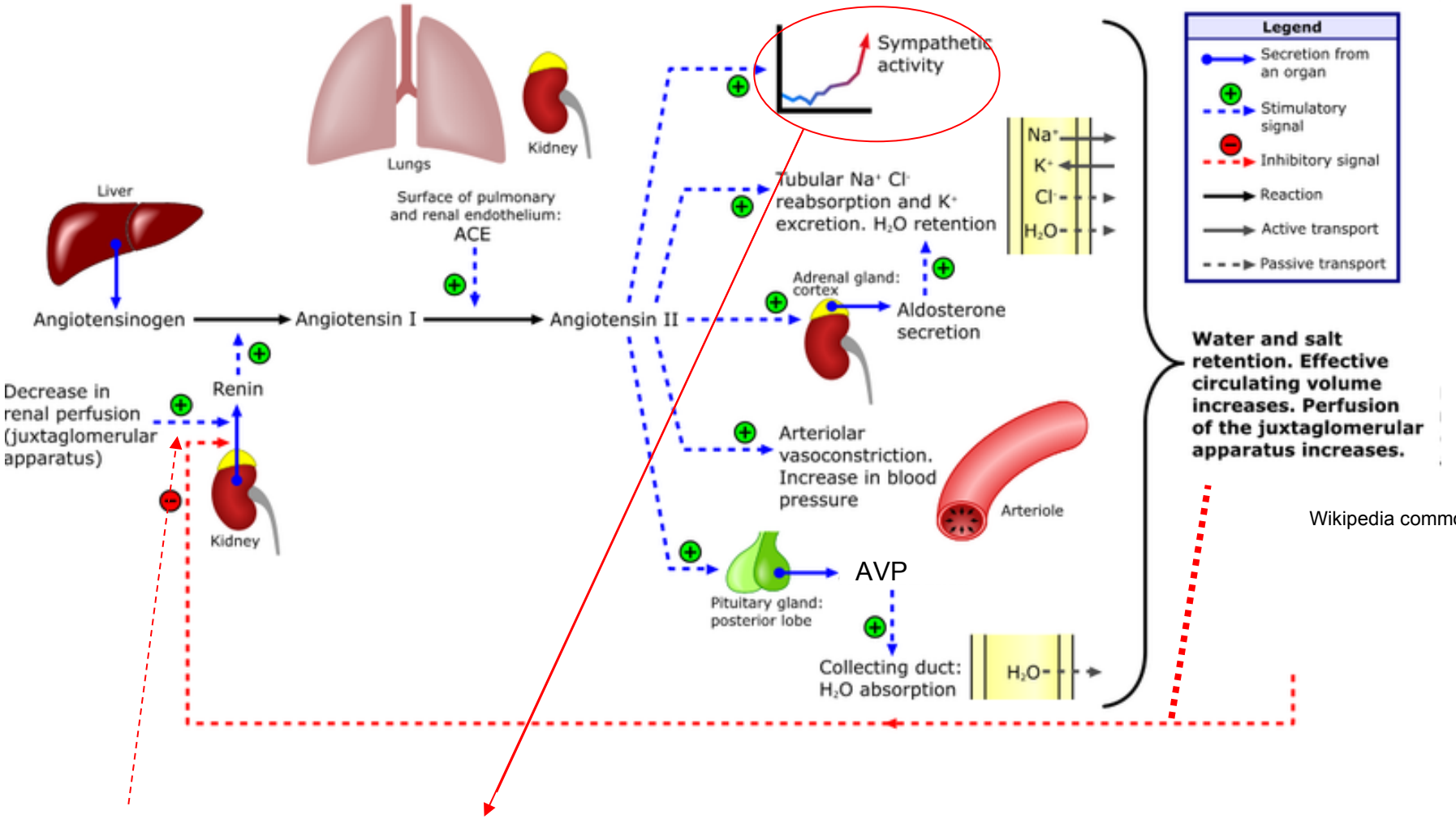


Image credit: Dr. Melanie Lawrence

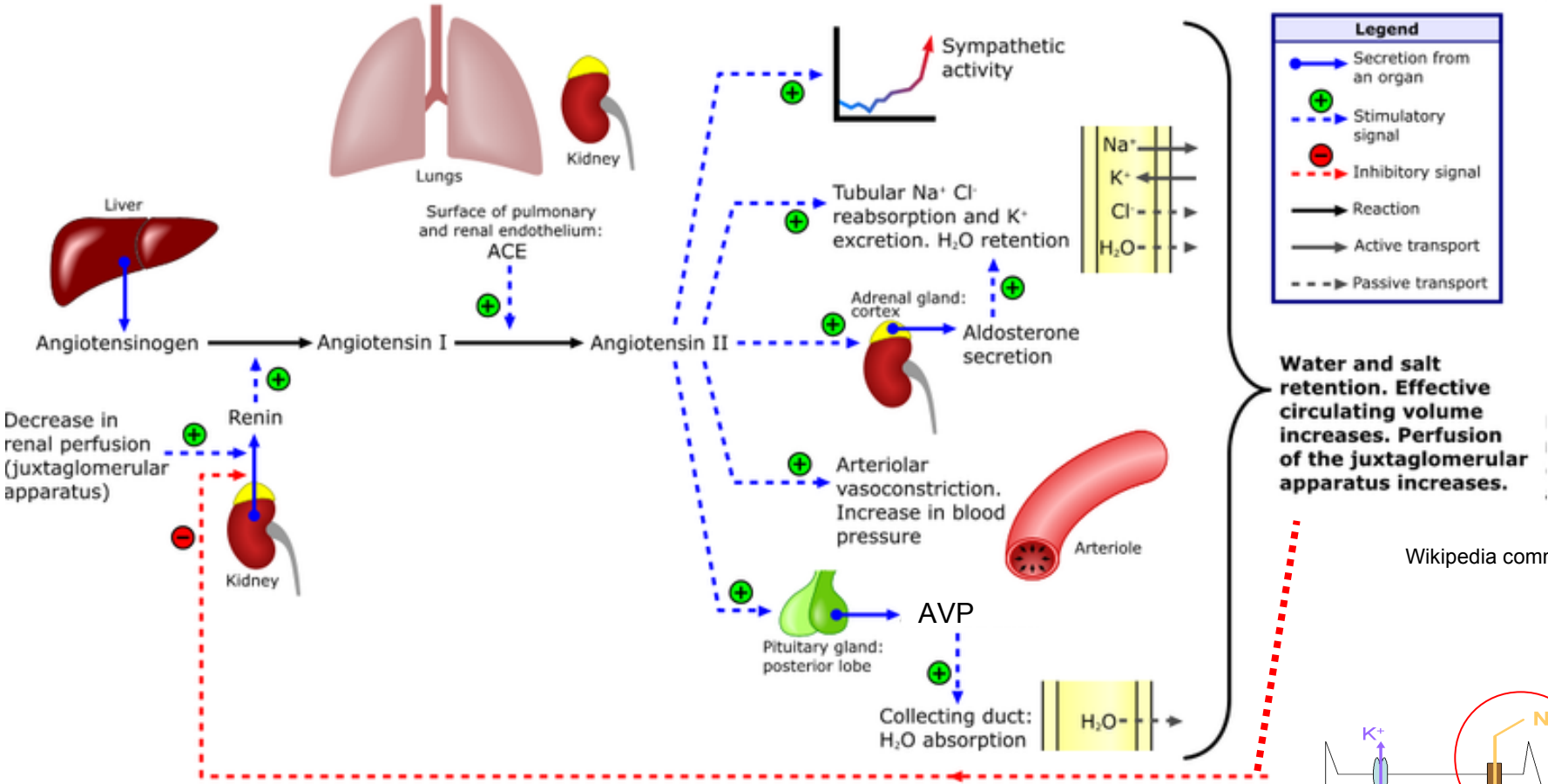
Renin-angiotensin-aldosterone system



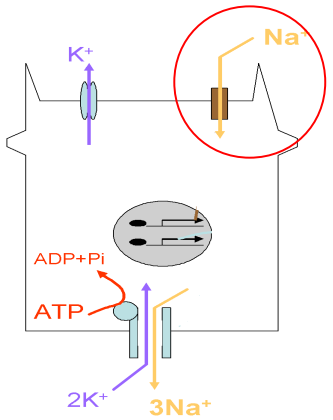
Wikipedia commons

Also, renal nerves (sympathetic – fight or flight) secrete noradrenalin: constricts both vessels serving glomerulus so reduces flow. Also directly promotes renin release.

