Pathophysiology of water and electrolyte metabolism

Ágnes Haris MD, PhD

Budapest

Sudden disaster on a Sunday afternoon .....

- 84 years old female, admitted to hospital 12 days earlier because she had had diarrhoea for 3 days
- On admission she looked volume depleted, had low BP (90/50 mmHg)
- Laboratory results: Hgb 9,86 g%, serum Na 134 mmol/l, K 3,0 mmol/l, BUN 21,9 mmol/l, creatinine 182 umol/l
- She got 0,9% NaCl infusion+KCl for 3 days
  the BP normalized (118/59 mmHg),
  the labs: Na 141 mmol/l, K 3,6 mmol/l, BUN 4,1 mmol/l, creatinine 86 umol/l
- The gastroenterology team decided to go on with GI work up in order to look for the cause of anemia

Sudden disaster on a Sunday afternoon .....

- Scheduled for colonoscopy on Monday (plan to preparing her by Fleet enema on Sunday evening)
- Instruction by the nurse on Sunday morning: „no solid food to eat, only fluids to drink”
- On Sunday morning – complaints free, ambulating, „looked nervous”
- In the afternoon: she suddenly lost her consciousness, had a convulsion, did not respond even to pain, had uncoordinated movements in all her extremities. Repeatedly vomited.

Sudden disaster on a Sunday afternoon .....

- Urgent labwork: serum Na 117 mmol/l, K 2,9 mmol/l, BUN 2,4 mmol/l, creatinine 98 umol/l
- Urinary osmolality 431 mOsm/kg, urinary Na 164 mmol/l, K 44 mmol/l hrs, 900 ml/12 hrs
- Brain CT:
  -no major abnormality can be seen
- She remained unconscious in the next day:
  Neurological examination:
  - no primary neurological abnormality,
  EEG: diffuse functional cortical abnormality

Sudden disaster on a Sunday afternoon .....

- Why was she mildly hyponatremic on admission?
- Why had she severe hyponatremia 12 days later?
- What do you think about the urinary osmolality of 431 mOsm/kg?
- And about the urinary Na of 164 mmol/l?
- What is your suggestion for treatment on the day of admission?
- What would you give on the 12th day? How much?

Hyponatremia

ADH secretion + Water intake

Both need to be present

Why ???

Why is ADH secreted in spite of hypoosmolality?

Where is the water coming from?

Is this an acute or a chronic condition?

ADH secretion

- In physiologic conditions
  - increased osmolaltity
  - increased serum Na

- In pathophysiologic conditions
  - stress, anxiety, pain, fever, nausea, vomiting
  - severe hypovolemia due to
    - fluid loss
    - diuretic use
  - effective volume depletion
  - SIADH
  - medications

Treatment on the first day

- The major stimulus for ADH was the volume depletion
- 0,9 % NaCl infusion shuts off the stimulus for ADH secretion
- How do you know this?
  The urine with high osmolality (evidence for ADH secretion) changes to less concentrated urine
  → the patient becomes able to excrete free water
  → the low serum osmolality and low serum Na are increasing and get normalized
- Hypertonic Na infusion is unnecessary and dangerous

Treatment on the 12th day

- Acute, severe hyponatremia, causing convulsion, coma, vomiting → very likely cerebral edema
- Urine osmolality: 431 mOsm/kg - proves strong influence of ADH (likely due to stress, anxiety, nausea)
- Lots of fluid intake according to the instructions
- Urine Na: 164 mmol/l means - no volume depletion
- Treatment: 3% NaCl infusion
- How much?

Treatment on the 12th day

- Weight of the patient: 72 kg. Body water: 42 l
  In order to elevate her serum Na by 1 mmol/l, she needs 42 mmol Na
  In order to elevate serum her Na by 5 mmol/l, she needs 210 mmol Na
  It means 408 ml of 3% NaCl infusion
- Follow urinary Na loss and replace it
- Check electrolytes frequently

Treatment on the 12th day

- She got 300 ml 3% NaCl infusion (154 mmol) and 4 g KCl
- 4 hours later serum Na 119 mmol/l, K 3,2 mmol/l
- During Sunday night 300 ml 3% NaCl infusion (154 mmol) and 4 g KCl
- On Monday morning 300 ml 3% NaCl infusion (154 mmol)
- In 24 hours: serum Na 130 mmol/l, K 3,9 mmol/l
- Urinary losses in 24 hrs: 230 mmol Na and 62 mmol K
- In summary she got 462 mmol Na in the 1st 24 hrs
- Next day: serum Na 134 mmol/l, she regained consciousness
- Two days later: serum Na 140 mmol/l

