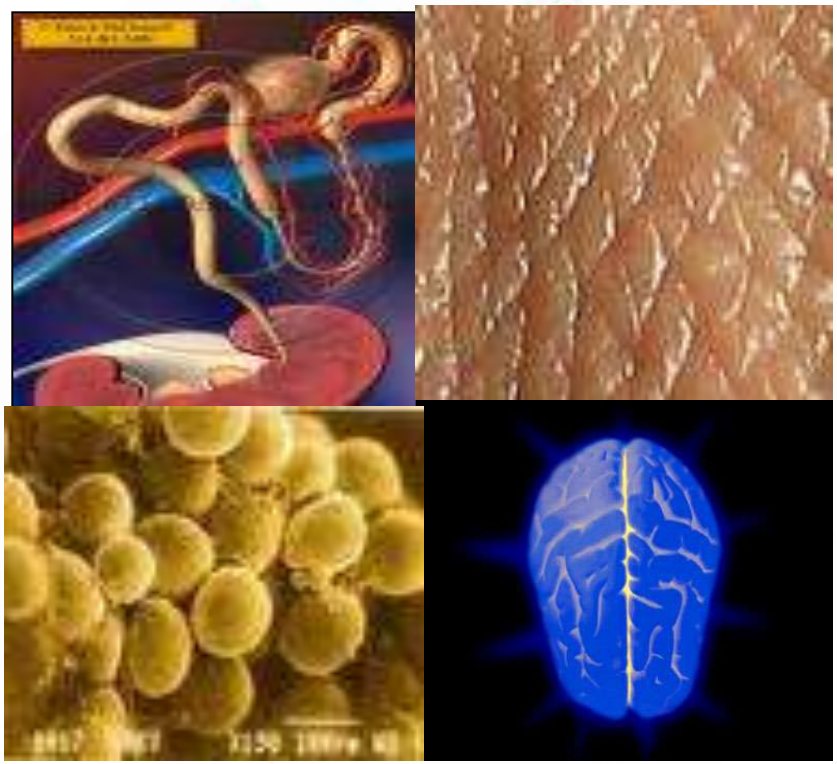
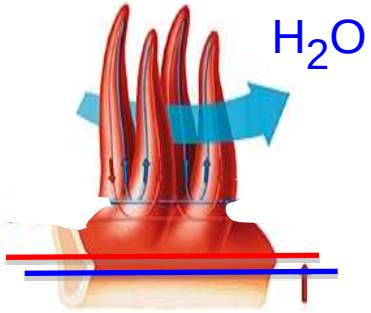
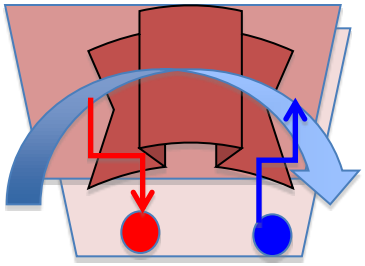
News from aquaporins: current aspects



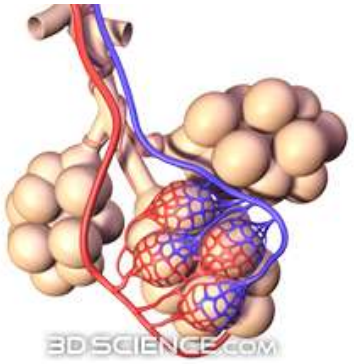
Jean Hamburger's Necker Seminar in Nephrology – April 20th, 2011

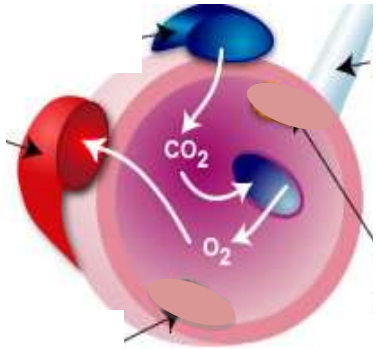
Going away from the pond: breathing in the air





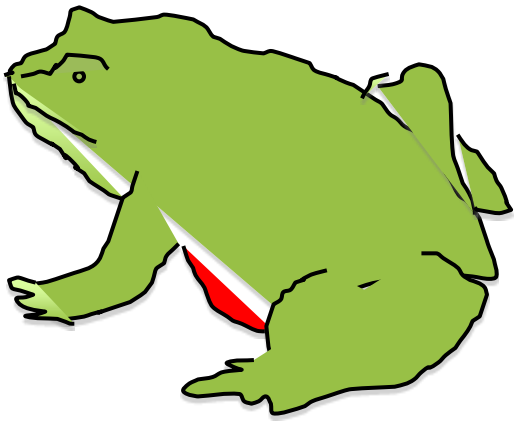
H_2O



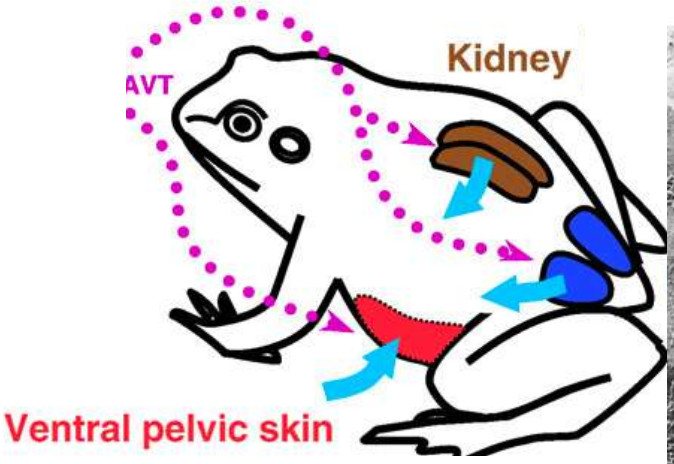


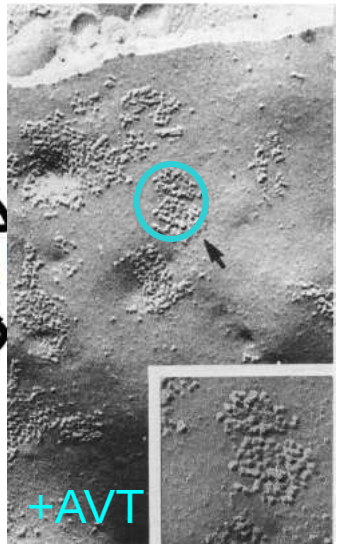
Courtesy of 3DScience.com

Going away from the pond: a water struggle for life



AVT = Arginine VasoTocyne

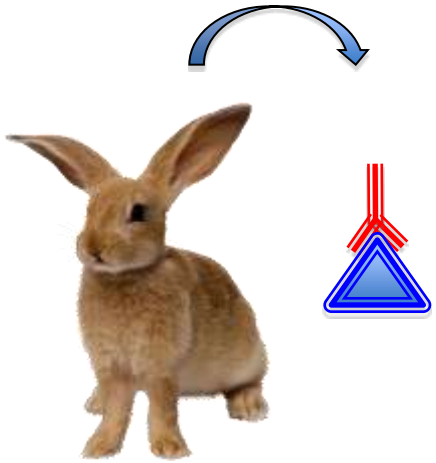




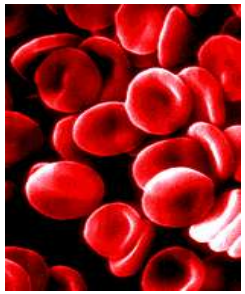
Adapted from Susuki & Tanaka, Comp Biochem Physiol, 2009

