به‌نام خدای بخشاینده مهربان

In the name of Allah, the Beneficent, the Merciful.

Drug Induced Hyponatremia

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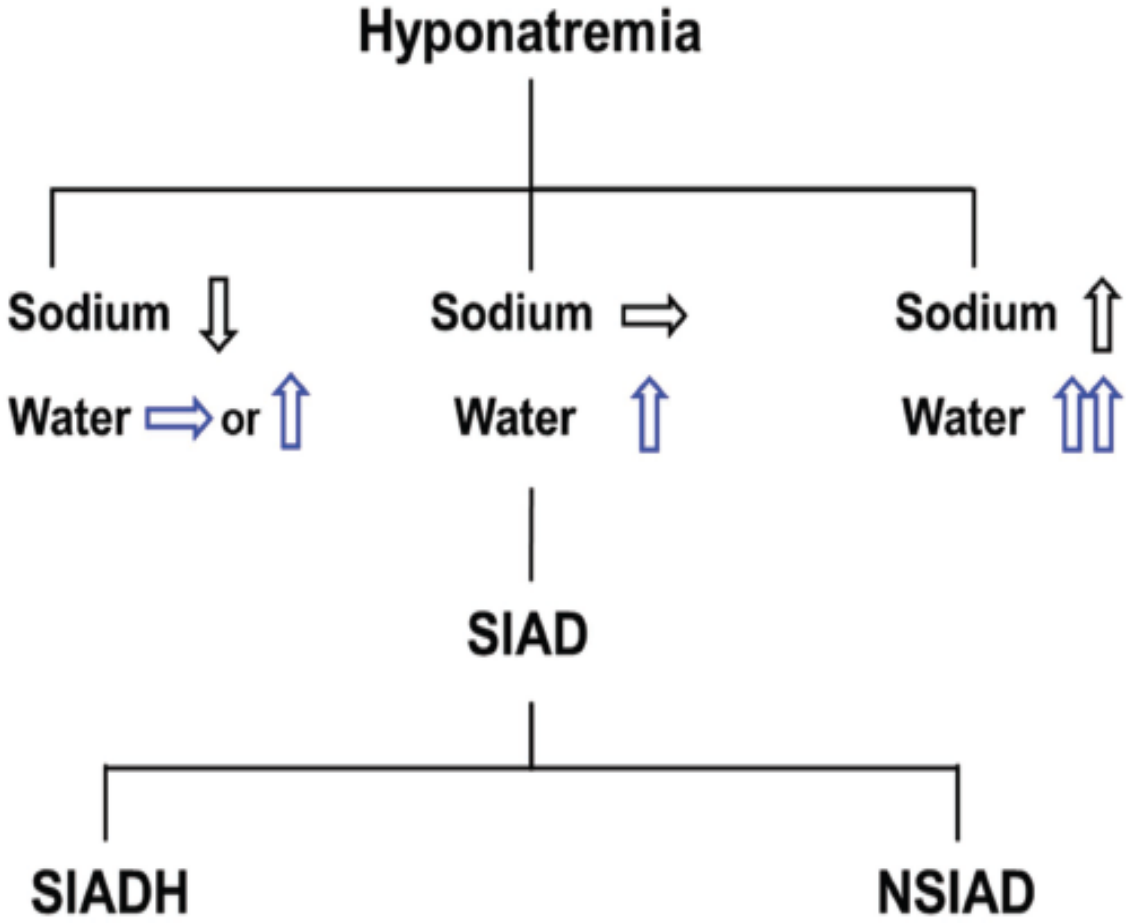
Introduction

- ✓Hyponatremia, [Na] < 135 mmol/L, most common electrolyte disorder in hospitalized patients
- ✓Often asymptomatic
- ✓Symptoms of increased ICP if severe or acute
- ✓Water balance disorder

Euvolomic Hyponatremia

- ✓SIAD: Syndrome of inappropriate antidiuresis
- ✓SIADH: Syndrome of inappropriate antidiuretic hormone
- ✓NSIAD: Nephrogenic syndrome of inappropriate antidiuresis



Etiology of SIAD

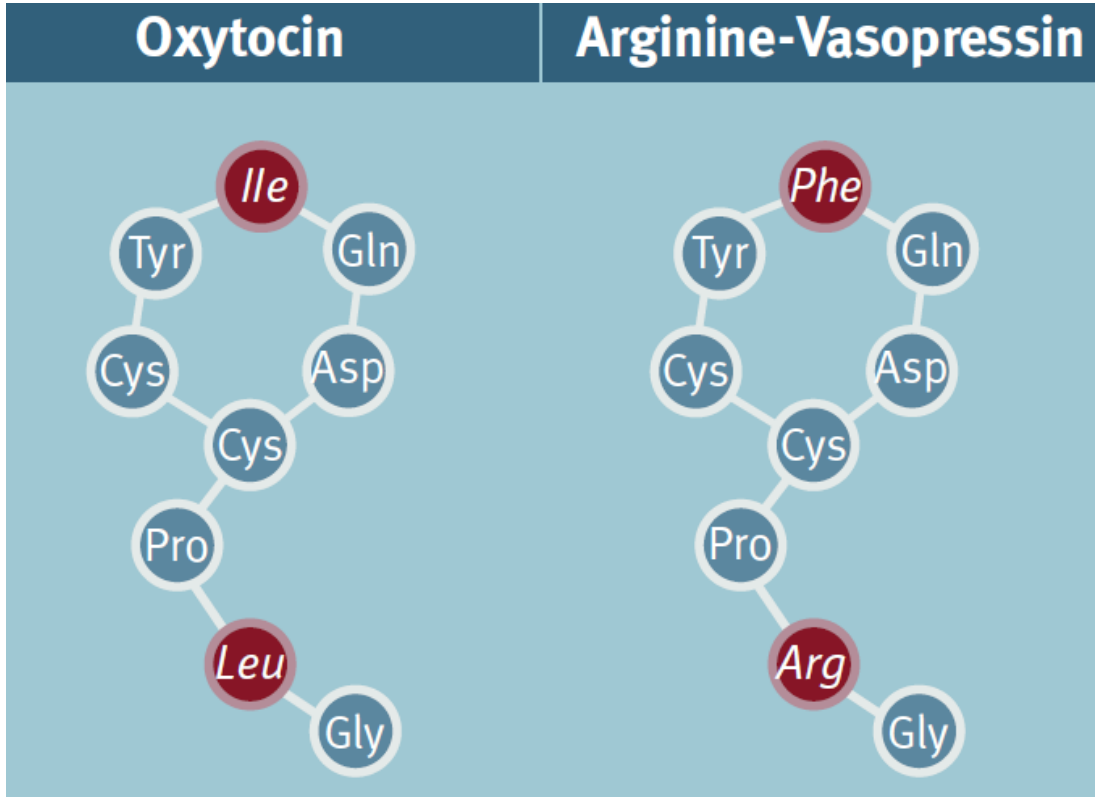
- ✓Malignancies
- ✓Pulmonary diseases
- ✓Disorders of the CNS
- ✓Drugs

Major drugs causing hyponatremia

- ✓AVP Analogs
- ✓Anticancer Chemotherapeutic Agents
- ✓Psychotropic Agents
- ✓Thiazide diuretics

AVP Analogs

- ✓Desmopressin
- ✓Oxytocin



Desmopressin

✓Used for:

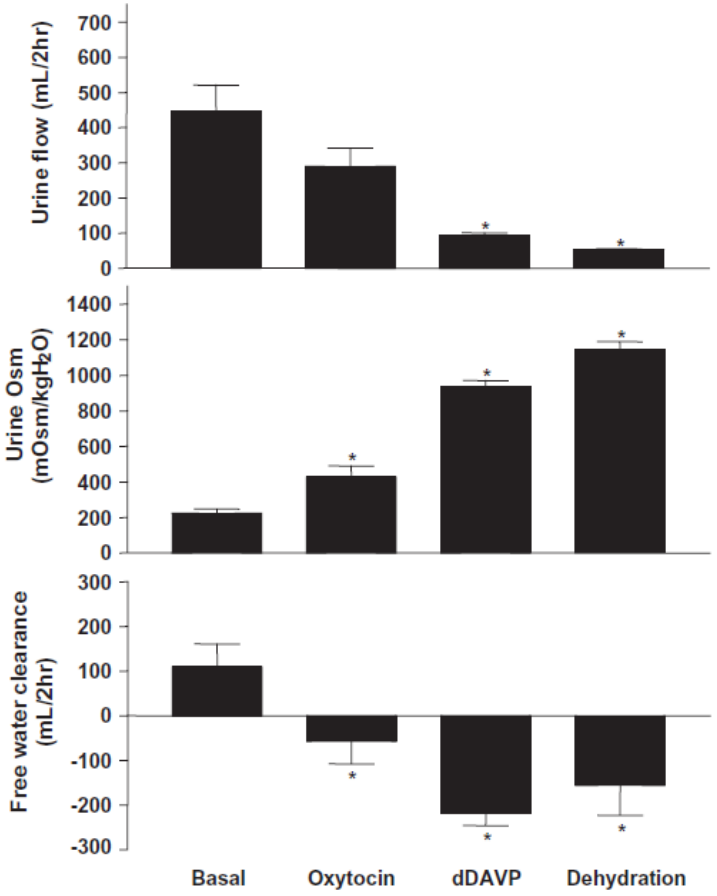
- Diabetes insipidus
- Nocturnal polyuria in elderly

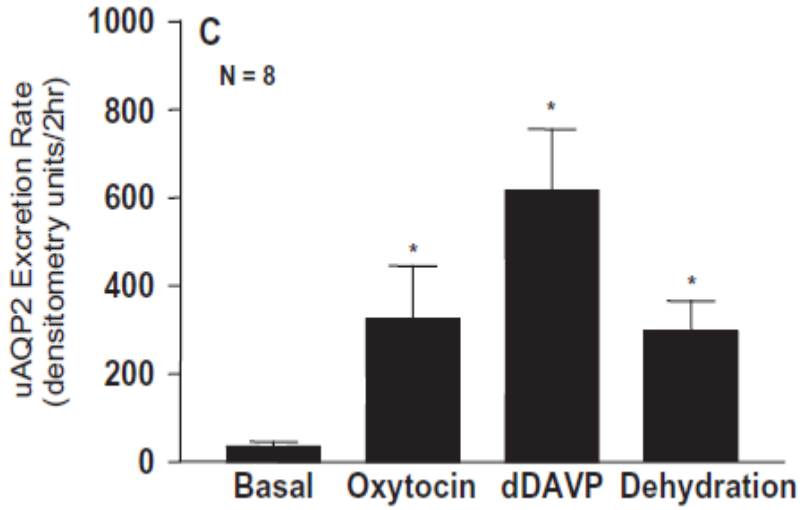
✓Greater antidiuretic effect:

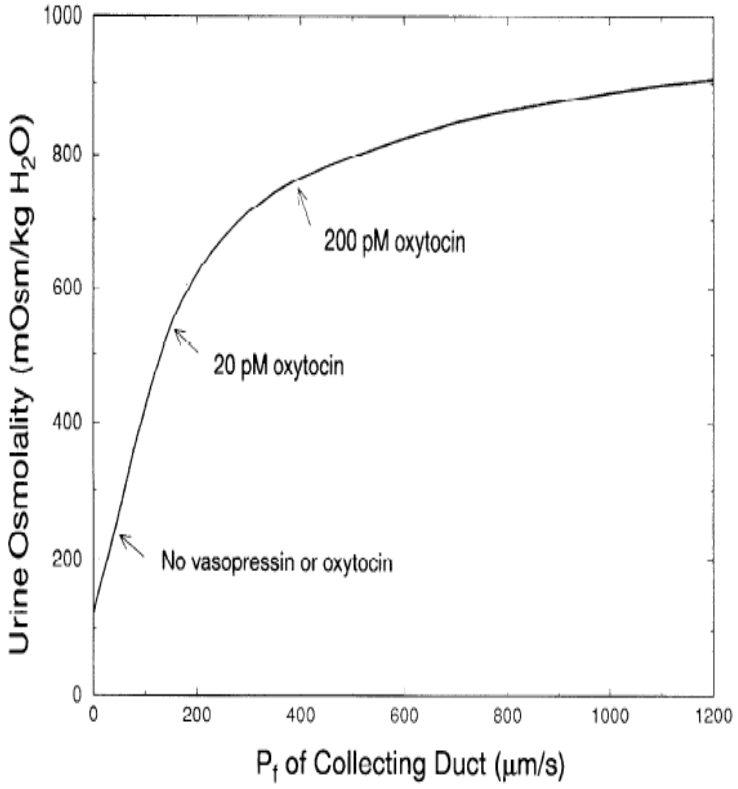
- Longer half-life
- Selective binding to V2R

✓desmopressin-induced hyponatremia: 7.6% in adults with nocturia

Oxytocin


Urine flow (mL/2hr)
Urine Osm (mOsm/kgH2O)
Free water clearance (mL/2hr)
Basal
Oxytocin
dDAVP
Dehydration


C
N = 8
uAQP2 Excretion Rate (densitometry units/2hr)
Basal
Oxytocin
dDAVP
Dehydration


Urine Osmolality (mOsm/kg H2O)
200 pM oxytocin
20 pM oxytocin
No vasopressin or oxytocin
Pf of Collecting Duct (µm/s)

Oxytocin

Water intoxication as differential diagnosis of obstetrical patients with convulsions and coma.

Case report: hyponatremia and generalized convulsion after intravenous oxytocin infusion

Olgu sunumu: İntravenöz oksitosin infüzyonu sonrası gelişen hiponatremi ve jeneralize konvülziyon

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Abstract

Most patients with drug-induced hyponatraemia are asymptomatic and the diagnosis is made incidentally following routine blood tests. Mild cases may be managed either by stopping the drug or by careful observation if the drug is considered essential. Severe hyponatremia (serum sodium levels less than 120 mmol/l) is associated with increased morbidity and mortality (confusion, convulsions, coma, congestive heart failure e.g.). We present a case of severe water intoxication with convulsion and prolonged coma, following the use of a high dose syntocinon infusion. A 22-year-old female who has intrauterine anencephalic fetus was refered to our hospital. Intravenous oxytocin was used to induce first-trimester abortion, eight hours later generalized tonic-clonic seizures occured and coma followed. Hyponatremia was found as the cause and treated by intravenous infusion of hypertonic 3% NaCl. The patient recovered and no seizure observed on follow-up. The central nervous system manifestations of acute hyponatremia may be related to cerebral edema. Drugs administration and electrolyte disturbances should be remembered as causes of coma and seizure in obstetric patients.