Renin-angiotensin-aldosterone system

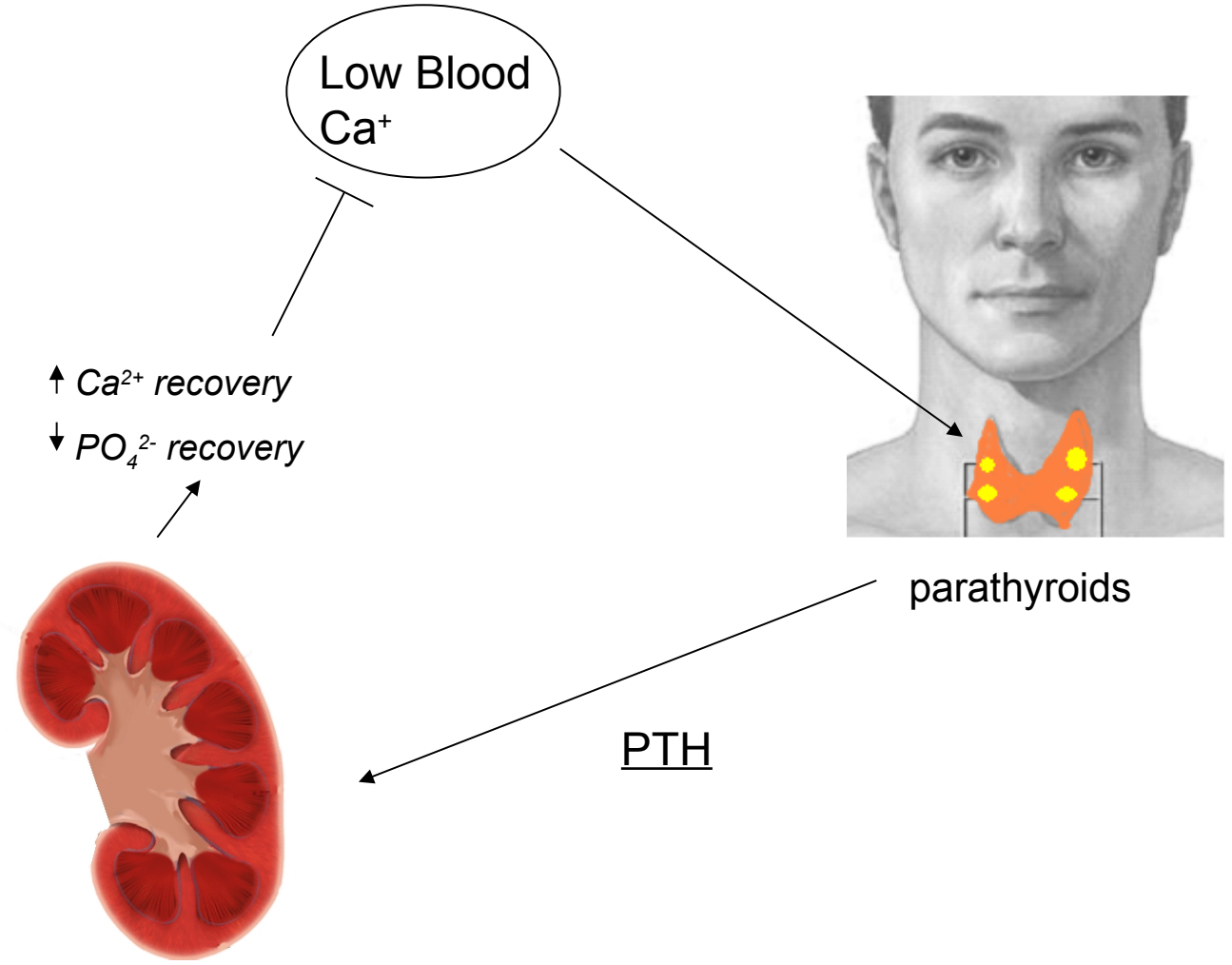


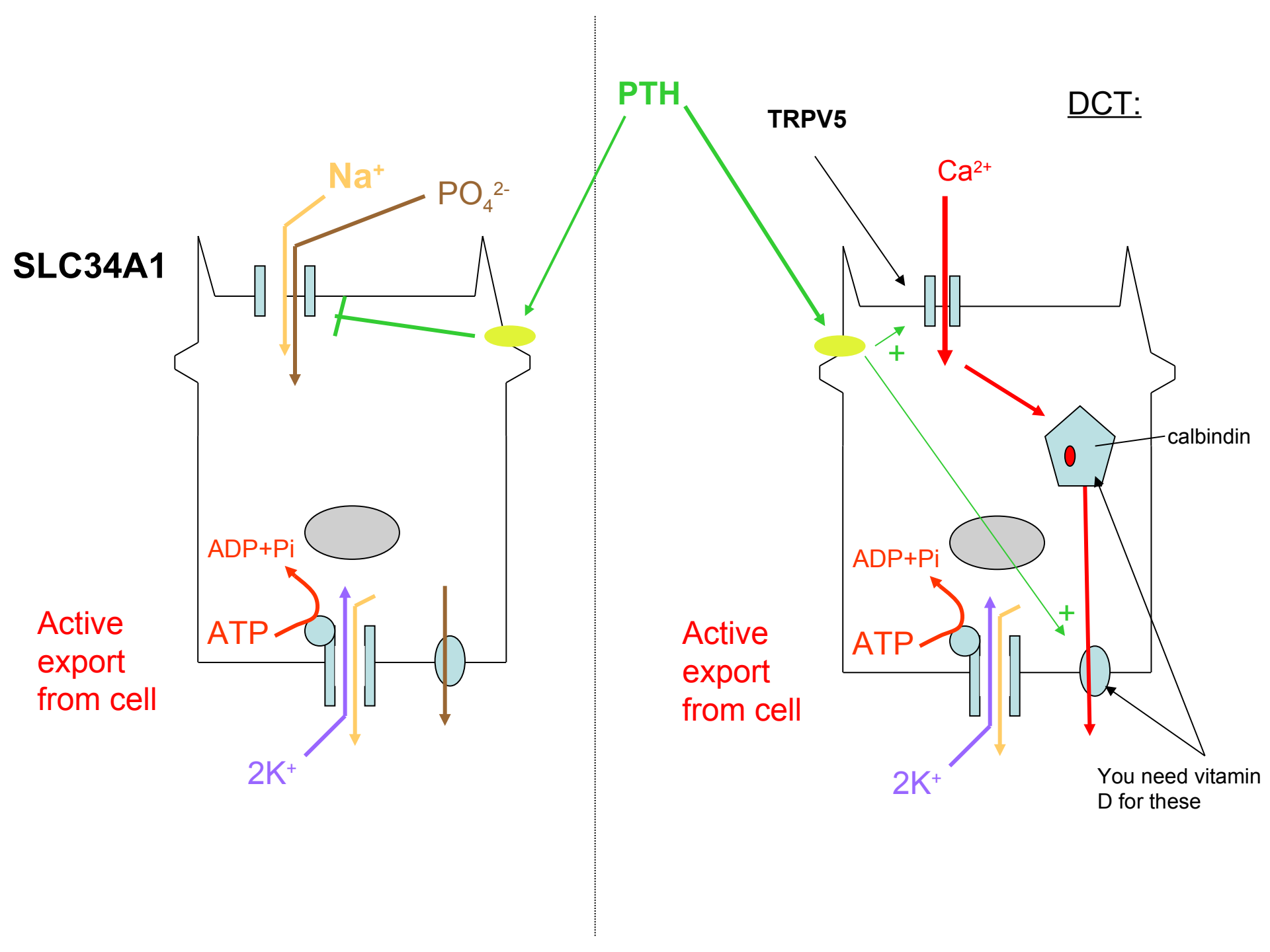
Wikipedia commons



ALSO – ANP (atrial natruietic peptide) from heart blocks the Na^+ re-uptake channel collecting ducts and causes more sodium loss.

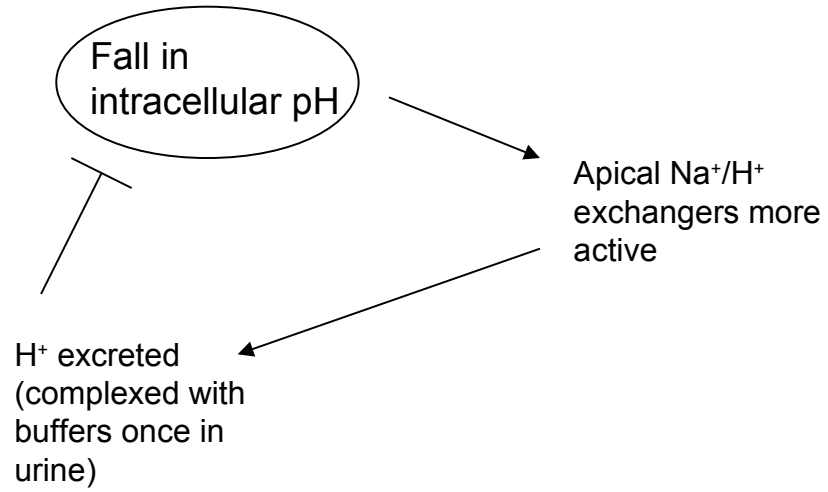
Calcium


Low Blood
Ca^{+}
$\uparrow Ca^{2+}$ recovery
$\downarrow PO_4^{2-}$ recovery
parathyroids
PTH


SLC34A1
Na+
PO4 2-
ADP+Pi
ATP
2K+
Active export from cell
PTH
TRPV5
DCT:
Ca2+
+
calbindin
ADP+Pi
ATP
+
2K+
Active export from cell
You need vitamin D for these

Acid-base

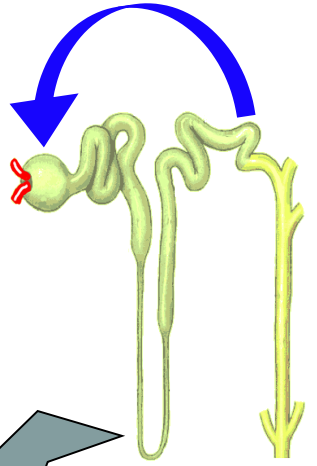
Usually, this means removing acid (oxidation of food leaves the body acid – see year 1 respiration lectures).



Summary of command-and-control (so far)