Acute hyponatremia

ADH secretion + Water intake

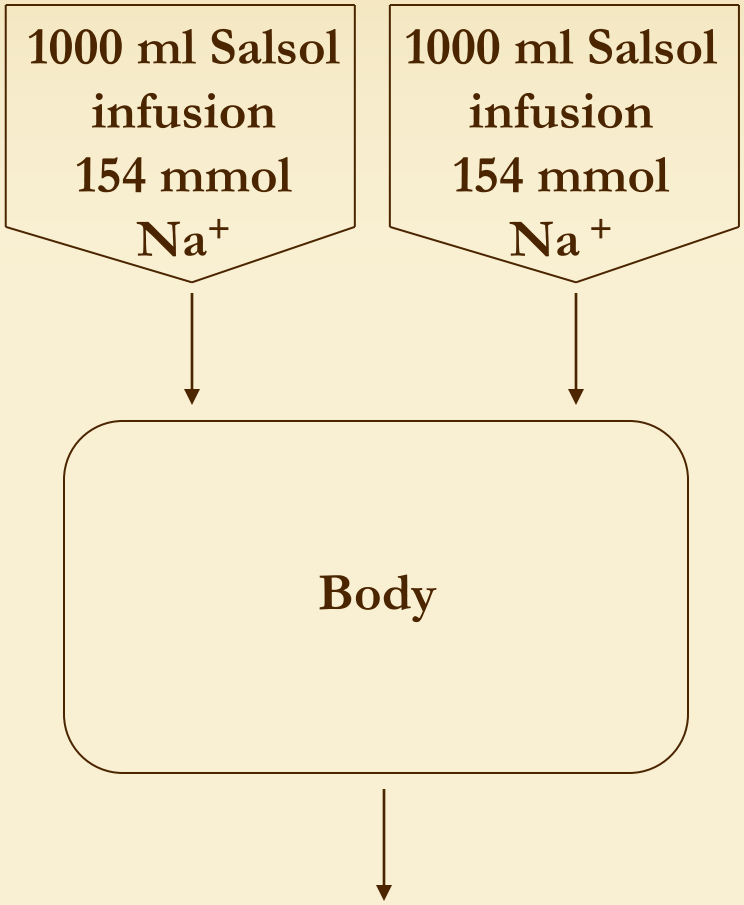
Both need to be present

Why ???

Why is ADH secreted in spite of hypoosmolality?
- stress, anxiety, pain, fever, nausea, vomiting,
typically in a perioperative situation

Where is the water coming from?
- hypotonic fluid intake, very often iv. infusions

Generation of EFW - Desalination



Persistent ADH action

No reason to retain NaCl

<u>Balance</u>:

Water intake: 2000 ml
Na^+ intake 308 mmol

Excreted free water: 1000 ml

Excreted Na^+: 308 mmol

1 L electrolyte free water is retained in the body, which causes hyponatremia

More tests than thoughts....

- 69 yrs female, in her past medical history:
  - 1990. Resection of malignant lung tumor
  - For 2 years hypertension, osteoporosis
  - Meds: indapamide, aspirin, carvedilol, vitamin D, Calcium suppl.
- 2008. october
  - dizziness, headache, unsteadiness, repeated falls
  - Once she invited guests, treated them, made conversation, but later did not remember these events
- SeNa oct. 3. 141, dec.19. 126,
  oct.29. 119, febr.20. 120 mmol/l.
  nov.17. 124,

More tests than thoughts....

- Tests because of her complaints (oct-febr):
  - head CT, 2x head MRI, neurosurgical consultation (some traumatic contusions)
  - chest XR and CT, mammography, abdominal US, carotid art. doppler scan, neurological examination
- Modification of the therapy:
  - Indapamide changed to ramipril+hydrochlorothiazide
  - Increased salt and fluid (!) intake suggested (although the patient did not whish to drink much)

- **What is wrong with this lady?**

Not so difficult....

- Febr. 20. Nephrology consultation: discontinue the thiazide, continue increased salt intake but limit fluid intake
- March 10. Free of complaints - SeNa 140 mmol/l.

The most frequent causes of hyponatremia

Clayton et al. Q.J.Med 2006

- Hyponatremia was found in 108 of the 9622 patients admitted to internal medicine department in 6 months
- Etiology
  - **Thiazide diuretics** - 29 cases
    („Thiazides: do they kill?" P.Gross, C.Palm, NDT 2005)
  - **Congestive heart failure -** 27 cases
  - **Liver cirrhosis** - 21 cases
  - In further cases: volume depletion, medications, malignancies, lung- and cerebral diseases, hypothyroidism, Addison disease, hypoNa postoperatively, primary polydipsia and chronic renal failure
- During the hospitalization 20% of the patients died

Risk factors for thiazid-induced hyponatremia

Chow et al. Q.J. Med 2003

- Between 1996-2002 223 thiazide caused hyponatremic patients were observed
- SeNa: 98-128 mmol/l (mean 116±7 mmol/l)
- Length of treatment 1-4479 day! (mean 105 day)
  - 42,8% indapamide,
  - 16,1% HCT,
  - 17,3% HCT+amiloride,
  - 15,4% HCT+triamterene
  - 8,4% bendrofluazide
- Thiazides were administered mainly for hypertension
- Risk factors for developing hyponatremia:
  age, low body weight, hypokalemia

Pathomechanism of thiazid-induced hyponatremia

- In most cases ADH secretion could not be explained by volume depletion!
- When thiazide is taken, the medulla can achieve high concentration – little ADH is enough to produce concentrated urine
- Decreased urinary dilution capacity in the elderly
- Increased fluid intake due to increased thirstiness (?)
- Decreased salt intake –adviced medically sec.to HTN (?)
- Na^+-K^+ transcellular shift in hypokalemia
- Activation of AQP-2 channels in cortical tubules due to thiazides – individual sensitivity (?)

Do cirrhotic patients need sodium in hyponatremia?

- 70 yrs old male, treated on an internal medicine department He is a regular alcohol drinker, has liver cirrhosis, oedema on the legs and huge ascites
- On admission: serum Na 132 mmol/l, K 4,2 mmol/l, BUN 5,7 mmol/l, creatinine 82 umol/l
- Initial treatment: 100 mg spironolactone, 160 mg furosemide, 50 mg ethacrynic acid, 50 mg hydrochlorothiazide, 3 g KCl
- In three days BW 115 → 111 kg, Na 132 → 125 mmol/l, creatinine 82 → 126 umol/l
- Treatment: furosemide discontinued, others continued, + 5 g NaCl in Ringer infusion

Do cirrhotic patients need sodium in hyponatremia?