Bourguet et al, Biophys J, 1976

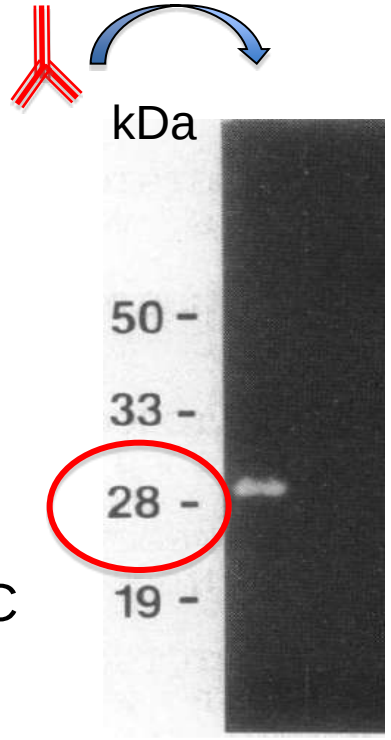
The discovery of CHIP-28 (AQP1)



Anti-Rh immunization



Protein extract from human RBC



Western blot

Purification

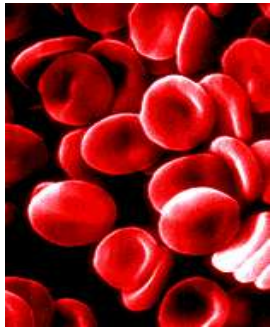
DNA cloning

3.1kb

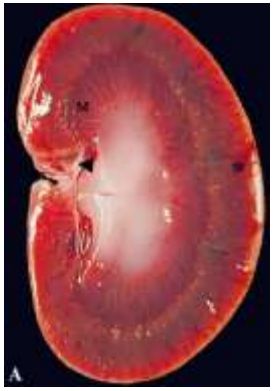
CHannel Integral Protein 28kDa, CHIP 28 (269 AA)

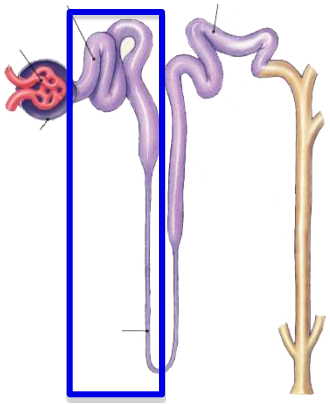
Adapted from Preston & Agre, PNAS 1992

CHIP28 (AQP1) is localised in highly water-permeable tissues

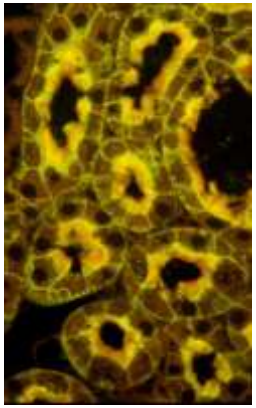


Colton (a): Alanine45
Colton (b): Valine45

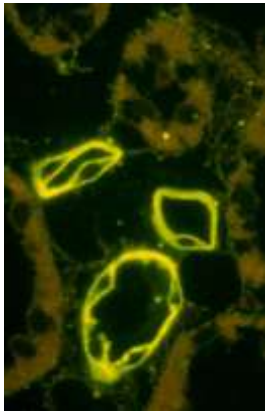




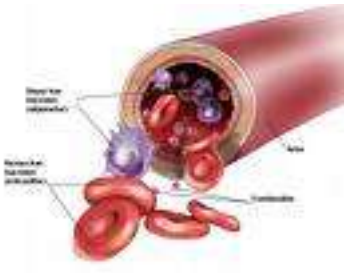
Proximal tubule



Thin descending Henle's loop



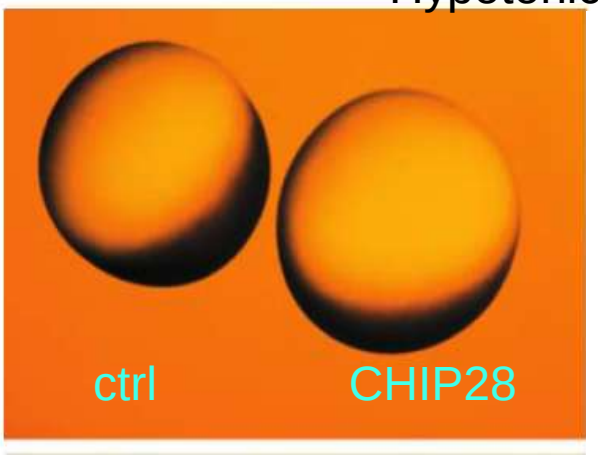
Vasa recta



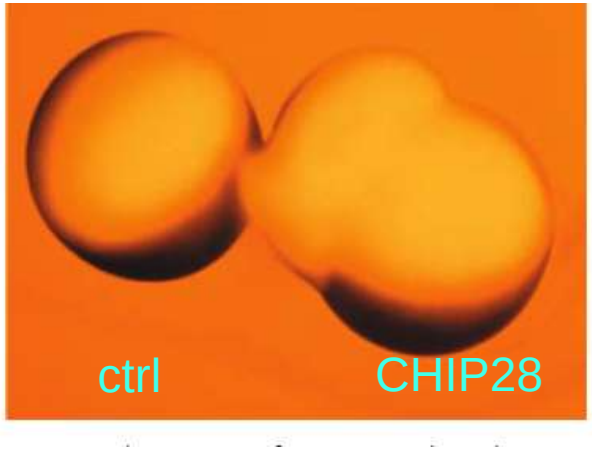
Sabolic et al, AJP, 1992

CHIP 28 (AQP1) enhances membrane permeability to water

Hypotonic medium



T= 30 sec



T= 3 min

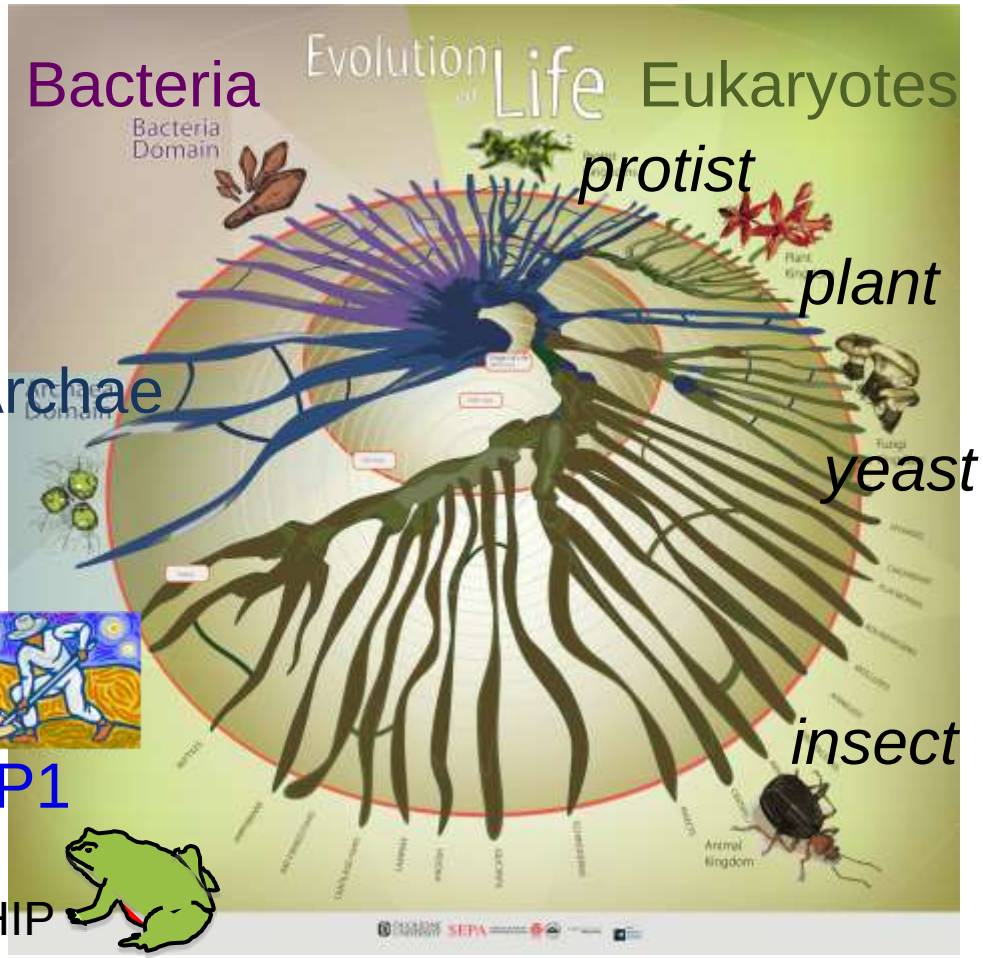
CHIP 28 is a water channel (rate: 3. 10^9 molecules/sec)