local

Renin helps maintain bp



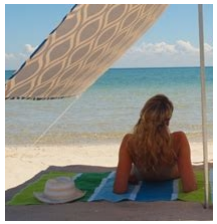
conversations between kidney and body

Blood vol, blood pressure

AVP, angiotensin II, aldosterone, PTH

Behaviour changing b.p. and fluid volume

other physiological responses

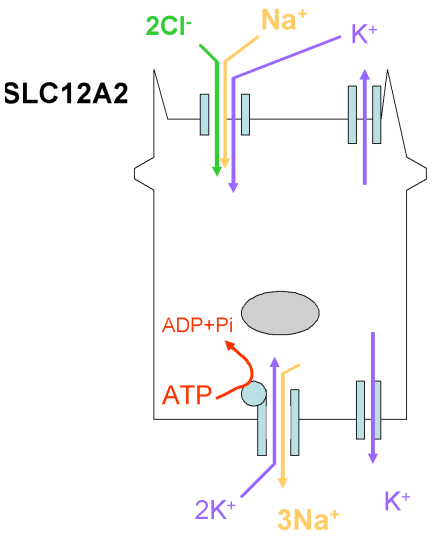


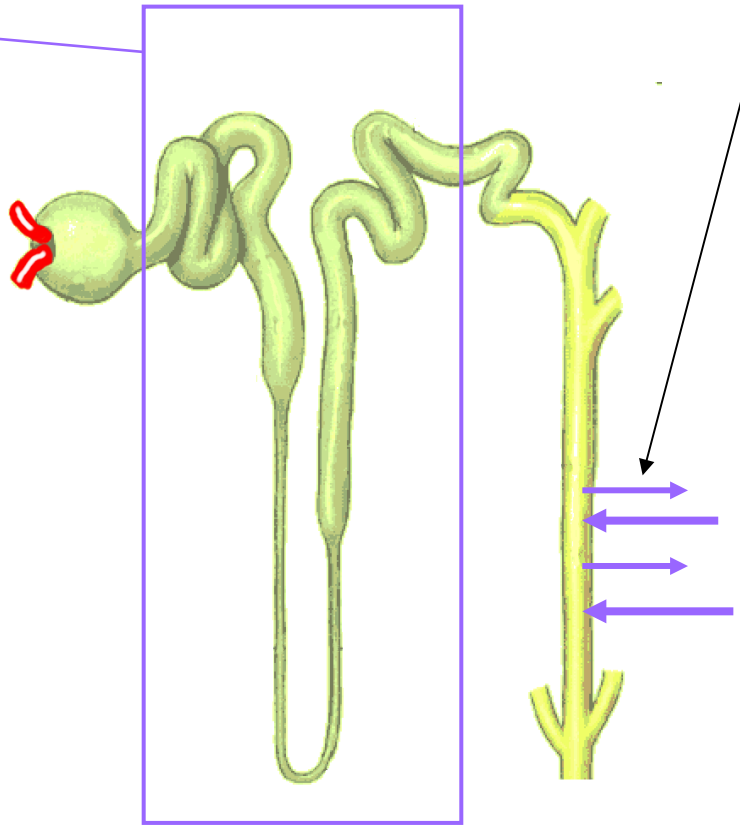
behavioural responses

Photos: Wikimedia commons anon CC3.0 and 4.0

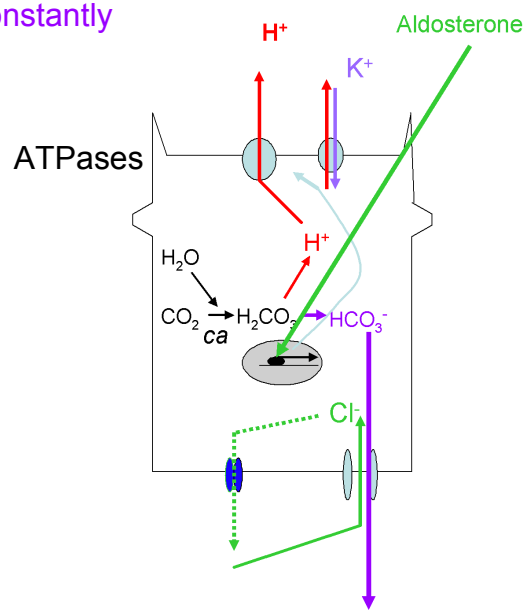
Potassium (only 2% of body K^+ is in extracellular fluids and it has to be regulated tightly)

Around 90% reabsorbed here, little regulation

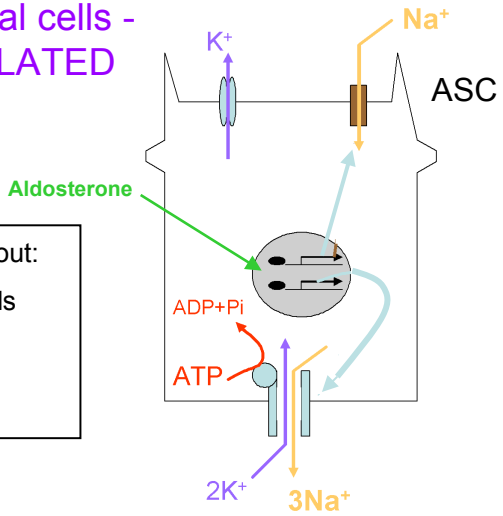




Re-absorption by intercalated cells constantly



Excretion by principal cells - REGULATED



1) High tissue K^+ increases K^+ flow into cells thence out:
2) Low K^+ diets ▶tyrP of apical K^+ channels ▶channels removed from membrane
3) High K^+ diets cause loss of tyrP and channels accumulate in membrane

Data from Giebisch GH. (2002) A trail of research on potassium. Kidney Int. 62:1498-512

Potassium _flux is sensitive to body pH:

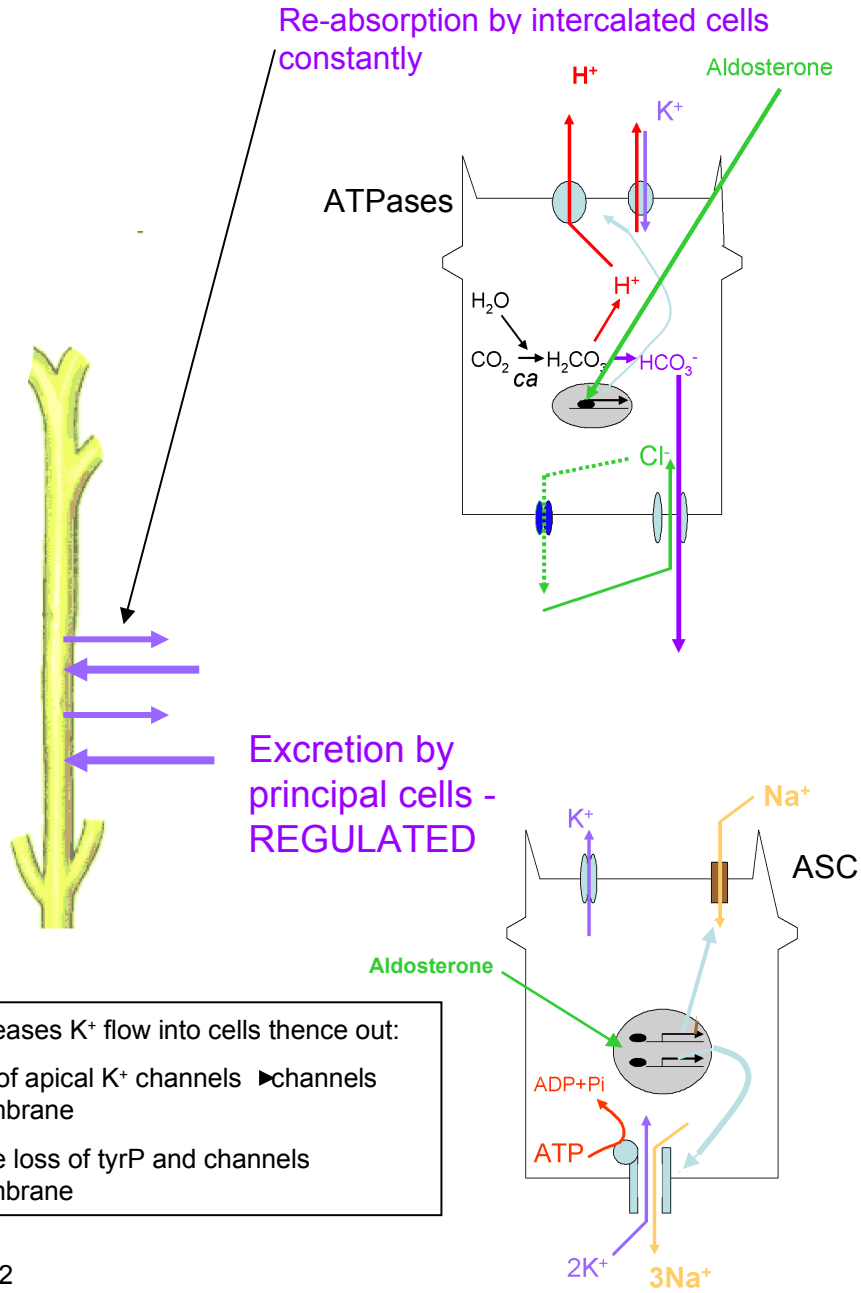
Alkalosis: H^+ out-pumping by intercalated cells reduced, so less K^+ re-uptake (AND apical K^+ channel activity increased in Prinicipal cells and so is the Na^+/K^+ ATPase -> more K^+ loss)

→ hypokalaemia

Acute acidosis: H^+ out-pumping by intercalated cells increases so K^+ reuptake increases. Also, apical K^+ channels on Principal cells less active (by an effect on their intracellular regulation) so K^+ secretion falls.

→ hyperkalaemia

(Chronic acidosis; Na pump less efficient in PCT, so urine more copious and helps flush K^+ away)



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Clinical Intervention in renal function

Why?

