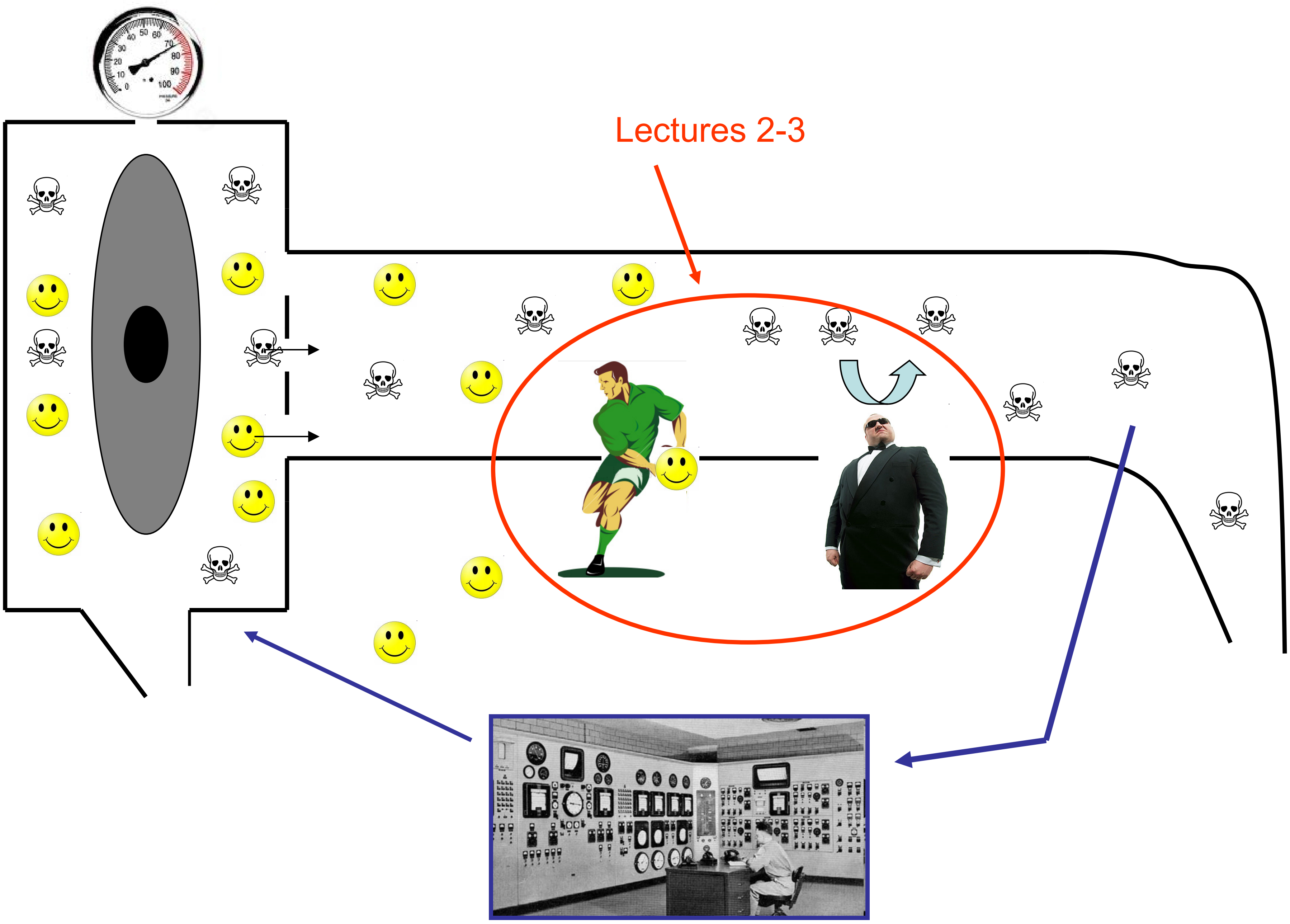
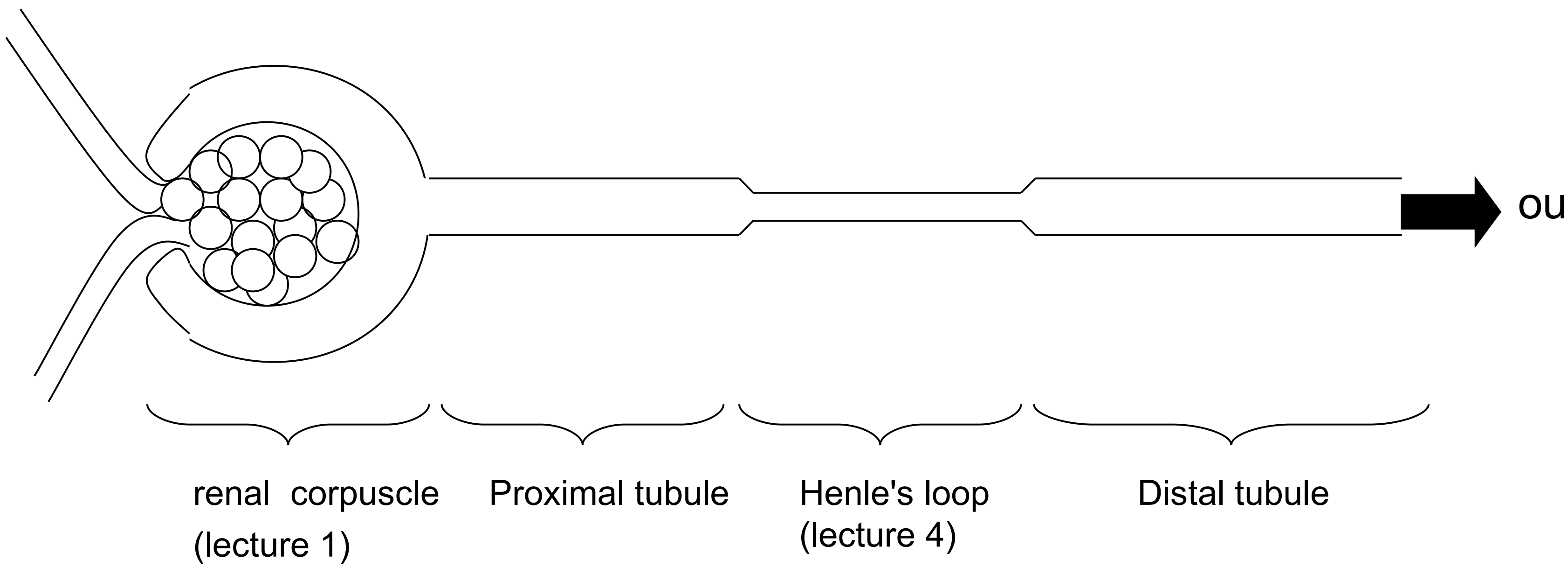
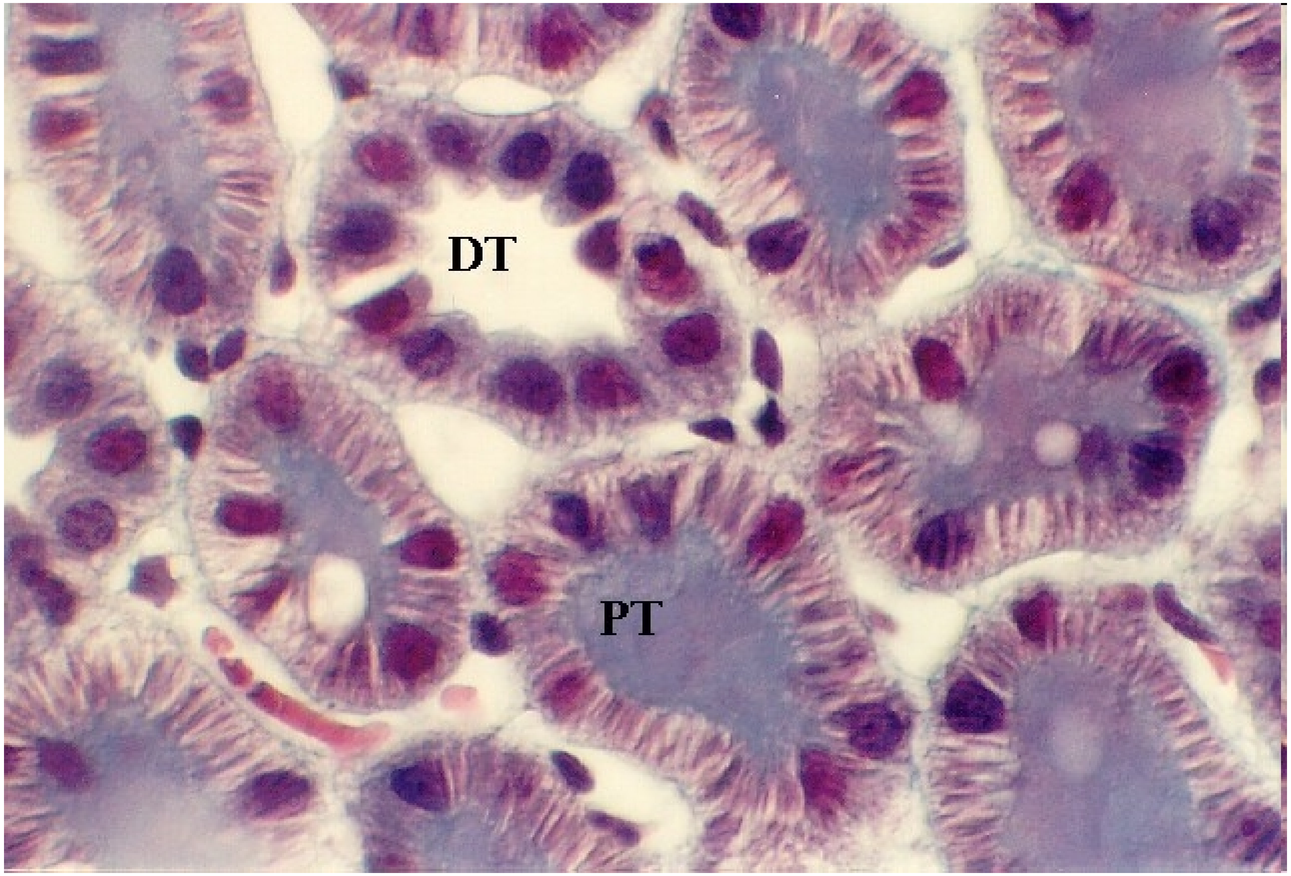

Lectures 2-3

The rest of the nephron is divided into 3 main zones:

(each is subdivided into segments, but we don't need to worry about that yet)



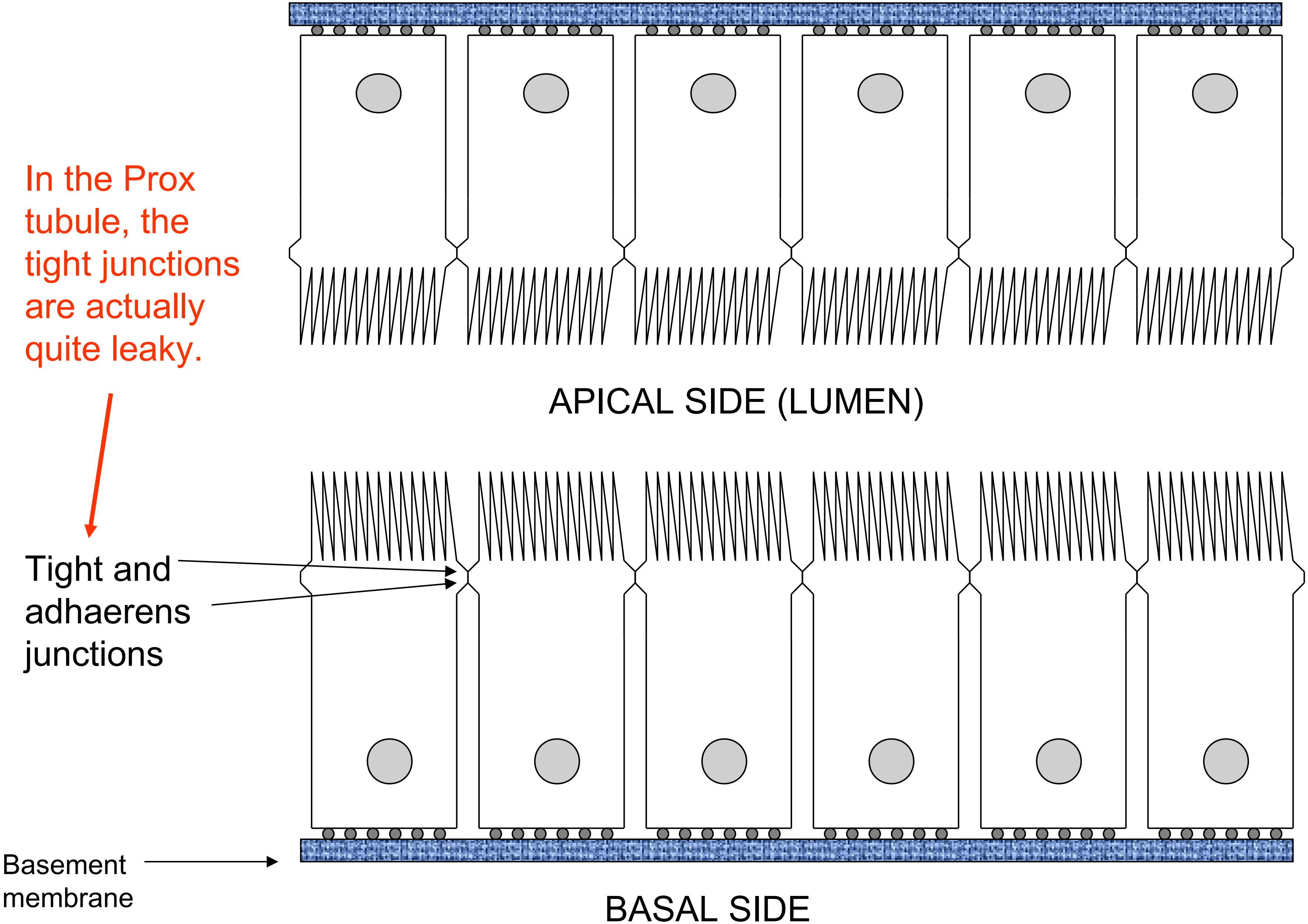
This is what the proximal and distal tubules look like in section:



Proximal tubules have microvilli, distal tubules don't

A reminder of epithelial structure:

In the Prox tubule, the tight junctions are actually quite leaky.



Things that nephron epithelia have to recover:

Na^+

K^+

Ca^{2+}

Mg^{2+}

Cl^-

HCO_3^-

PO_4^{2-}

H_2O

Amino acids

Glucose

Proteins

This lecture – we are going to consider the cell biology of recovering things

(*you need to know it as medics, because so many components of the transport system are drug targets used to control renal function, and because this transport activity makes kidneys vulnerable to damage by drugs*).