CHIP 28 = AQuaPorin1 (AQP1)

Preston et al, Science 1992

Aquaporins in all Life domains

1990 GlpF
(aquaglyceroporin)
1995 AQPZ
(aquaporin)



2004 PfAQP

1990 TIP

2003
AQPM

1995
AQY

1992
CHIP28=AQP1

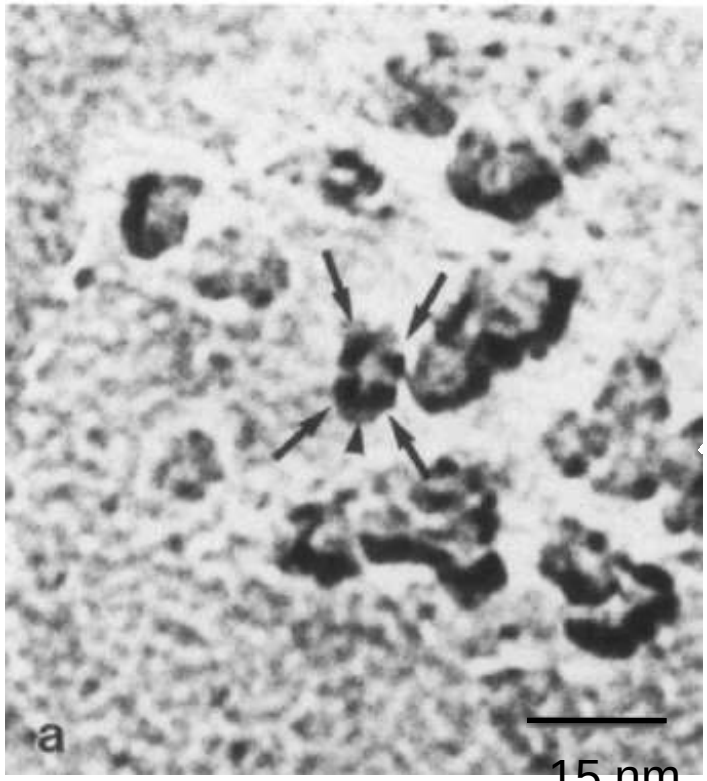
1995 AQPcic
DRIP

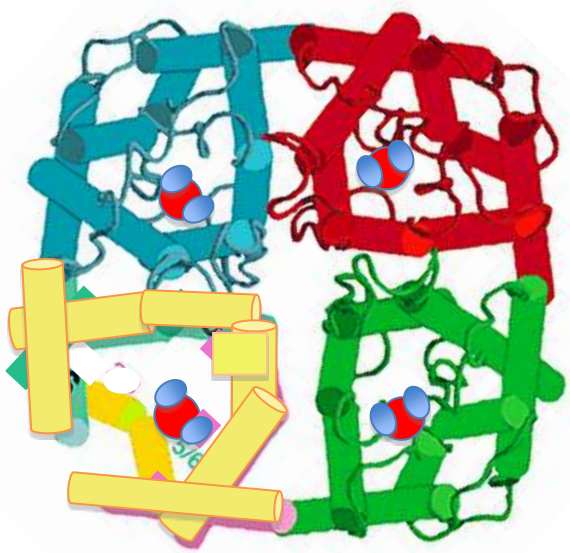
FaCHIP
1994

Adapted from the Duquesne Univ's Tree of Life

The tetrameric organisation of AQP

Erythrocyte membrane



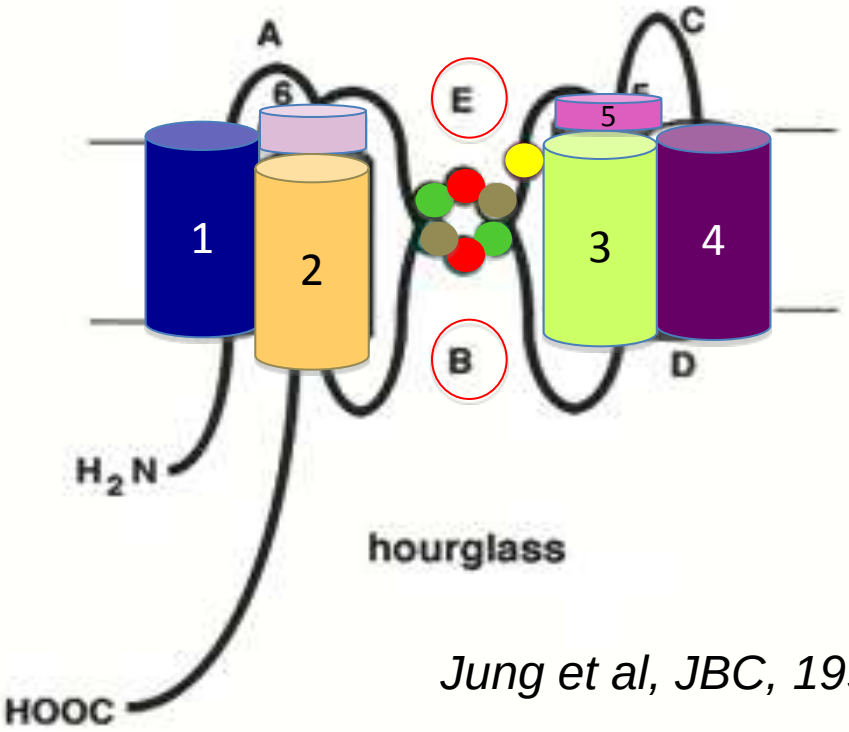


AQP1: 200 000 copies/erythrocyte

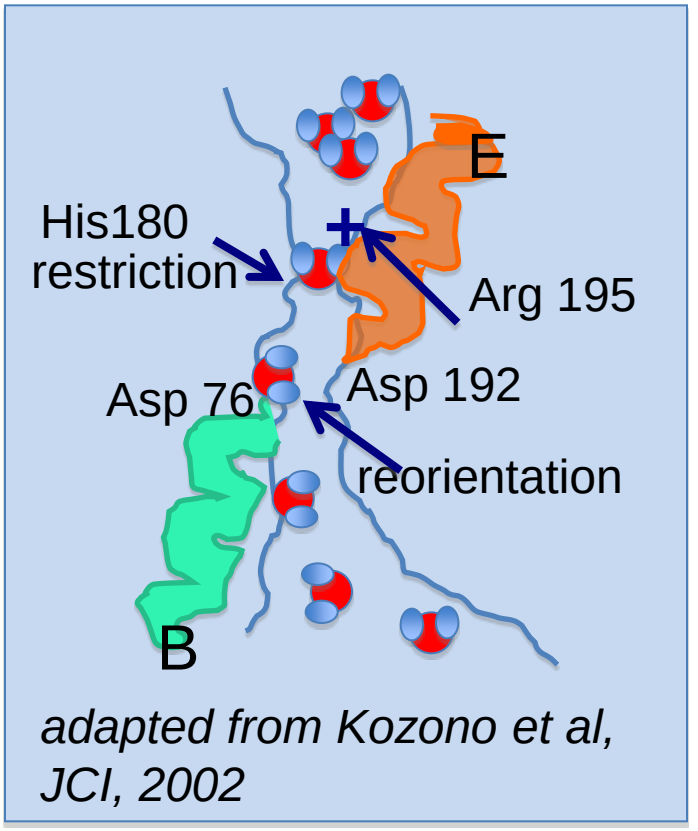
Verbavatz et al, J Cell Biol 1993

Adapted from Murata et al, Nature, 2000

The monomeric structure of AQP



Jung et al, JBC, 1994



adapted from Kozono et al, JCI, 2002

The AQP's signature **Asparagine-Proline-Alanine (NPA)** is located in B and E loops