Control of hypertension

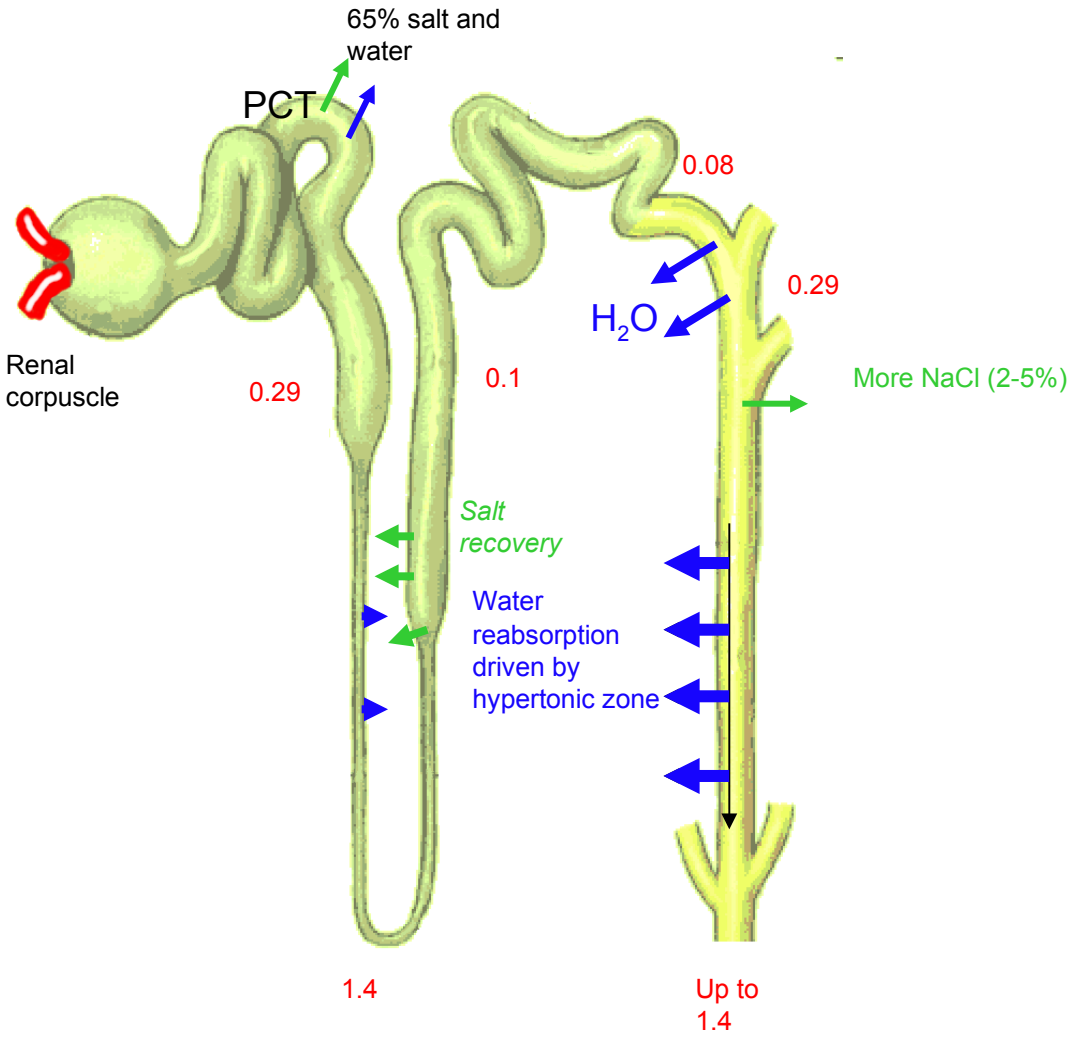
Control of oedema

Control of ion imbalances

Control of acid-base disturbances

Diuresis: increasing the amount of water (+ salts) lost from the body

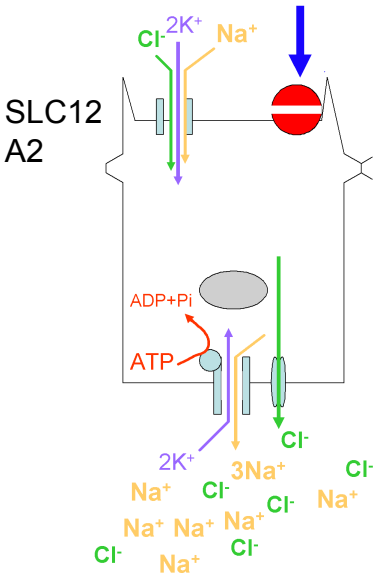
through / of urine



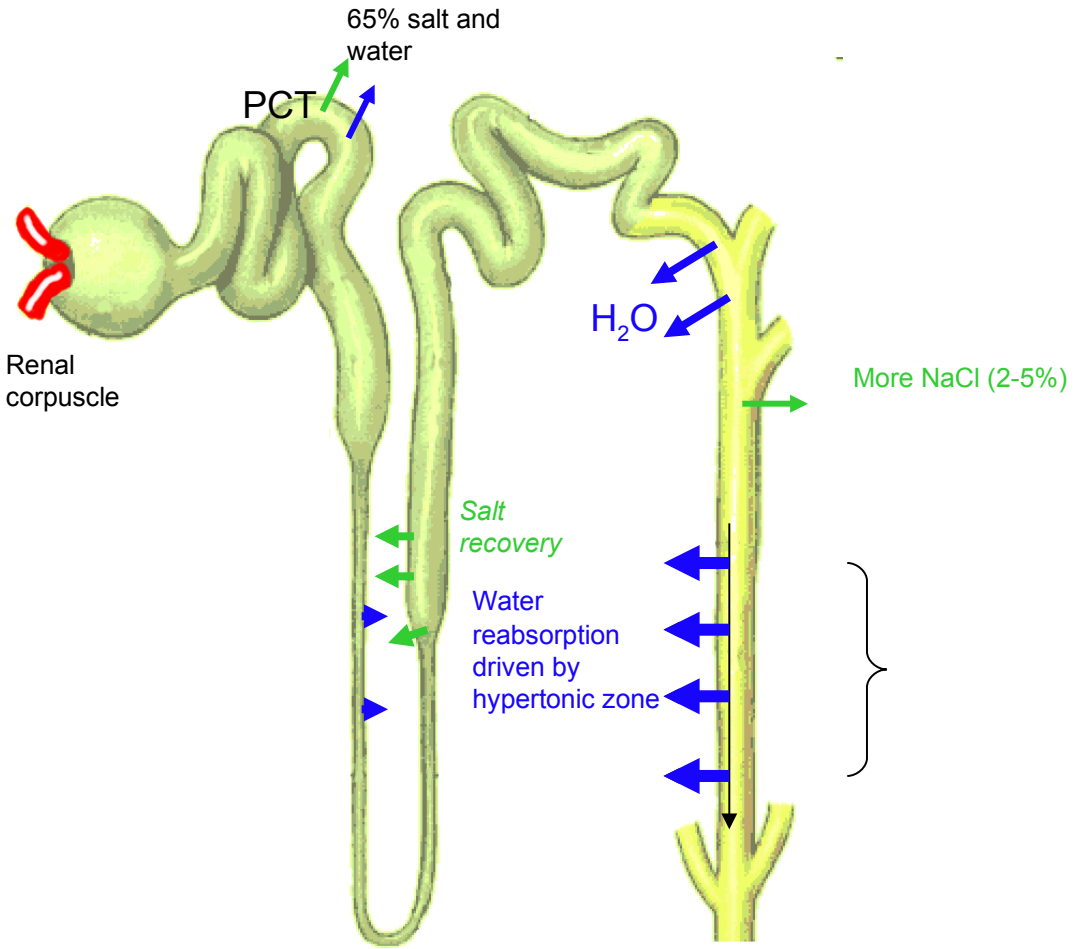
(you have seen this before)

Diuresis: increasing the amount of water (+ salts) lost from the body

TAL:



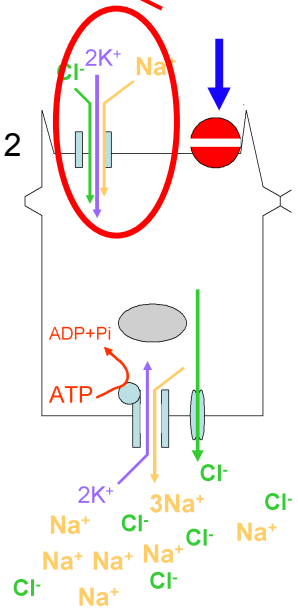
(you have seen this before)



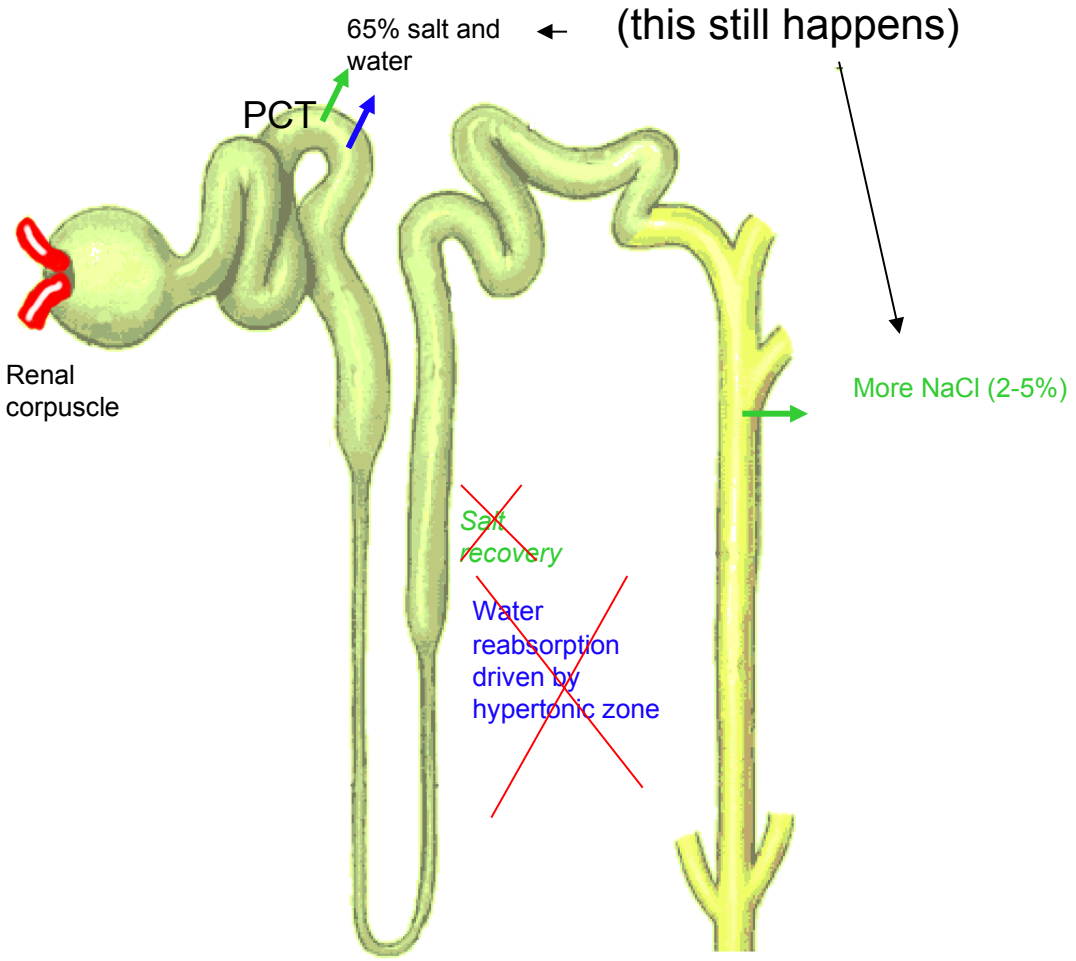
(Henle's) Loop Diuretics:

If we block SLC12A2, we stop the salt being moved into the interstitium

TAL:



(you have seen this before)



Features of loop diuretics:

They are powerful (up to 20% of filtrate to bladder: usually around 0.4%) ☺

They result in loss of Na^+, K^+ and Cl^- because of failure to recover in the TAL of LoH ☹

They can result in hypercalcuria – less pull for Ca^{2+} recovery – and kidney stones.