NEXT LECTURE we'll consider what is recovered where (and why).

What parts have we got to do this?

Primary Active Transporters (Na^+/K^+ ATPase and H^+ ATPase are the only common ones in the plasma membrane).

Solute Carrier Family (SLC) proteins – about 300 – many are co-transporters powered by established conc gradients (eg in Na^+) – 'secondary active transporters'

Aquaporins (Water channels)

Ion Channels

Protein endocytosis receptors

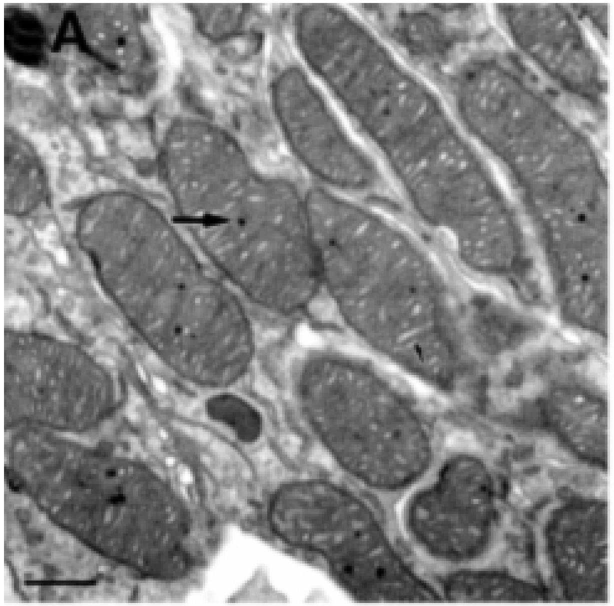
(Note that we do *not* have a water pump!)

The filtrate and the plasma will be around equilibrium.

If we want to move things from filtrate to plasma, we will be moving from equilibrium, so we will need to do work (ie move a lot of food towards equilibrium to move some solute away from it – 2nd law).

So we are going to need to burn up ATP.

Notice how packed kidney cells are with mitochondria!



Peng M, *Kidney International* (2004) **66**, 20–28

(you've just seen this slide)

What parts have we got to do this?

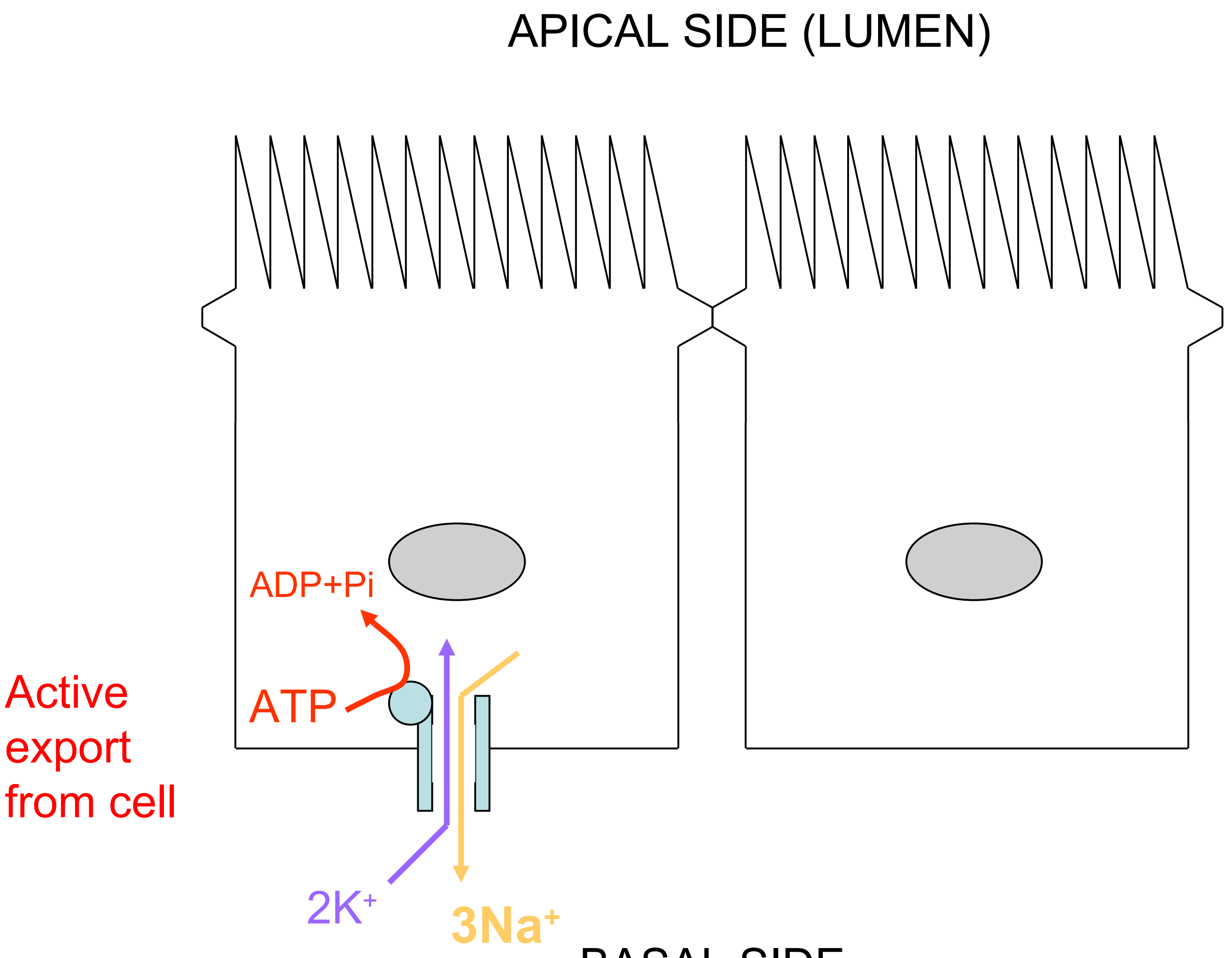
Primary Active Transporters (Na^+/K^+ ATPase is the only common one in the pm).

Solute Carrier Family (SLC) proteins – about 300 – many are co-transporters powered by established conc gradients (eg in Na^+) – 'secondary active transporters'

Aquaporins (Water channels)

Ion Channels

This, then, will be our main engine:

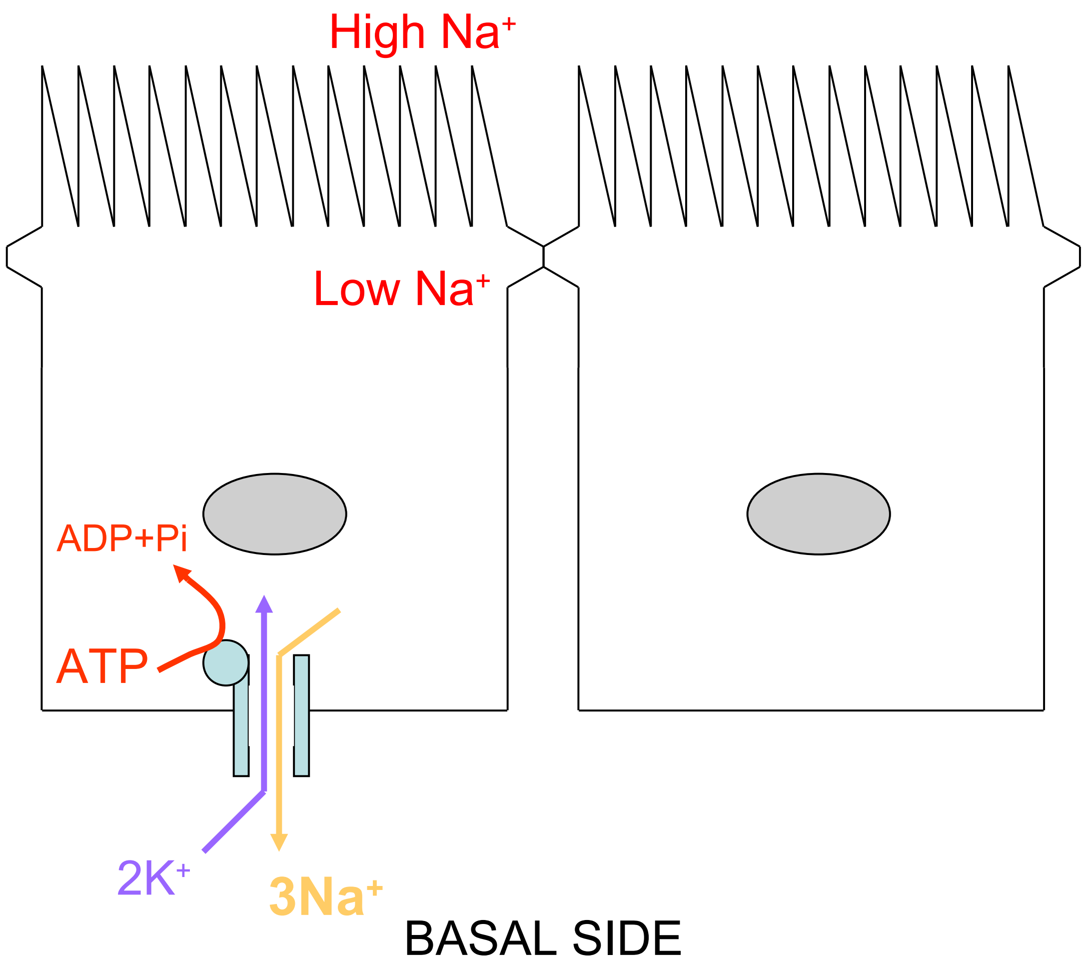


(obviously, the Na^{+}/K^{+} ATPase is drawn very over-scale)

This, then, will be our main engine:

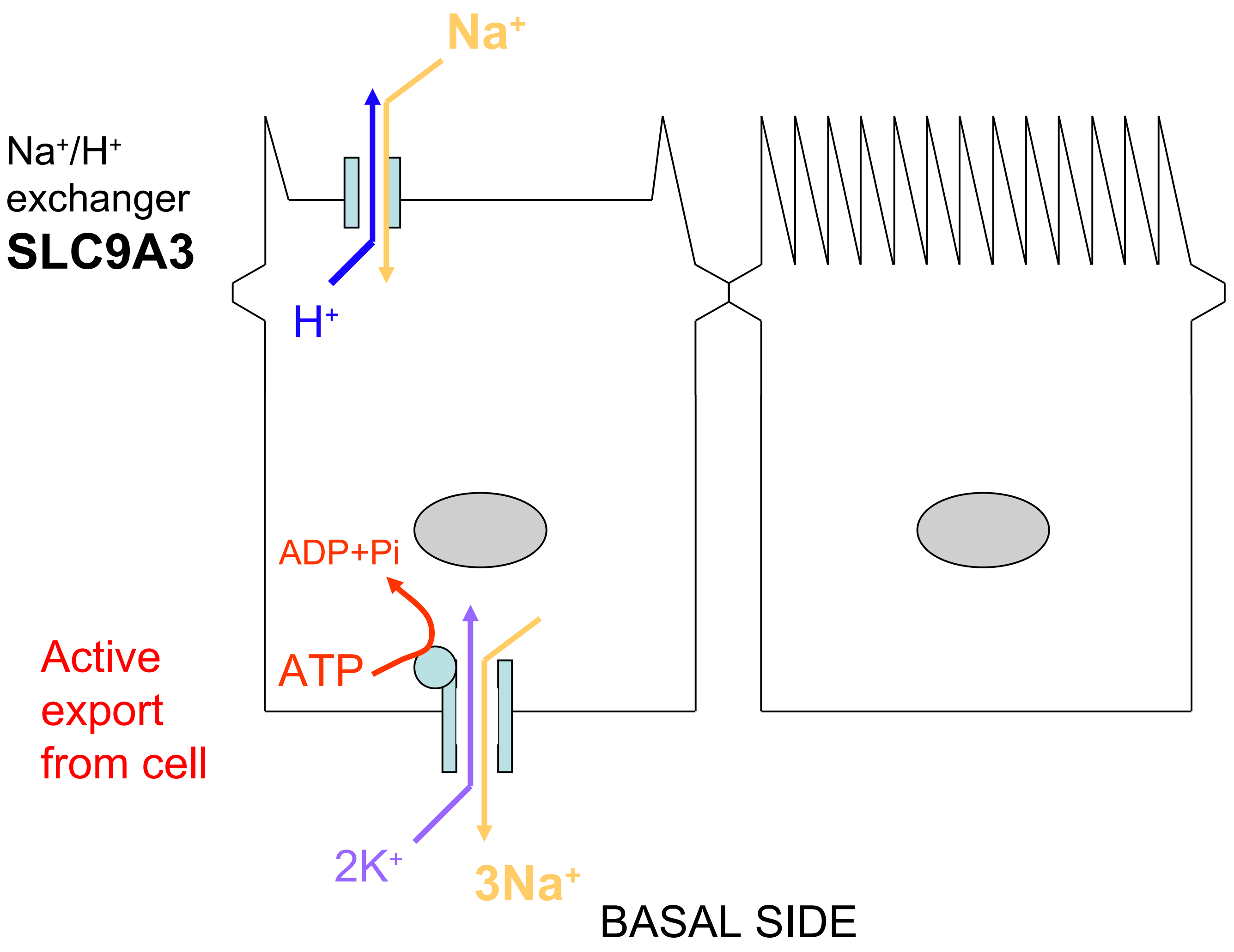
Creates a gradient that can power passive import, if channels permit

Active export from cell



Sodium recovery (proximal tubule):

(microvilli flattened out for clarity)



Aside; we will **NOT** ask you anything like this;

SLC9A3 transports;

a) Sodium and protons
b) Calcium and protions
c) Calcium and chloride
d) Amino acids
e) potassium