(J Turkish-German Gynecol Assoc 2009; 10: 47-8)

Key words: Oxytocin, seizure, coma

Özet

İlaca bağlı gelişen hiponatremi olgularının çoğu asemptomatiktir ve tanı rutin kan incelemesini takiben tesadüfen konur. Hafif olgular, ilaç kesilerek ya da ilaç kullanımı gerekli ise dikkatli bir şekilde gözlenerek takip edilir. Şiddetli hiponatremi (serum sodyum düzeyi 120 mmol/l'den düşük) artmış morbidite ve mortalite ile (konfüzyon, konvülziyon, koma, konjestif kalp yetmezliği v.s) birliktedir. Bu yazıda, yüksek doz oksitosin infüzyonu kullanımını takiben gelişen konvülziyon ve uzamış komalı ciddi su intoksikasyonu olan bir olguyu sunuyoruz. Hastanemize 22 yaşında intrauterin anensefalik fetusa sahip bayan hasta yönlendirilmişti. İlk trimester abortusu sağlamak için intravenöz oksitosin kullanılmış ve takiben sekiz saat sonra jeneralize tonik-klonik nöbet ve uzamış koma gelişmişti. Neden olarak hiponatremi saptandı ve iv hipertonik %3 NaCl infüzyonu ile tedavi edildi. Hasta klinik olarak düzeldi ve takipte nöbet gözlenmedi. Akut hiponatreminin santral sinir sistemi bulguları, serebral ödemle ilişkili olabilir. İlaç uygulamaları ve elektrolit bozuklukları obstetrik hastalarda nöbet ve komanın nedeni olarak akla gelmelidir.

(J Turkish-German Gynecol Assoc 2009; 10: 47-8)

Anahtar kelimeler: Oksitosin, nöbet, koma

NEPHRON

Letter to the Editor

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An Unforgotten Cause of Acute Hyponatremia: Water Intoxication due to Oxytocin Administration in a Pregnant Woman

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Dear Sir,

Water intoxication, a kind of acute hyponatremia, is characterized by confusion, lethargy, vomiting, convulsion, periods of violent behavior, coma, and death due to cerebral edema. To develop hyponatremia, one needs both a source of electrolyte-free water gain and/or the generation and the action of arginine vasopressin (AVP) to prevent excretion of this electrolyte-free water [1]. Oxytocin has an antidiuretic-hormone-like effect as well as a contractile activity on uterine smooth muscle. We describe a case of acute hyponatremia (plasma sodium 115 mmol/l) with generalized convulsive seizure attacks due to administration of oxytocin and electrolyte-free water administration.

A 22-year-old woman at 24 weeks' gestation underwent induced abortion in a gynecologic clinic with intravenous oxytocin infusion. Within these 2 days, she received 6 liters of 5% dextrose water and 50 U of oxytocin (approximately 18 mU/min). Dilatation and curettage were done smoothly under intravenous administration of morphine. Postoperatively, the patient had a generalized convulsive seizure and loss of consciousness 3 h later. Oxytocin infusion was withdrawn, intravenous diazepam was given immediately, and the patient was transferred to the Tri-Service General Hospital. Her past history was otherwise insignificant. Physical examination was unremarkable. On neurological

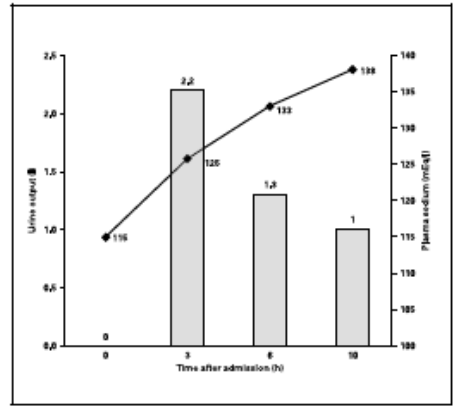


Fig. 1. Time course of spontaneous diuresis and corresponding changes of plasma sodium in a woman with water intoxication.

Chemotherapeutic Agents

- ✓Vincristine, Vinblastine
- ✓Cisplatin, carboplatin
- ✓Cyclophosphamide
- ✓Ifosfamide

Vincristine

✓Case reports of hyponatremia following vincristine

✓SIADH: direct toxic effect of vincristine on neurohypophysis and the hypothalamic system

Cisplatin

- ✓Rare cases of hyponatremia via increasing plasma AVP levels

- ✓|Cisplatin nephrotoxicity: renal salt wasting and hypovolemic hyponatremia

Cyclophosphamide

- ✓Plasma AVP concentration **not** elevated following IV cyclophosphamide

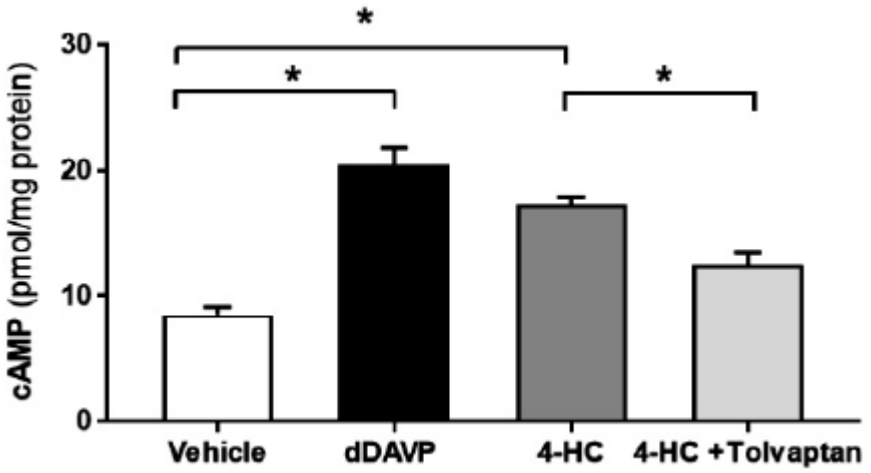
- ✓Antidiuresis occur in patients with central DI

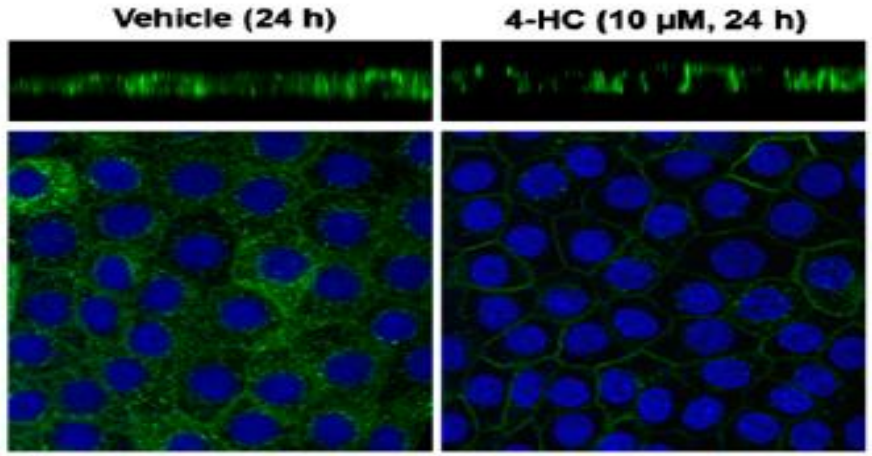
Excluding the possibility of SIADH

Cyclophosphamide

- ✓In the absence of vasopressin stimulation, 4-HC increased:
  - cAMP production
  - AQP2 protein and mRNA expression,
  - V2R mRNA expression

