Osmoprotection

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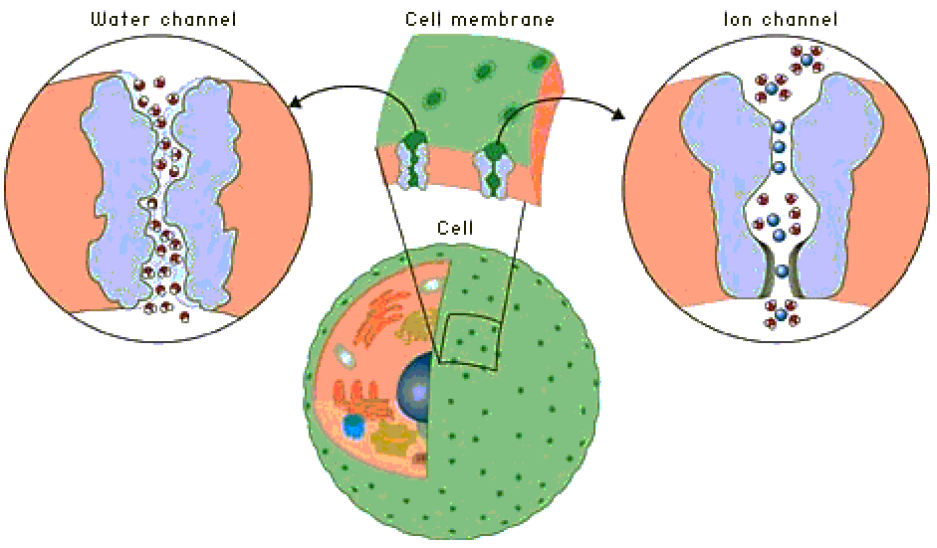
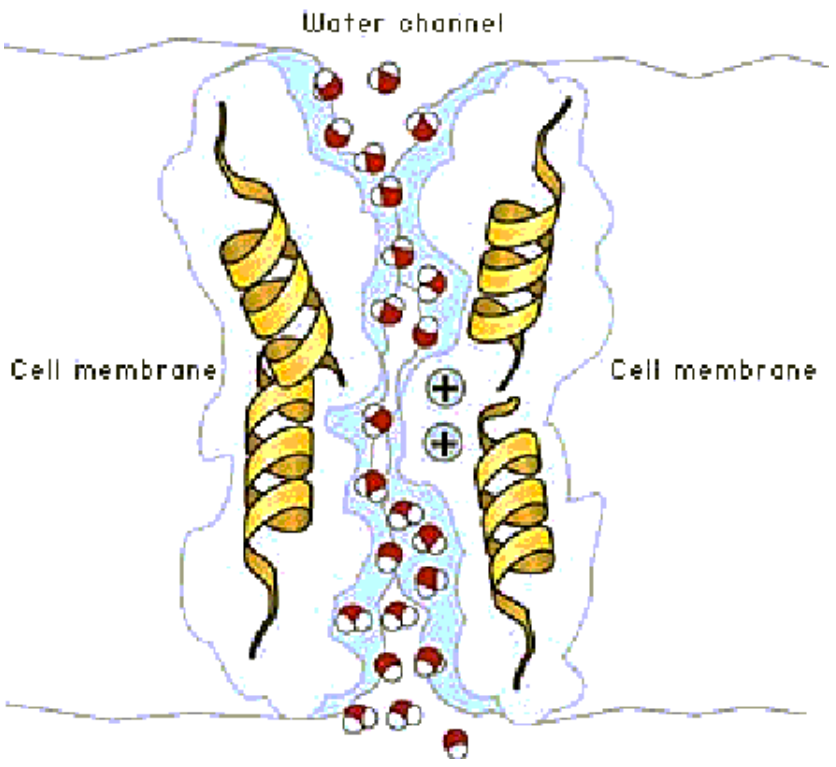
For the Discovery of AQUAPORIN FAMILY



What are aquaporins?

Aquaporins are proteins embedded in the cell membrane that regulate the flow of water. They are "the plumbing system for cells."