- In the nex three days: BW → 120 kg, SeNa → 117 → 109 mmol/l, creatinine → 270 umol/l,
- Even more NaCl given
- Consultation asked for nephrology service because oliguria, deteriorating renal functions:
  SeNa 112 mmol/l, K 3,8 mmol/l, BUN 8,8 mmol/l, creatinine 307 umol/l
  Urinary Na excretion 2 mmol/day, K 8,6 mmol/day
- **How would you manage this patient?**

Hyponatremia in cirrhotic patients

Splanchnic vasodilatation,
↓ systemic vascular resistance, ↓ MAP

↓

Baroreceptor activation - „effective volume depletion”

↓

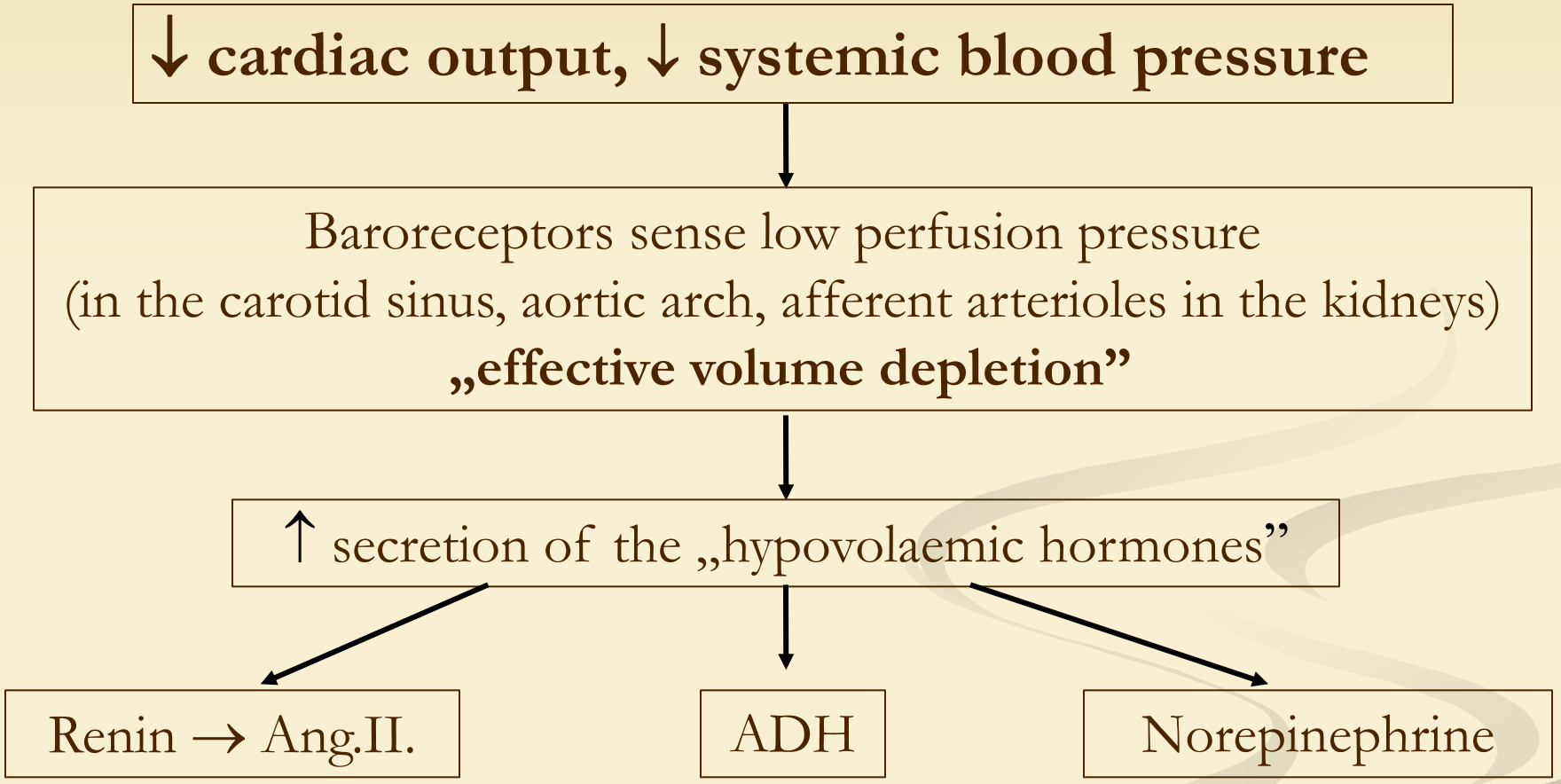
↑ secretion of the „hypovolaemic hormones”

↙ ↓ ↘

Renin → Ang.II. | ADH | Norepinephrine

Further factors contributing to hyponatremia:
-overgenerous diuretic treatment
-too much fluid intake (e.g. Beer drinkers)

