Sildenafil for the Treatment of Congenital Nephrogenic Diabetes Insipidus (NDI)

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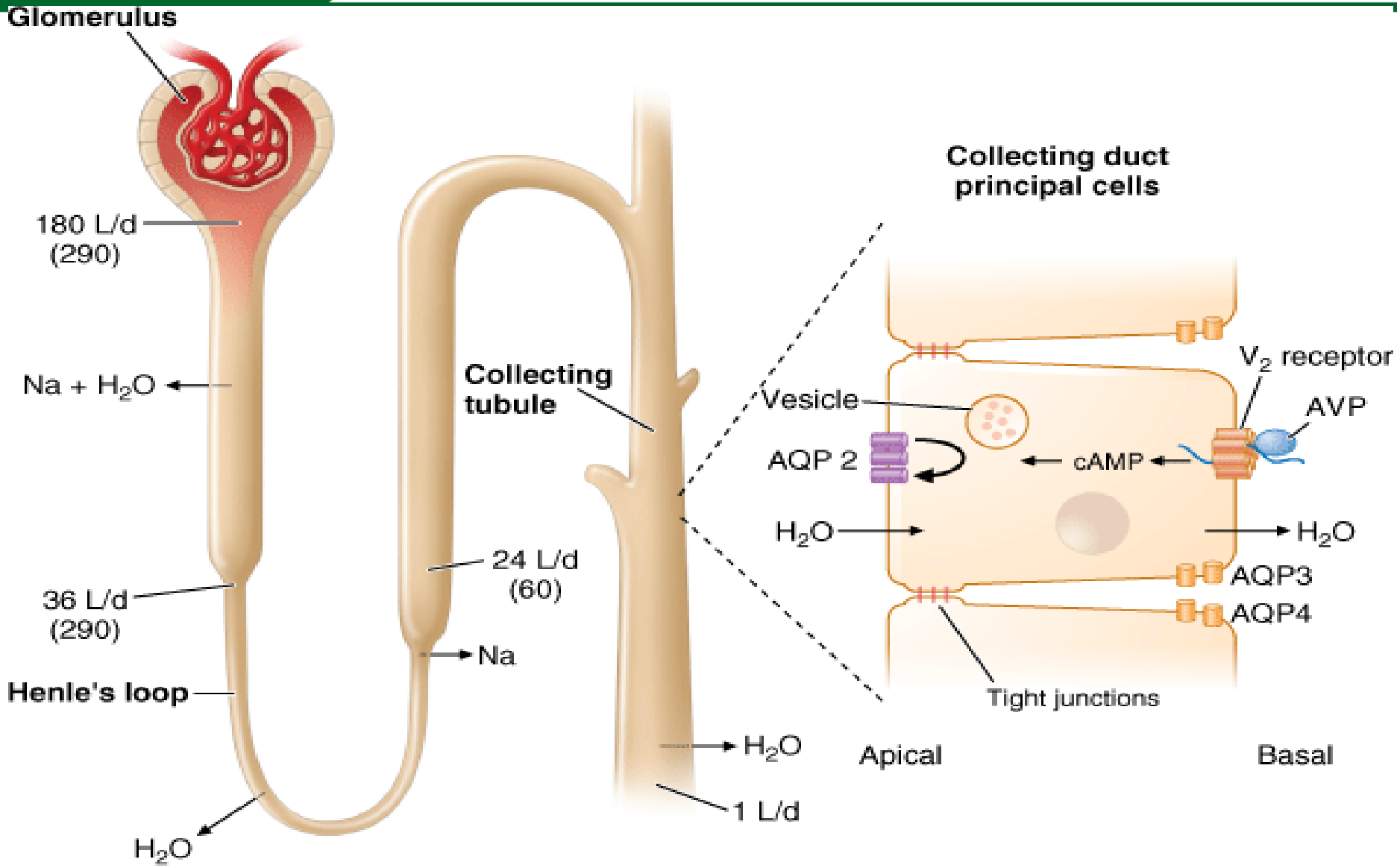
Renal Handling of Water



