NIYAMATULLAH MEMORIAL ESSAY WRITING COMPETITION

"WATER METABOLISM AND DISORDERS OF WATER BACANCE"

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WATER METABOLISM AND DISORDERS OF WATER BALENCE

INTRODUCTION

Disorders of body fluids are among the most commonly encountered problems in clinical practice. Since body water is primary determinant of osmolality of extracellular fluid (ECF), disorders of water metabolism can be broadly divided into

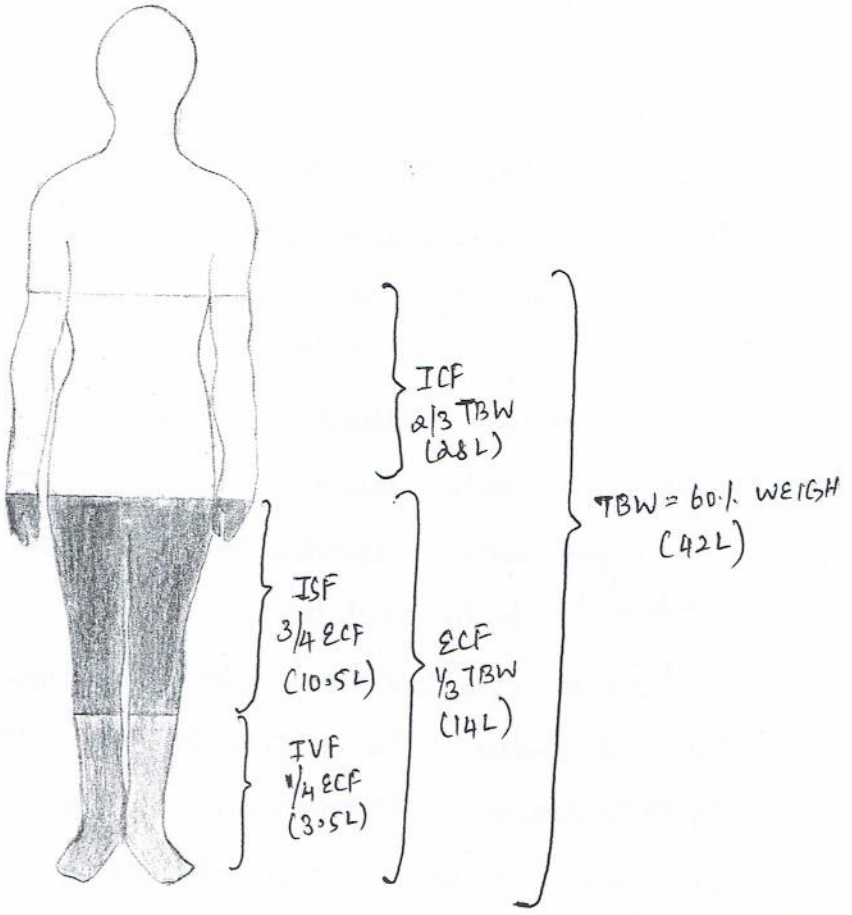
1) hypoosmolar disorder, in which there is excess of body water relative to body solute.

2) hyperosmolar disorder, in which there is deficiency of body water relative to body solute.

Because sodium is main constituent of plasma osmolality (Posm), these disorders are characterised by hyponatremia and hypernatremia respectively. Before discussing these disorders, lets first review the regulatory mechanisms underlying water and sodium metabolism, two major determinants of body fluid homeostasis.

BODY FLUID COMPARTMENTS

Water constitutes ~ 55-65% of body weight (BW), varying with age, sex and amount of body fat. TBW is distributed between ~~the~~ Intracellular Fluid (ICF) and ECF compartments.



SCHEMATIC REPRESENTATION OF BODY FLUID COMPARTMENTS

The shaded areas depicts the approximate size of each compartments in 70 kg adult.

TOTAL AND EFFECTIVE OSMOLALITY

Osmolality is defined as concentration of all solutes in given weight of water. Posm can be measured

(i) directly (via determination of freezing point depression (or) vapour pressure, since each of these are colligative properties of number of free solute particles in a given volume of plasma.

(or).

(ii) estimated as

$$P_{osm}\ (osm/kg\ H_2O) = 2 \times plasma\ [Na^+]\ (meq/L) + \frac{glucose\ (mg/dl)}{18} + \frac{BUN\ (mg/dl)}{2.8}$$

. Both (i) and (ii) produce comparable results under most conditions. However, Total osmolality of plasma is not always equivalent to "effective" osmolality. (K/A Tonicity of plasma) because the latter is function of relative solute permeability properties of membrane separating two compartments. Solute that are impermeable to cell membrane (Na^+, mannitol) are restricted to ECF compartments and are effective osmoles, since they create osmotic pressure gradient across cell membrane, leading to osmotic movement of water from ICF to ECF compartments. Solute that are permeable to cell membrane (urea, ethanol, methanol) are ineffective solutes, do not create osmotic pressure gradient and not associated with water shift. Glucose is unique solute, at normal physiologic plasma concentrations, taken up by cells via active mechanisms and therefore act as ineffective solutes, But under condition of impaired cellular uptake (eg. insulin deficiency) it becomes an effective solute.

WATER BALANCE AND OVERALL RENAL HANDLING OF WATER

3 major sources of water -

1) water ingested.

2) Water contained within food
3) Water produced by aerobic metabolism as mitochondria convert foodstuffs and O_2 to CO_2 and H_2O

INPUT

SOURCE	AMOUNT (ml)
Ingested fluids	1200
Ingested foods	1000
metabolism	300
	2,500

OUTPUT

ROUTE	AMOUNT (ml)
Urine	1500
Feces	100
Skin / sweat	550
Exhaled air	350
	2,500

* Kidney can generate a urine as dilute as 30 mosm (1/10 plasma osmolality) or as concentrated as 1200 mOsm (4x plasma osmolality).