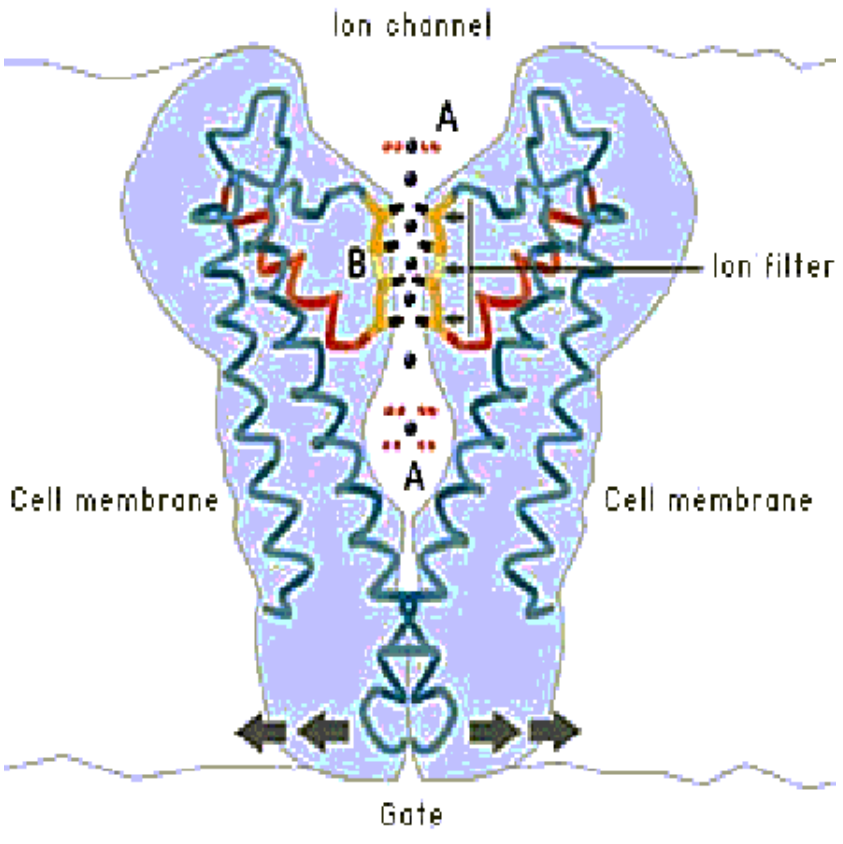
Passage of water molecules through the aquaporin AQP1. Because of the positive charge at the center of the channel, positively charged ions such as H3O+, are deflected. This prevents proton leakage through the channel.



AQP 1 = Corneal Endothelium - DYSTROPHY
AQP 3 = Conjunctional Epithelium - TFD
AQP 3 & 5 = Corneal Epithelium - DYSTROPHY
AQP 0 = Lens Epithelium – CONGENITAL CATARACT
AQP 1 & 4 = Ciliary Body Epithelium GLAUCOMA
AQP 4 = Retinal Muller Cells – RP / DYSTRO

The Ion Channels

The ion channel permits passage of potassium ions but not sodium ions. The oxygen atoms of the ion filter form an environment very similar to the water environment outside the filter. The cell may also control opening and closing of the channel



Osmoprotection - Response to hypertonicity

Numerous tissues and organs (eg. kidney, heart, brain) experience hypertonicity

Cells protect themselves by either synthesizing or importing compatible solutes

Compatible solutes are small, non-ionic organic compounds that build intracellular osmotic strength withoutdamaging proteins

Osmoprotection: *cell function is maintained without damage under hypertonic conditions*

Compatible Solutes:

Amino-acids: L-carnitine, betanine, taurine
Polyols: Glycerol, Erythritol, Xylitol, Mono-inositol

Carnitine and glycerol enter cells through specific channels, and xylitol and erythritol may use the same channel as glycerol

In a healthy ocular surface, the tear film:

- Is uncompromised
- The epithelial cells are hydrated and in osmotic balance
- Provides maximum comfort

Compromised tear film. Cells are dehydrated and out of balance

When tear film is healthy, it maintains a constant osmolarity

In dry eye, the quantity of water in the tear film is decreased:

- As the result of high evaporation
- Or because sufficient water is not produced in the first place

Because there is less water in the tear film, the concentration of solutes such as sodium and potassium increases

This raises the osmolarity and upsets the isotonic balance between the tear film and the ocular epithelial cells

Dry eye and Osmoprotection

Osmoprotection is a new approach to treating dry eye by providing cellular protection against the effects of hyper tonicity

Osmoprotectants protect against hypertonicity below the ocular surface and provide hydration to the epithelial surface

Carboxymethylcellulose has been shown to bind directly to corneal cells, and to accelerate wound healing
Corneal cells are able to use compatible solutes to protect themselves from hyperosmolar stress

The combination of CMC with compatible solutes in an artificial tear should provide an incremental benefit in the management of dry eye conditions

OPTIVE (TM)

Active ingredients:

0.5% CMC, patented blend of molecular weights for enhanced viscosity between Refresh Tears (Cellufresh) and Refresh Liquigel

0.9% glycerin, acts as a compatible solute, carries moisture into the cells

Additional ingredients:

- L-carnitine and erythritol as compatible solutes (buffers and osmotic agents)
- Essential electrolytes
- Preserved with Purite®

Formula is isotonic with no added NaCl

OPTIVE™ Lubricant Eye Drops provides hydrating and osmoprotective action
Hydrating:

- CMC
- Glycerin

Osmoprotection