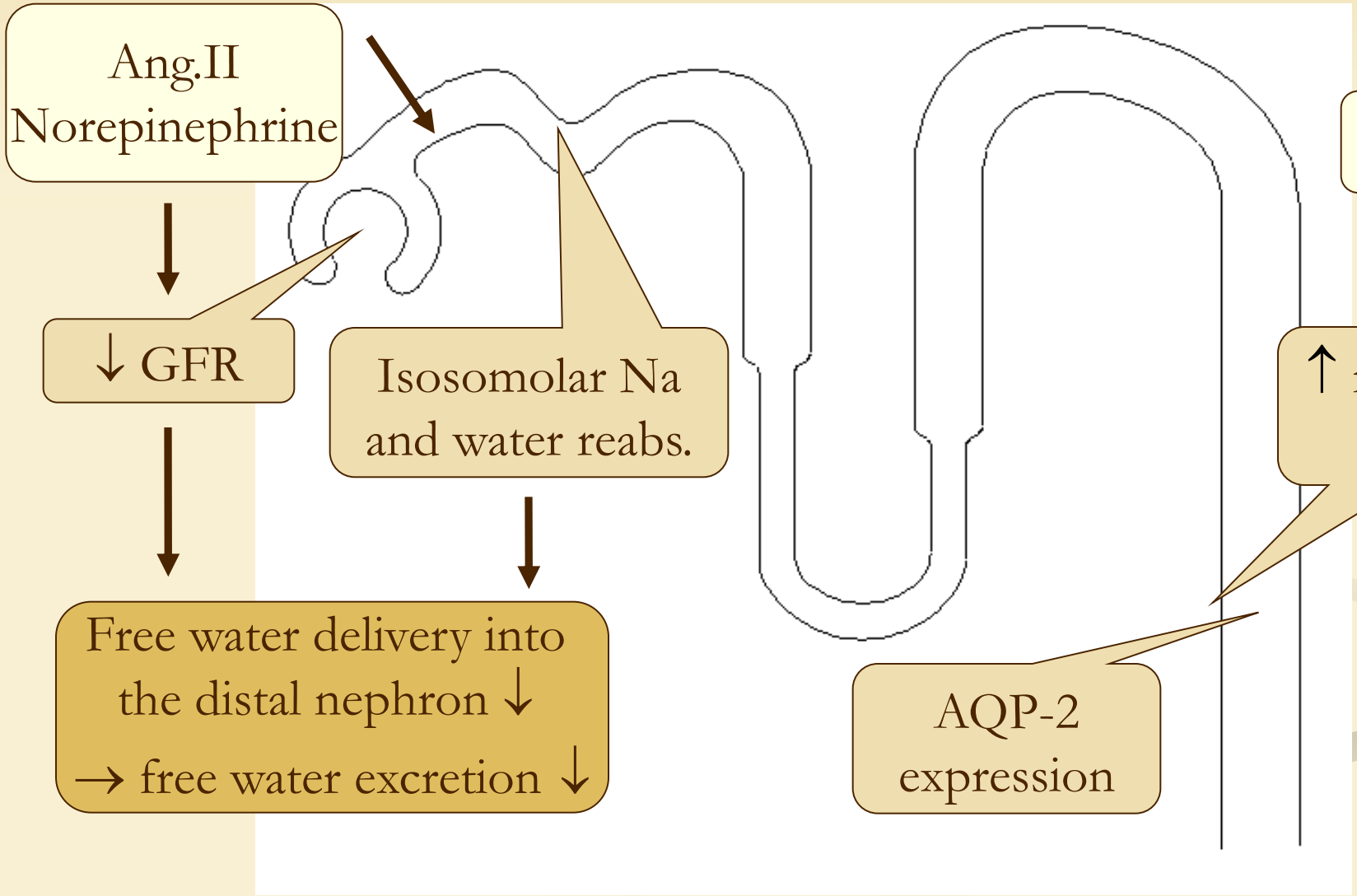
Hyponatremia in congestive heart failure



Other factors causing hyponatremia:

Low cardiac output, high level of Ang II. → increased thirstiness

Disturbed free water clearance – effects of the „ hypovolaemic hormones”



Hyponatremia in cirrhotic patients

- Severity of hyponatremia is proportional to the prognosis
- Correction of hyponatremia does not change the hemodynamical, pathophysiological abnormalities
- Mild hyponatremia usually does not cause major complaints, do not have to be treated (≈>125mmol/l)
- Treatment: decrease fluid intake in order to achive negative fluid balance
- „Delicate" diuretic administration, mainly loop diuretics (if peripheral edema present, ↓ BW: by 1-2 kg/d, if only ascites: <0,5 kg/d)
- Hypertonic saline infusion is contraindicated !!
- Vasopressin receptor antagonists: aquaretics (vaptans)

Therapy in CHF

- Survival is proportional to the degree of hyponatremia
- Its correction does not improve the prognosis of CHF
- ACEI/ARB
  - Cardiac output improves
  - ACEI decreases ADH's effectivity in the cortical collecting duct, therefore water reabsorption ↓
  - Decreased thirstiness
- Moderate fluid restriction
- Administration of moderate doses of loop diuretics
- Vasopressin receptor antagonists: aquaretics (vaptans)

A case of SIADH

- 66 years old male, ALL diagnosed 9 months ago
- Got monthy bolus cytostatic treatments
- Developed aspergillus pneumonia - Rx intaconazole
- Admitted secondary to feeling unwell, weak, dizzy, but he was ambulating, can properly communicate
- Labs: Na 117 mmol/l, K 3,5 mmol/l, Cl 85 mmol/l, bicarb 23 mmol/l, BUN 6,5 mmol/l, creatinine 75 umol/l, BS 8,3 mmol/l, serum osmolality 237 mOsm/kg, urinary Na 83 mmol/l, osmolality 456 mOsm/kg, normal TSH
- According to his chart: serum Na 123-133 mmol/l previously
- **Why does he have ADH? Acute or chronic?**

Inappropriate ADH secretion - SIADH

- Malignancies
  - small lung cell carcinoma
  - prostate, uterus cc.
  - pancreas, duodenum cc.
  - leukemia, lymphoma

- Central nervous syst.dis.
  - Tumors, abscess
  - infections
  - Demyelinization diseases
  - SAH, trauma