Krane & Goldstein, Mamm Genome, 2007

H.sapiens aquaporins

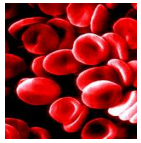
4 exons water transport	AQUAPORINS AQP0 AQP1 AQP2 AQP4 (Hg-insensitive?) AQP5 AQP6 (anion-permeable, Hg-activated) AQP8 (ammonium-permeable)
6 exons water+glycerol transport	AQUAGLYCEROPORINS AQP3 AQP7 AQP9 (heavy metals-permeable) AQP10
3 exons ?	SUPERAQUAPORINS AQP11 AQP12

Aquaporins localisation

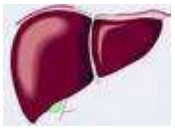
AQP **1 3 4**

AQP **1 3 4 5**

AQP **1 4 5**



AQP **1 3**



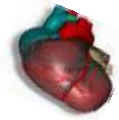
AQP **1 4 8 9**

AQP **1 5 8**

AQP **7**

AQP **0 1 3 4 5**

AQP **1 4 5 8**



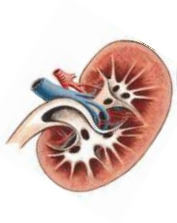
AQP **1 7**

AQP **1 2 3 4 6 7 11**

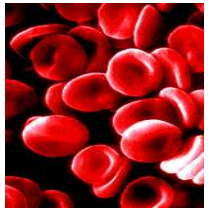
AQP **1 3 4**

AQP **4 7**

Aquaporins and diseases



Genetic NDI
Lithium-induced NDI
AQP2



Transfusional incompatibility
Colton AQP1
GILL AQP3

Metabolic syndrom
AQP7

Inherited autosomal dominant cataract
AQP0

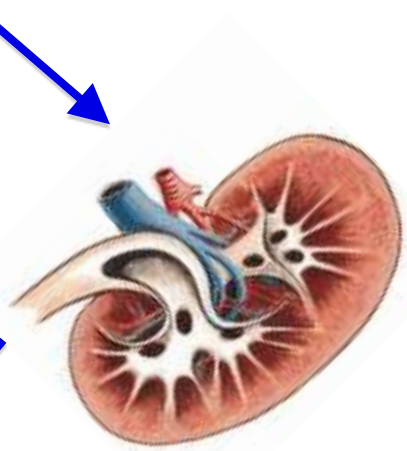
Neuromyelitis optica (Devic's disease)
AQP4

Sjögren's syndrom
AQP 1 & 5

Other roles in cellular (dys)functions

Renal water absorption

180 L/24h

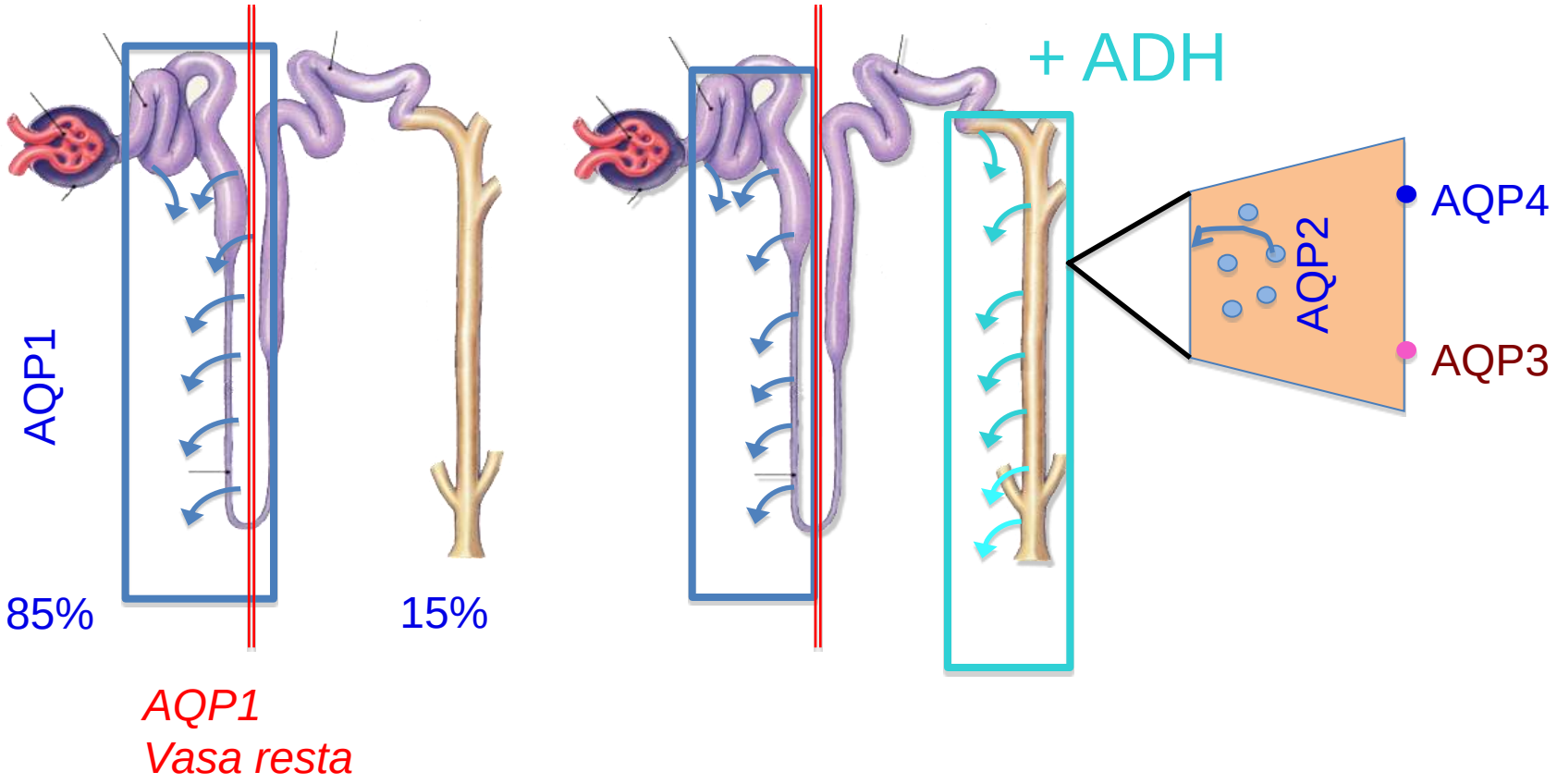


1,8 L/24h

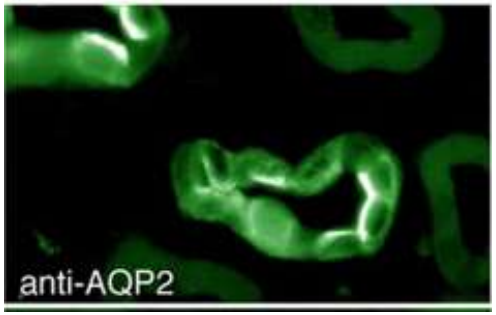
Dependent on the hydration status :
- dehydration: < 0.2%
- hyperhydration: 7%