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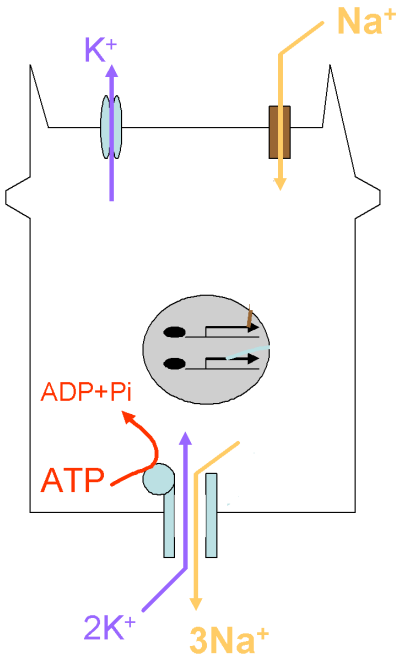
They result in loss of Na^+, K^+ and Cl^- because of failure to recover in the TAL of LoH ☹

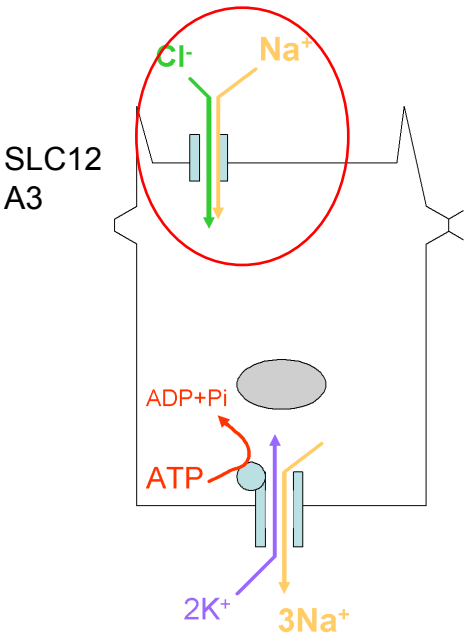
They can result in hypercalcuria – less pull for Ca^{2+} recovery – and kidney stones.

More Na^+ getting to the Coll Duct means more uptake there and more K^+ loss ☹

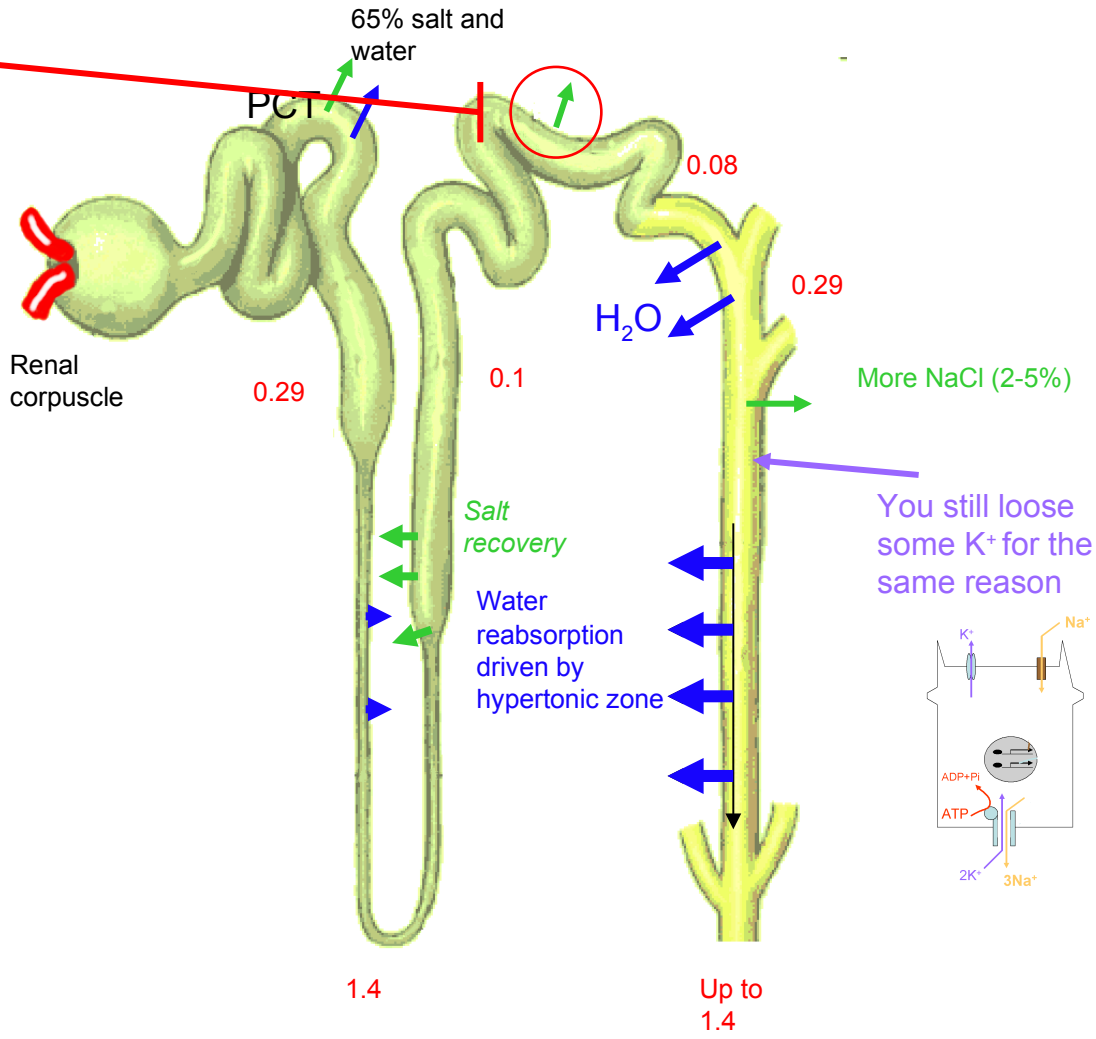


Alternative diuretics:

Distal tubule diuretics ('thiazides')



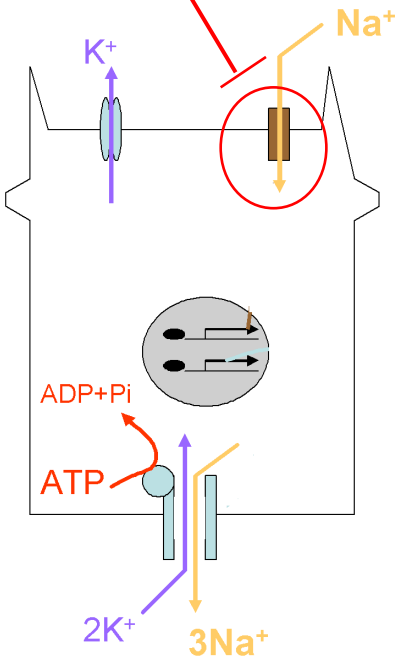
(you have seen this before)



Alternative diuretics:

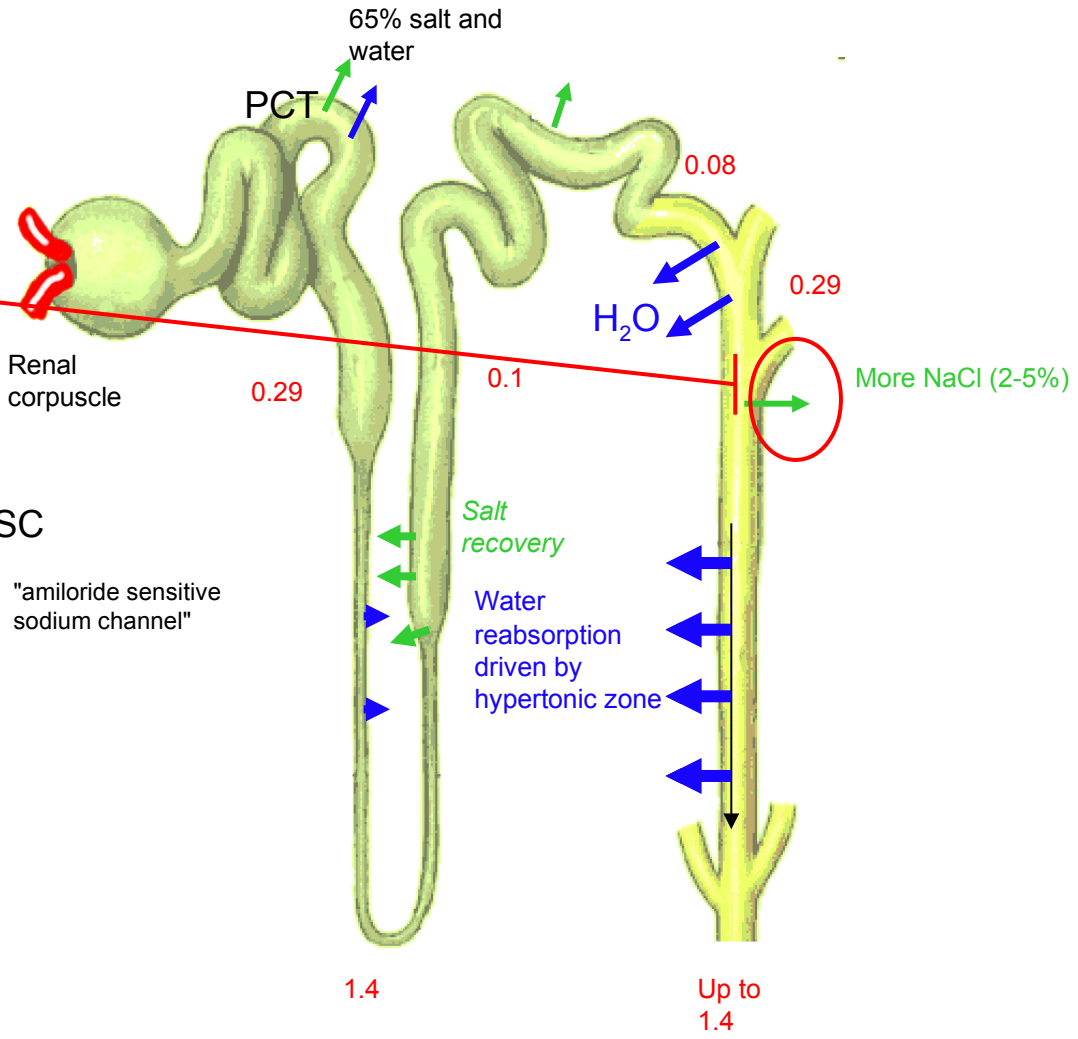
Distal tubule diuretics ('thiazides')