- Medications
  - dDAVP, oxytocin, NSAID
  - antidepressants,
  - narcotics, nicotine
  - cytostatics
  - chlorpropamide
  - carbamazepine

- Lung diseases
  - TBC, aspergillosis
  - pneumonia, abscess
  - obstructive lung disease
  - ventillation

Vaptans

- Vasopressin receptor antagonists – increase electrolyte-free water excretion
- Conivaptan (V1a and V2), tolvaptan, satavaptan, lixivaptan (V2 receptor antagonists)
- Indicated (in general) in euvolemic and hypervolemic hyponatremia
- Contraindicated in hypovolemic hyponatremia
- Overcorrection of hyponatremia has to be avoided!
- Very expensive drugs

Tolvaptan – EVEREST trial
Gheorghiade M et al., JAMA 2007. 297:1332

- Short and long term administration of tolvaptan
  - randomised controlled trial
  - 4133 patients admitted with chronic heart failure
- Body weight, dyspnea, edema ↓, serum Na ↑ more in patients who received tolvaptan
- But no effect on mortality, comparing to placebo
- Mental functioning showed small but significant improvement in the tolvaptan group

Tolvaptan – SALT1 and SALT2 trials
Schrier RW et al. NEJM 2006. 355:2099

- Two multicenter RCTs for 30 days
- Tolvaptan 225 pts, placebo 223 pts with SIADH, CHF, and cirrhosis
- Serum Na increased more in the tolvaptan group
- Hyponatremia recurred after tolvaptan was discontinued
- Patients in the tolvaptan group had increased thirst, dry mouth, increased urination

Hyponatremia in chronic renal failure

- Our case: 72 years old lady, regularly seen on clinic
  - eGFR 10 ml/min
  - Nausea, vomiting, feeling unwell
  - Se Na 129 mmol/l, urine output 3400 ml/day
- On the next visit:
  - Se Na 135 mmol/l
  - urinary osmolality 284 mOsm/kg
  - urine output 2800 ml/day
- **Why was she hyponatremic?**

What does the maximal urinary diluting capacity mean?

- Healthy persons:
  - Minimal urine osmolality: 50-80 mOsm/kg
  - Average solute excretion: 600-900 mOsm/day (300-450 mmol Na, K + the anions, and 300-450 urea)
- How much can we drink without the risk of hyponatremia?

  Solute excretion / diluting capacity / L
  - 900 mOsm and 50 mOsm /kg = 18 L
  - 600 mOsm and 80 mOsm /kg = 7,5 L
  - 200 mOsm and 50 mOsm /kg = 4 L
- Beer potomania („Tea and toast" hyponatremia):
  - Low protein and salt intake, therefore low osmolar excretion and too much fluid intake

Hyponatremia in chronic renal failure

- The urine is „isostenuric" ≈ 300 mOsm/kg
- The kidneys are not able to dilute significantly better (nor concentrate)
- If the daily solute excretion 900 mOsm – maximally 3 L fluid can be excreted, without causing hyponatremia
- But on low protein and low salt diet the daily solute excretion ↓, therefore exaggerated fluid intake can cause hyponatremia
- Therapy: adjust fluid intake to the actual diluting capacity of the kidneys

What kind of i.v. infusion has to be given in hypernatremia?

- 81 yrs old male patient, admitted to hospital because of volume depletion and pneumonia. He was febrile, desoriented.
- Lab results: serum Na 156 mmol/l, K 5,0 mmol/l, BUN 22 mmol/l, creatinine 173 umol/l, glucose 6,1 mmol/l.
- Chest XR: pneumonia and pulmonary congestion
- Initial treatment: 500 ml of Ringer lactate infusion and 500 ml 5% glucose infusion
- **Was this appropriate? What kind of change do you expect in serum Na concentration?**

What kind of i.v. infusion has to be given in hypernatremia?

- Next morning:

  - Serum Na 157 mmol/l, osmolality 330 mOsm/kg
  - Urinary Na 40 mmol/l, K 48 mmol/l,
    osmolality 463 mOsm/kg

  (24 hrs collection could not be done)

What kind of i.v. infusion has to be given in hypernatremia?

- Na balance

  - the patient excreted 40 mmol/l sodium,
  - intake by RL: 67 mmol
  (Ringer lactate contains 132 mmol/l)

- Treatment on the following day

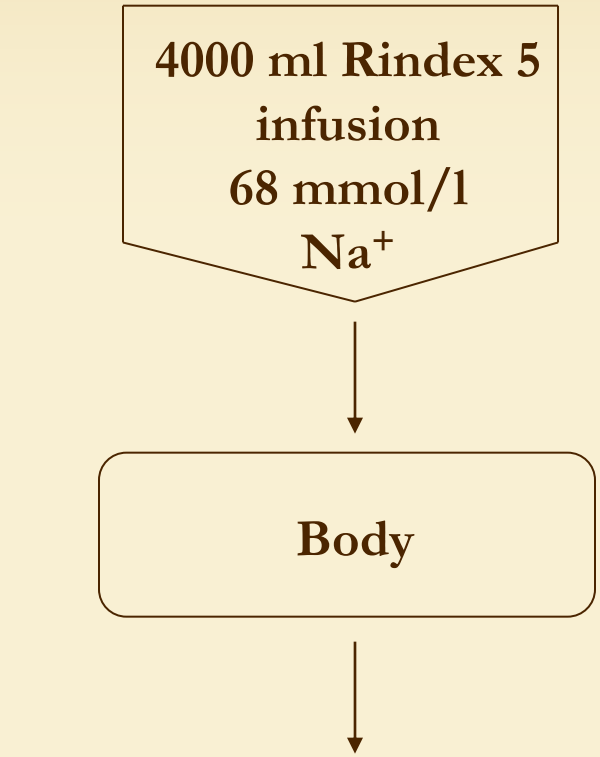
  1500 ml 5% glucose infusion, and he was eating and drinking a litte
  Serum Na 159 mmol/l

- **Why? What can we do now?**

What kind of i.v. infusion has to be given in hypernatremia?