This will never be a 'catch' mismatch to the words next to it

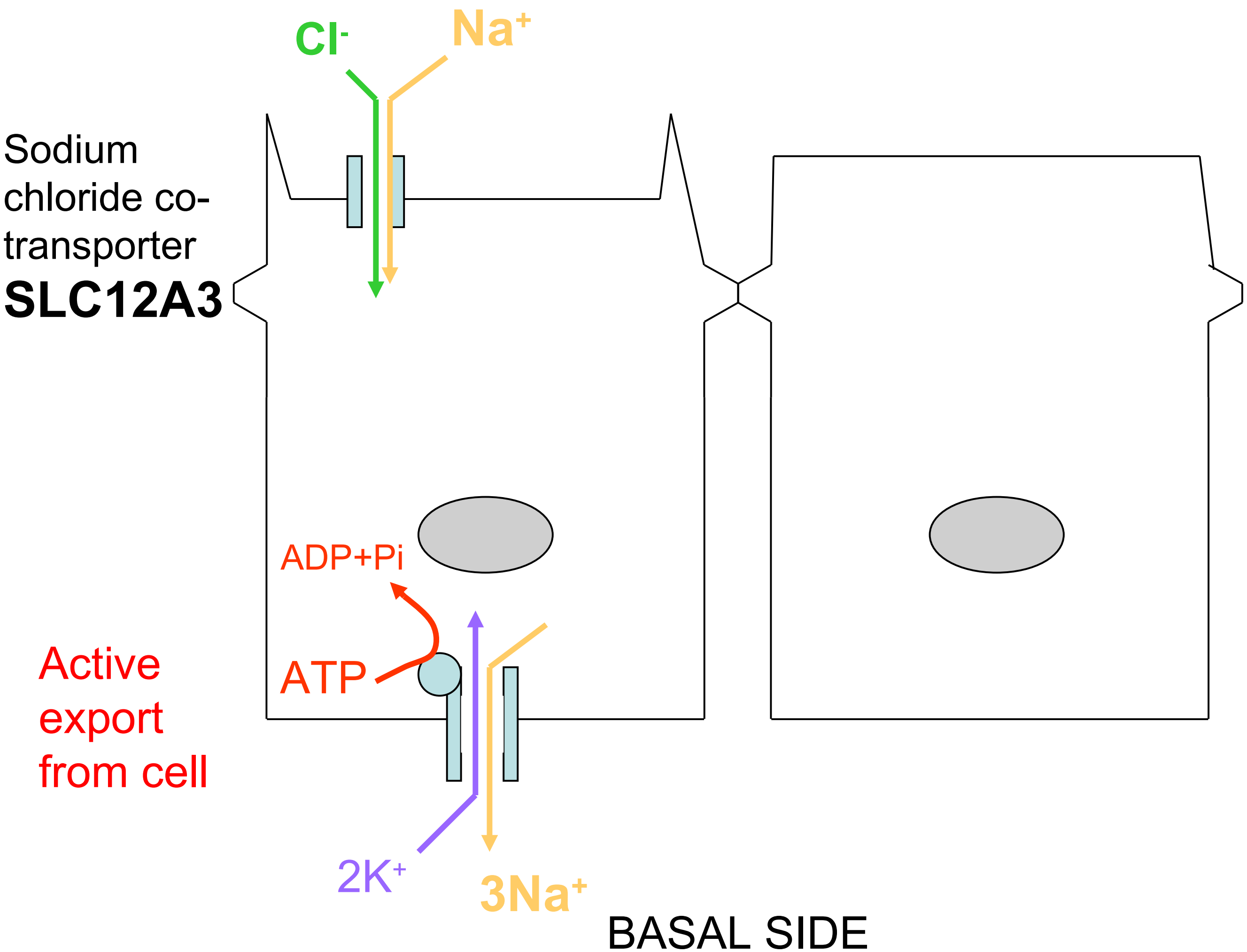
We may ask you something like this;

The apical Na^+/H^+ exchanger SLC9A3 allows

a) Na^+ and H^+ export from the cell
b) Na^+ export and H^+ import
c) Na^+ import and H^+ export
d) Na^H and H^+ import to the cell

….. From the urinary space

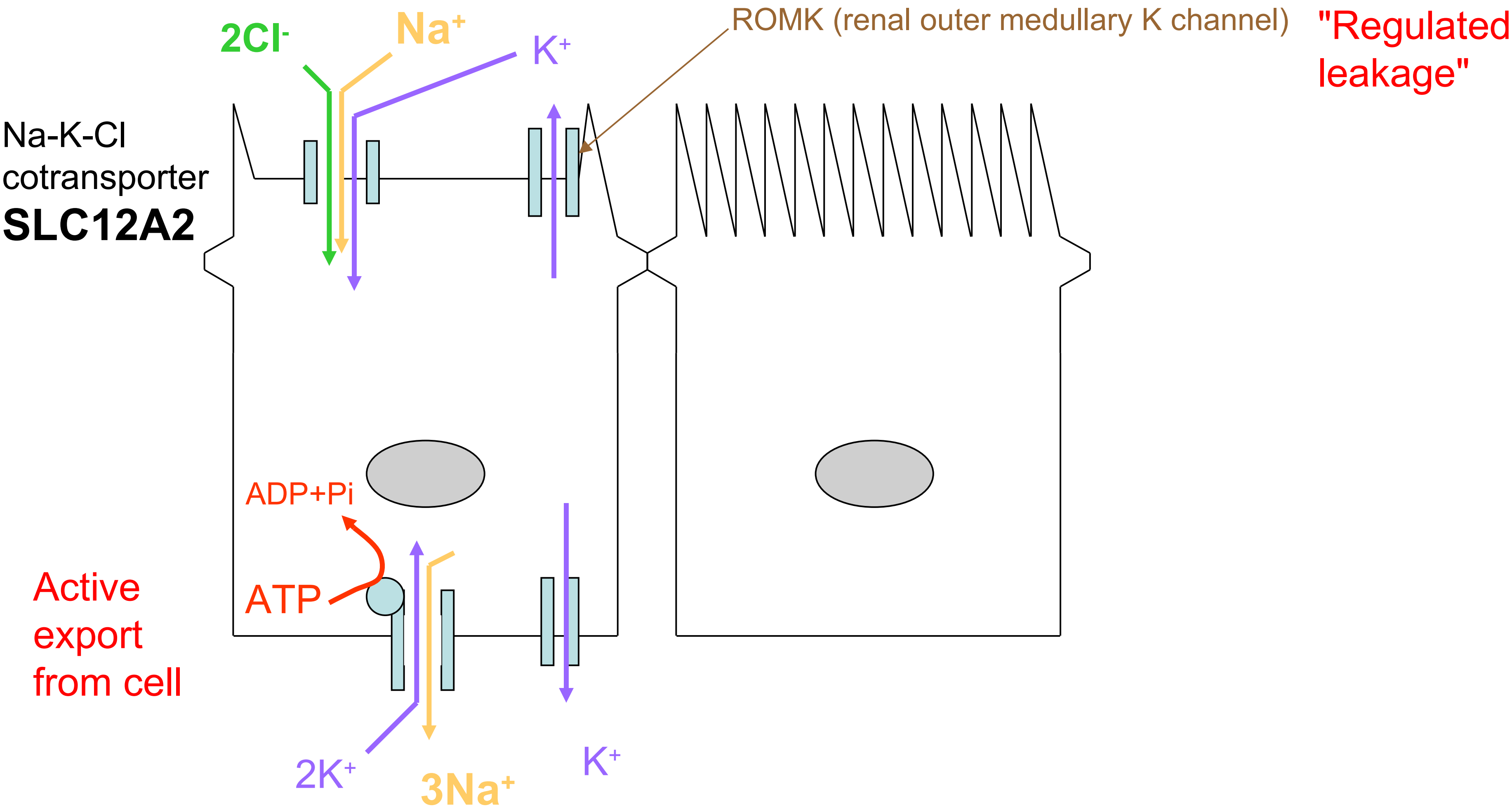
Sodium recovery (distal tubule):



NB – don't worry yet about why the systems are different in different parts of the tubule – we'll deal with that in lecture 3.

(obviously, the Na^+/K^+ ATPase is drawn very over-scale)

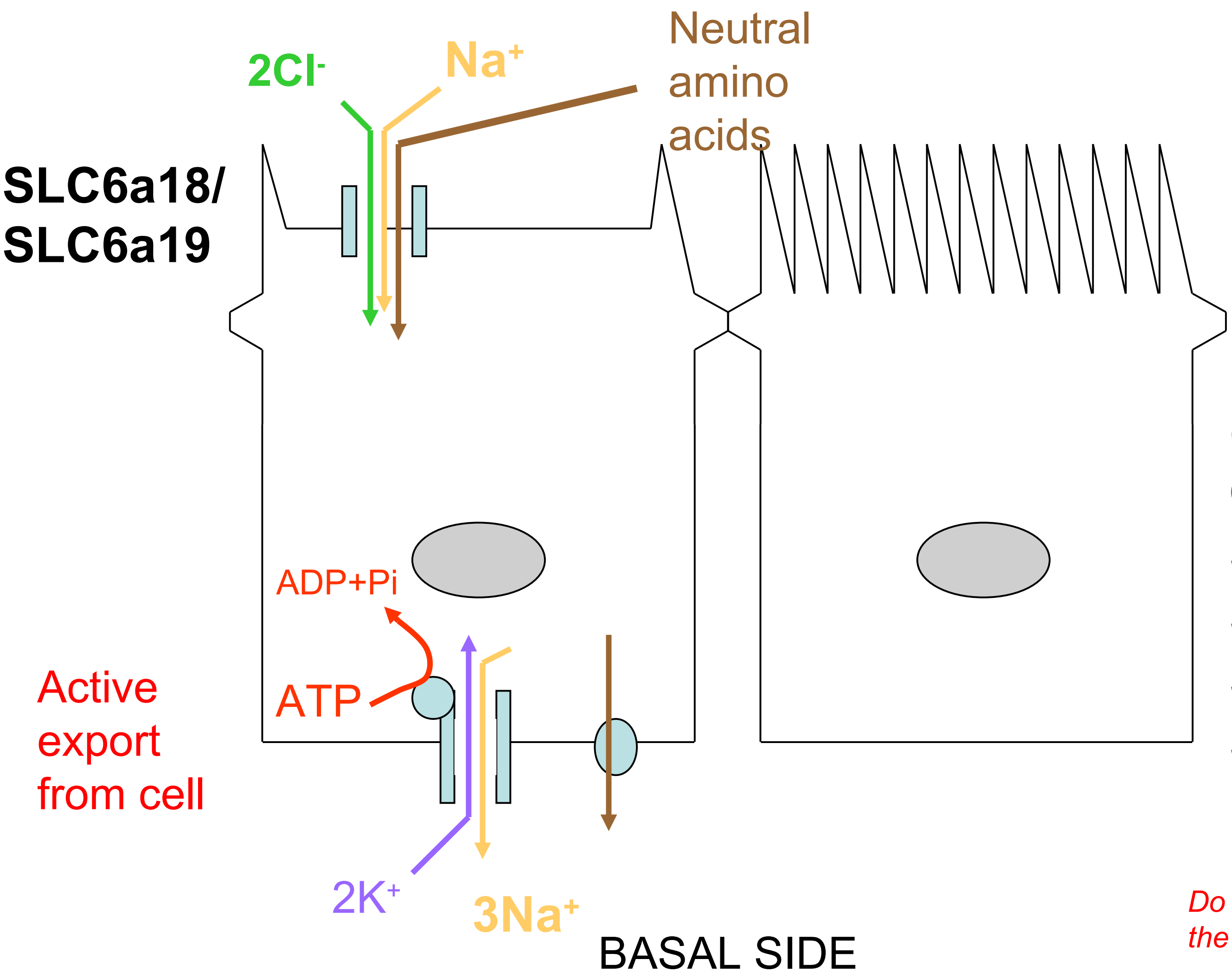
Potassium recovery (Loop of Henle):



BASAL SIDE

Ref: **Welling & Ho (2009)** ***Am J Physiol Renal Physiol*** **297: F849-F863**

Amino acid recovery (Prox tubule):



Other channels carry other amino acids:

SLC1A1 –ve

SLC36A2 Gly, Ala, Pro with H^+

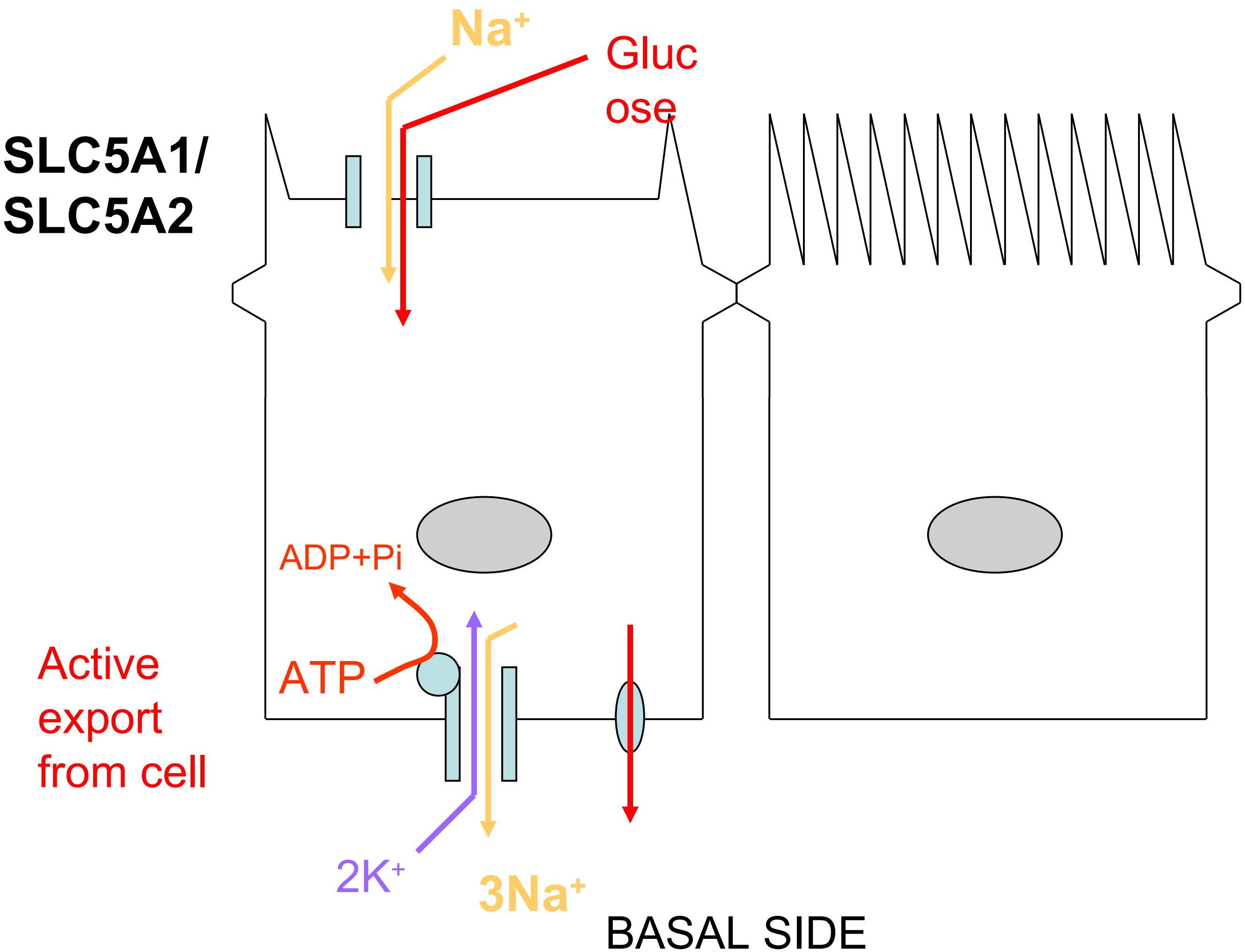
SLC6A20 Pro with Na^+

SLC3A1 cysteine

Do not try to learn all these! – just see the general picture.