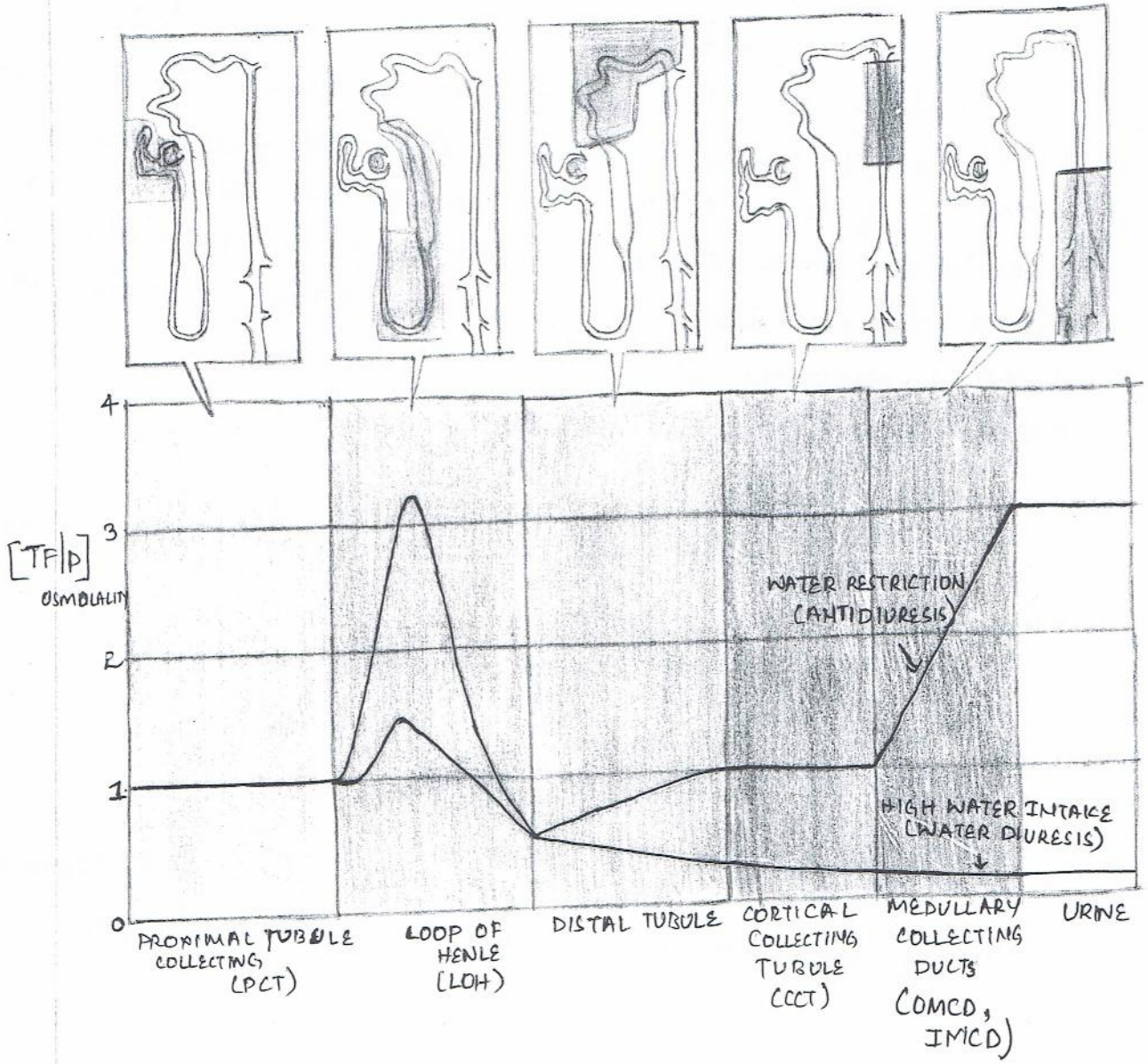
* Free water clearance is positive if kidney produces urine that is less concentrated than plasma and negative if kidney produces urine that is more concentrated than plasma.

$$\underset{\text{(Urine Output)}}{\dot{V}} = \underset{\text{(Osmolal clearance)}}{C_{osm}} + \underset{\text{(Free water clearance)}}{C_{H2O}}.$$

$$\boxed{C_{H2O} = \dot{V} - C_{osm}}$$

WATER TRANSPORT BY DIFFERENT SEGMENTS OF NEPHRON

* kidney generate concentrated Urine by using osmosis to desire water from tubule lumen, across a water-permeable epithelium into hyperatonic interstitium.



. RELATIVE OSMOLALITY OF TUBULE FLUID ALONG NEPHRON. PLOTTED ON Y-AXIS IS RATIO OF OSMOLALITY OF TUBULE FLUID (TF) TO OSMOLALITY OF PLASMA (P). ON X-AXIS REPRESENT DISTANCE ALONG NEPHRON

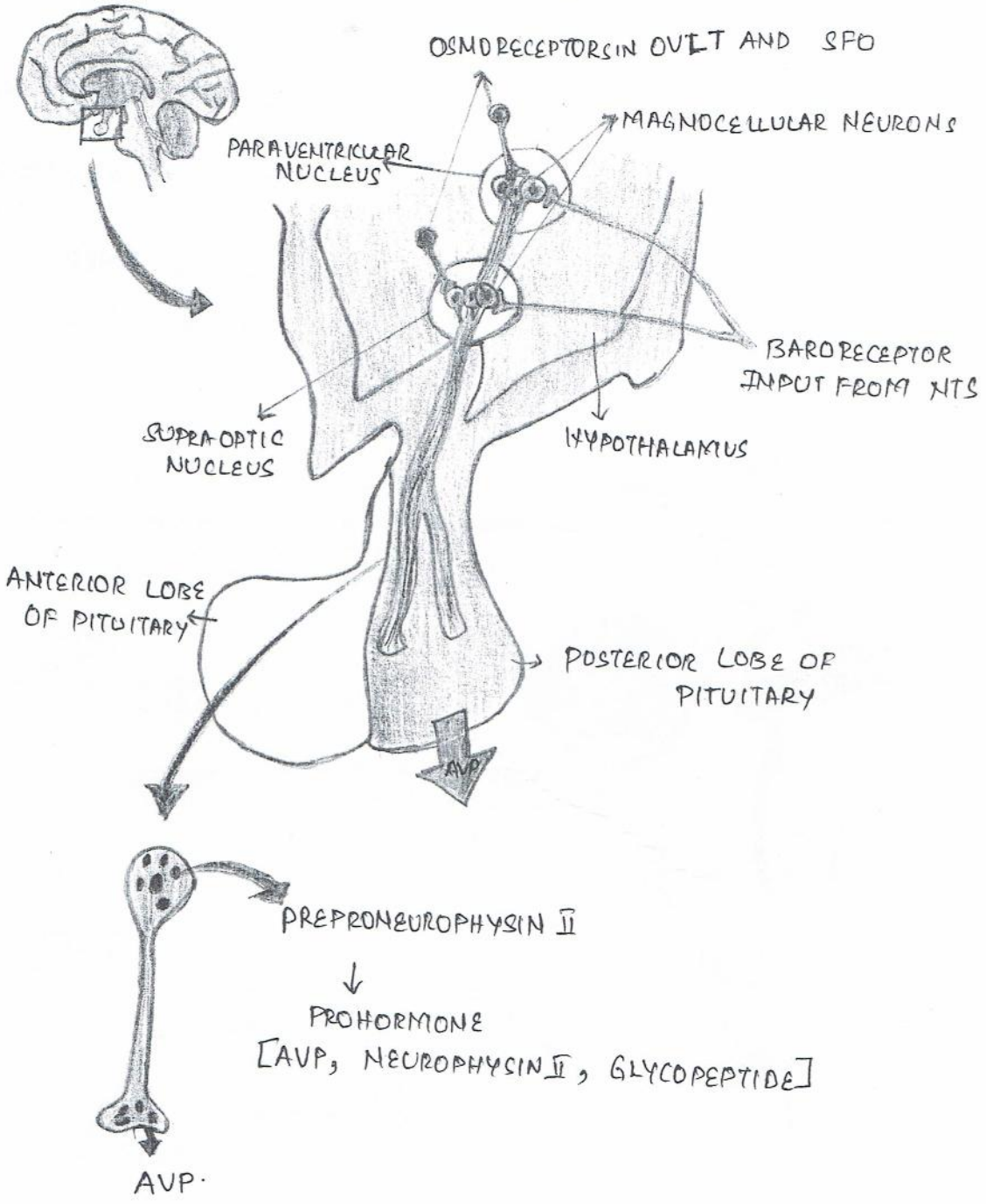
Tubular fluid is isotonic in PCT, become dilute in LOH and then either remains dilute or become concentrated by end of collecting duct.

Recurve: Under restricted water intake; elevated levels of Arginine Vasopressin (AVP), increase water permeability from Initial collecting Tubule (ICT) to end of Inner Medullary Collecting Duct (IMCD). So osmolality of tubular fluid increased along ICT, achieving osmolality of cortical interstitium (same as plasma osmolality ~290mOsm) by end of this nephron segment. MCD, luminal osmolality rises sharply as tubular fluid equilibrates with surrounding medullary interstitium, which become increasingly more hyperosmotic from corticomedullary junction to papillary tip MCDs responsible for concentrating final Urine.