V2R-mediated NSIAD





Ifosfamide

- ✓Elevated plasma AVP levels in few cases of ifosfamide induced hyponatremia

- ✓ *SIADH underlies ifosfamide-induced hyponatremia*

Psychotropic Agents

- Antipsychotics
- Antidepressants
- Anticonvulsants

Psychotropic Agents

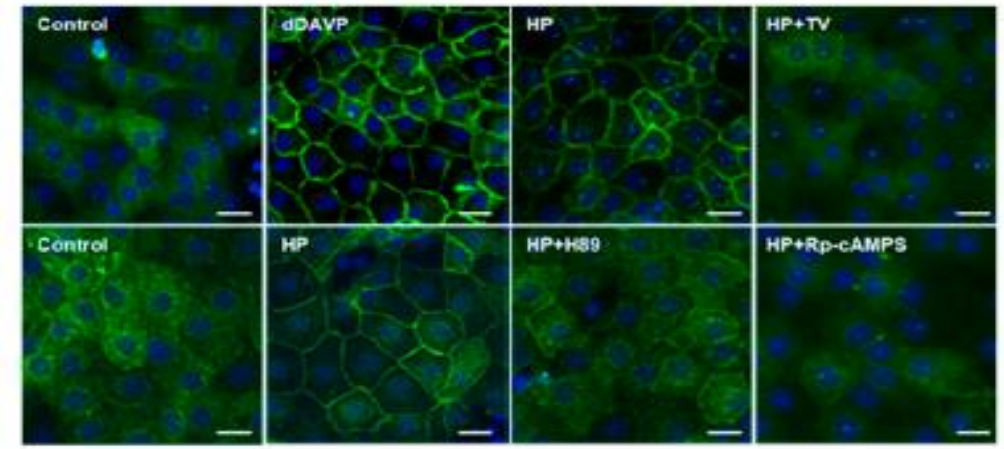
- ✓Plasma AVP levels not increased
- ✓Diagnosis of SIAD is more appropriate
- ✓Psychotropic agents act as V2R agonists to induce nephrogenic antidiuresis

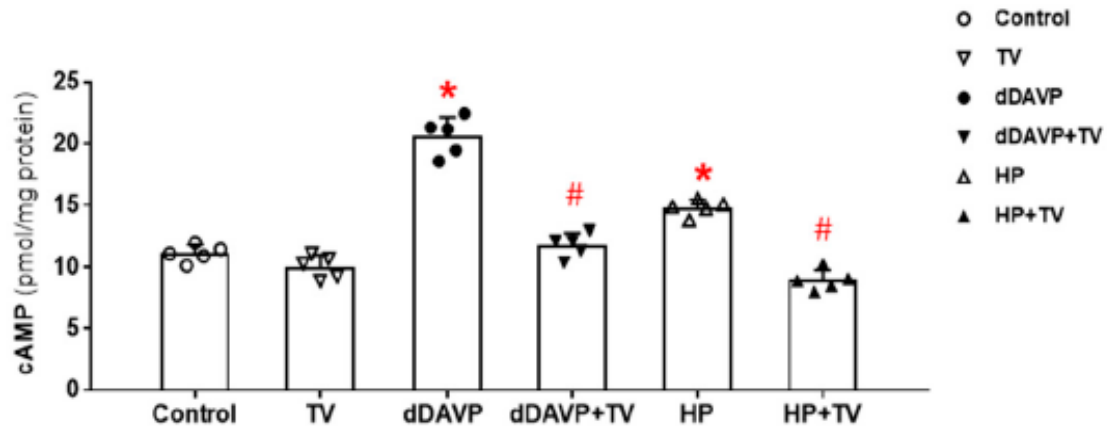
NSIAD

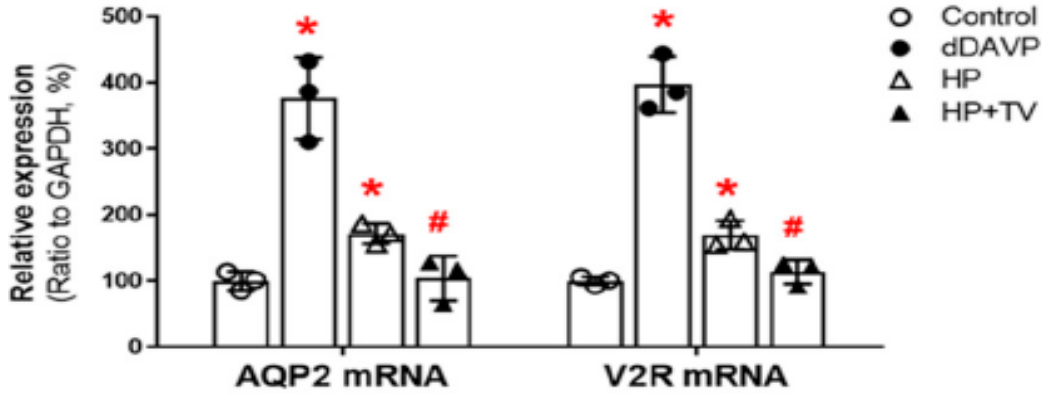
Antipsychotics

Haloperidol: V2R agonist in the kidney

- ✓ accelerating AQP2 transcription
- ✓ AQP2 dephosphorylation at S261
- ✓ AQP2 upregulation







Antipsychotics

Antipsychotic-induced hyponatremia:

- NSIAD
- Primary polydipsia

Association between antipsychotic therapy and hospitalization due to hyponatremia

The association was stronger for first-generation antipsychotics than secondgeneration

Antidepressants

- ✓SSRI
- ✓SNRI
- ✓TCA
- ✓MAO Inh
- ✓mirtazapine

Antidepressants

✓highest risk of hyponatremia with:
- SSRI
- SNRI

✓Most common SSRI:
- fluoxetine
- Paroxetine
- Sertraline

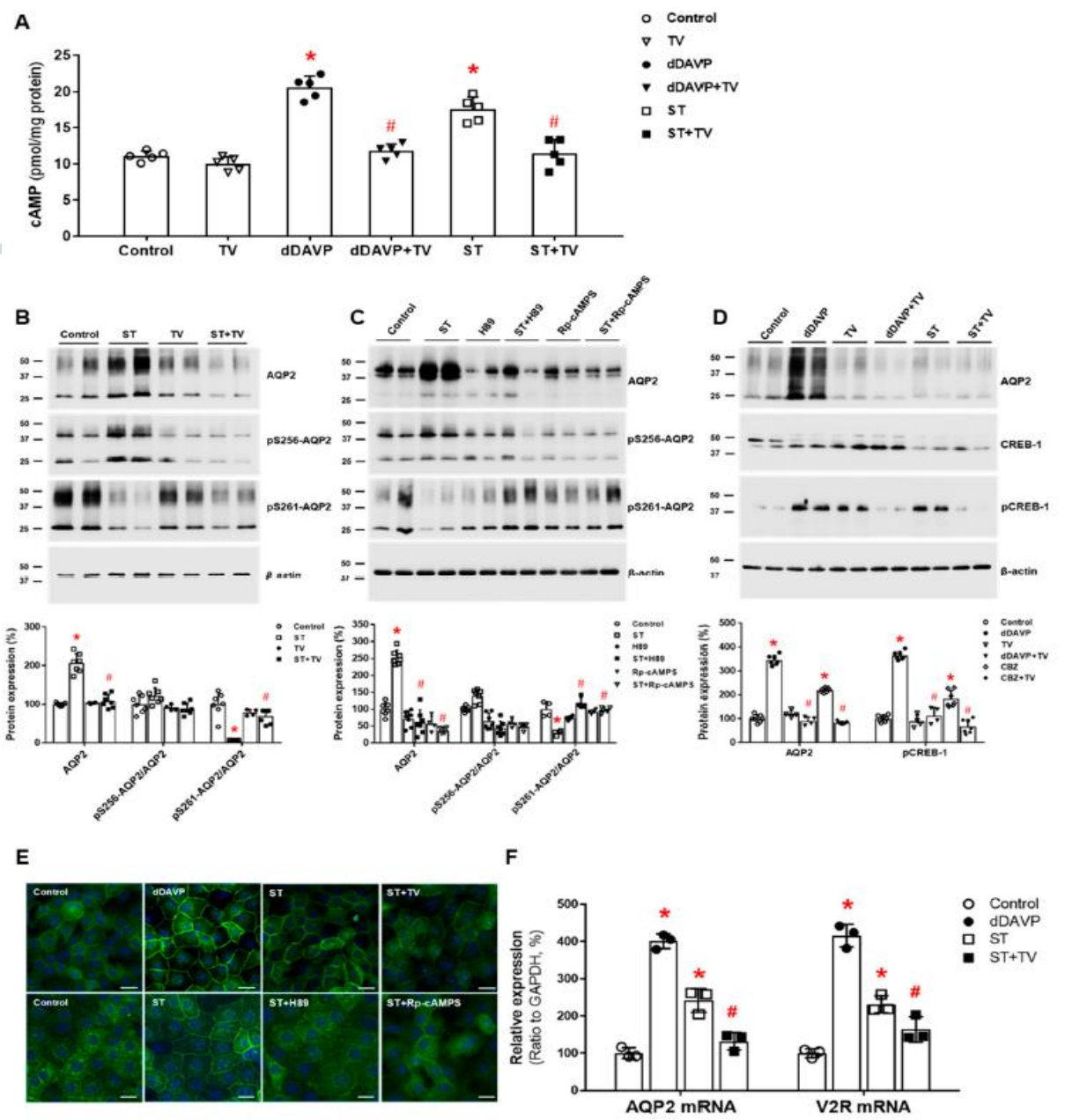
✓most important risk factors:
- Older age
- concomitant use of diuretics