Verrey F, Singer D, Ramadan T, Vuille-dit-Bille RN, Mariotta L, Camargo SM. (2009) Kidney amino acid transport. Pflugers Arch. 2009 May;458(1):53-60

<u>Glucose recovery: (mostly proximal tubule; a little in LoH)</u>

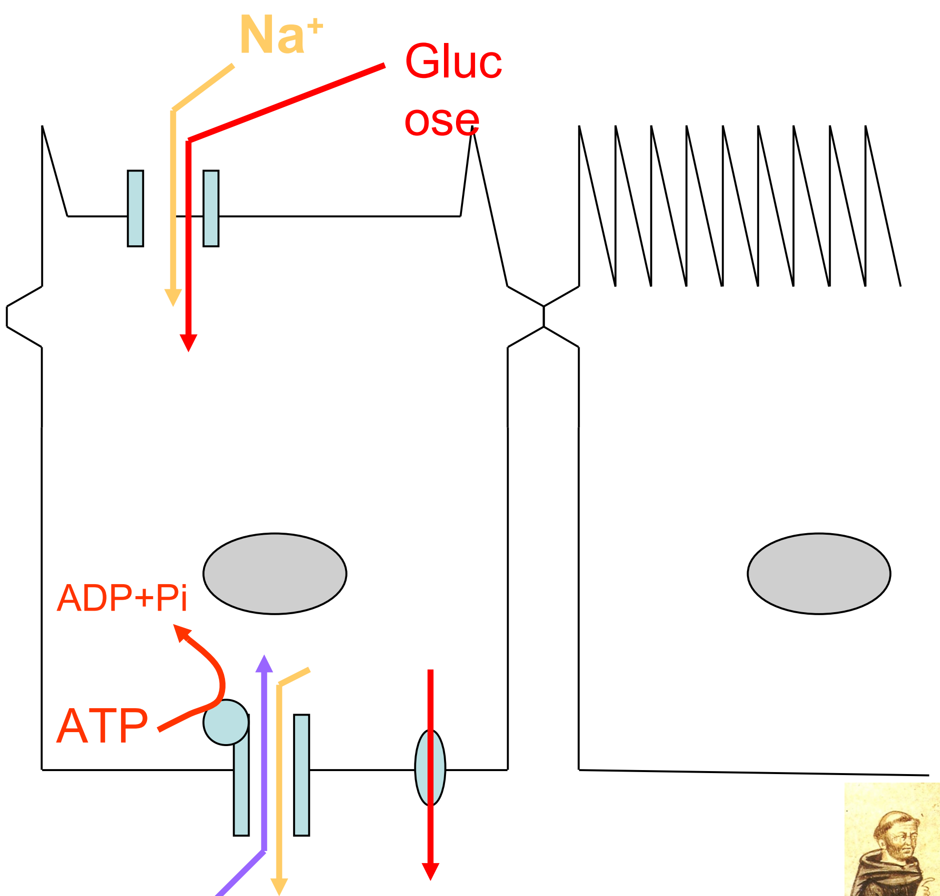


Most is done by SLC5A2; Na^+:glucose = 1:1

SLC5A1 has a 2:1 ratio

Glucose recovery:

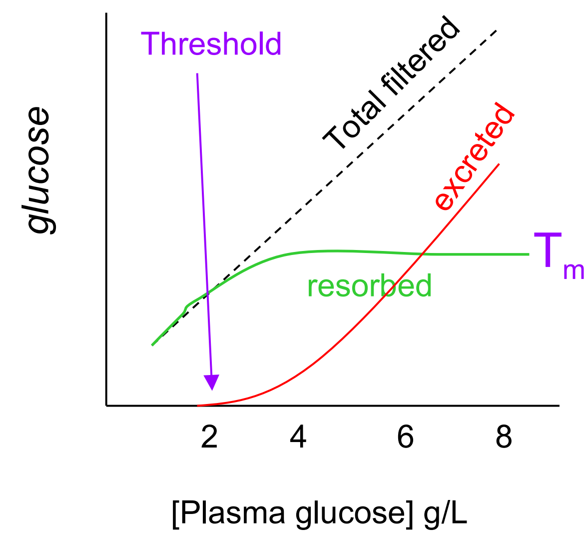
SLC5A1/
SLC5A2



Active
export
from cell

BASAL SIDE

This is rate-limited:



Diabetes mellitus

(*sweet*)

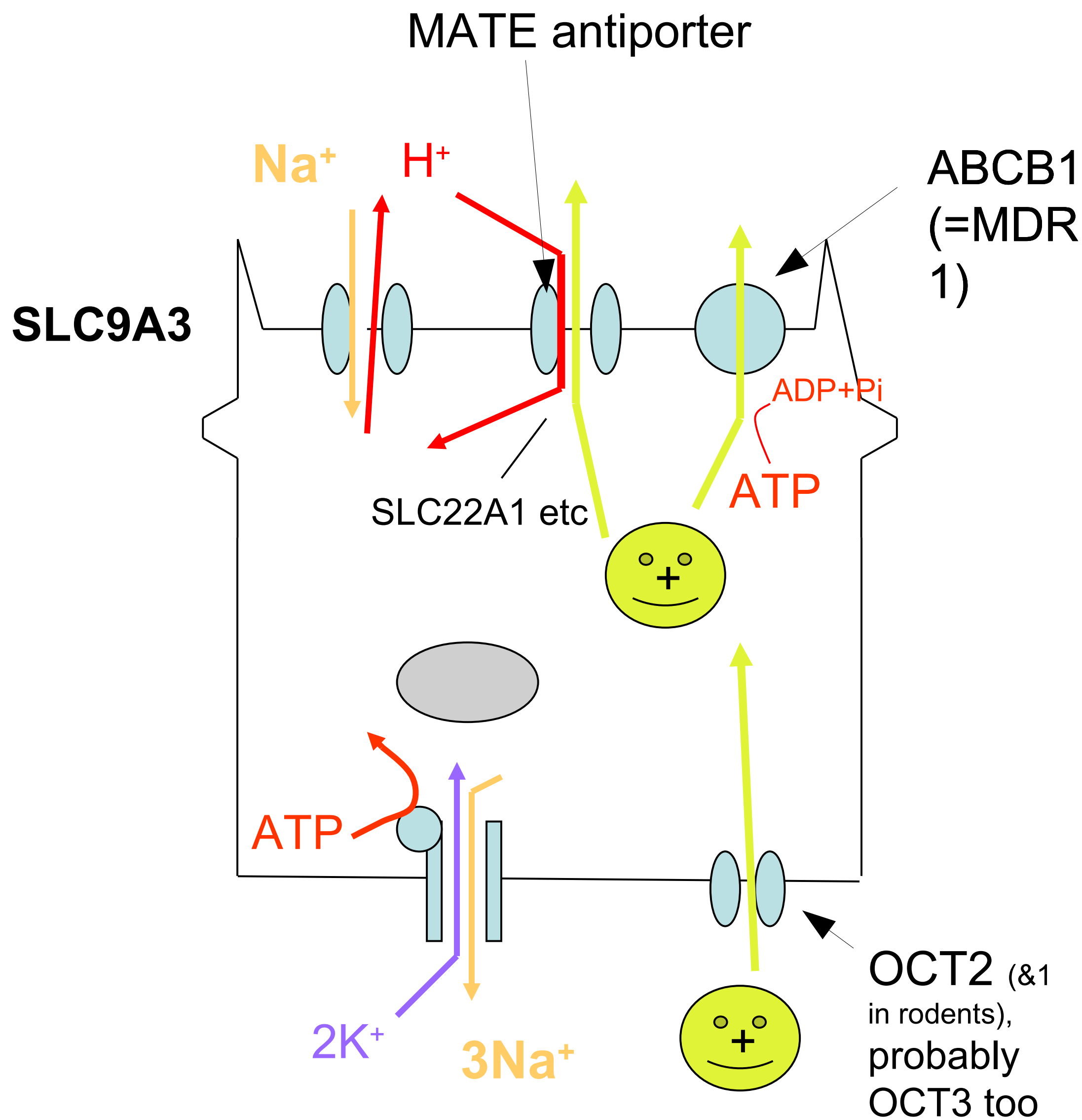
Organic anions and cations (including drugs & metabolites)

SLC22 family: Organic anion transporters (OATs)
Organic cation transporters (OCTs)
Organic Cation/ Carnitine transporters (OCNTs)

Useful review in the introduction of: Jacobsson JA, Haitina T, Lindblom J, Fredriksson R. (2007) Genomics. 90:595-609.

OCTs (SLC22A1-3)

Fairly simple: allow passive movement in either direction (so things go down-gradient)



Examples of things carried:

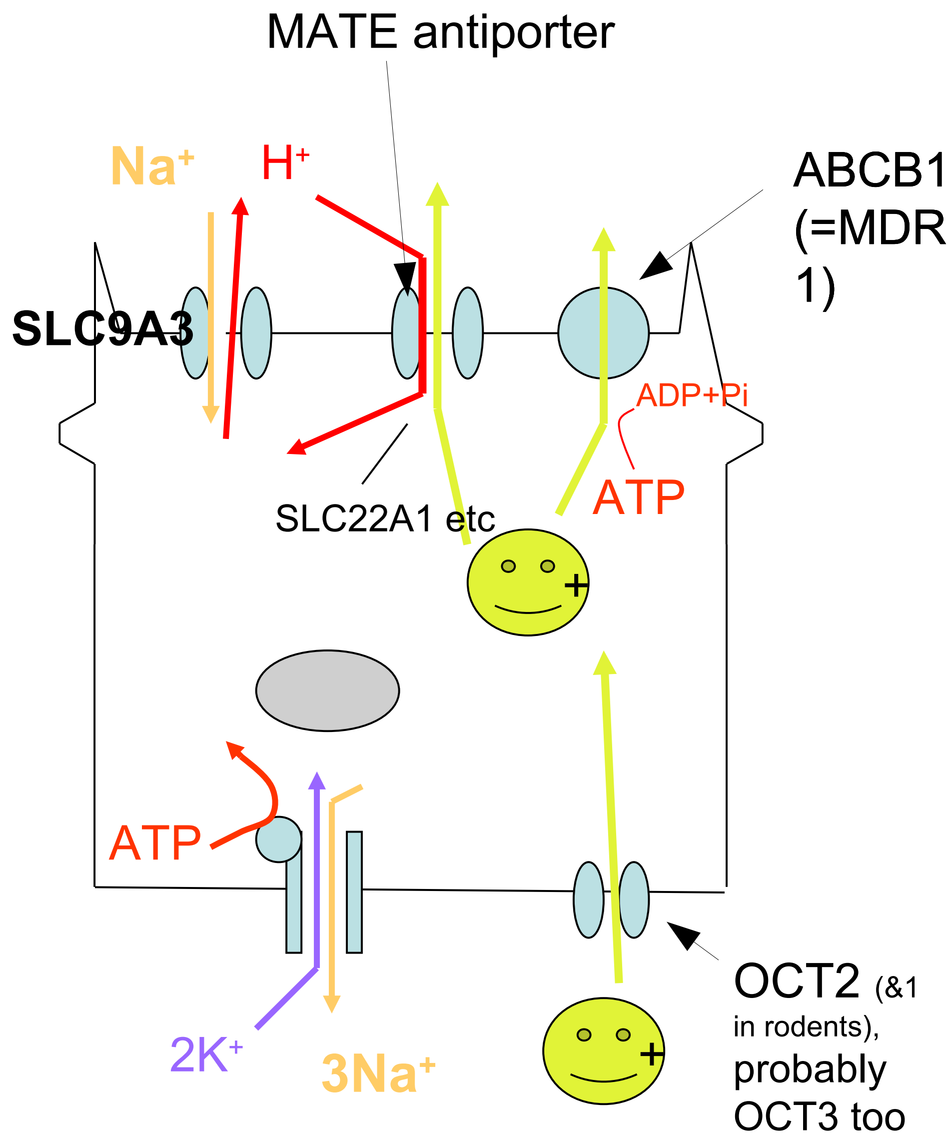
- tetraethylammonium (TEA)
- 1-methyl-4-phenylpyridinium (MPP)
- endogenous amines, such as dopamine
- therapeutic drugs, such as cimetidine and morphine
- cationic xenobiotics, such as antihistamines

Karbach U, Kricke J, Meyer-Wentrup F, Gorboulev V, Volk C, Loffing-Cueni D, Kaissling B, Bachmann S, Koepsell H. (2000) Am J Physiol Renal Physiol. 279:F679-87.

OCTs (SLC22A1-3)

Fairly simple: allow passive movement in either direction (so things go down-gradient)

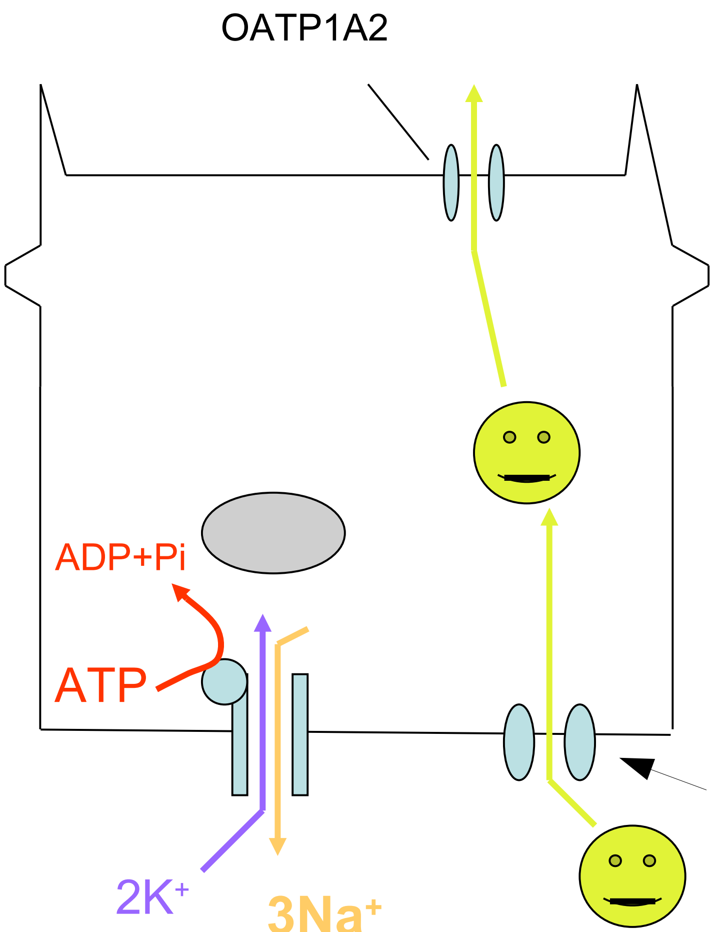
Note this is 'safe' in the sense that cations drift into the cell and are pumped out. The cytoplasmic concentration should therefore not exceed that of plasma.