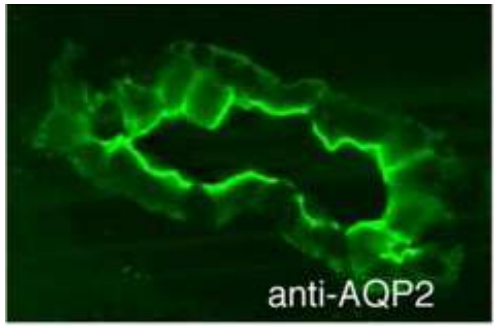
150 -1 200 mOsm/L

Water absorption along the nephron



AQP2 translocation to apical membrane of principal cells induces water transport





+ ADH

Ser256AQP2

PKA

Ca^{2+}

cAMP

ATP

V2R

Gs

AC

ADH

H_2O

Ser256AQP2

AQP2

AQP3

AQP4

Adapted from Lu et al, JBC, 2007

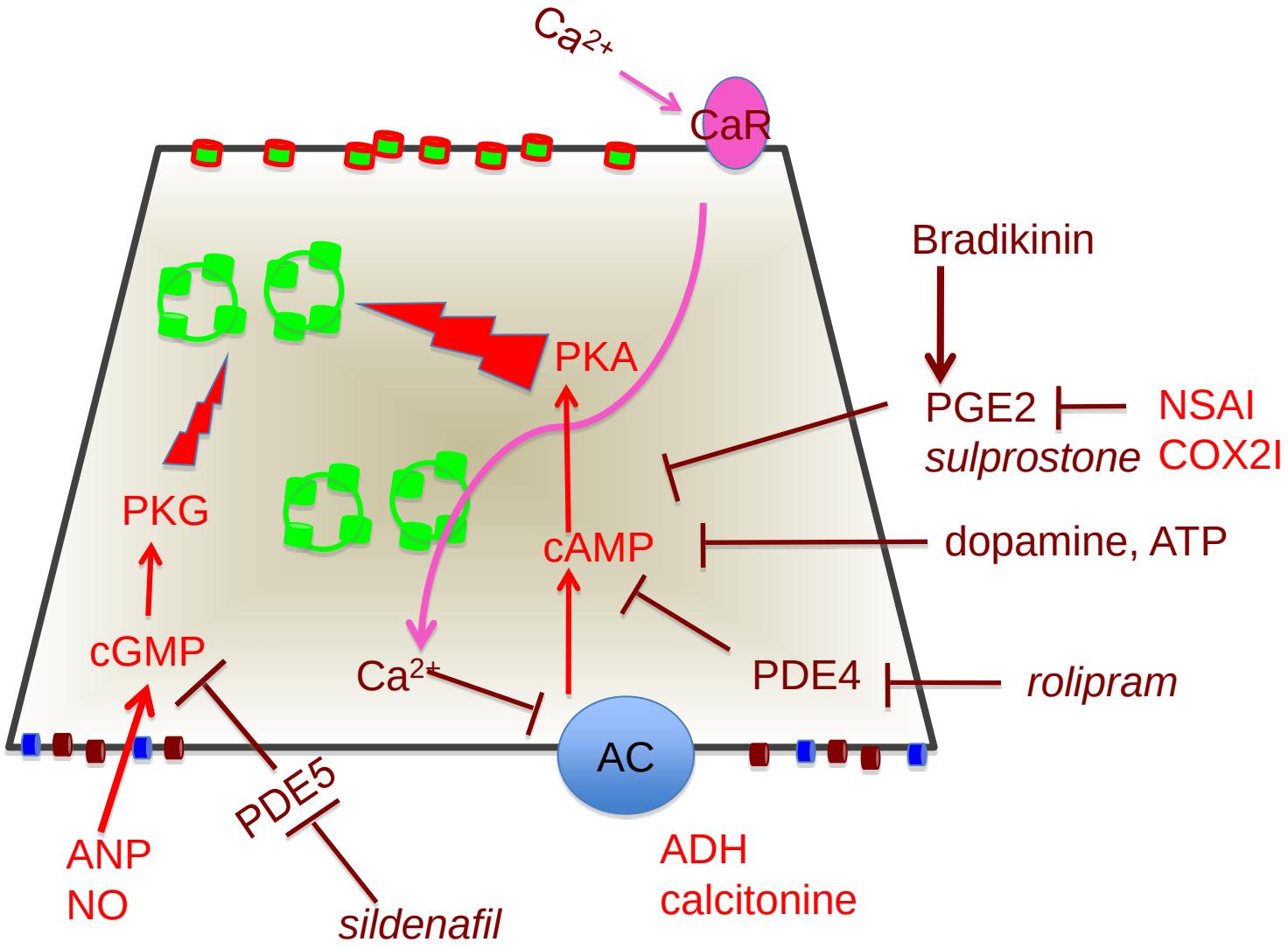
Phosphorylated AQP2 translocates to apical membrane of principal cells

Ser 256
Ser 264
Ser 269

ANP: atrial natriuretic peptide

CaR: Ca receptor

PDE: phospho diesterase



Short and long term AQP2 regulation : trafficking, gating and protein abundance

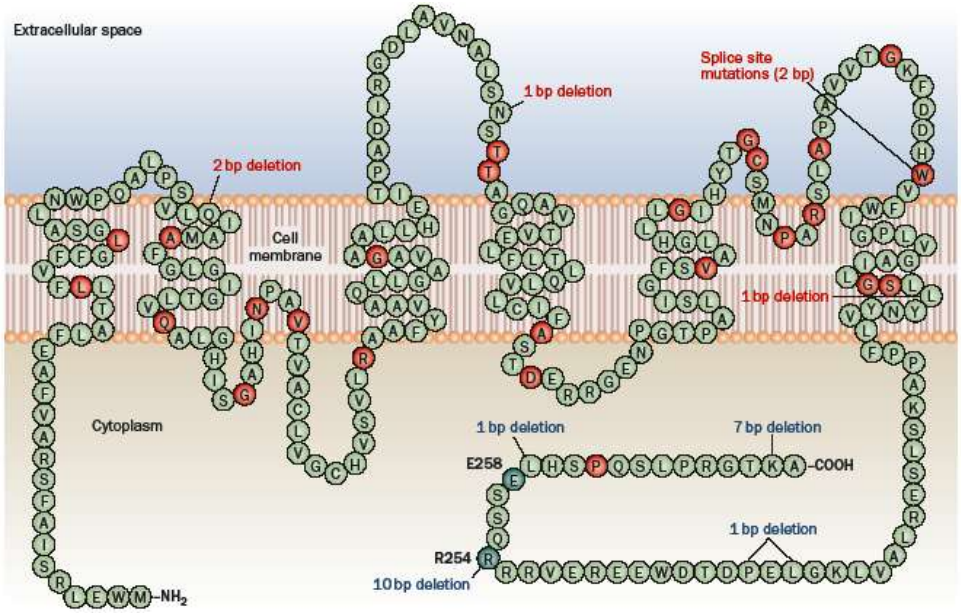
cAMPi-mediated regulation

- induces trafficking to plasma membrane
- decreases endocytosis
- prevents proteasomal degradation (reduced polyubiquitinylation)
- enhances AQP2 gene transcription (CREBP)
- increases the intrinsic water permeability of the channel

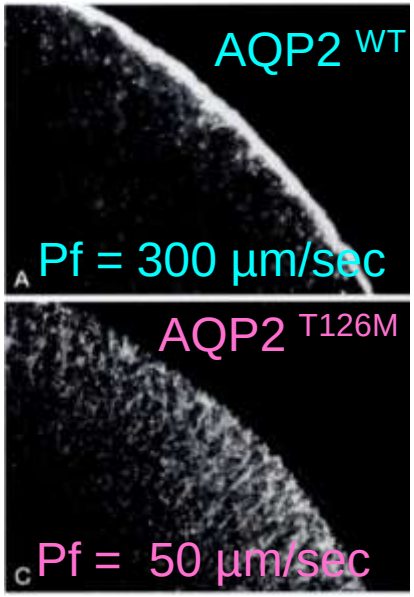
Other regulations

- high extracellular tonicity enhances AQP2 gene transcription (TonEBP)
- inflammatory stimuli decrease AQP2 gene transcription (nFkB)
- aldosterone targets AQP2 to the basolateral membrane
- hypokalemia, hypercalcemia, ureteral obstruction decrease AQP2 abundance