Potassium-sparing diuretics (amiloride etc)



ASC

"amiloride sensitive sodium channel"



(you have seen this before)

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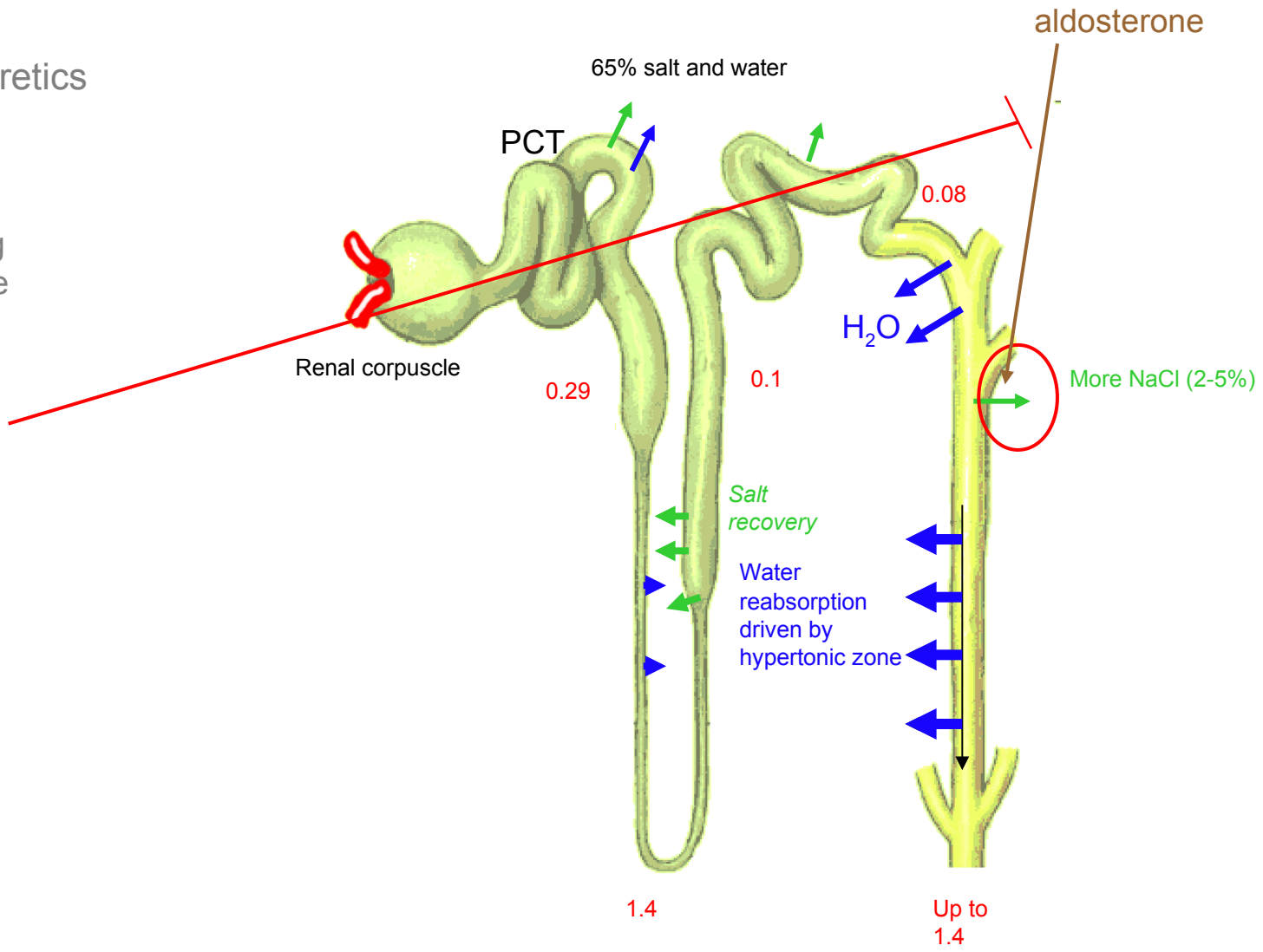
Distal tubule diuretics ('thiazides')

Potassium-sparing diuretics (amiloride etc)

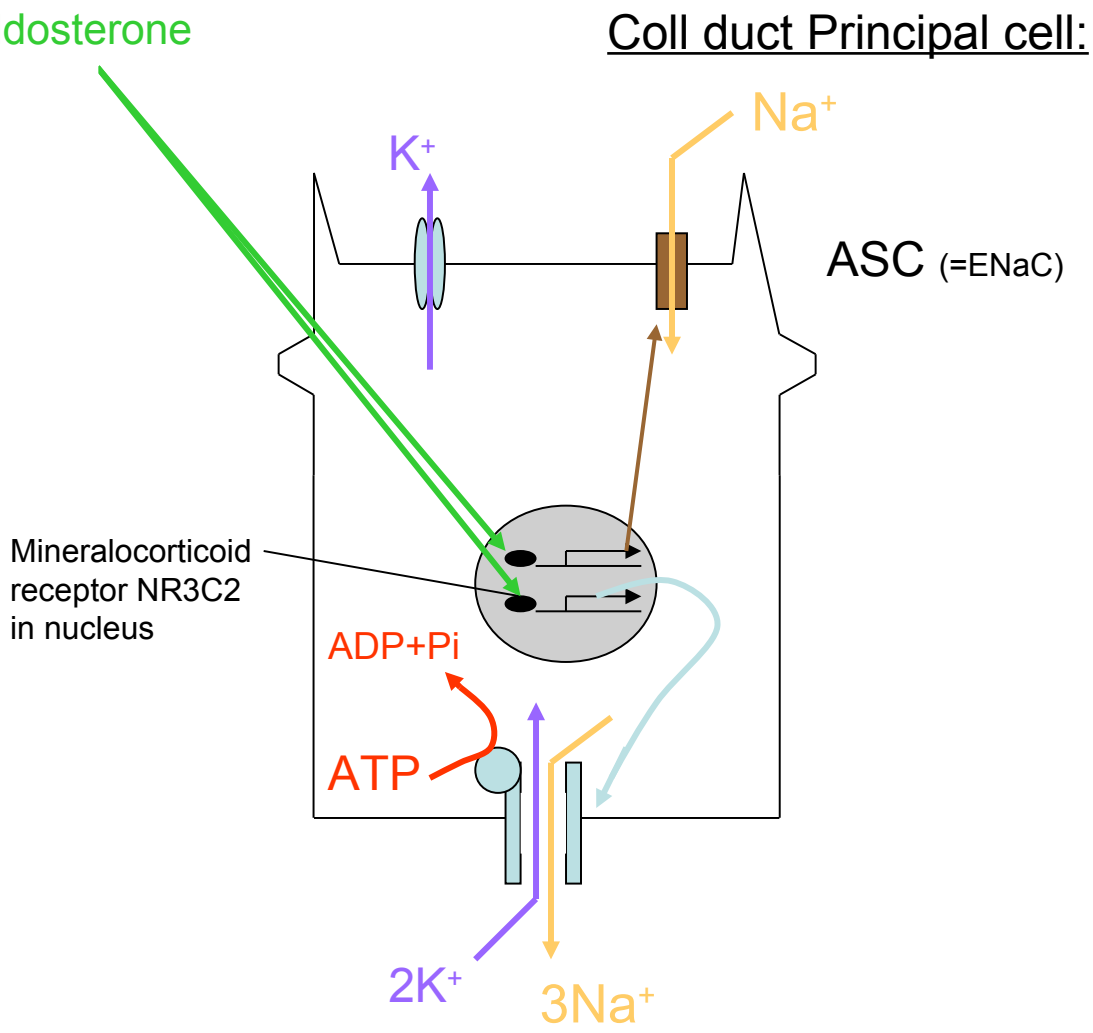
Spironolactone



(you have seen this before)

Action of Aldosterone on kidney cells:

(you have seen this before)



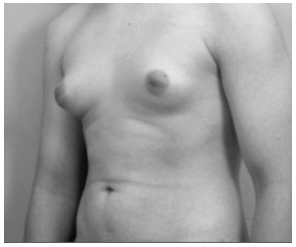
-> and more Na recovery and K secretion

Alternative diuretics:

Distal tubule diuretics ('thiazides')

Potassium-sparing diuretics (amiloride etc)

Spironolactone (problem – also antiandrogenic)



(this is a man – gynaecomastia)

(you have seen this before)