- Checking again the urinary excretion:
  Na 11 mmol/l, K 9,5 mmol/l osmolality 439 mOsm/kg
- He was excreting very little Na
- He was not able to increase his urine osmolality
- We gave 40 mg furosemide i.v. and 2500 ml 5% glucose infusion daily
- The urinary Na excretion increased to 52 mmol/l, K excretion to 30,2 mmol/l
- The serum Na decreased gradually and in 3 days normalized to 137 mmol/l

Sodium balance in diabetes insipidus



Balance:

Water intake: 4000 ml/24 hr
Na^+ intake 272 mmol
Excreted water: 4000 ml/24 hr
Excreted Na^+: 140 mmol/24 hr

The patients retains 33 mmol Na^+ by each L of infusion
In 24 hours 132 mmol Na^+ surplus created in the body.

Potassium disorders

Hypokalemia – where does this huge amount of K go?

- A 62 yrs old female
- PMHx: collagen colitis – she had been well for years
- She presented with profuse, watery diarrhoea, several times daily. In the last days nausea and vomiting also occurred
- On admission: severly volume depleted, very weak, completely anuric, BP 60/40 mmHg.

Hypokalemia – where does this huge amount of K go?

- Labs on admission:
  Na 124 mmol/l, K 1,8 mmol/l, BUN 31,5 mmol/l, creatinine 665 umol/l

Days	KCl g/day	HD-Dialysate K	Serum K	
1	4	3 mmol/l	1,5	anuric
2	14	3 mmol/l	2,3	anuric
3	12	-	2,6	oliguric
4	14	-	3,0	diuresis
5	14	-	3,6	diuresis
6	10	-	3,8	diuresis

Hypokalemia – where does this huge amount of K go?

- **Why did she need so much K?**
  (83 g = 1079 mmol)
- **Did this patient have renal K wasting tubulopathy?**

Hypokalemia – first step in differential diagnosis

- Urinary K excretion
  - In our patient: 19,5 mmol/day
    18,8 mmol/day

Hypokalemia – where does this huge amount of K go?

- Body weight of the patient: 60 kg
  Extracellular water: 10 l
  Intracellular water: 20 l
- K content of EC: 10x4= 40 mmol
  K content of IC: 20x150=3000 mmol

An other hypokalemic patient ...

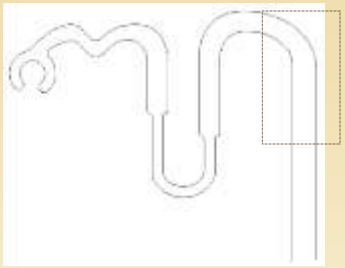
- 48 years old male
- PMHx: hypertension since his age of 30
- His mother, his sister and his son also have HTN
- Serum potassium between 2,5-2,9 mmol/l for years
- Meds on the first consultation: 20 mg amlodipin, 2x20 mg enalapril+hydrochlorothiazide, 4 mg prasosin, 2x2 g KCL
- Labs: serum Na 145 mmol/l, K 2,9 mmol/l, CN 7,7 mmol/l, creatinine 100 umol/l
- **What kind of tests would you order?**

An other hypokalemic patient ...