✓Hyponatremia within the few weeks of drug administration

✓serum sodium level normalized within 2 weeks of drug withdrawal

Antidepressants

- ✓Sertraline upregulates AQP2 by inducing V2R-cAMP-PKA signaling.
- ✓Sertraline as a V2R agonist *NSIAD*
- ✓Antidiuretic effect of sertraline: reduced number of wet episodes in enuresis



Anticonvulsants

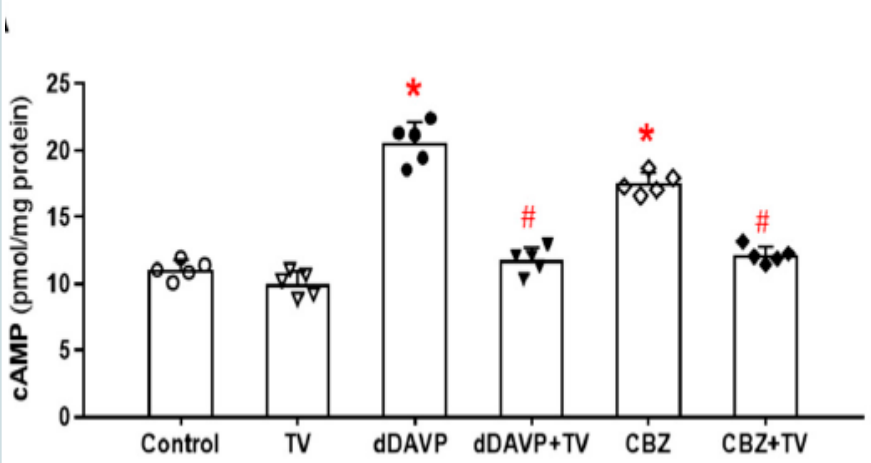
✓Carbamazepine

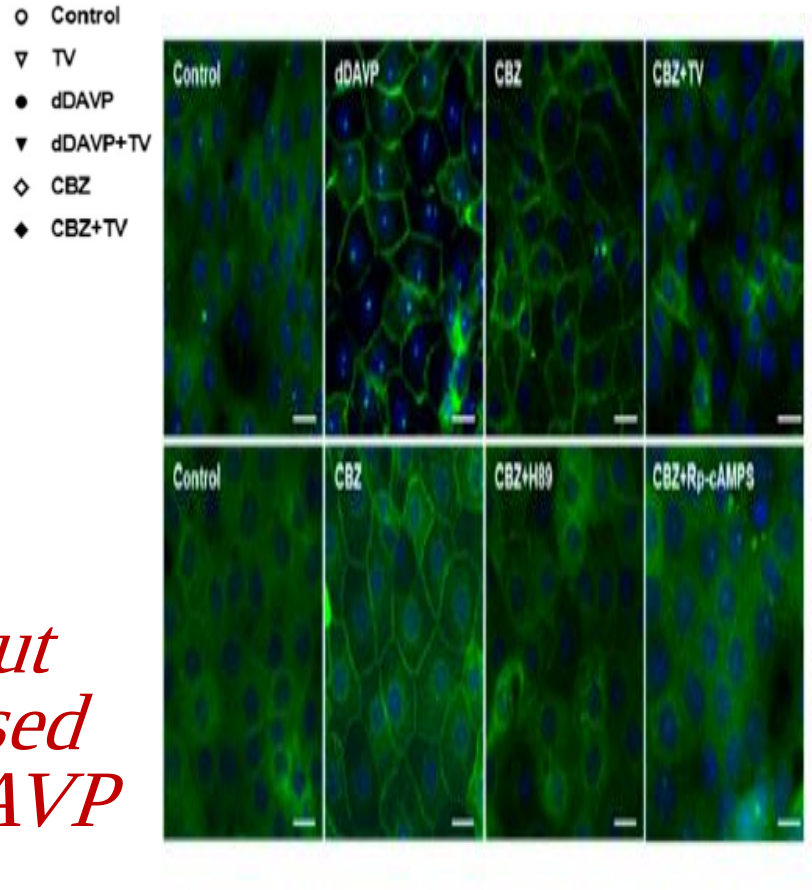
✓Oxcarbazepine: more associated with hyponatremia

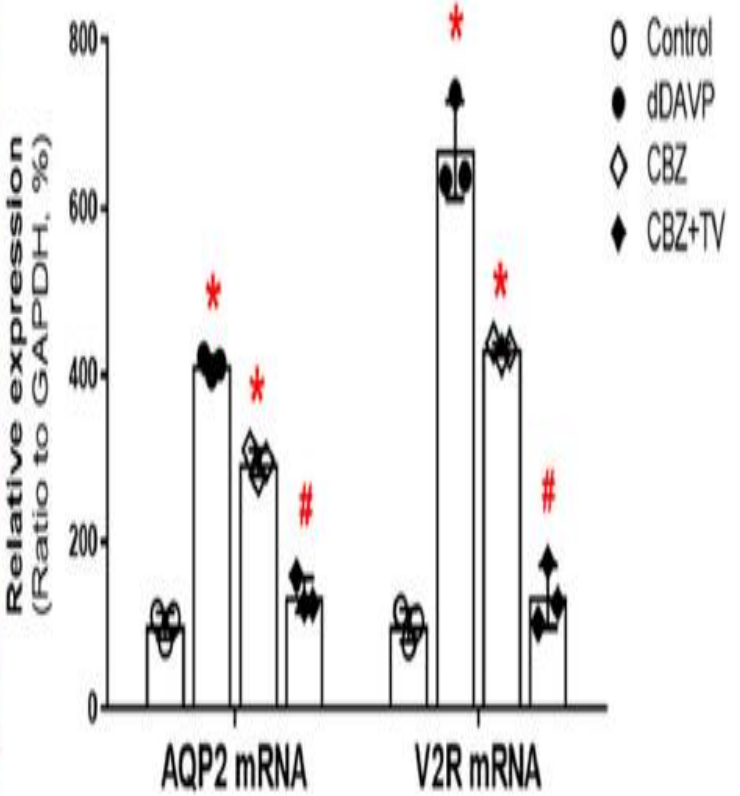
✓risk of hyponatremia is increased in:

- older adults
- use other medications causing hyponatremia
- higher carbamazepine doses
- serum carbamazepine levels
- lower initial serum sodium concentration

Anticonvulsants







V2R stimulation without evidence of the increased release of endogenous AVP

Thiazides

✓5-fold risk for any degree of hyponatremia

✓8-fold risk of severe hyponatremia (Na ≤ 125 mmol/L)

✓The 2 major electrolyte abnormalities associated with thiazides:

- *hypokalemia* :
  - universal effect of thiazides
  - dose dependent
- *Hyponatremia*:
  - in minority of susceptible individuals
  - conflicting results about dose-dependency

✓More patients may develop frank hyponatremia (Na < 135 mmol/L) than frank hypokalemia (K< 3.5 mmol/L).