AQP2 mutations : inherited Nephrogenic Diabetes Insipidus



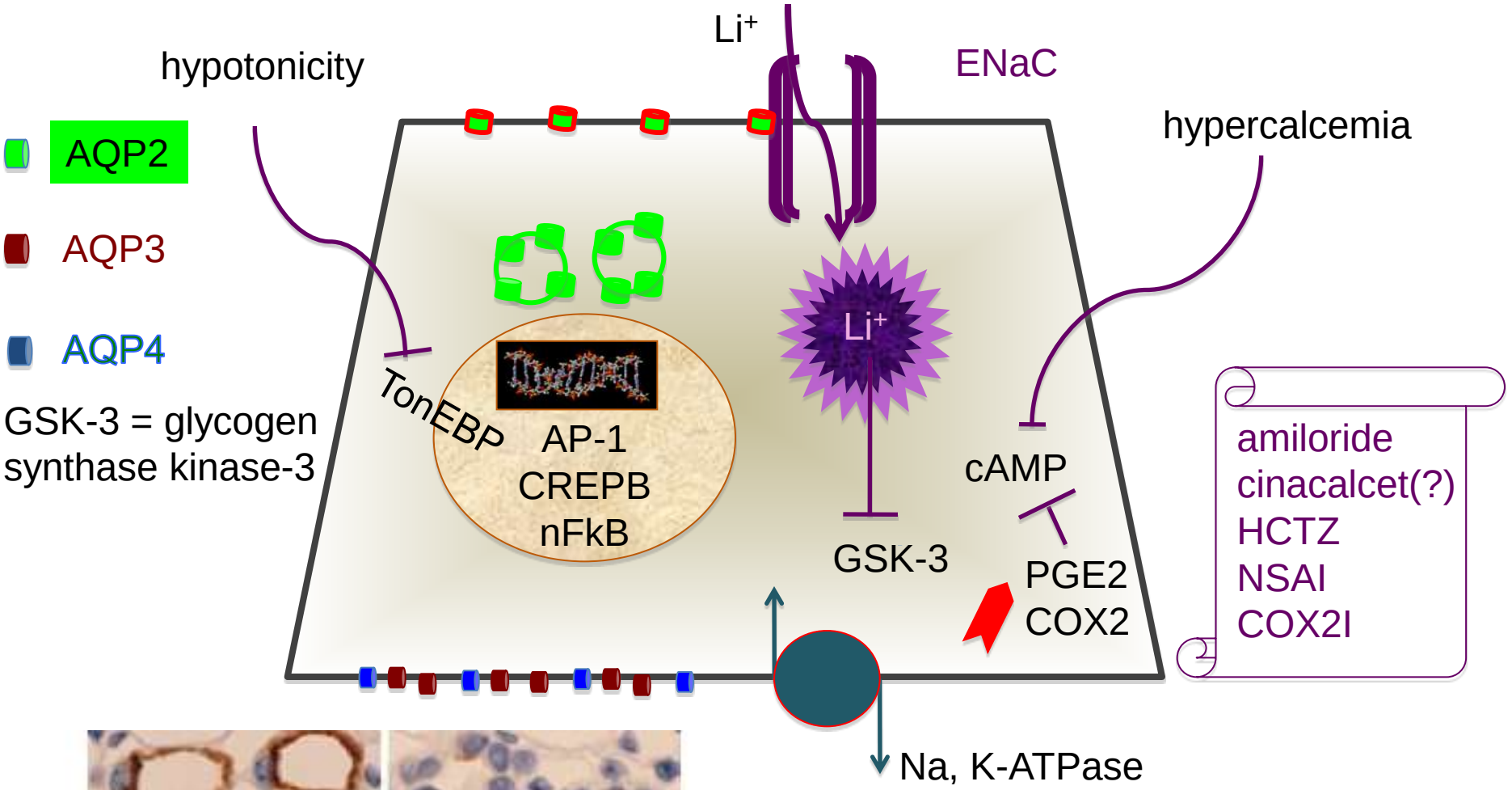
Mulders et al, JASN, 1996

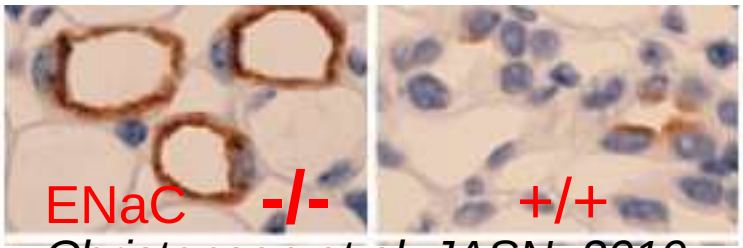


- (32) Mutations located in the core causing autosomal recessive NDI
  ➡ misfolding and degradation
- (8) Mutations located in Cter causing autosomal dominant NDI (dominant-negative effect) ➡ reduced or wrong trafficking of heterotetramers

Noda et al, Nat Rev Nephrol, 2010

Acquired NDI: lithium-induced NDI





Christensen et al, JASN, 2010

→ A major role for ENaC

Towards a better understanding of *H.sapiens* aquaporins: mouse models

AQUAPORINS

AQP0

* ~~AQP1~~ — polyuria

* ~~AQP2~~ — diabetes insipidus

* ~~AQP4~~ — no renal phenotype

* AQP5

* AQP6

AQP8

AQUAGLYCEROPORINS

* ~~AQP3~~ — mild polyuria

* ~~AQP7~~ — glyceroluria

AQP9

AQP10 — polykystic kidney

SUPERAQUAPORINS

* ~~AQP11~~

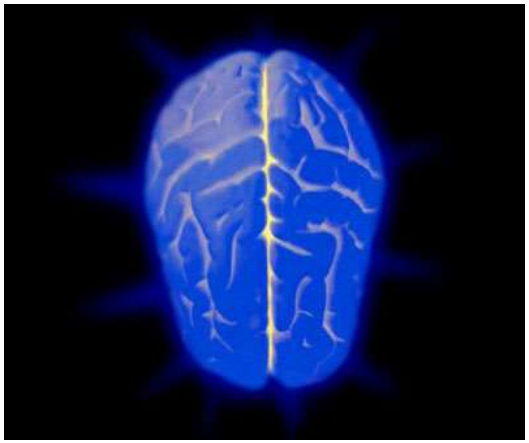
AQP12

Morishita et al, Mol Cell Biol, 2005

Renal AQP beyond the kidney

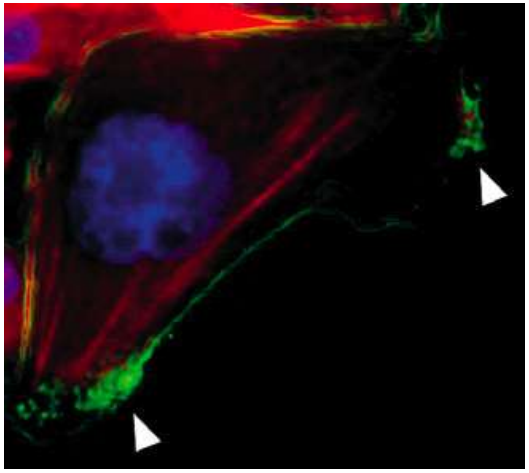
AQP3
and skin

AQP4
and brain

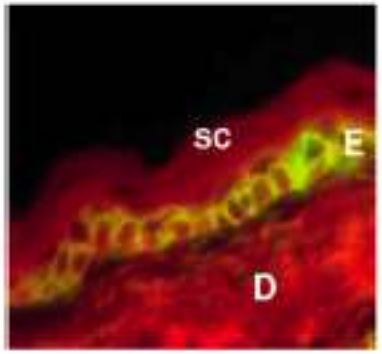


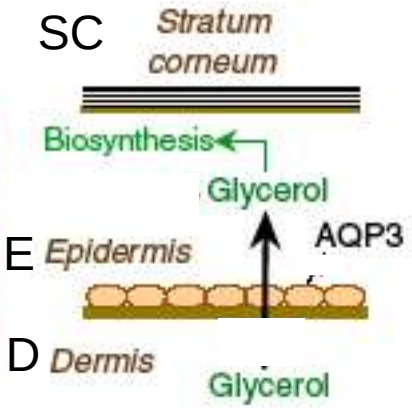
AQP7
and fat

AQP1
and cell
migration



AQP3 in skin

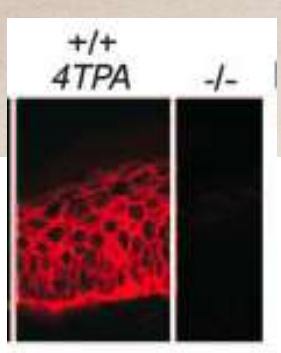




AQP3-/- mice have a delayed wound healing, a reduced skin elasticity, and a reduced hydration of the striatum corneum… which are corrected by topical application of glycerol.