* Two major mechanisms responsible for regulating water metabolism are
  (i) pituitary secretion of hormone vasopressin
  (ii) Thirst.

Arginine Vasopressin (AVP)

Large bodied neurons in paraventricular and supraoptic nuclei of hypothalamus synthesize AVP, 9-aminoacid peptide (aka ADH)



CONTROL OF AVP SYNTHESIS & RELEASE BY OSMORECEPTORS.

Signals from atrial, low pressure baroreceptor travel with vagus nerve to nucleus tractus solitarius (NTS).

2 ACTIONS OF AVP

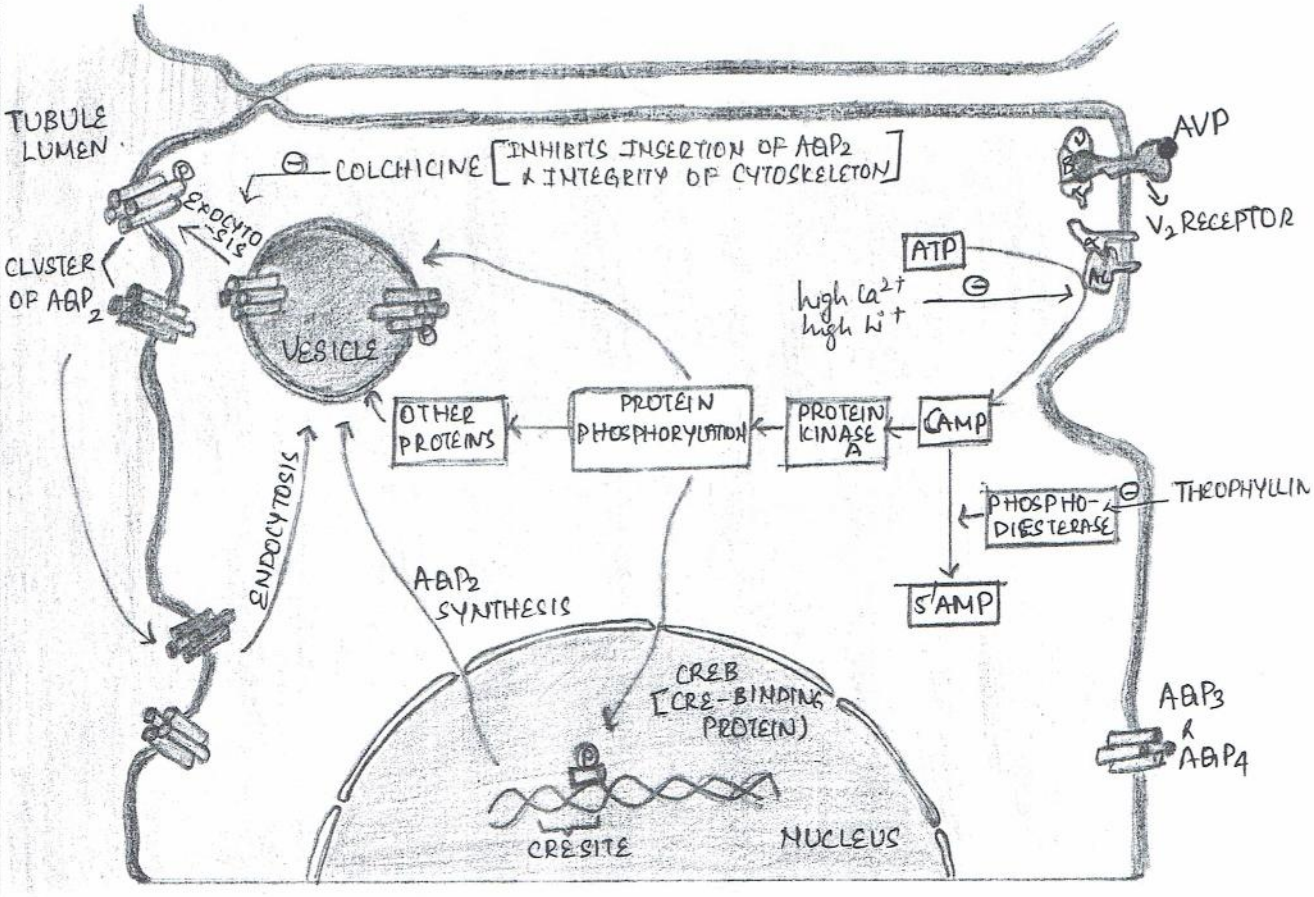
(i) IN HYPOVOLEMIC SHOCK – acts on vascular smooth muscle to cause vasoconstriction.