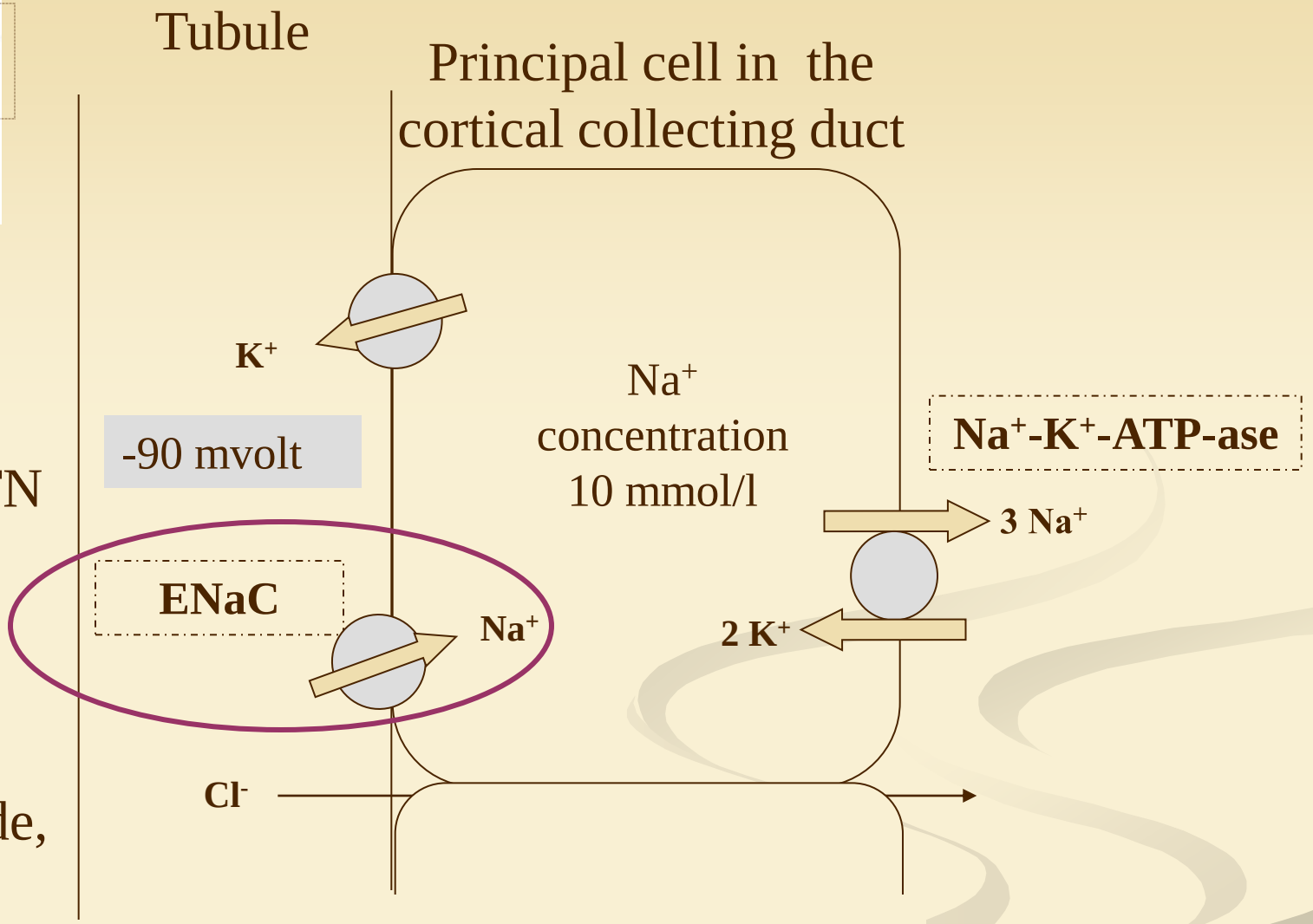
- 24 hr urinary Na: 262 mmol/day
  24 hr urinary K: 104 mmol/day
- Blood gas analysis:
  pH 7,46
  HCO_3 28,8 mmol/l
  pCO_2 41 mmHg
- **What is the differencial diagnosis?**

An other hypokalemic patient ...

- Renin and aldosterone levels - repeatedly normal
- RAS - excluded
- Glucocorticoid overproduction – serum cortisol normal
- Rx: spironolactone – no change
- **What is your diagnosis and how would you treat this patient?**