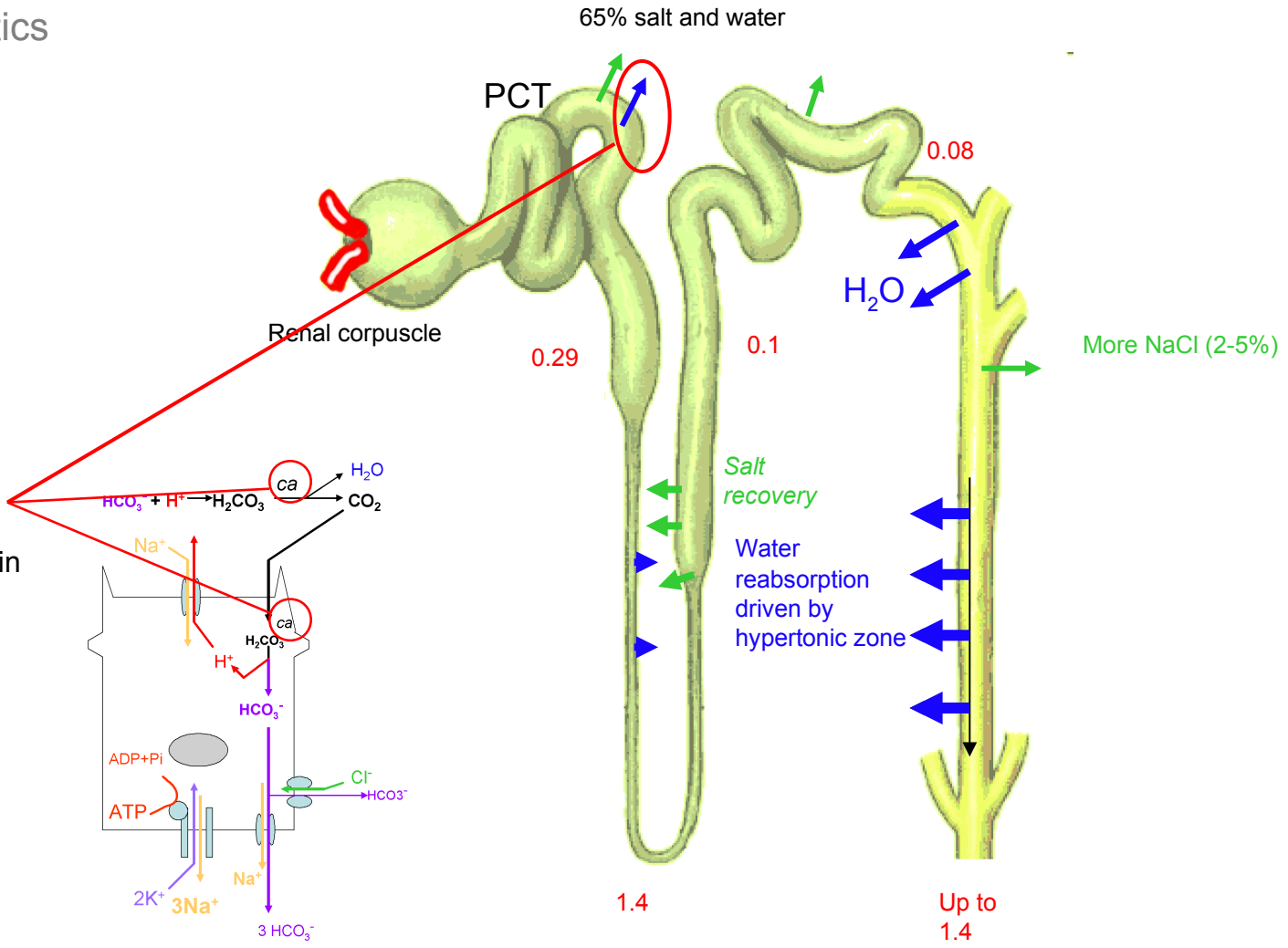
Alternative diuretics:

Distal tubule diuretics ('thiazides')

Potassium-sparing diuretics (amiloride etc)

Spironolactone

Carbonic anhydrase inhibitors (more bicarb in lumen, resists egress of water osmotically)



(you have seen this before)

Alternative diuretics:

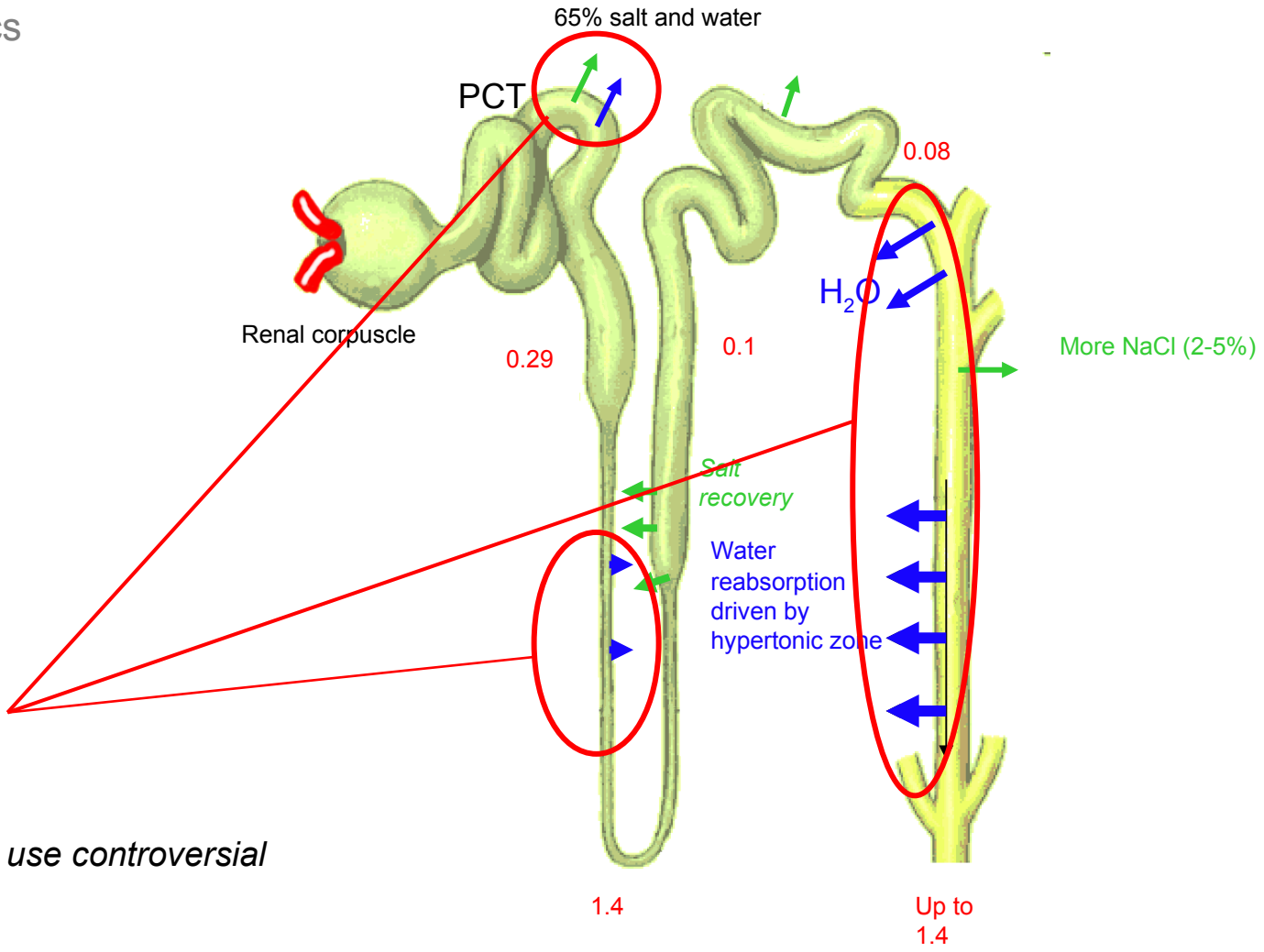
Distal tubule diuretics ('thiazides')

Potassium-sparing diuretics (amiloride etc)

Spironolactone

Carbonic anhydrase inhibitors

Osmotic agents (eg mannitol): stay in the lumen and resist water egress osmotically) *Clinical use controversial*