(ii) ACTS ON KIDNEY – Major regulator of water excretion by

a) increasing water permeability in all segments beyond DCT

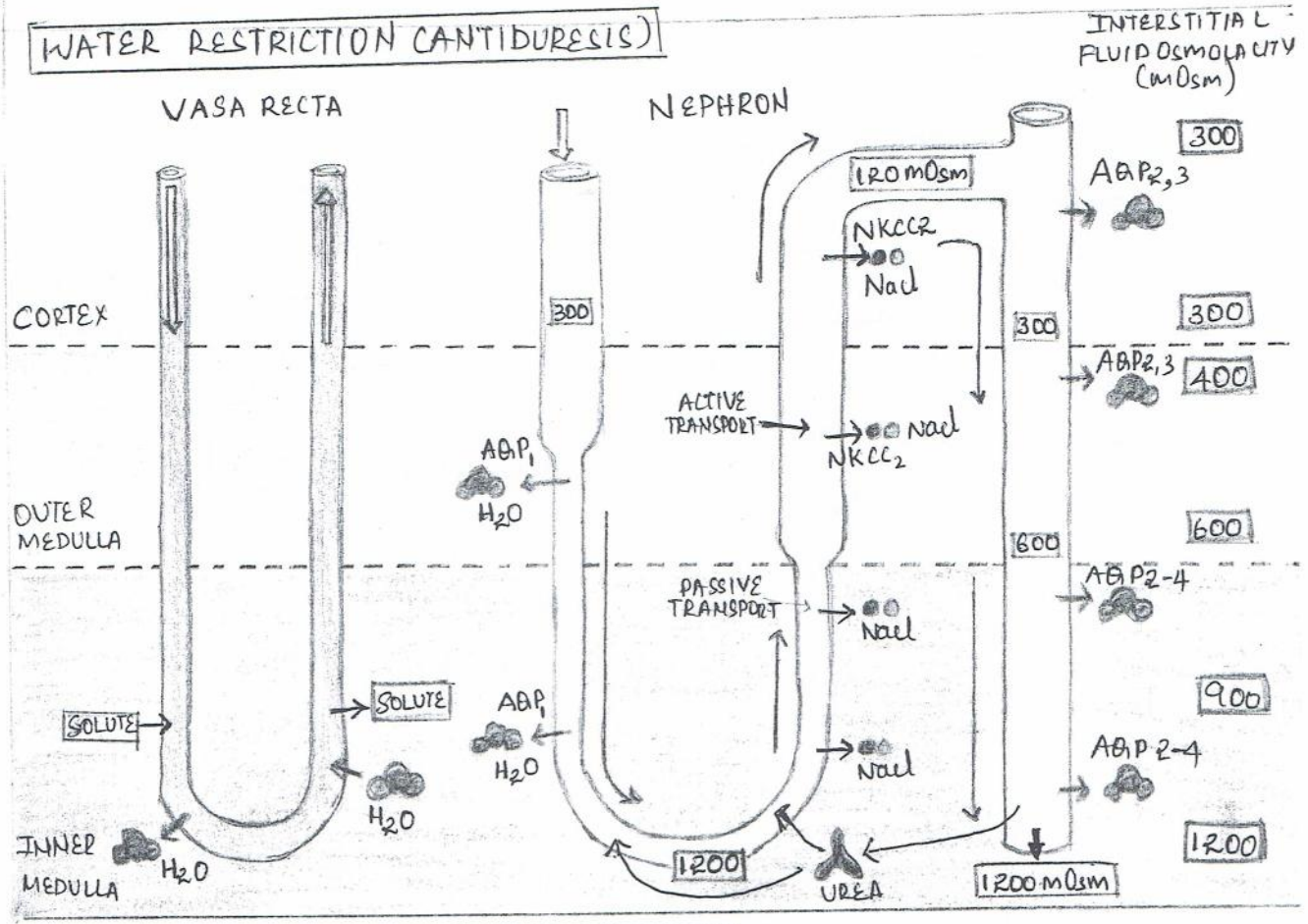
b) Increase Urea permeability in IMCD

3) Increase active NaCl reabsorption in TAL

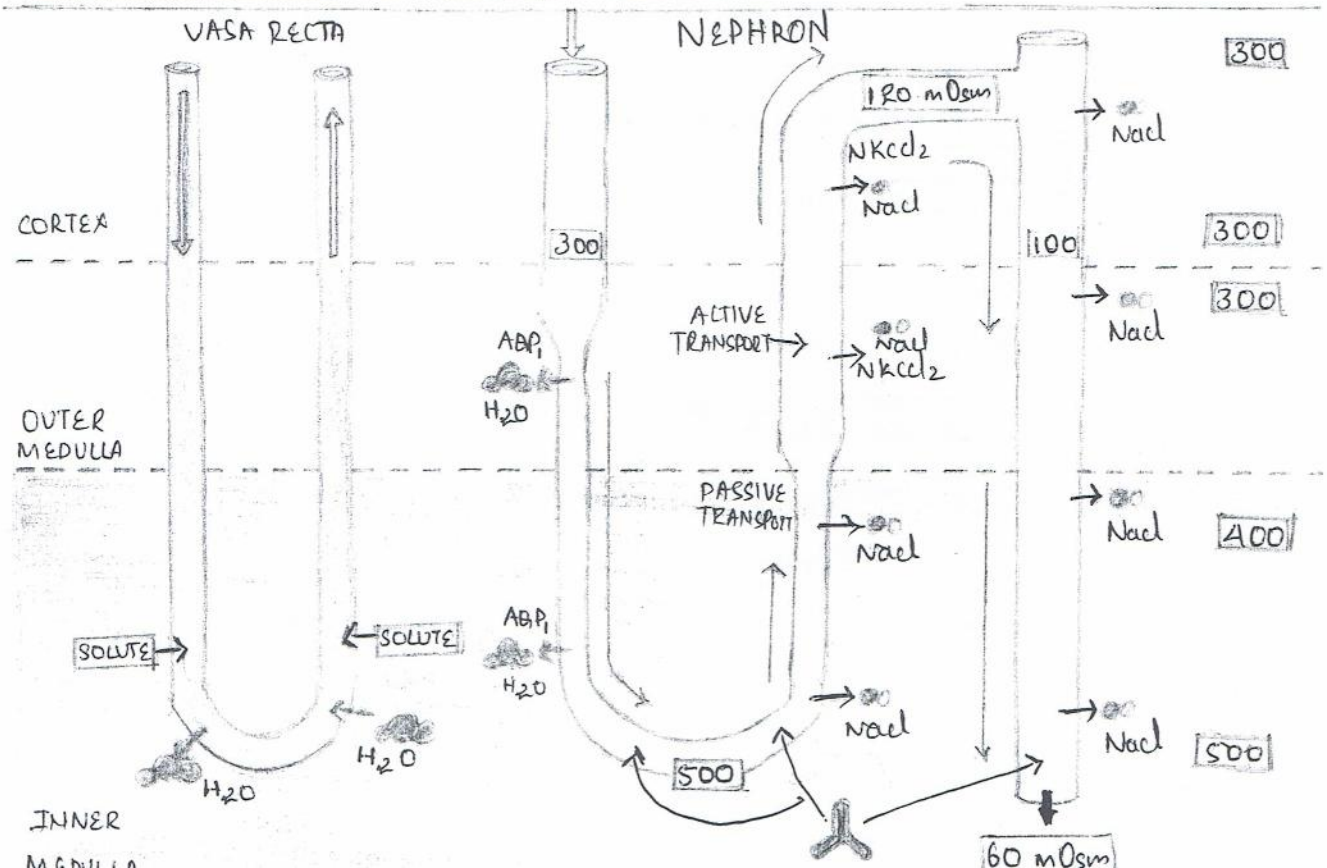


CELLUAR MECHANISM OF AVP ACTION IN COLLECTING TUBULE

WATER RESTRICTION (ANTIDURESIS)



HIGH WATER INTAKE (WATER DIURESIS)