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

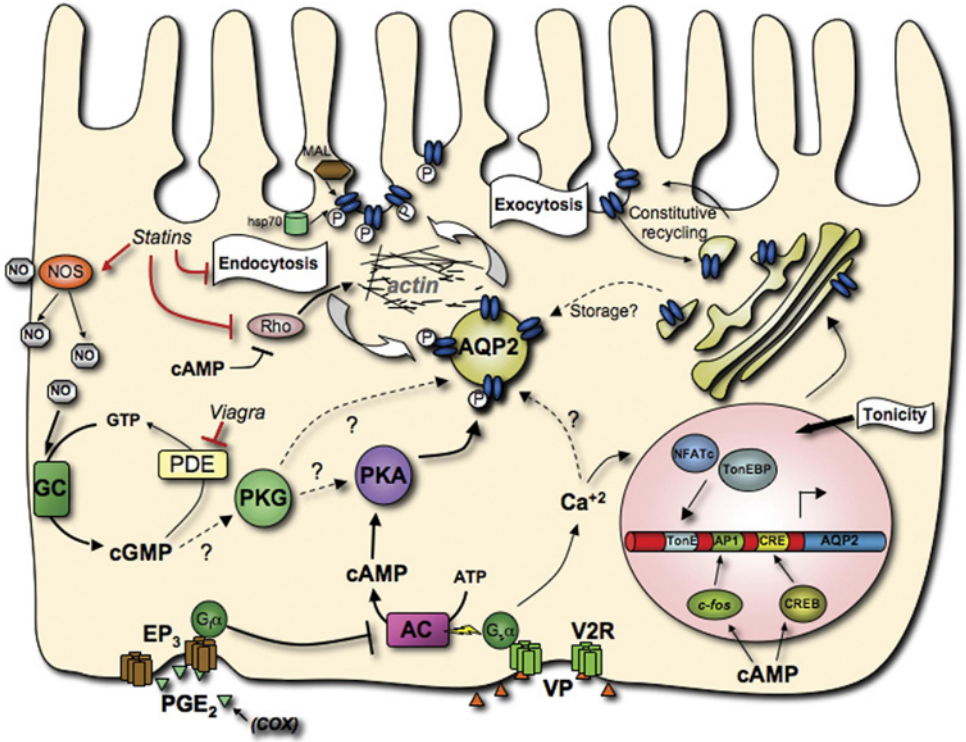
Introduction

- Congenital NDI is a rare hereditary disorder, characterized by inability of the kidney to concentrate urine in response to arginine vasopressin (AVP)
- X-linked NDI can result from mutations in the type 2 vasopressin receptor (*V2R*) [90%]
- The autosomal recessive and dominant forma of NDI are caused by mutations in the aquaporin 2 (*AQP2*) water channel [10%].

Background

- Children with NDI may experience frequent episodes of hypertonic dehydration which can complicated by seizures, cerebral edema, and acute kidney injury.
- Current conventional treatment regimen including adequate hydration, low sodium and protein diet, hydrochlorothiazide (HCTZ-amiloride) and non-steroidal anti-inflammatory (NSAID) can only partially control the NDI symptoms.

Regulation of water permeability in the renal collecting duct cells



Experimental animal studies

- Recent experimental studies have suggested that treatment with sildenafil citrate, a phosphodiesterase type 5 (PDE5) inhibitor, may enhance cyclic guanosine monophosphate (cGMP)-mediated apical trafficking of AQP2 and may be effective in increasing water reabsorption in patients with congenital NDI.

Sildenafil in Human with NDI

- Although, the use of sildenafil in experimental animals has been shown to result in AQP2 membrane accumulation of the principal cells of collecting duct in the absence of vasopressin via its G-protein coupled V2R, it has not yet been evaluated for the treatment of NDI in humans

The first case study

- A 4-year old boy with X-linked NDI due to a mutation in V2R (12bp-deletion, delta R247-G250 at Xq28 position) resistant to conventional therapy (HCTZ-amiloride and indomethacin) treated with sildenafil citrate 2.0 mg/kg/day for 10 days after a 2-day washout period between the two treatment regimen.

Methods

- Aliquots of the entire 24-hr urine collections before and after sildenafil treatment were analyzed for urine volume, osmolality, cGMP, and AQP2 determinations.
- Urinary cGMP and AQP2 excretion were measured by quantitative radioimmunoassay (RIA).

Methods (cont'd)

- Blood samples were also obtained at the completion of each treatment regimen for, sodium and osmolality measurements.
- The primary endpoint was 24-hour urine volume after 10 days of sildenafil and conventional treatments.

Results

- Compared to conventional therapy, treatment with sildenafil resulted in significant reduction in 24-hr urine volume and an increase in cAMP and AQP2 excretion
- Patient tolerated sildenafil well and experienced no adverse effect

Results

Table 1. Desmopressin acetate (DDAVP) test

Parameter	Serum sodium (mEq/L)	Serum osmolality (mOsm/L)	Urine osmolality (mOsm/L)	Urine output (mL/kg/hr)
Baseline	148	307	104	5.5
DDAVP (2 µg injection) 2 hours later	147	309	96	5.3

Results

Table2. Comparison of sildenafil with HCTZ/amiloride plus indomethacin treatment

Parameter	Hhdrochlorothizide-amiloride plus indomethacin	Sildenafil
Serum sodium (mEq/L)	148	139
Serum osmolality (mOsm/L)	307	291
Urine osmolality (mOsm/L)	104	215
24-hr Urine volume (mL)	1698	1050
Average number of voids per day	9	4
Urine AQP2 concentration (fmol/mg creatinine)	37	129
Urine cGMP concentration (nmol/mg creatinine)	0.41	1.68

AQP2, aquaporin2 ; GAMP, Cyclic guanosine-3,5-monophosphate;

Conclusion

- Treatment with sildenafil citrate for 10 days demonstrated a clear correlation between the correction of polyuria and an increase of urinary cGMP and AQP2 membrane expression.
- Sildenafil citrate should be considered as an alternative agent in treatment of X-linked NDI resistant to conventional therapy.

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