Electrolyte abnormalities of thiazides

Thiazide diuretic prescription and electrolyte abnormalities in primary care

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Keywords
electrolytes, hypokalaemia, hyponatraemia, primary care, thiazide diuretics

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Aims
Thiazide diuretics have a number of well-documented metabolic adverse effects. The aim of this study was to estimate the frequency of hyponatraemia and hypokalaemia amongst patients taking a thiazide diuretic in primary care.

Methods
A computerized search of the electronic prescribing and laboratory records of six UK general practices was performed. Of the 32 218 adult patients identified, 3773 had received at least one prescription for a thiazide between the years 1990 and 2002.

Results
Detailed prescribing data were available for 2942 patients of whom 951 (32.3%) had a recorded check of their electrolytes. One hundred and ninety-six (20.6%) had a sodium and/or potassium concentration below the normal range. The sodium distribution had a negative skew (−1.8) and in 130 (13.7%) patients was within the hyponatraemic range. Hypokalaemia was less common, occurring in 79 (8.5%) patients. Hyponatraemia was significantly associated with increased age; the odds ratio for developing hyponatraemia in patients over 70 years was 3.87 compared with those of ≤70 years. Hypokalaemia was significantly associated with increased thiazide dose.

Conclusions
Prescription of a thiazide diuretic in primary care is associated with a high frequency of hyponatraemia and hypokalaemia. Thiazides should be prescribed at low dose and the risk of hyponatraemia, especially in the elderly, should be considered and monitored for when prescribing these agents.

Thiazide Associated Hyponatremia

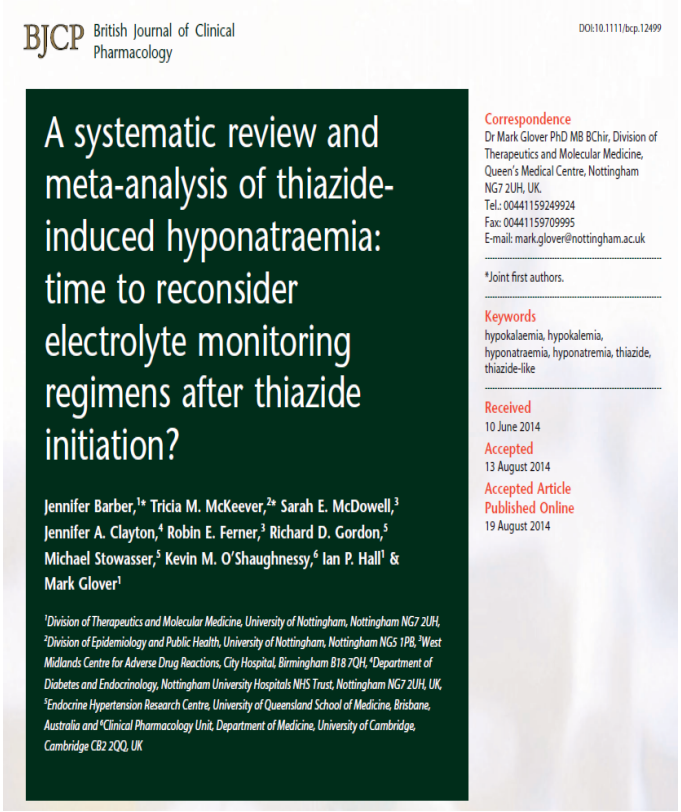
- ✓euvolemic patient
- ✓receiving a thiazide
- ✓hyponatremia

Thiazide Induced Hyponatremia

- ✓Euvolemia by clinical assessment
- ✓Improvement following cessation of thiazide treatment (by 3 mEq/L in 1 d or 5 mEq/L in 2 d)
- ✓No significant improvement before cessation of thiazide use (unless specifically treated, eg, with 3% saline solution, urea, or a vaptan)
- ✓No recurrence after resolution in the absence of a thiazide

Epidemiologic Features of TAH

Variable	Mean	95% CI	I^2 (%)	Pop Studies/Patients	Summary of case report data n	Mean	SD	Range
Gender (Female)*	0.79	0.74, 0.82	65	43/3269	32 (66%)			
Age (years)	74.9	73.0, 76.8	93	36/2840	48	63.8	14.8	31–88
BMI (kg m^{-2})	24.9	20.0, 29.8	100	2/2025	3	21.3	2.8	18.2–23.7
Time to TIH (days)	19.0	7.9, 30.1	97	19/446	26	189	817	1–3650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A systematic review and meta-analysis of thiazide-induced hyponatraemia: time to reconsider electrolyte monitoring regimens after thiazide initiation?

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Clinical Features of TAH

Symptoms	Prop	95% CI	I^2 (%)	Pop Studies/Patients	Summary of case report data *n*	%
Falls	0.48	0.20, 0.77	84	5/252	2	4
Fatigue	0.46	0.21, 0.72	92	8/333	18	38
Weakness	0.45	0.32, 0.58	49	14/247	13	27
Confusion	0.44	0.33, 0.56	85	22/710	16	33
Nausea	0.36	0.24, 0.48	76	14/405	10	21
Neurological symptoms	0.51	0.22, 0.80	76	8/37	10	21
Vomiting	0.35	0.25, 0.45	68	13/549	9	19
Dizziness	0.31	0.15, 0.51	92	8/488	5	10
Unconsciousness	0.30	0.15, 0.48	75	11/181	13	27
Seizures	0.19	0.08, 0.33	84	10/405	10	21

Which thiazides?

Drugs	Prop.	95% CI	I^2 (%)	Pop Studies/Patients	Summary of case study data *n*	%
Thiazide or thiazide-like drug						
Moduretic® (HCTZ with amiloride)	0.73	0.57, 0.87	92	19/633	8	16
HCTZ	0.68	0.52, 0.82	97	19/2583	14	29
Bendroflumethiazide (bendrofluazide)	0.52	0.15, 0.88	97	8/429	4	8
Indapamide	0.47	0.23, 0.72	99	8/1313	2	4
Dyazide® (HCTZ with triamterine)	0.18	0.08, 0.32	36	3/59	4	8
Chlortalidone	0.07	0.02, 0.14	85	6/2174	2	2
HCTZ with losartan	0 studies				2	4
Other drugs						
ARB	0.59	0.00, 0.96	99	3/1844	3	6
Non-thiazide diuretics	0.58	0.19, 0.91	86	5/1815	3	6
ACE inhibitor	0.51	0.27, 0.75	96	5/2000	6	12
NSAID	0.33	0.18, 0.49	89	6/2036	2	4
Antidepressants	0.32	0.19, 0.47	68	6/1882	4	8
Potassium supplements	0.16	0.15, 0.18		2/1805	2	2