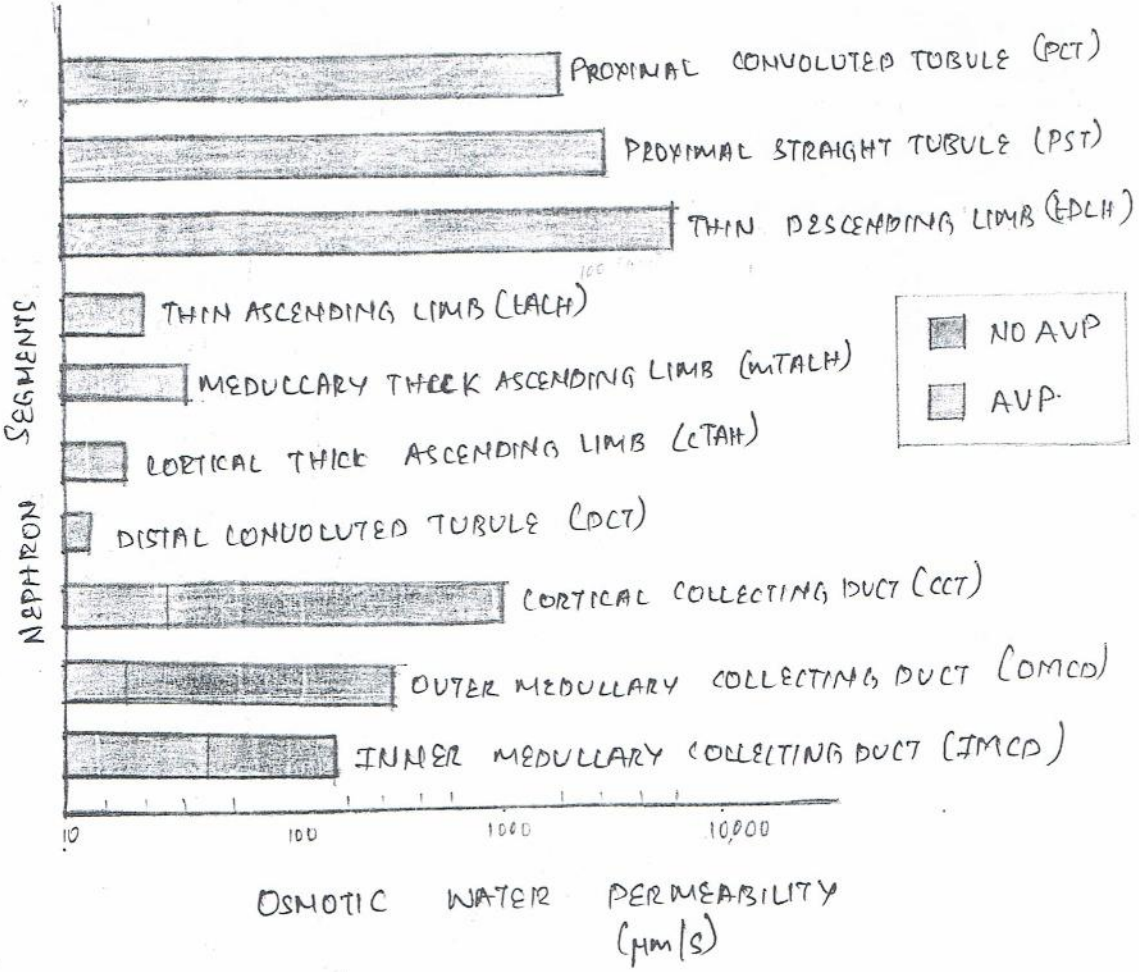


* Higest water permeability seen in PCT and tDLH → reflects abundant presence of AQP1 water channel in apical and basolateral cell membrane.

* AVP dramatically increases water permeabilities of collecting Tubules (JCT and CCT) and ducts (OMCD and IMCT) by causing AQP2 water channel to insert into apical membrane.

* AQP3, AQP4 → present in Basolateral cell membrane of MCDs

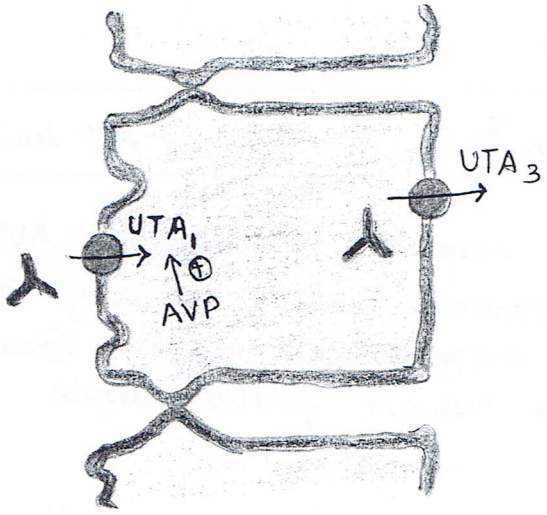
AQP_2 ⇒ sensitive to AVP
AQP_1, AQP_3, AQP_4 ⇒ insensitive to AVP.



WATER PERMEABILITY IN DIFFERENT NEPHRON SEGMENTES

In inner medullar, AVP enhances Urea permeability of terminal 2/3rd of IMCD. AVP- dependent increase in cAMP that triggers apical insertion of AQP_2- containing vesicles, also leads to phosphorylation of apical UT-A_1 (Urea transporter) & increases its activity. Substantial increase in Urea reabsorption and thus high interstitial Urea i.e indirectly responsible for generating osmotic gradient that drives water reabsorption in IMCD

IMCD



REGULATION OF WATER PERMEABILITY

SHORT TERM

AVP - through cAMP - stimulates vesicle containing water channel fuse to apical membrane from subapical pool

LONG TERM

AVP - by enchancing transcription of AQP_2 gene - increase abundance of AQP_2 protein in principle cells

* Breakdown of AVP take place in liver and kidney
* $t_{1/2}$ of AVP is 18 minute

congestive heart failure, congestion of liver, Renal impairment } can compromise breakdown of AVP → high circulating levels of AVP.

* 1% rise in plasma osmolality, 5 to 10% reduction in effective circulatory volume } ⊕ AVP release.

OSMOTIC REGULATION

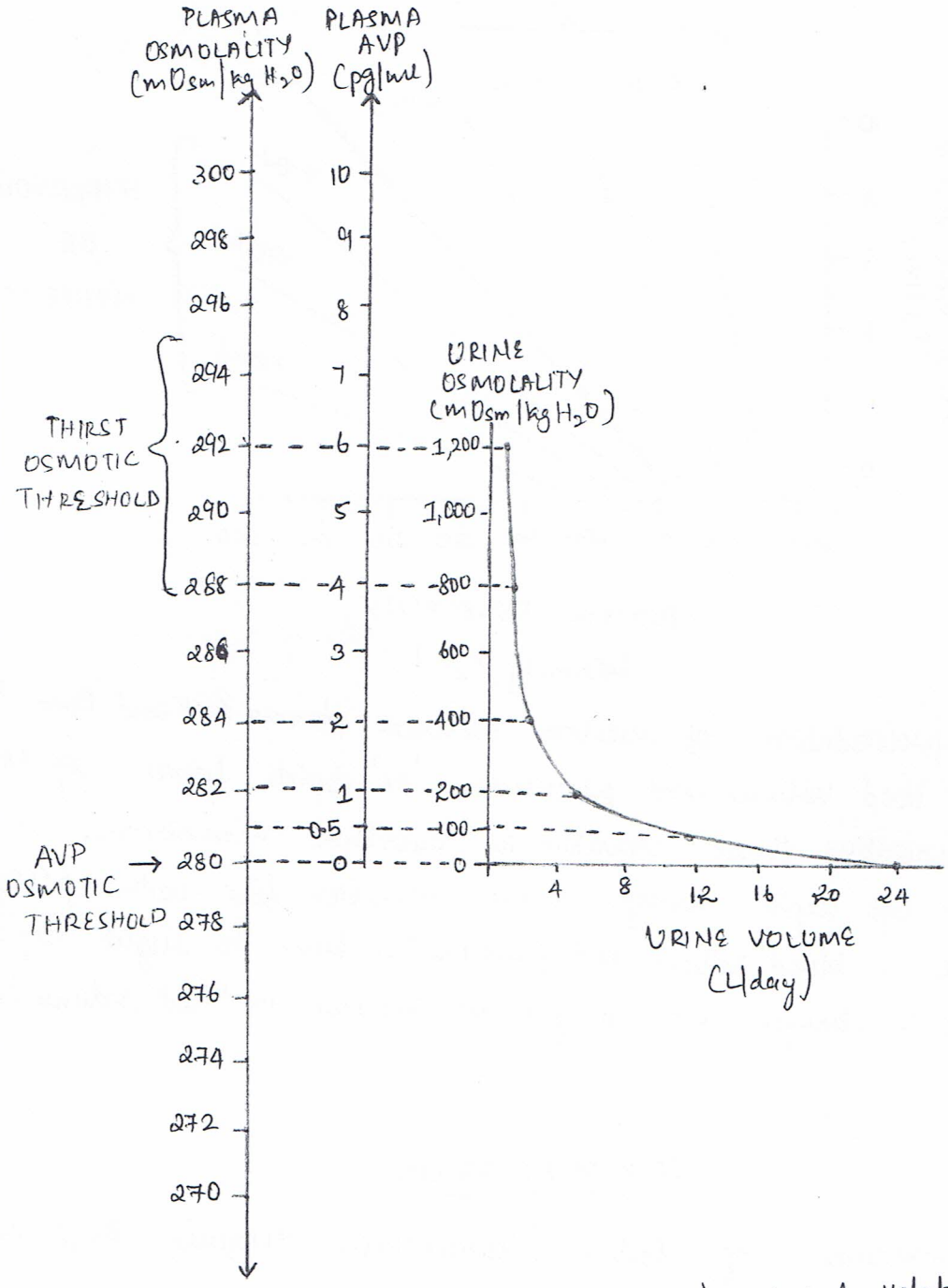
for each 1mOsm/kg H_2O ↑ in Posm ⇒ ↑ plasma AVP level of 0.4 to 0.8 pg/ml

* The renal response to circulating AVP is similarly linear, with Urinary concentration that is directly proportional to AVP levels from 0.5 to 4-5 pg/ml after which Urine Osmolality is maximal and cannot increase further despite additional increase in AVP level.