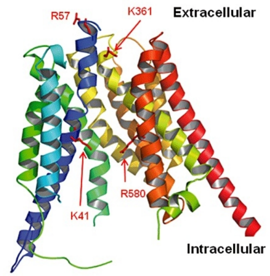


Karbach U, Kricke J, Meyer-Wentrup F, Gorboulev V, Volk C, Loffing-Cueni D, Kaissling B, Bachmann S, Koepsell H. (2000) Am J Physiol Renal Physiol. 279:F679-87.

OATPs (SLC21 A1,2,3 = OATP1A2, 1B1, 1B3)

No need to learn this list!





Transport larger and somewhat hydrophobic organic anions including many xenobiotics.

Examples:

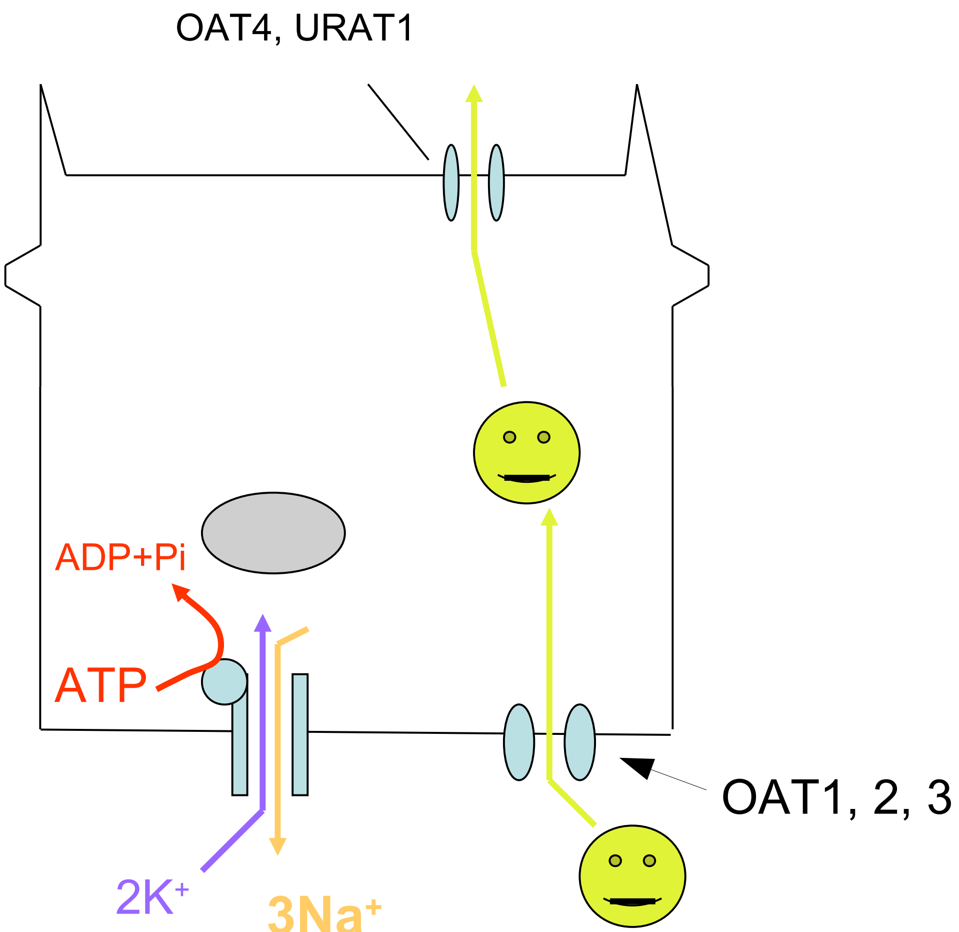
- Prostaglandins
- Cholate
- Ciprofloxacin
- Cyclic peptides

NB – there is evidence that OATPs are electroneutral transporters, so something else must move too.

Roth M, Obaidat A, Hagenbuch B. (2012) OATPs, OATs and OCTs: the organic anion and cation transporters of the SLCO and SLC22A gene superfamilies. Br J Pharmacol. 2012 Mar;165(5):1260-87.

OATs (SLC22 A6,7,8,911,12,19,20 = OAT1,2,3,4,7, URAT1, OAT5,6)

No need to learn this list!



Examples of transported things:

- methotrexate
- furosemide
- penicillin

← this drawing is incomplete – revise from the next slides, not this one.

NB – labels are right for human – mice are different

Roth M, Obaidat A, Hagenbuch B. (2012) OATPs, OATs and OCTs: the organic anion and cation transporters of the SLCO and SLC22A gene superfamilies. Br J Pharmacol. 2012 Mar;165(5):1260-87.

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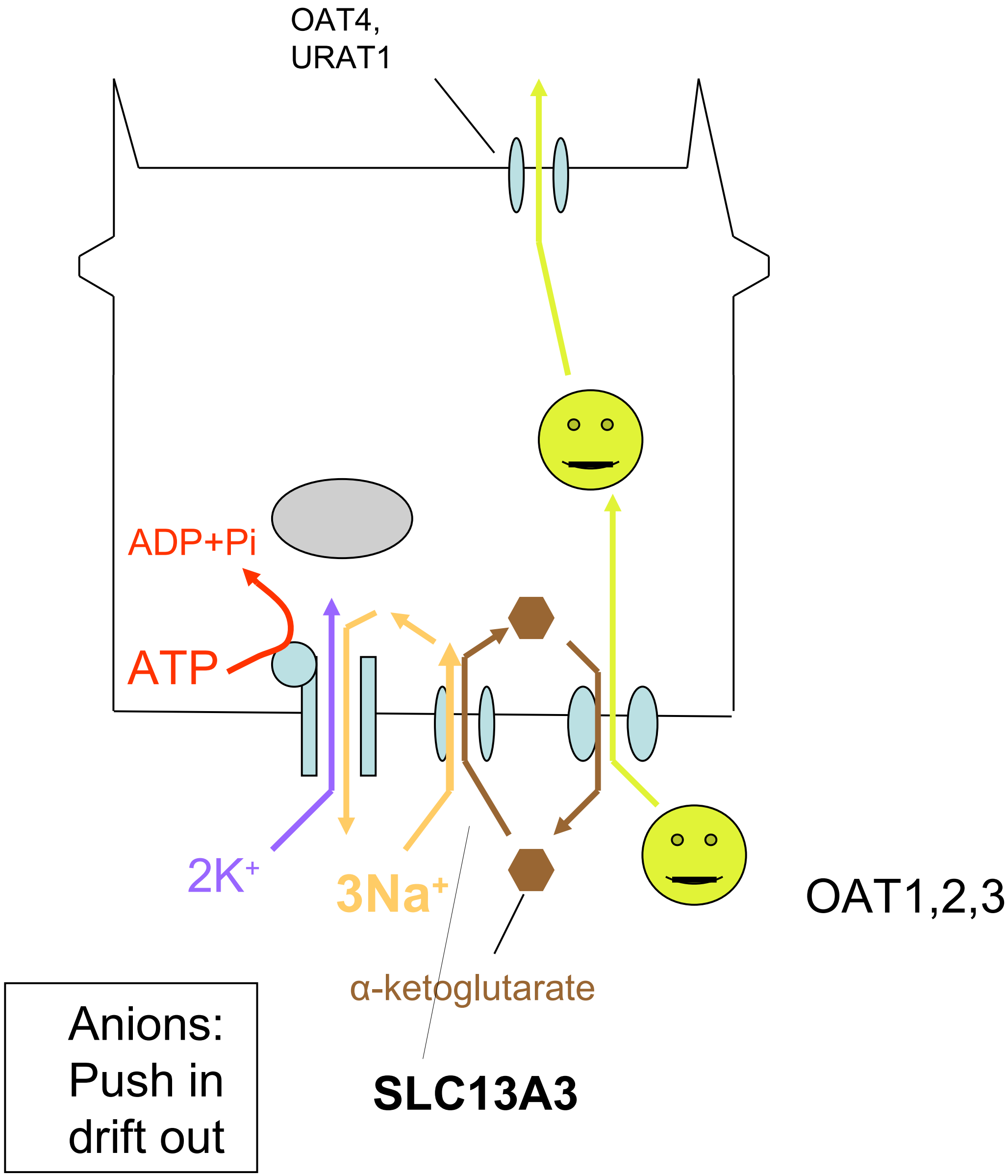

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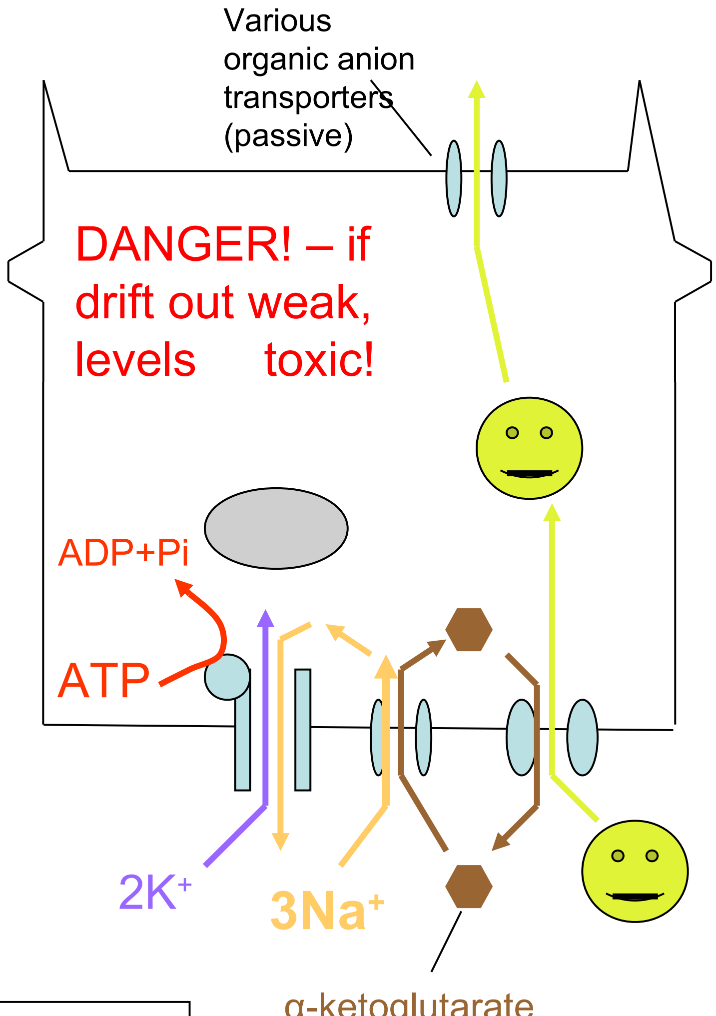

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Anions:
Push in
drift out

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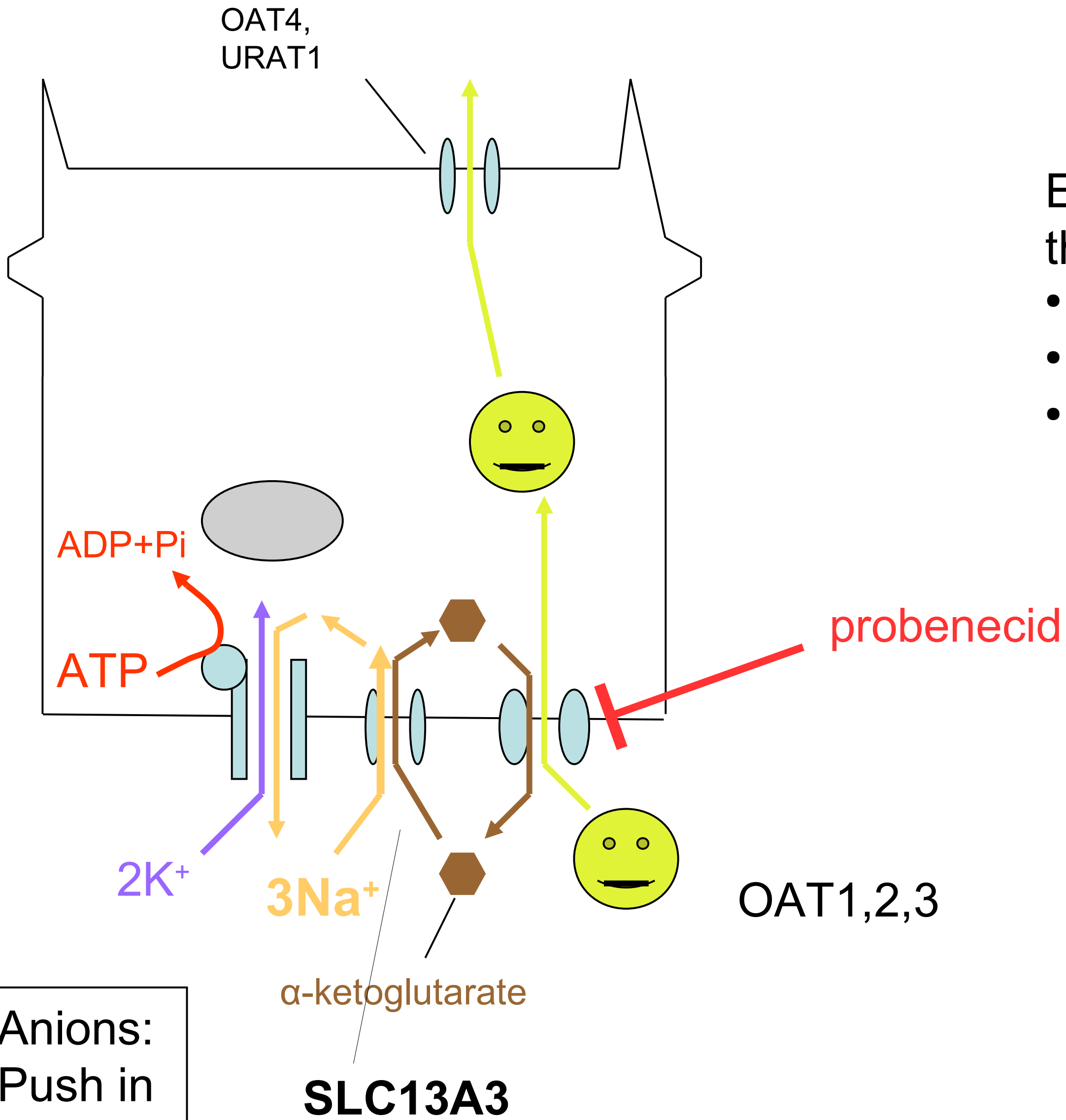