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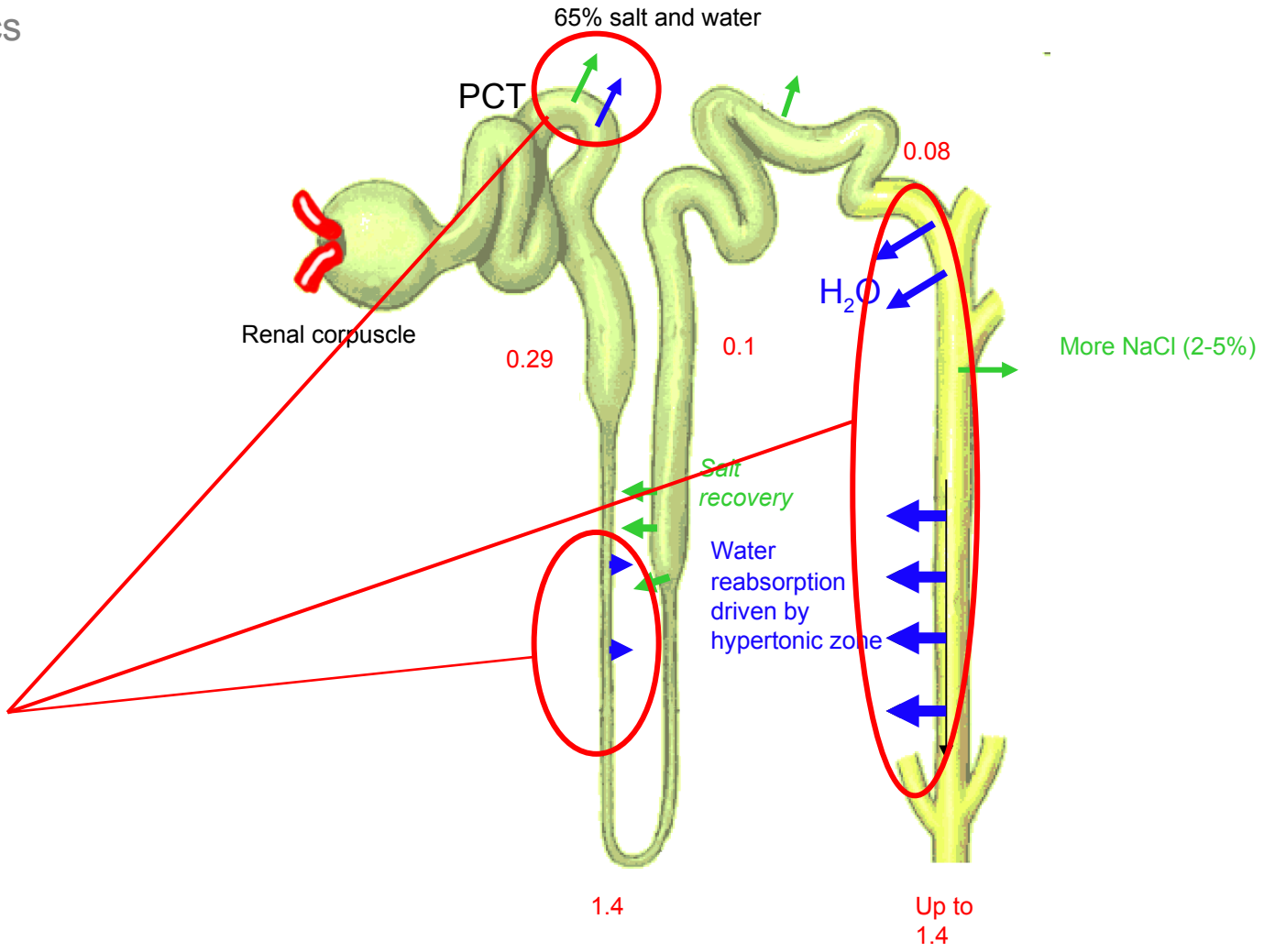
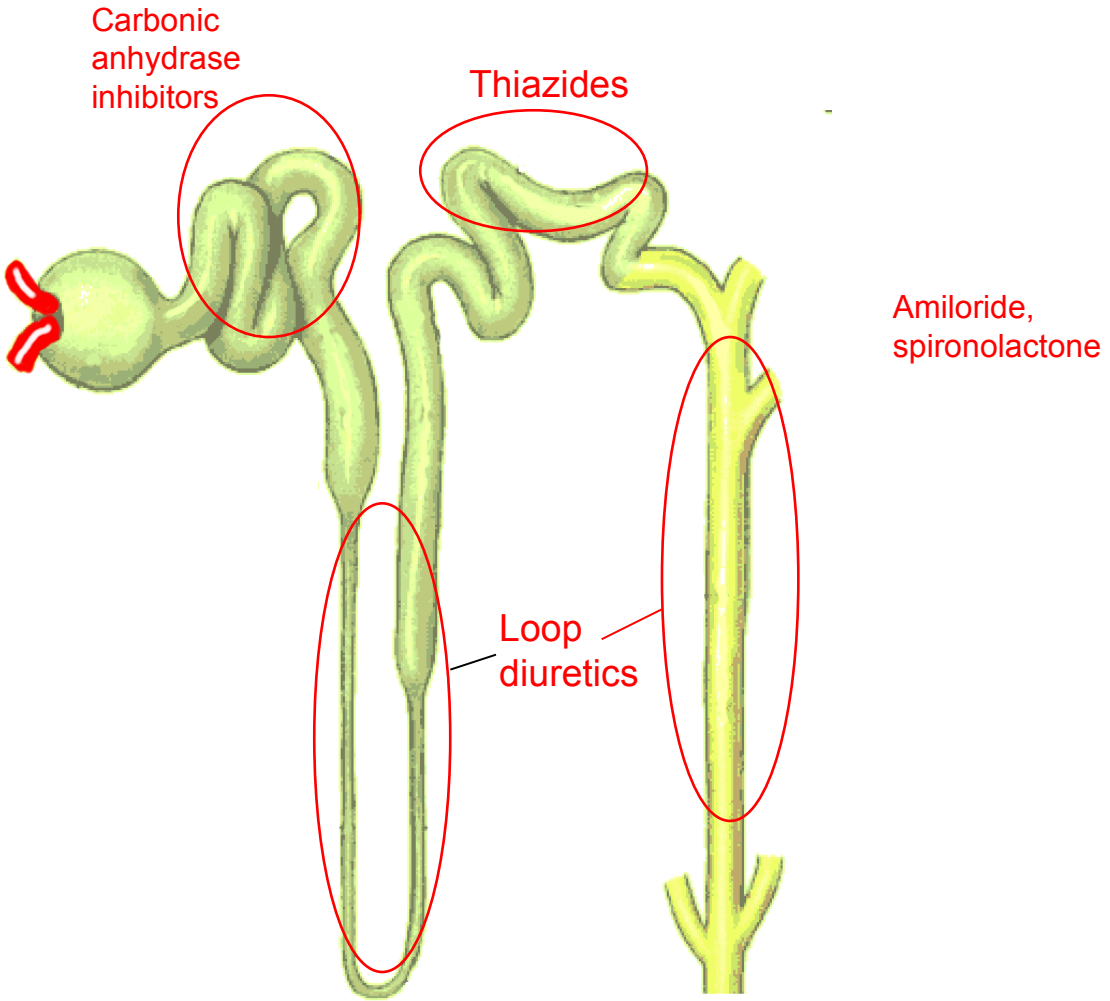


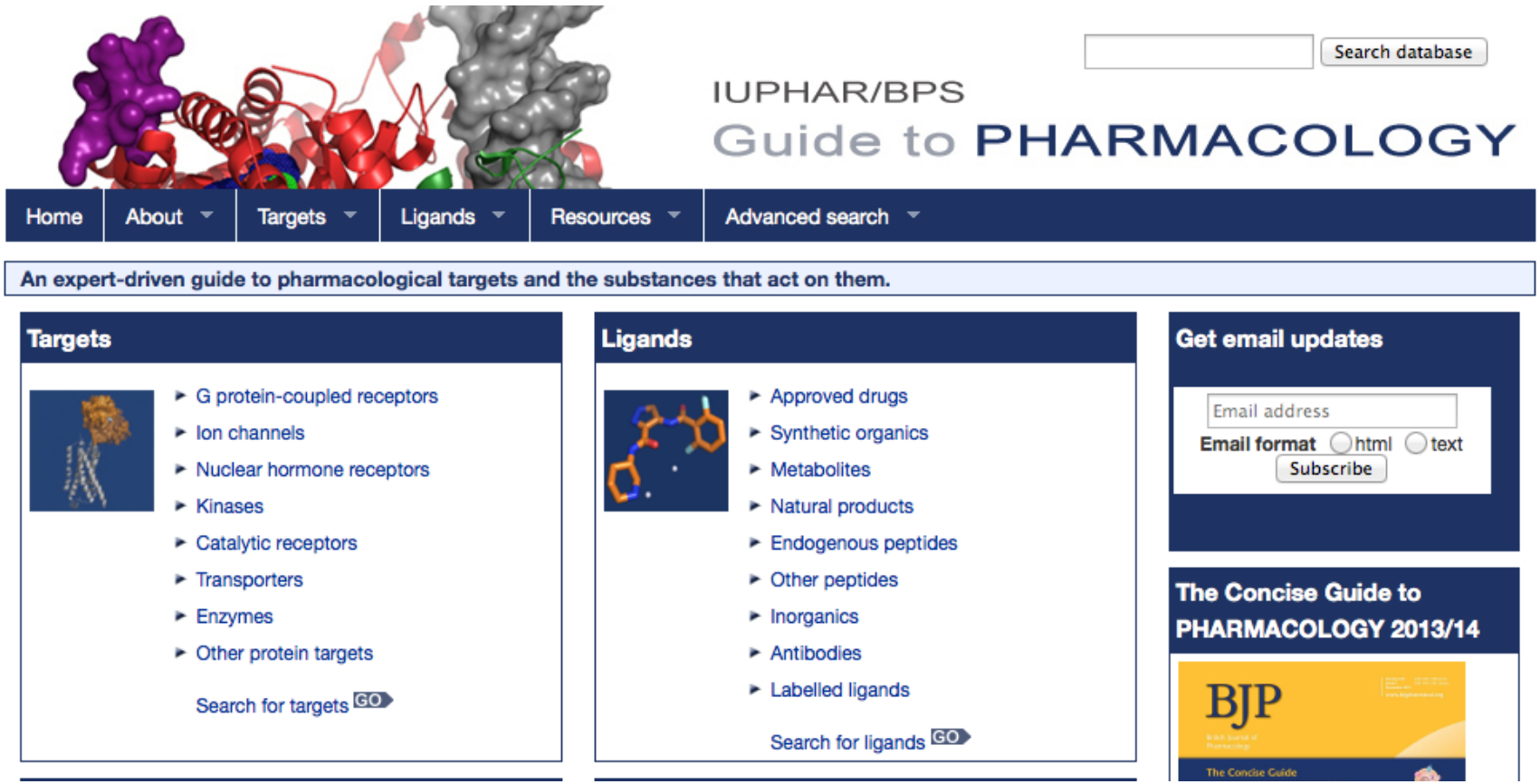
Very high plasma glucose can exceed recovery capacity and act in this way: diabetic thirst because water lost but Na^+ not lost as much -> hypernatraemia.

Diuretics summary slide:



NB – this info is given from the point of view of basic understanding – the pharmacology vertical theme will give you the clinical details.

Advert: you do know about this, don't you?

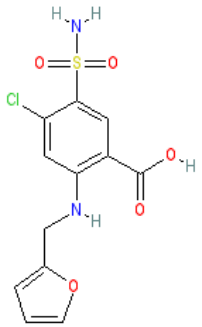


Run on behalf of BPS/IUPHAR from Edinburgh Med sch

furosemide

Ligand Id: 4839	
Ligand name	**furosemide**

2D Structure



Calculated Physico-chemical Properties

Hydrogen bond acceptors	6
Hydrogen bond donors	3
Rotatable bonds	5
Topological polar surface area	131.01
Molecular weight	330.01
XLogP	0.88
No. Lipinski's rules broken	0

Molecular properties generated using the CDK

Summary | Biological activity | **Clinical data** | References | Structure | Similar ligands

Summary of Clinical Use

Furosemide is used to treat edema associated with chronic heart failure, liver cirrhosis and renal disease. Furosemide is also used in the treatment of hypertension, either alone or in combination with other agents.

Mechanism Of Action and Pharmacodynamic Effects

Furosemide inhibits SLC12A1 (sodium-(potassium)-chloride cotransporter 2) and reduces water reabsorption in the thick ascending limb of the loop of Henle, thereby increasing urine output.