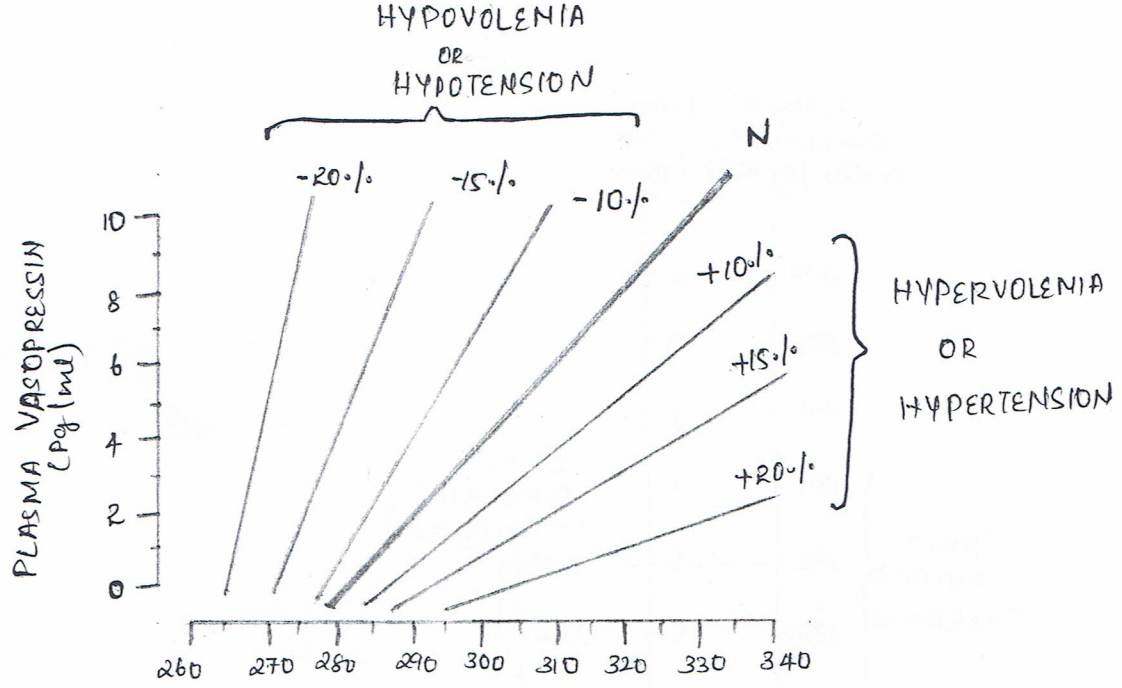
Thus, changes of 1% in Posmo are sufficient to cause significant ↑ in AVP levels and maximal antidiuresis is achieved ~~is~~ and after increase in Posm of 5-10 mOsm/kg H_2O (2-4%) above threshold for AVP secretion.

VOLUME REGULATION

In case of thirst, hypovolemia is stimulus for AVP secretion. AVP secretion is much less sensitive to small changes in Blood volume and Blood pressure than to changes in Osmolality



Schematic representation of normal physiological relationships among Posm, Plasma AVP, Uosm and Urine Volume. Note particularly inverse relationship between Uosm and Urine Volume, resulting in disproportionate effects of small changes in Plasma AVP on Urine [illegible] AVP levels



Representation of relation between plasma AVP and Posm under varying blood volume and pressure. 'N' depicts linear regression line associating these variable in euvolemic normotensive subjects. Lines to left depict change in this regression line with progressive decrease in blood volume and pressure. Lines to right depict the opposite changes with progressive increase in blood volume and pressure.

SODIUM METABOLISM

Maintainence of sodium homeostasis require simple balance between intake and excretion.

SALT APPETITE: A robust salt appetite occurs predominantly in adrenal insufficiency and related to high ACTH, produced as a result of loss of cortisol feedback on pituitary.

DISORDERS OF WATER BALANCE

HYPEROSMOLALITY AND HYPERNATREMIA

Hyperosmolality refers to deficiency of water relative to solute in ECF.
Hypernatremia → can be caused by excess of body sodium. Vast majority of cases due to loss of body water in excess of body solute.

Pathogenesis of hyperosmolar disorder

WATER DEPLETION (DECREASE IN TOTAL BODY WATER IN EXCESS OF BODY SOLUTE).

1. INSUFFICIENT WATER INTAKE:
   - Hypodipsia (osmoreceptor dysfunction, age)
   - Neurological deficits (cognitive dysfunction, motor impairment).

2. HYPOTONIC FLUID LOSS:

   A. RENAL: Diabetes insipidus
   - Insufficient AVP secretion (central DI, Osmoreceptor dysfunction)
   - Insufficient AVP effect (nephrogenic DI)

   B. RENAL: Other fluid loss
   - Osmotic diuresis (hyperglycemia, mannitol).
   - Diuretic drugs (furosemide, ethacrynic acid, thiazides)
   - Postobstructive diuresis
   - Diuretic phase of acute tubular necrosis

   C. NONRENAL FLUID LOSS:
   - Gastrointestinal (vomiting, diarrhoea, nasogastric suction).
   - cutaneous (sweating, burns).
   - Pulmonary (hyperventilation).
   - Peritoneal dialysis.

SOLUTE EXCESS (INCREASE IN TOTAL BODY SOLUTE IN EXCESS OF BODY WATER)

1. SODIUM:
   - Excess Na^+ administration ($NaCl$, $NaHCO_3$)
   - Sea water drowning.
2. OTHER:
   - Hyperalimentation (intravenous, parenteral).

COMMON ETIOLOGIES OF POLYDIPSIA AND HYPOTONIC POLYURIA

CENTRAL (NEUROGENIC) DIABETES INSIPIDUS

- Congenital (congenital malformations; autosomal dominant: AVP-neurophysin gene mutation)
- Drug | Toxin - induced (ethanol, diphenylhydantoin, snake venom)
- Granulomatous (histiocytosis, sarcoidosis)
- Neoplastic (craniopharyngioma, meningioma, germinoma, metastases, pituitary tumour)
- Infectious (meningitis, encephalitis)
- Inflammatory | autoimmune (lymphocytic infundibulo neurohypophysitis)
- Trauma (neurosurgery, deceleration injury)
- Vascular (cerebral hemorrhage or infarction).

Nephrogenic diabetes insipidus

- Congenital (X-linked recessive: AVP V_2 receptor gene mutation; Autosomal recessive: AQP_2 gene mutation).
- Drug induced (demeclocycline, lithium, cisplatin, methoxyflurane)
- hypercalcemia
- hypokalemia
- Infiltrating lesions (sarcoidosis, amyloidosis)
- Vascular (sickle cell anemia).

OSMORECEPTOR DYSFUNCTION:

- Granulomatous (histiocytosis, sarcoidosis)
- Neoplastic (craniopharyngioma, pinealoma, meningioma, metastasis)
- Vascular (anterior communicating artery aneurysm/ ligation, intrahypothalamic hemorrhage)
- other (hydrocephalous, ventricular/suprasellar cyst, trauma, idiopathic)

Increased AVP metabolism:

- pregnancy.