Examples of transported things:

- methotrexate
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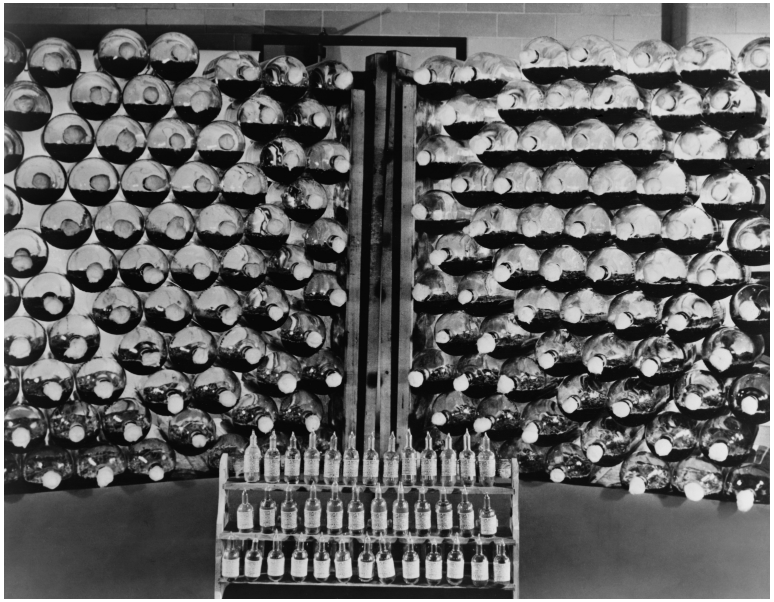
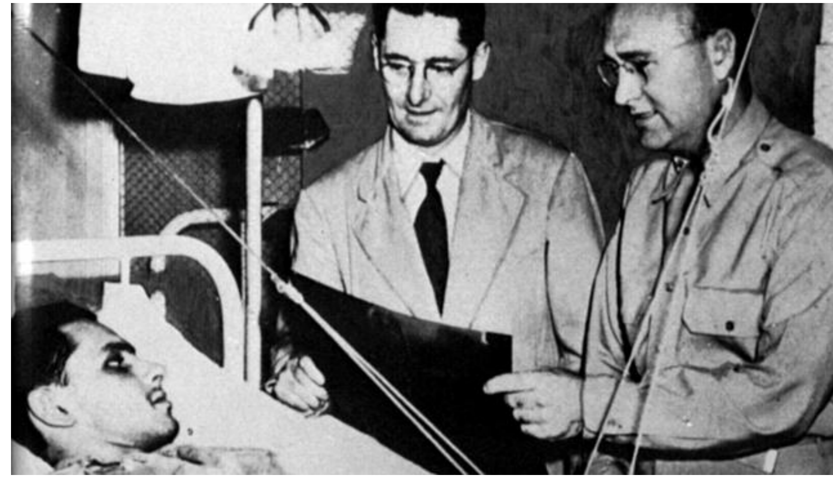
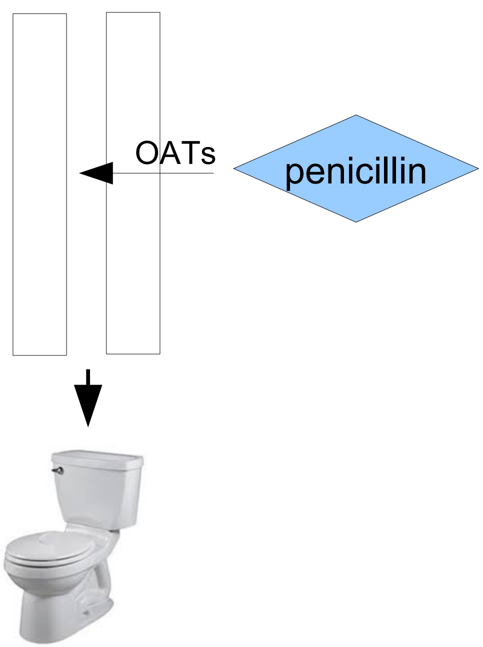
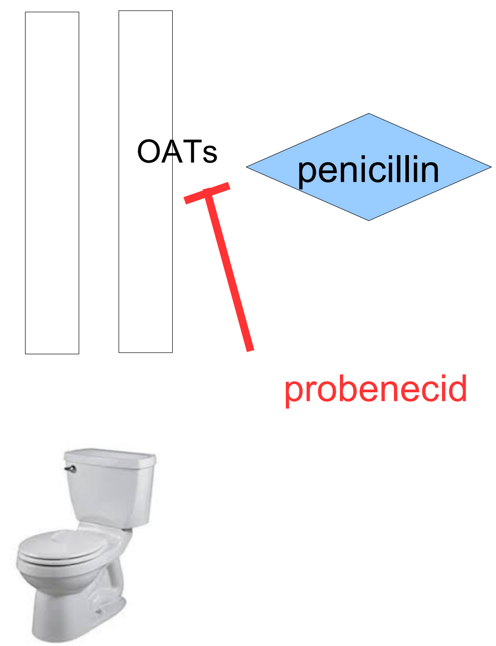
- penicillin

Anions:
Push in
drift out

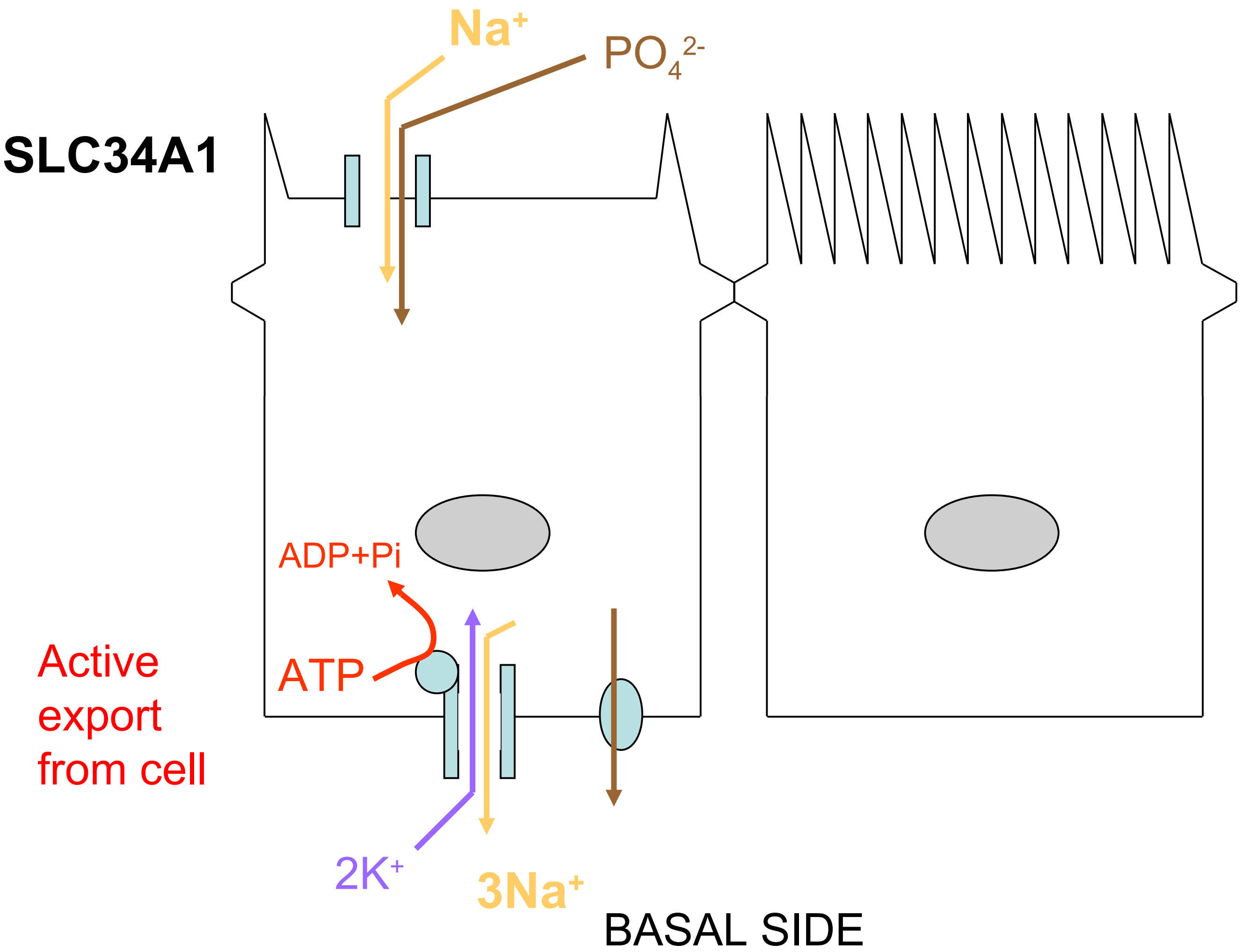




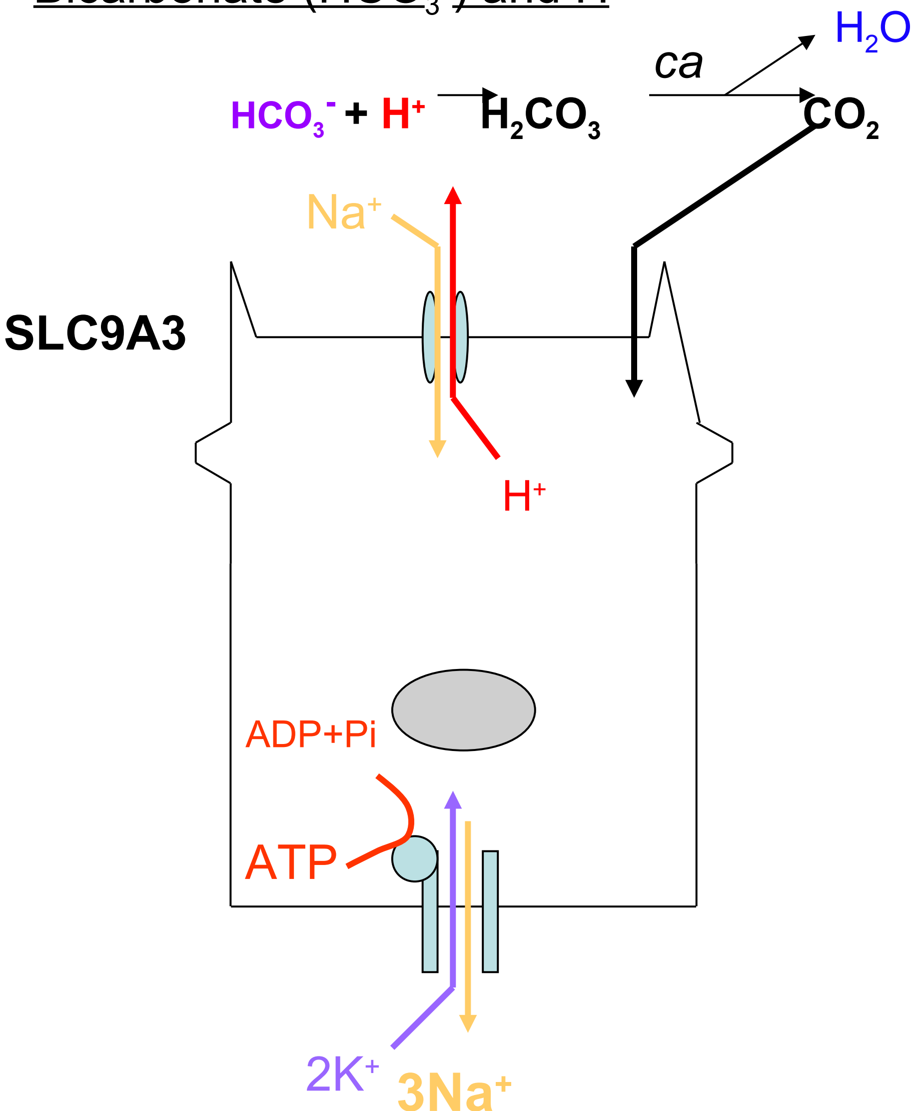

OATs
penicillin


OATs
penicillin
probenecid

Phosphate recovery (Proximal tubule):



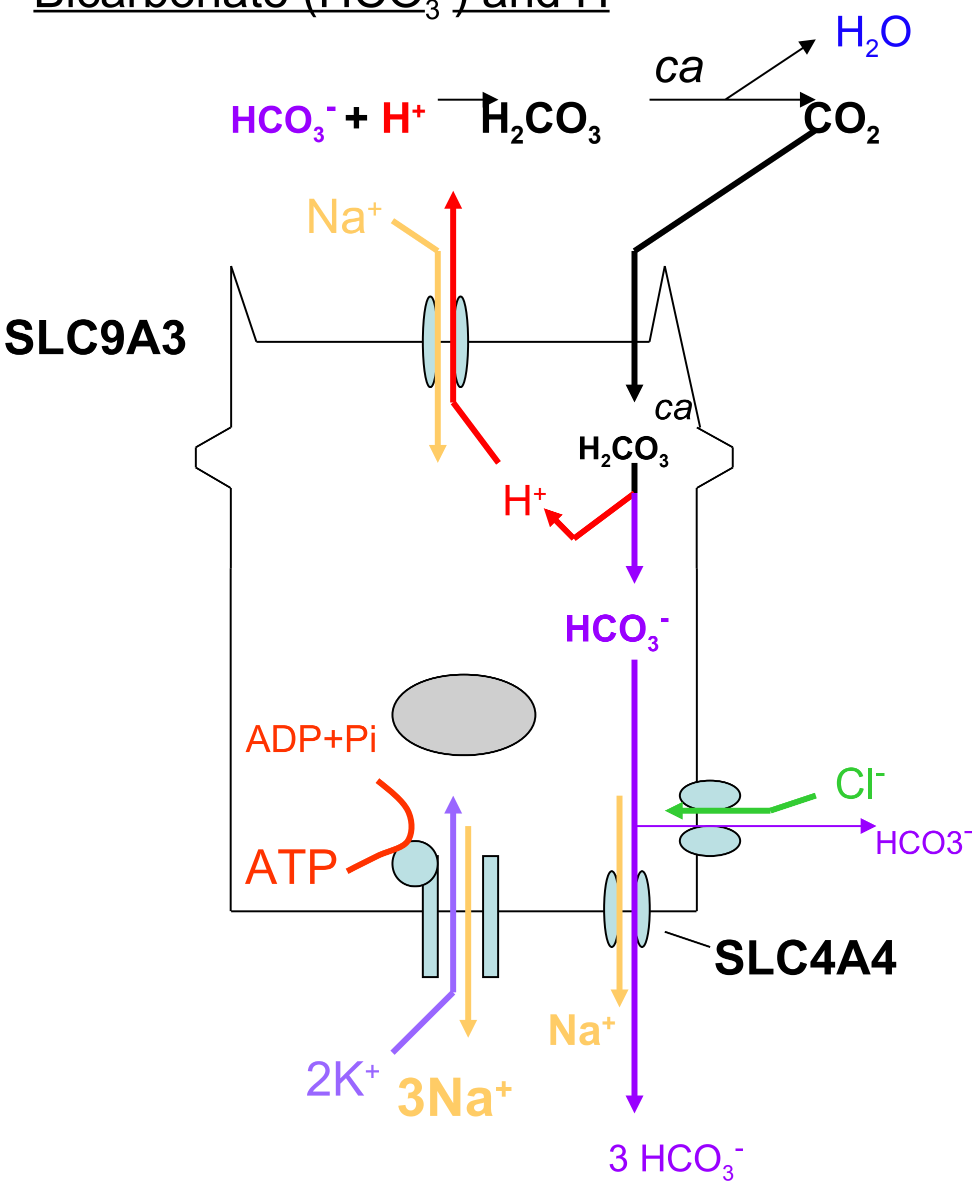
Bicarbonate (HCO_3^-) and H^+



ca = carbonic anhydrase

Proximal tubule

Bicarbonate (HCO_3^-) and H^+



ca = carbonic anhydrase

NB – this mechanism results in no net loss of $HCO3^-$ or H^+ (as ions)