Lab Features of TAH

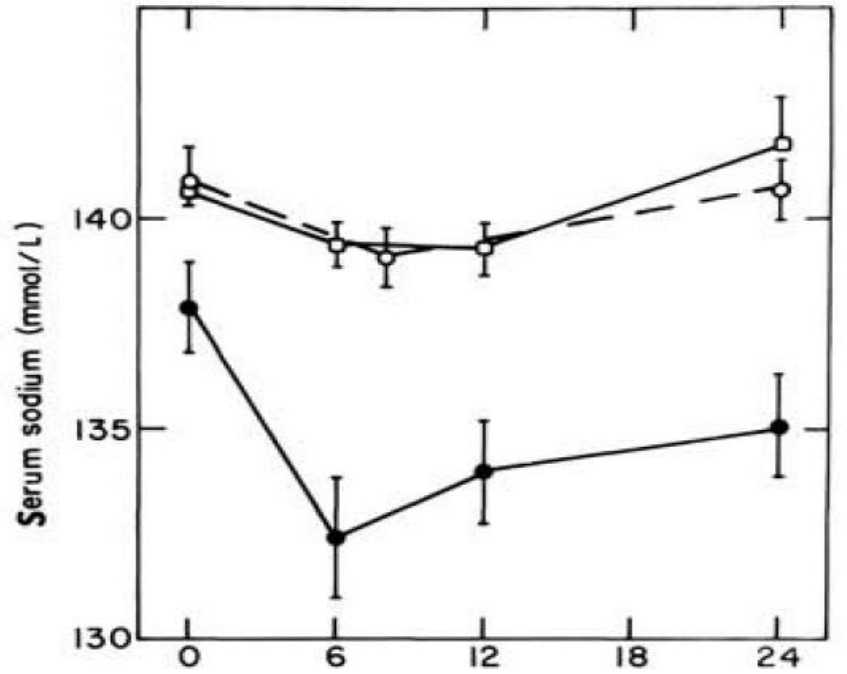
	Mean	95% CI	I^2 (%)	Contributing population Studies/Patients	Summary of case study data *n*	Mean (SD)
Serum sodium (mM)	116.4	113.4, 119.5	99	37/1042	48	111.2 (8.2)
Serum potassium (mM)	3.3	3.0, 3.5	97	28/902	41	3.3 (1.0)
Serum creatinine (μmol l^{-1})	76.8	64.1, 89.4	99	17/504	28	75.2 (30.2)
Serum osmolality (mosm kg^{-1})	240.4	235.9, 244.8	80	11/229	28	221.3 (65.3)
Urine sodium (mM)	64.0	47.0, 81.0	94	13/98	22	55.2 (39.5)
Urine osmolality (mosm kg^{-1})	401.5	370.3, 432.6	81	14/322	27	438.3 (200.7)

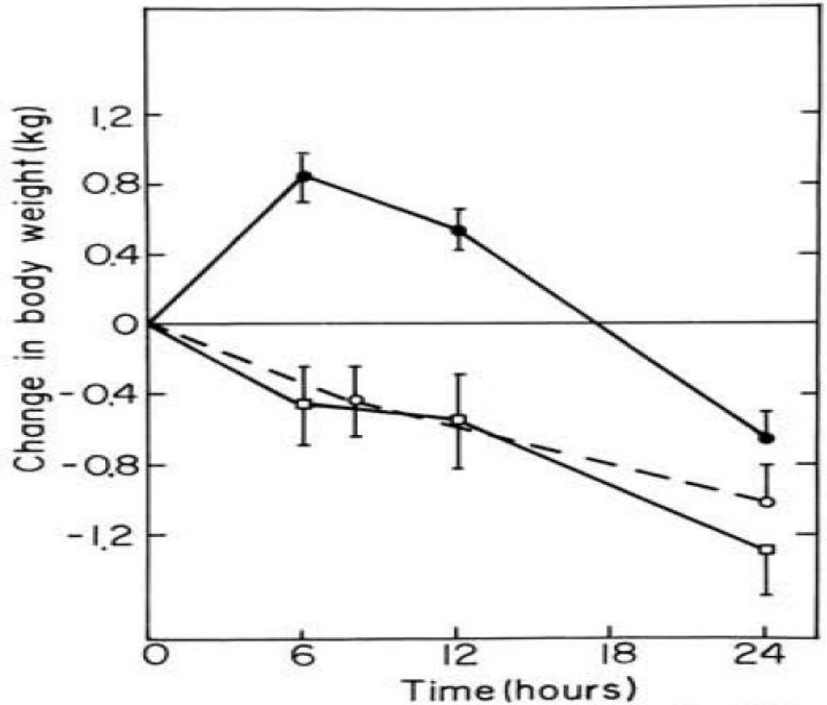
Pathophysiology of TAH

- ✓Excessive Water Intake
- ✓Impaired Free Water Excretion
- ✓Solute Depletion
- ✓Osmotic Inactivation of Cations

Excessive Water Intake

- ✓More modest fluid intake in patients with TAH
- ✓Rechallenge of thiazide in patients with a history of TAH:
  - Polydipsia
  - weight gain





Impaired Free-Water Excretion

1) Reduced distal delivery of filtrate
   - Reduced GFR
   - Enhanced proximal tubule reabsorption
2) Reduced solute load (urea)
3) Inhibition of NCC impairing maximal dilution
4) Increased collecting duct water permeability
   - ADH dependent: hemodynamic ADH release mediated by diuretic-induced volume depletion
   - ADH independent:
     - Increased luminal PGE_2 from enhanced production and reduced prostaglandin transporter activity
     - Direct effect of thiazides on collecting duct permeability independent of ADH
     - Increased medullary tonicity fostering water reabsorption in the absence of ADH

Impaired free water generation

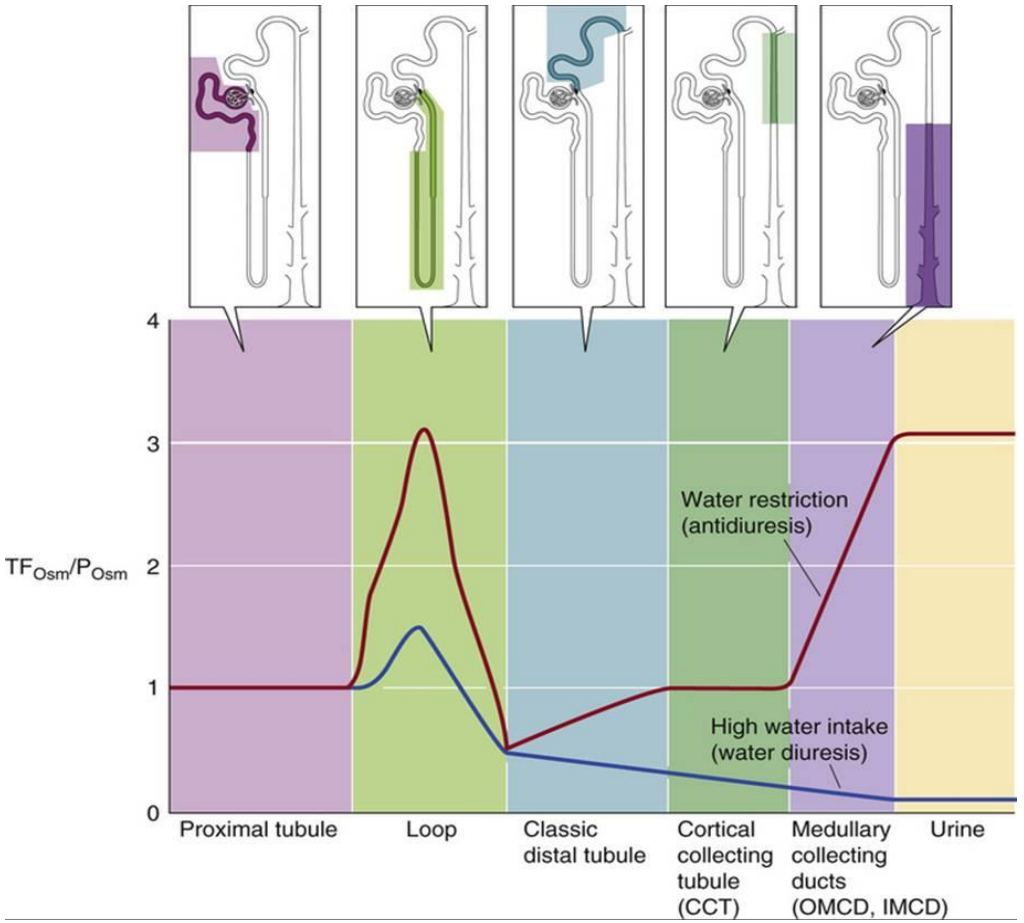
Volume depletion by thiazide:

- Reduced GFR
- Enhanced proximal tubule reabsorption

→ Reduced distal delivery of filtrate

Impaired maximal urine dilution

- ✓The osmolarity of fluid entering the DCT: 100-150mOsm/L
- ✓NCC-mediated sodium reabsorption in DCT:maximally dilute urine: 50mOsm/L
- ✓Thiazides prevents reduction of urine osmolarity from 100 -150 to 50 mOsm/L



Increased water permeability

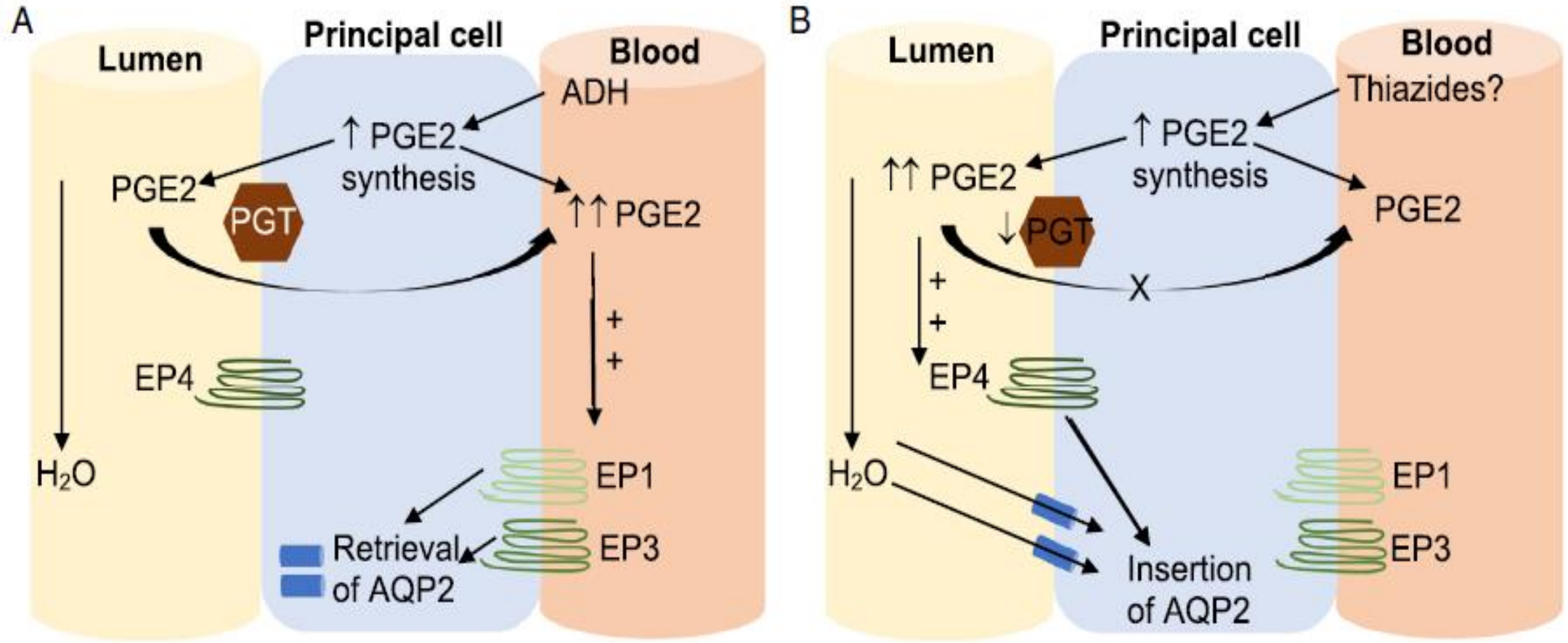
- ✓If the sole mechanism for TAH was NCC inhibition: *Uosm=150*
- ✓higher urine osmolarity in TAH: 400

Increased water permeability

- ✓ADH dependent: hemodynamic ADH release by volume depletion

- ✓ADH independent
  - Increased luminal PGE
    - enhanced production
    - reduced prostaglandin transporter activity
  - Direct effect of thiazides on collecting duct permeability
  - Increased medullary tonicity

Role of PG in TAH



Conclusion

Hypothalamus ⟸ **Drugs for SIADH**

↓

Posterior pituitary

↓

Arginine vasopressin

↓

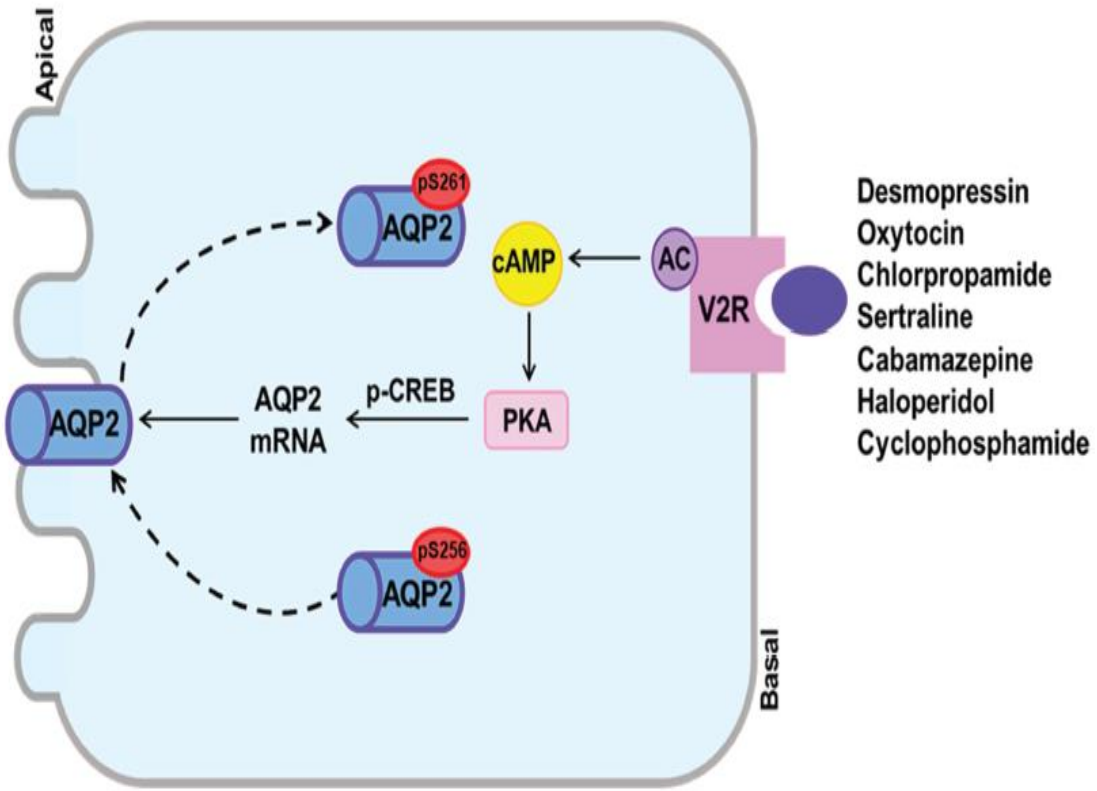
Kidney V2R ⟸ **Drugs for NSIAD**

↓

cAMP-PKA

↓

AQP2 upregulation ⟸ PG E2? **Thiazide diuretics**



Thanks a lot for your attention