Primary polydipsia:

- psychogenic (schizophrenia)
- Dipsogenic (downward resetting of thirst threshold: ≈ to central DI).

DISTINGUISHING BETWEEN CENTRAL AND NEPHROGENIC DI

Evaluating response to administration of desmopressin (d DAVP) 1μg SC (@1) IV → significant increase in Uosm within 1 (@1) 2 hr after injection indicates insufficient endogenous AVP secretion (central DI). Although conceptually simple, interpretation of difficulties often arise because water diuresis produced by AVP deficiency produces a 'wash-out' of renal medullary concentration gradient, so increase in Uosm in response to AVP are not as great as would be expected.

Increase in Uosm of 50% → central DI

Increase in Uosm of <10% → nephrogenic DI

Response between 10-50% are less certain.

For this reason, plasma AVP level is measured to aid in this distinction.

MANAGEMENT OF HYPERNATREMIA

Hypernatremia is frequently a preventable electrolyte disorder if water losses are recognized and appropriately replaced. Treatment depends on two important factors:

(i) ECF volume status
(ii) Rate of development of hypernatremia

Correction of ECF volume depletion:

Primary goal is to administer isotonic saline until restoration of ECF volume is achieved, as assessed by neck veins, absence of orthostatic hypotension and tachycardia. Hypotonic (0.45%) NaCl (or) 5% glucose solutions can be used to correct plasma osmolality.

Correction of ECF volume expansion:

Diuretics (eg furosemide) with liberal fluid intake can be used to correct hyponatremia. In presence of advanced renal failure, may need to be dialyzed.

Water replacement method of calculation:

eg: method of calculation of necessary water replacement in a 75kg man with plasma sodium of 154 meq/L is as

$$\boxed{TBW = \text{Body weight} \times 60\%}$$

$$TBW = 75 \times 0.6 = 45L$$

$$\boxed{\frac{\text{Actual Plasma sodium}}{\text{Desired plasma sodium}} \times TBW} = \frac{154\ meq/L}{140\ meq/L} \times 45L = 49.5L$$

- Therefore repletion of 4.5L (49.5 - 4.5L) positive water balance

Rate of correction :

Depends on rate of development of hypernatremia and symptoms. More neurological signs and symptoms are associated with acute hypernatremia, therefore this biochemical abnormality should be corrected rapidly, over few hours

Concurrently idiogenic osmoles appear to accumulate in brain cells during chronic hypernatremia, as mechanism to protect against shrinkage. So correction is done gradually, at a rate not to exceed 2mOsm/hour. One half of correction can be achieved in 24 hours and other half in next 24 hours or longer.

Management of Diabetes insipidus

Central DI :* Desmopressin (DDAVP), a synthetic analogue of AVP

* Increases urine concentration and decrease Urine flow in a dose-dependent manner.

* can be given by IV or sc injection, Nasal inhalation, or oral.

* Onset of action ~15 mins after injection, 60 mins after oral route.

* produces slight increase (1-3 l) in total body water and a decrease in plasma osmolarity, that eliminates thirst and polydipsia.

Nephrogenic DI :* Thiazide diuretic and/or amiloride in conjunction with low-sodium diet and prostaglandin synthesis inhibitor (eg. Indomethacin) usually reduces polyuria and polydipsia by 30-50% and may eliminate completely in some patients.

HYPO OSMOLALITY AND HYPONATREMIA

Hypo osmolality indicates excess water relative to solute in ECF, because water moves freely between ECF and ICF. It indicate an excess of TBW relative to total body solute.

HYPONATREMIA AND HYPOOSMOLALITY ARE USUALLY SYNONYMOUS WITH TWO EXCEPTIONS

① pseudohyponatremia: produced by marked elevation of serum lipids and proteins

② HIGH concentration of effective solutes other than sodium
eg: glucose - can cause relative decrease in serum [Na⁺] despite an unchange in Posm

misdiagnosis can be avoided by
1) direct measurement of Posm
2) correcting serum [Na⁺] by 1.6 meq/L for each 100mg/dl increase in plasma glucose concentration above 100mg/dl.

PATHOGENESIS OF HYPOOSMOLAR DISORDERS

SOLUTE DEPLETION (Primary decrease in total body solute plus secondary water retention

I RENAL SOLUTE LOSS:
- Diuretic use
- Solute diuresis (glucose, mannitol)
- Salt wasting nephropathy
- mineralocorticoid deficiency.

2. NON RENAL SOLUTE LOSS:

- Gastrointestinal (diarrhoea, vomiting, pancreatitis, bowel obstruction
- Cutaneous (sweating, burns)
- Blood loss.

SOLUTE DILUTION (primary increase in TBW ± secondary solute depletion)

1. IMPAIRED RENAL FREE WATER EXCRETION

A. INCREASED PROXIMAL NEPHRON REABSOPTION:

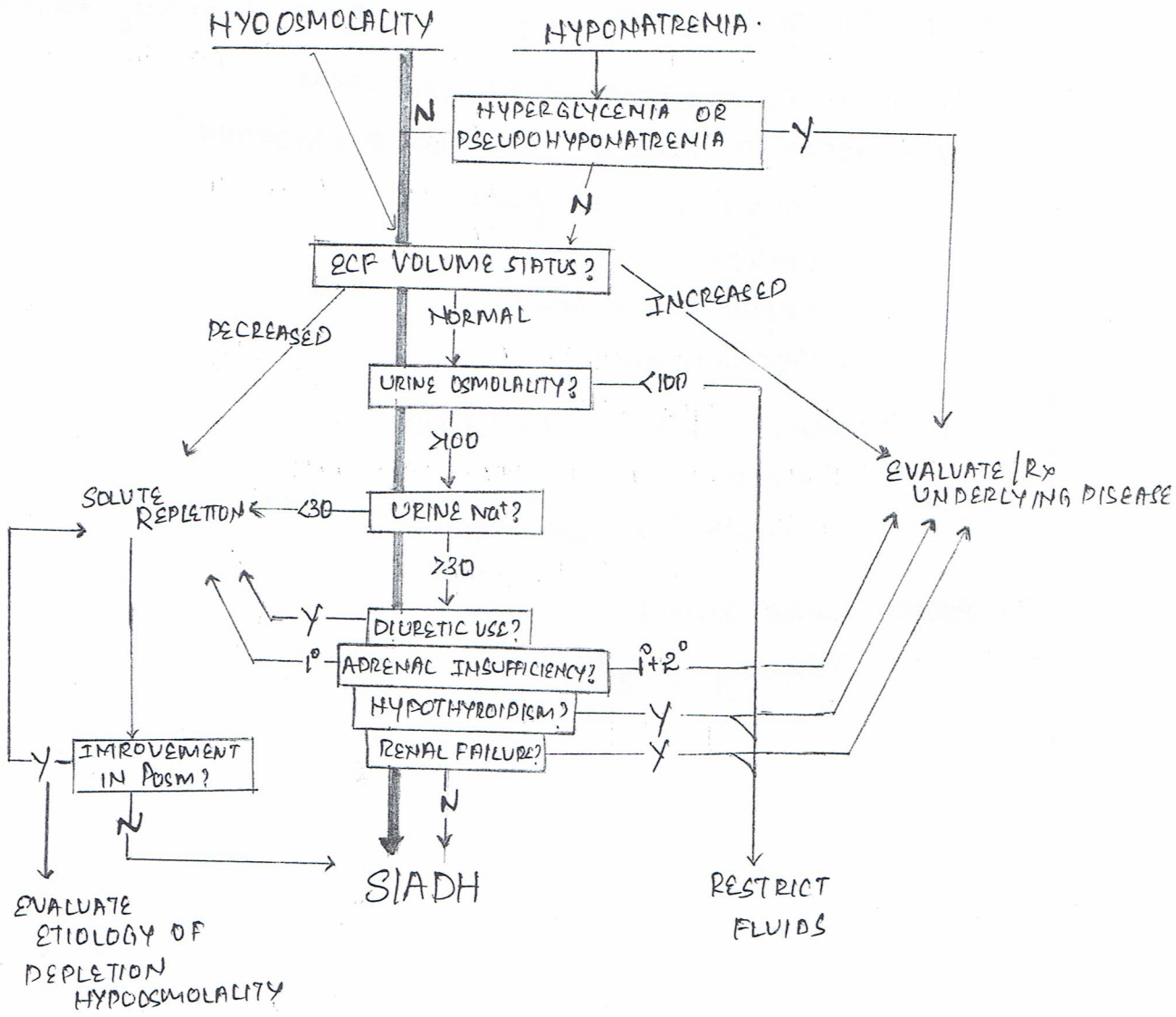
- Congestive heart failure
- cirrhosis
- Nephrotic syndrome
- Hypothyroidism