…so no effect on acid/base

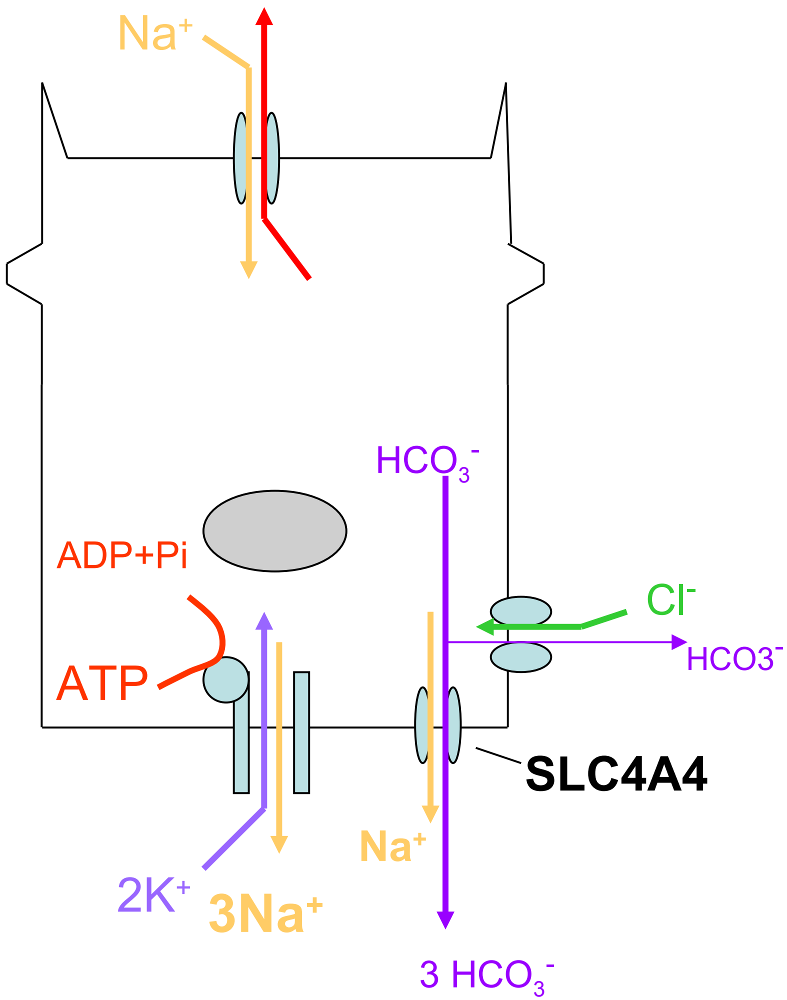
(the Cl^- just gets out again through a chloride channel).

Proximal tubule

If there is remaining H^+ when the bicarbonate has been taken up (1);

HPO_4^{2-} + H^+ → $H_2PO_4^-$ (leaves body in urine)

Still some left when bicarb mostly gone



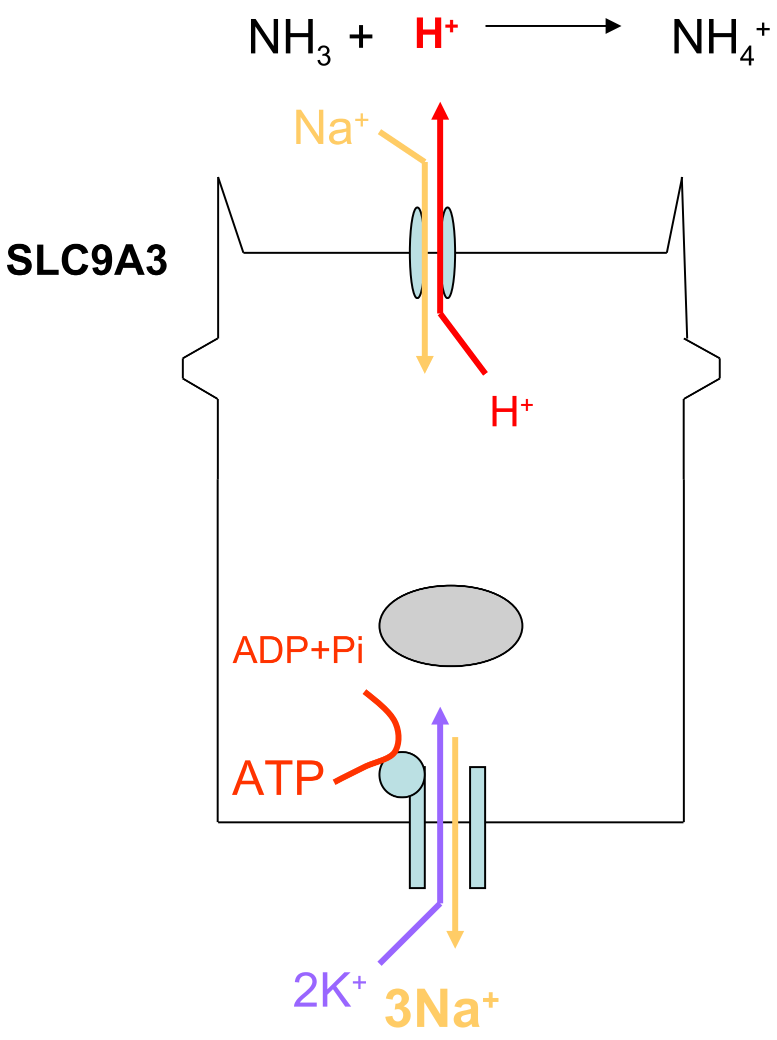
Proximal tubule

NB – this mechanism results in net secretion of H^+

…so DOES affect acid/base

(Useful! - if you are short of bicarbonate – ie in acidosis – you throw out some H^+).

<u>When the bicarbonate has been taken up (2);</u>

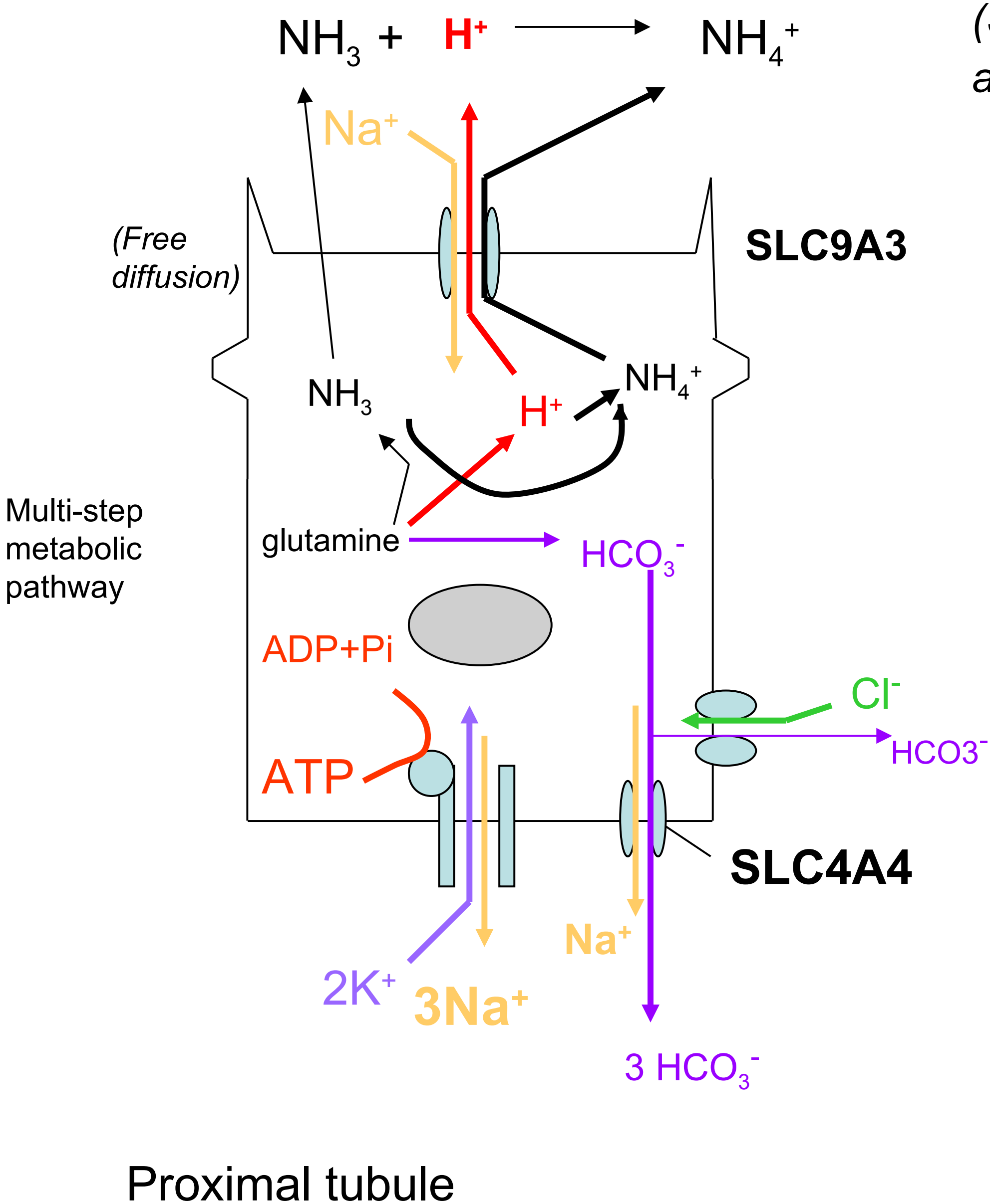


NB – this mechanism results in net secretion of H^+

…so DOES affect acid/base

Proximal tubule

Where does the ammonia/um come from?

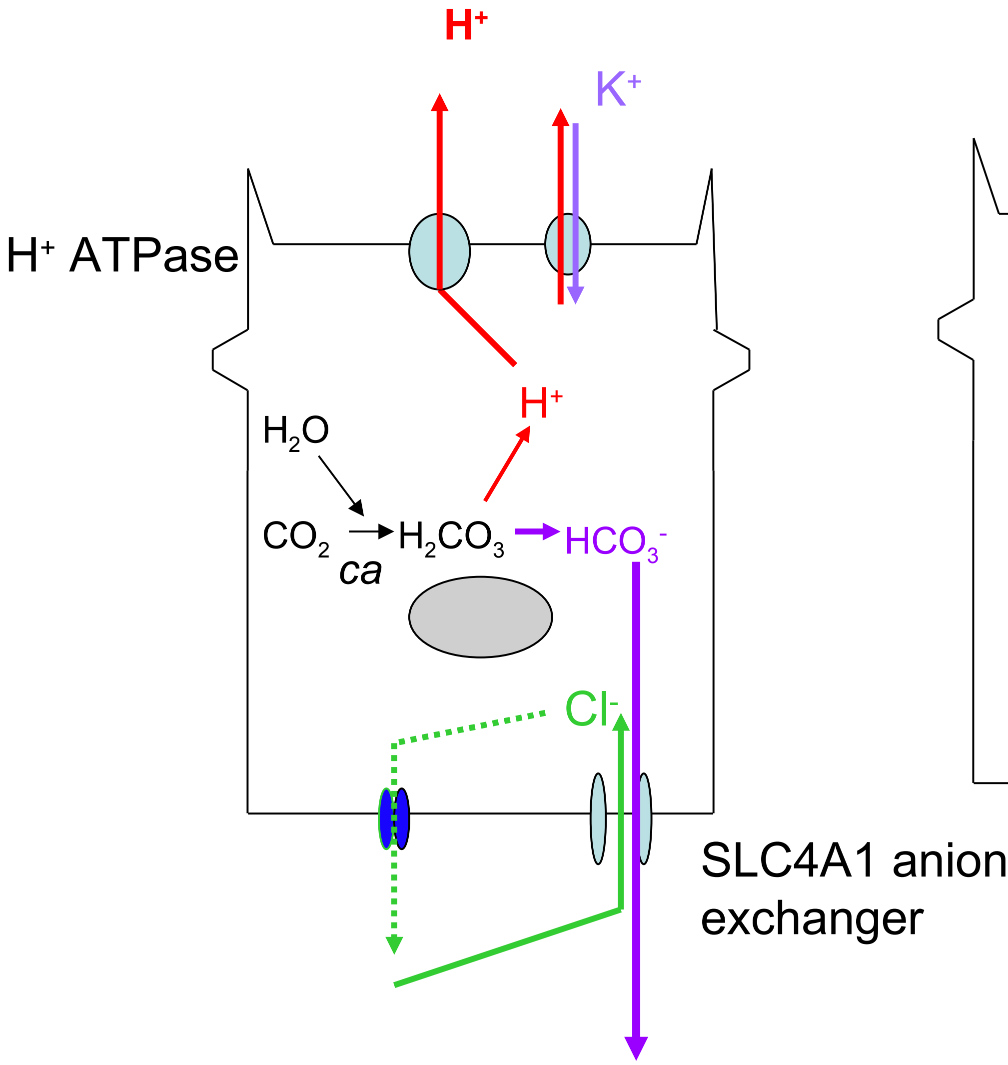


(SLC9A3 can transport either H^+ or NH_4^+ against Na^+)