AQP3 is expressed at the plasma membrane of basal epidermal skin cells.

Glycerol retains water
and has a biosynthetic role.

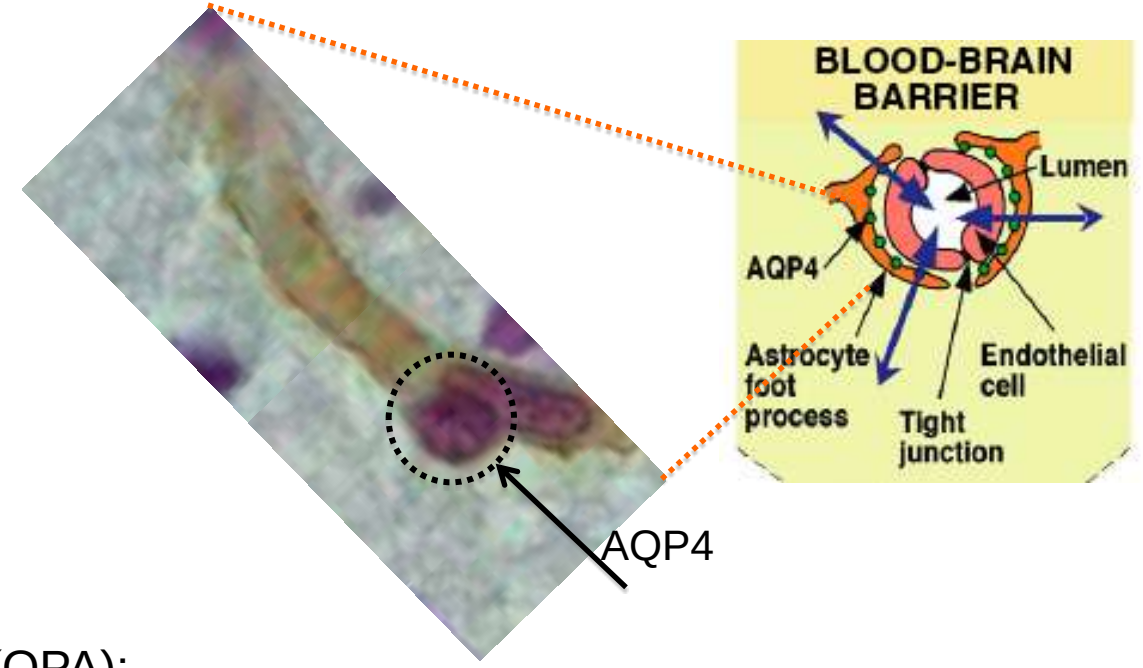


Verkman, J Cell Sci, 2005

Hara-Chikuma & Verkman, Mol Cell Biol, 2008

AQP4 in brain

Orthogonal Particules Arrays (OPA):
a supramolecular complex of
the short M23 isoform of AQP4.



AQP4 is concentrated in glial cells
at the fluid/parenchymal interface

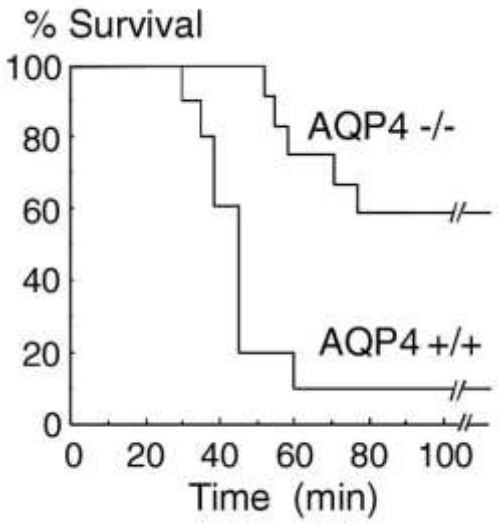
AQP4 is a major actor of brain water balance.

Verbavatz et al, J Cell Sci, 1997

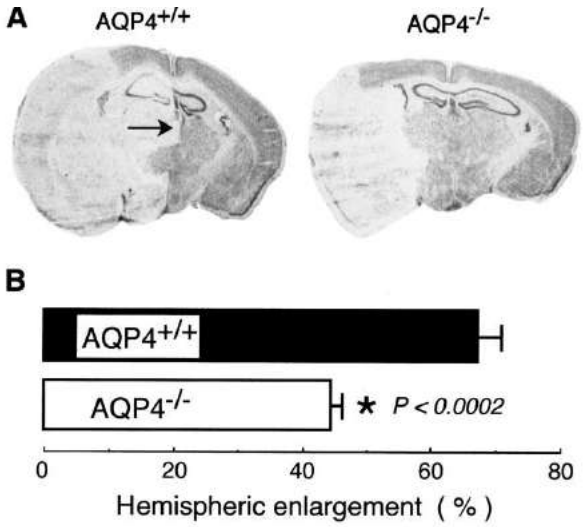
Saadoun & Papadopoulos, Neuroscience, 2010

AQP4 in brain

WATER INTOXICATION
(20% bw water ip +DDAVP)



CYTOTOXIC OEDEMA
Middle cerebral artery occlusion



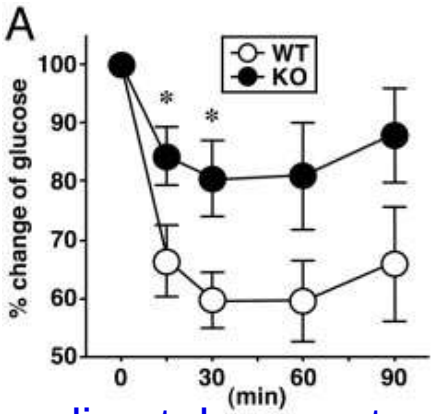
24h: reduced mortality in AQP4 -/-
reduced neurological deficit in AQP4 -/-

AQP4 deletion reduces cytotoxic brain oedema (BBB intact), but is beneficial to reduce vasogenic brain oedema (BBB disruption).