B. IMPAIRED DISTAL NEPHRON DILUTION:

- SIADH
- Glucocorticoid deficiency

2. EXCESS WATER INTAKE

- Primary polydipsia



SCHEMATIC SUMMARY OF EVALUATION OF HYPOOSMOLAR PATIENTS.
DARK ARROW IN CENTRE → emphasize presence of CNS dysfunction due to hyponatremia should always be assessed immediately, so that appropriate therapy can be started as soon as possible in symptomatic patients

ABBREVIATIONS

N → no
Y → yes
ECF → extracellular fluid volume
Rx → Treat
1° → primary
2° → secondary
SIADH → Syndrome of inappropriate antidiuretic hormone secretion.

COMMON ETIOLOGIES OF SIADH

TUMORS:
- pulmonary/mediastinal (bronchogenic carcinoma, mesothelioma, thymoma)
- Nonchest (duodenal carcinoma, pancreatic carcinoma, urethral/prostate carcinoma, uterine carcinoma, nasopharyngeal carcinoma, leukaemia)

CNS DISORDERS:
- Mass lesion (Tumors, brain abscesses, subdural hematoma)
- Inflammatory disease (encephalitis, meningitis, systemic lupus)
- Degenerative/demyelinative disease (Guillain-Barre, spinal cord lesions)
- Miscellaneous (subarachnoid hemorrhage, head trauma, acute psychosis, delirium tremens, pituitary stalk lesions).

Drug induced:
- Stimulated AVP release (Carbine, phenothiazines, tricyclic)
- Direct renal effects and/or potentiation of AVP effects (dDAVP, oxytocin, prostaglandin synthesis inhibitors)
- Mixed or uncertain actions (chlorpropamide, clofibrate, carbamazepine, cyclophosphamide, Vincristine)

Pulmonary disease :

- Infections (Tuberculosis, aspergillosis, pneumonia, empyema)
- mechanical/ventilatory (acute respiratory failure, chronic obstructive pulmonary disease [COPD], positive pressure ventilation).

CRITERIA FOR DIAGNOSIS OF SIADH

ESSENTIAL :

1. Decreased effective osmolality of ECF (P_{osm} < 275 mOsm/kg H_2O)
2. Inappropriate Urinary concentration (U_{osm} > 100 mOsm/kg H_2O with normal renal function) at some level of hypoosmolality.
3. clinical euvolemia, as defined by absence of signs of hypovolemia (orthostasis, tachycardia, decreased skin turgor, dry mucous membr or hypervolemia (subcutaneous edema, ascites).
4. Elevated Urinary sodium excretion which on a normal salt and water intake
5. Absence of other potential causes of euvolemic hypoosmolality: hypothyroidism, hypocortisolism (Addison's disease or pituitary ACTH insufficiency) and diuretic use.

SUPPLEMENTAL :

6. Abnormal water load test (inability to excrete atleast 80% of 20 ml/kg water load in 4hr and/or failure to dilute Urine to < 100 mOsm/kg H_2O
7. Plasma AVP level inappropriately elevated relative to P_{osm}
8. No significant correction of serum [Na^+] with volume expansion but improvement after fluid restriction.

MANAGEMENT OF HYPONATREMIA

Factors affecting approach to treatment?

* presence (or) absence of symptoms
* duration of hyponatremia [because time dependent process are involved in adaptation to tonicity change and presence of cerebral symptoms reflect a failure of adaptation]

In this regard, hyponatremia developing within 48hours carries greater risk of permanent neurologic sequale from cerebral edema, if plasma sodium correction is not corrected expeditiously. Conversely, Chronic hyponatremia are at risk of osmotic demyelination, if corrected too rapid.

Acute symptomatic hyponatremia:

* Aim to raise serum[Na^+] by 2mmol/L/hr until symptoms subside
* Hypertonic saline (3% NaCl) is infused at rate of 1 to 2ml/kg/hour and Loop diuretic – furosemide, enhances solute-free water excretion and hastens, return to normal serum [Na^+]
* If severe neurological symptoms (Obtundation or coma) are present, 3% NaCl infused at 4 to 6ml/kg/hour.

chronic symptomatic hyponatremia:

[hyponatremia >48hrs ordination is unknown].

FOLLOWING GUIDELINES ARE FUNDAMENTAL TO SUCCESSFUL THERAPY

1. Because cerebral water is increased only by ~10% in severe chronic hyponatremia, promptly increase serum[Na^+] level by 10%.

(or) by ~10meq/L.

2. After initial correction, do not exceed a correction rate of 1.0 to 1.5 meq/L/hour

3. Do not increase serum[Na^+] by more than 12meq/L/24 hours

(or) 18meq/L/48hours.

chronic asymptomatic hyponatremia:

Hypothyroidism & adrenal insufficiency are sought as possible etiologies and hormone replacement if deficient.

MANAGEMENT OF SIADH

1) FLUID RESTRICTION

2) PHARMACOLOGICAL AGENTS:

DEMECLOCYCLINE: Inhibits formation and action of cAMP in renal CT

* Onset: 5 to 6 days after treatment started
* metabolized by liver
* DO not combine with calcium, aluminium, magnesium containing antacids.

VASOPRESSIN ANTAGONIST

CONIVAPTANS
* IV formulation
* antagonize both V_{1a} and V_2 receptors
* approved for SIADH and hypervolemic hyponatremia associated with cardiac failure

(which V_{1a} component may improve heart function by decreasing cardiac afterload)

* CI: cirrhosis (increases splanchnic flow).

TOLVAPTANS
LIXIVAPTANS
SATAVAPTANS
→ * available as oral formula
* increase solute-free water excretion in cardiac failure, cirrhosis & SIADH

SOLUTE DEPLETION: Restoration of ECF volume with crystalloids (or) colloids interrupts non osmotic release of vasopressin

SOLUTE DILUTION: requires attention to underlying disorder of CHF, CRF and CLD.
* $[Na^+]$ and water restriction
* Refractory patients → treated with combination of ACE inhibitors and diuretics

[Resultant increase in cardiac output with ACE inhibitor may increase solute free water excretion and correct hyponatremia.
LOOP DIURETICS - diminish action of vasopressin on collecting tubules thereby increasing solute free water excretion. THIAZIDE DIURETICS IMPAIRS URINARY DILUTION & WORSEN HYPONATREMIA]