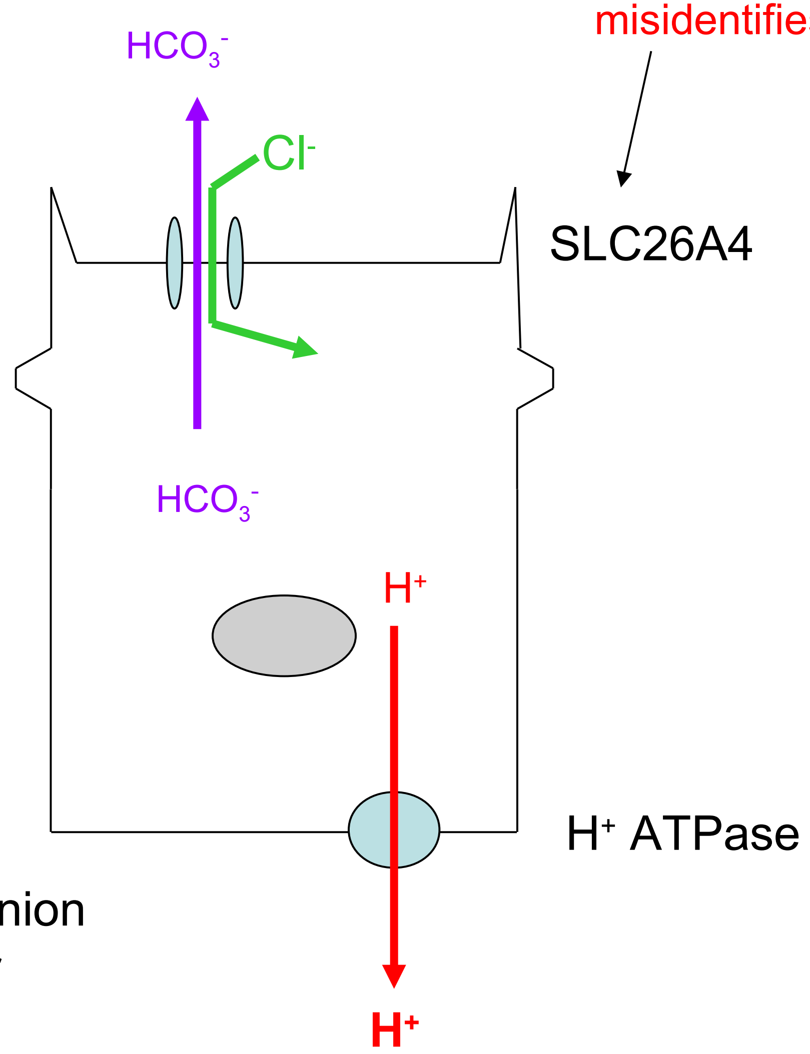
Essentially, H^+ goes out and bicarbonate comes in...

… which is exactly what you want if you were short of bicarbonate (remember, these reactions happen mainly when all lumen bicarbonate has been recovered)

More acid base: Intercalated cells

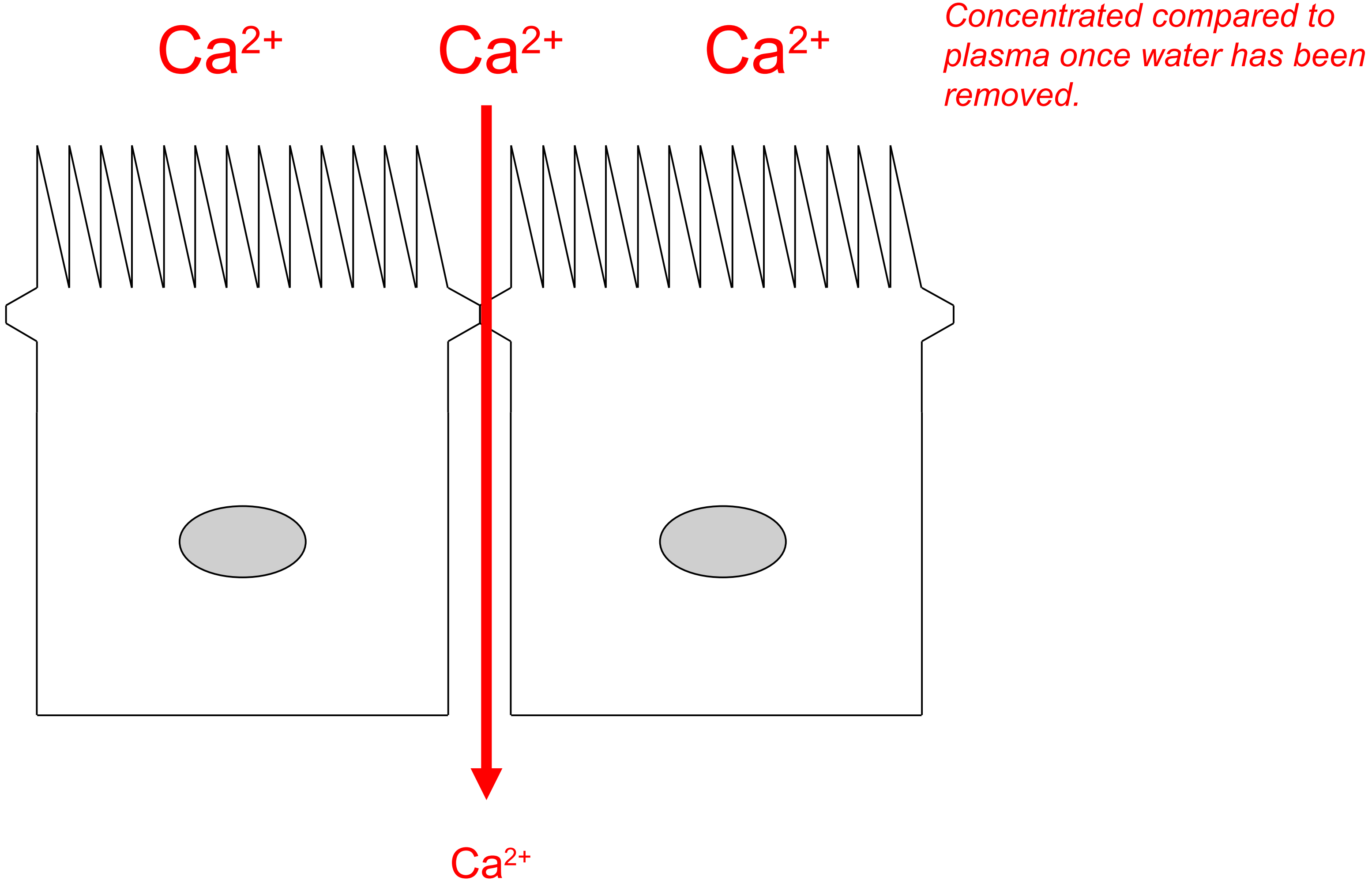


These type A cells throw H^+ out of the body



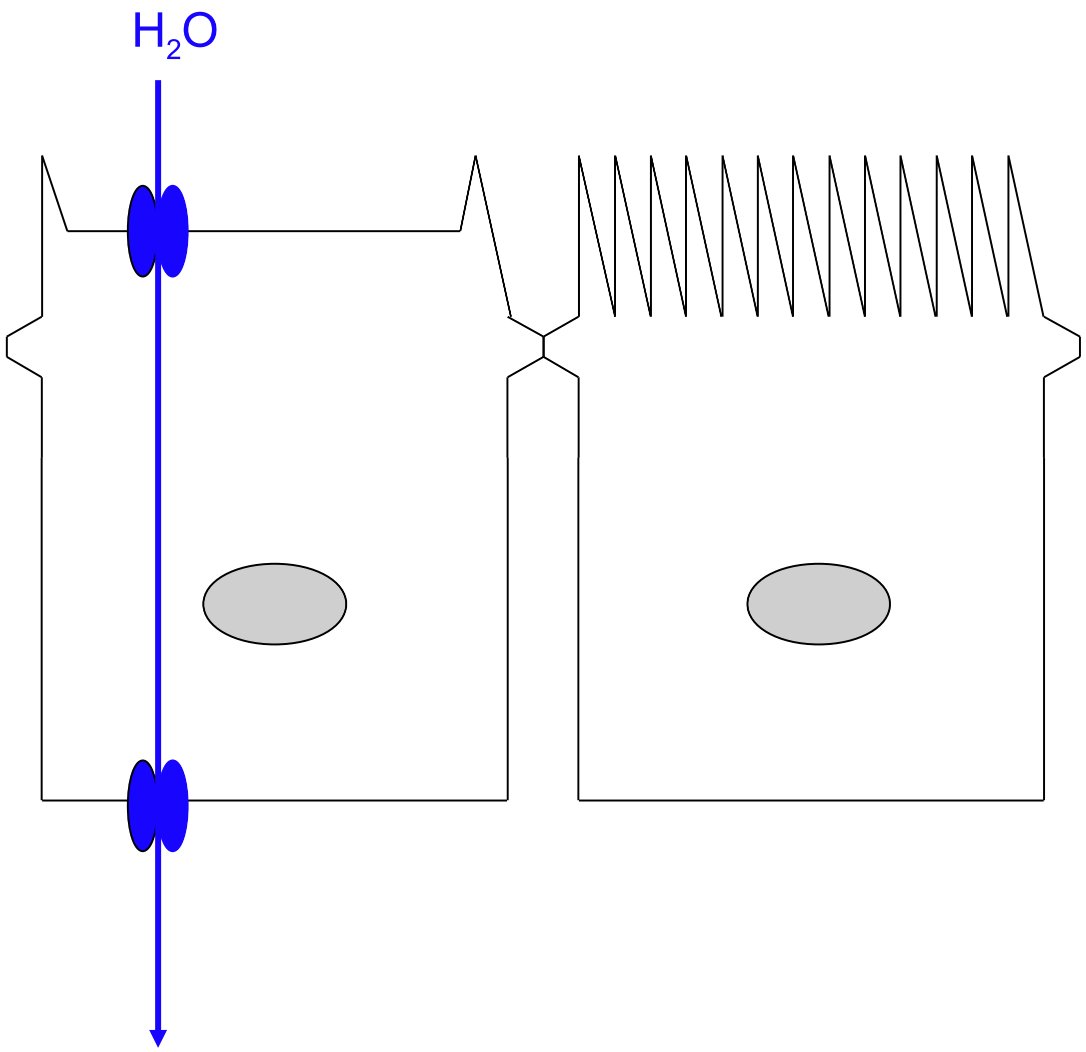
These type B cells throw H^+ back into the body

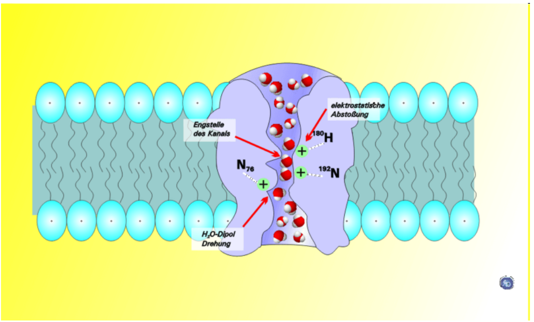
Calcium is mainly paracellular, passive, and driven by osmosis once the urine has become more concentrated:



(We'll meet a regulated system in lecture 4)

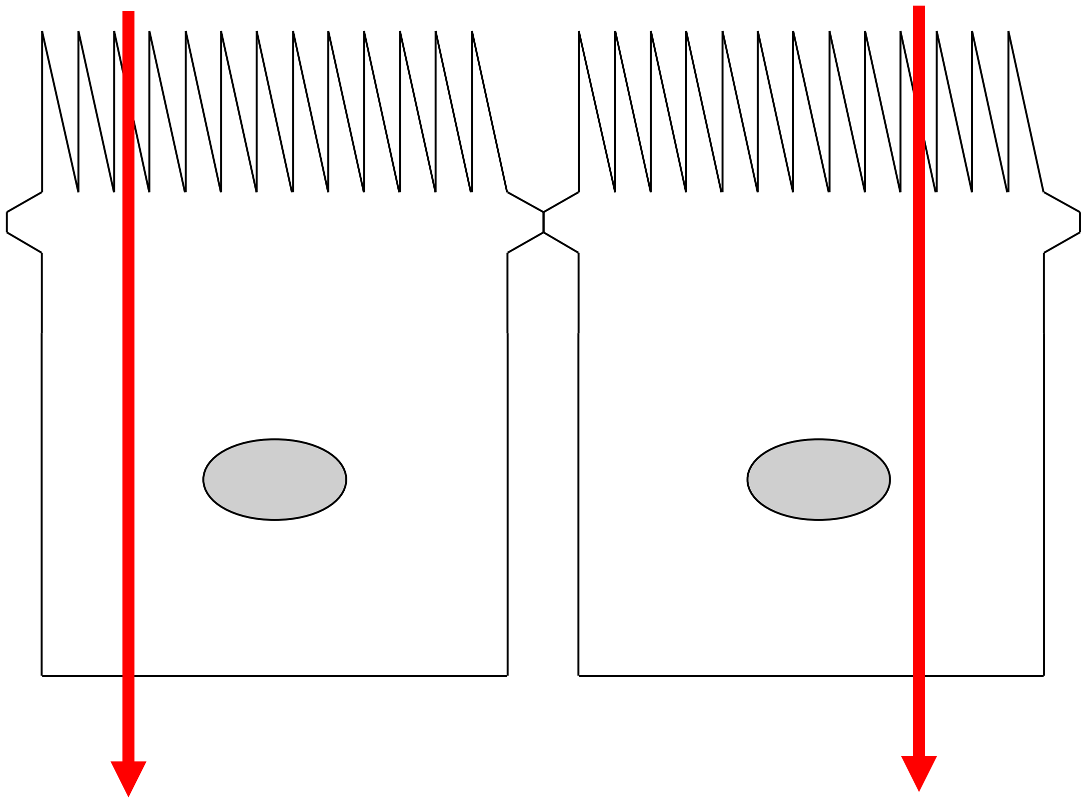
Water: aquaporins.





Aquaporin1 (wikipedia commons)

Protein uptake in the proximal tubule cells, using general receptors such as Megalin:



Summary (2)

Solute recovery mostly parasitizes the sodium gradient created by the pump.

Each recovery has its own systems (SLCs etc)

There are very many SLC (solute carrier) proteins: you need to learn them only in so far as you need to for drug targets: we are not going to test you on remembering SLCs

The kidney has several ways to play with acid-base balance of the body

Some things, like water, can move only passively.

Next lecture, we consider what is absorbed and where…