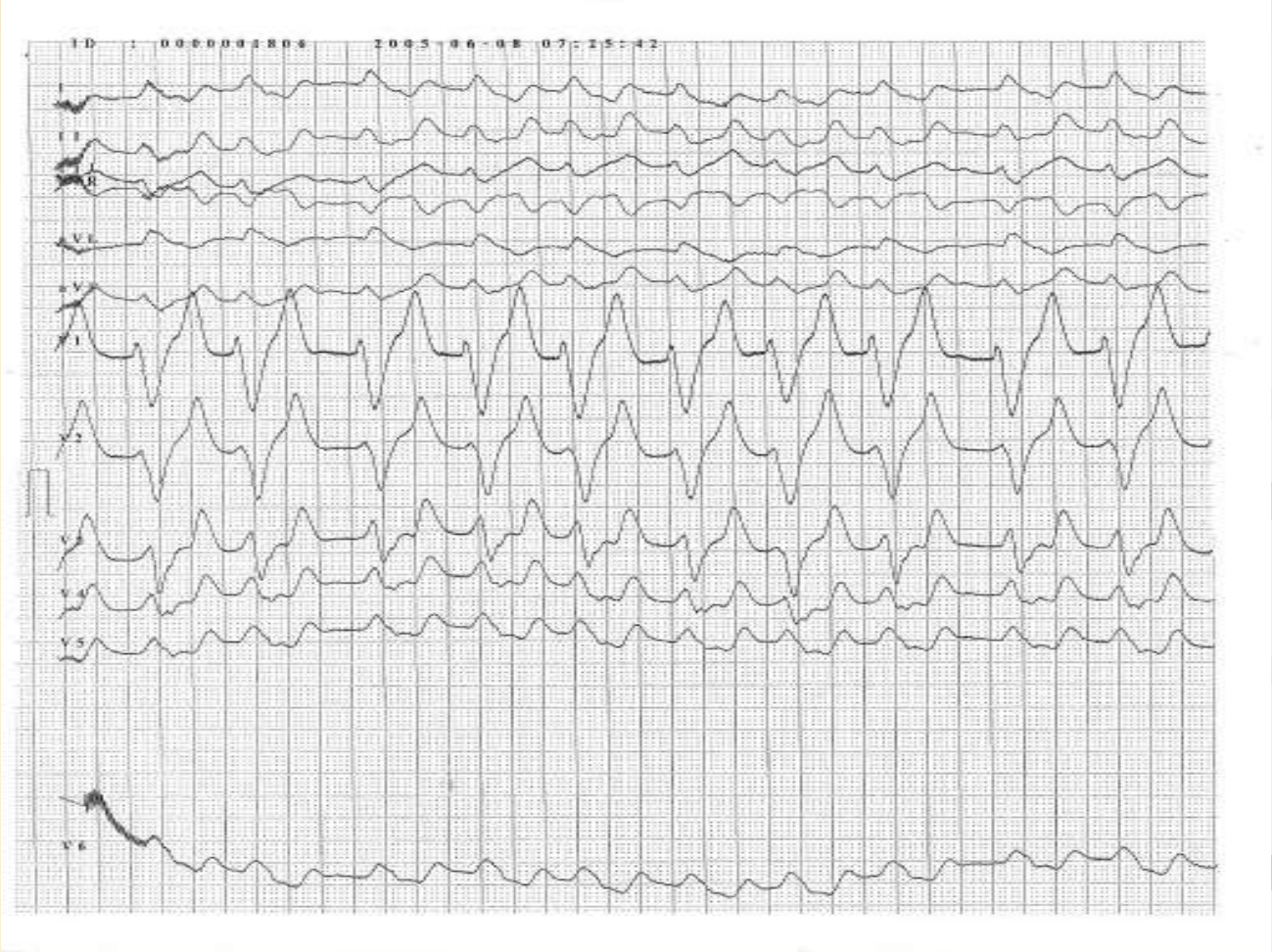


- Continually open ENaC
- Familiar HTN
- Suppressed renin and aldosterone
- Rx: amiloride, triamterene

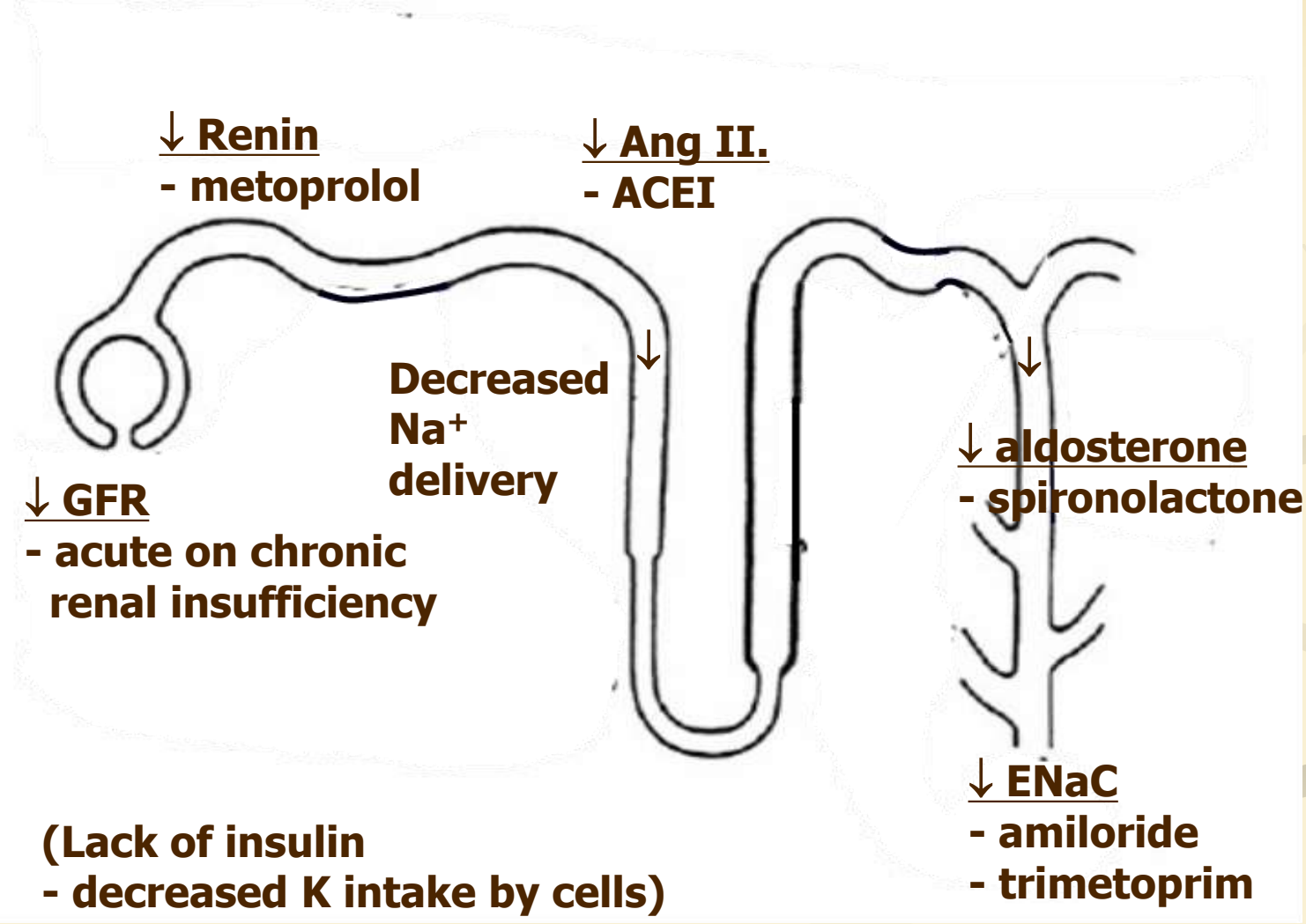


Liddle syndrome

Is this an emergency?



Life threatening hyperkalemia

- 82 years old female with HTN, DM, and CRF
- Serum creatinin earlier 150 umol/l
- Rx: 20 mg lisinopril, 20 mg spironolactone, 5 mg amiloride, 50 mg hydrochlorotiazide, 100 mg metoprolol, trimetroprim-sulfamethoxasol for one week
- Extremely week, unable to walk, than respiratory insufficiency developed
- Labs: serum Na 133 mmol/l, K 10,0 mmol/l, Cl 102 mmol/l, HCO3 18 mmol/l, kreat 265 umol/l, CN 31,5 mmol/l, Vc 26,4 mmol/l, urinary K 16 mmol/l.
- **How many reasons did she have for hyperkalemia?**

Inhibitors of renal potassium excretion