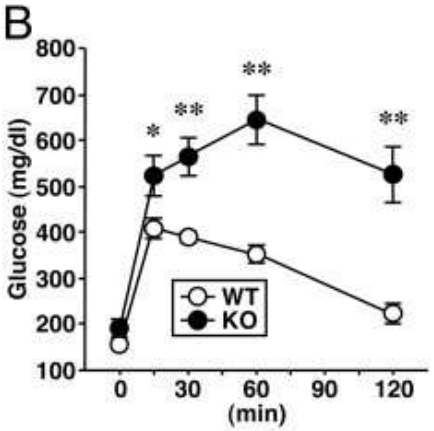
Manley et al, Nature Med, 2000

AQP7 in fatty tissues

20 weeks

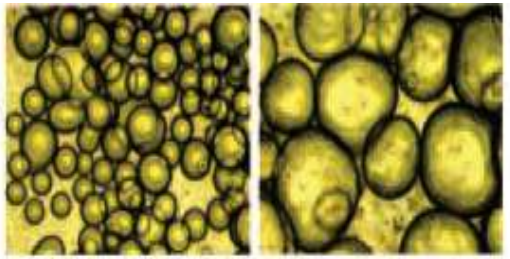


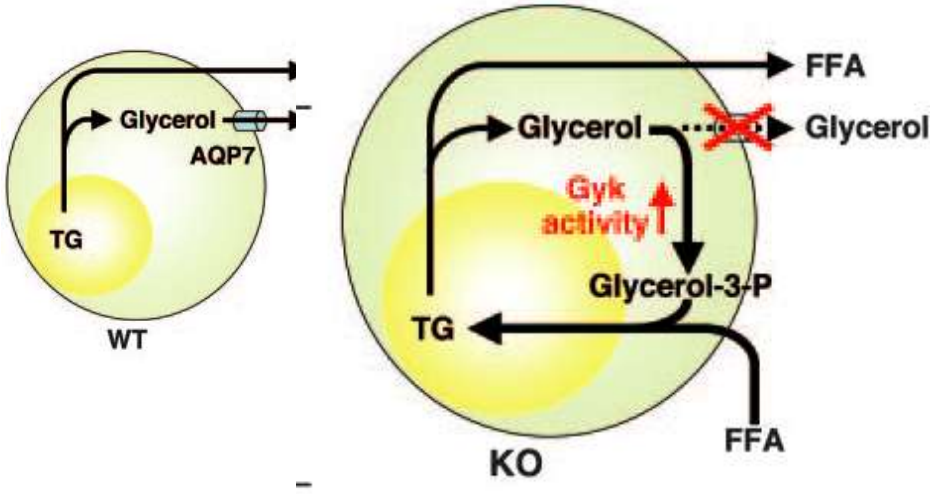
insuline tolerance test



glucose tolerance test

+/+ AQP7-/-



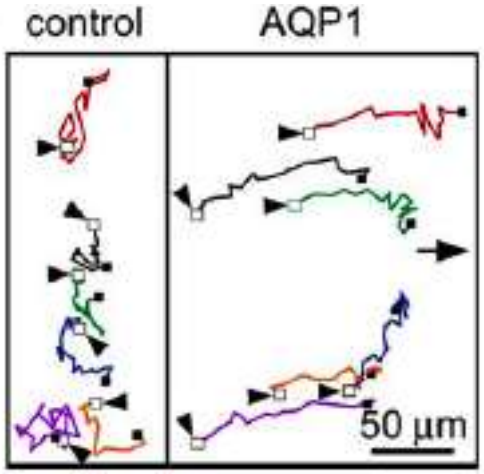


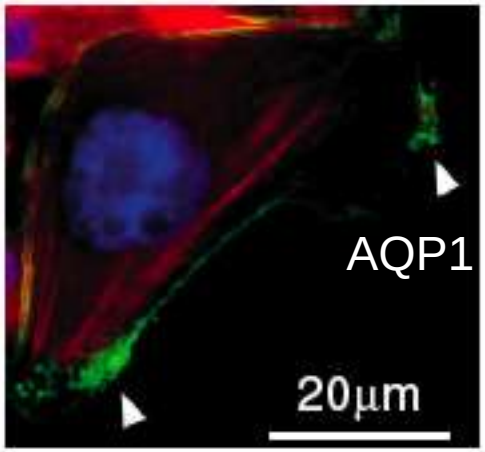
G3P glycerol3 Phosphate
GK glycerol kinase

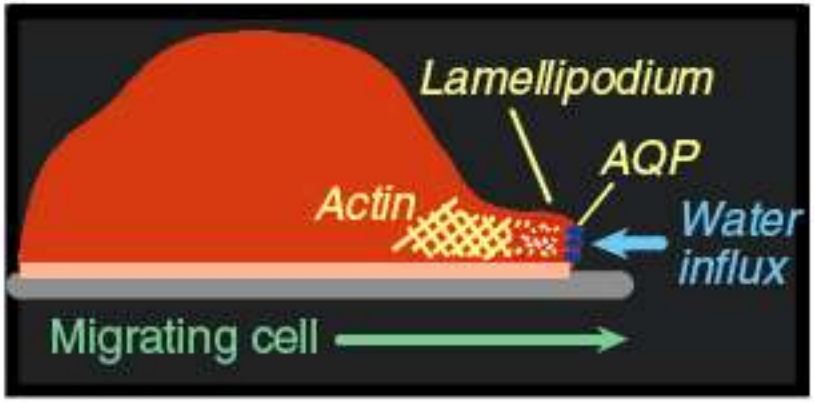
Hibuse et al, PNAS, 2005

Hara-Chikuma et al, JBC, 2005

AQP1 in migrating cells





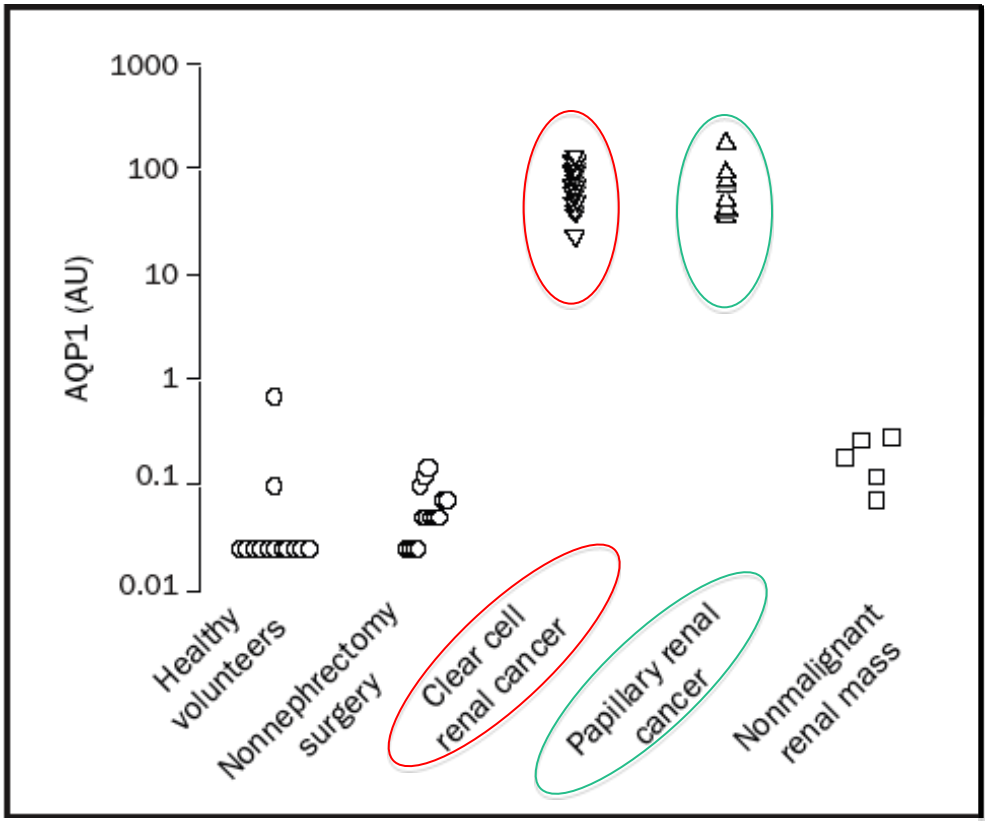


AQP1 facilitates cell migration

AQP1 is over-expressed in different tumor cell types.
AQP1 expression level and tumor grade may be correlated.

Saadoun et al, Nature, 2005
Verkman, J Exp Biol, 2009

Urinary AQP1 as a marker of renal cancer



Morrissey et al, Mayo Clin Proc, 2010

AQP polymorphisms

- AQP1

ajusted body loss in 10 km-runners

- AQP2

venous thrombosis

- AQP3

Meynière's disease

- AQP4

stroke outcome

- AQP7

obesity, type 2 diabetes