M.Sc. 4th Semester
Subject: Human Physiology
Paper: PHY-401
Unit:33
Module: 02
Topics: Neurohypophysial hormones
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NEUROHYPOPHYSIAL HORMONES

Dr. Ankita Das

Posterior Pituitary

Comprised of the endings of axons from cell bodies in the hypothalamus (supraoptic and paraventricular nuclei)

Axons pass from the hypothalamus to the posterior pituitary via the hypothalamohypophysial tract

Posterior pituitary hormones are synthesized in the cell bodies of neurons in the supraoptic and paraventricular nuclei

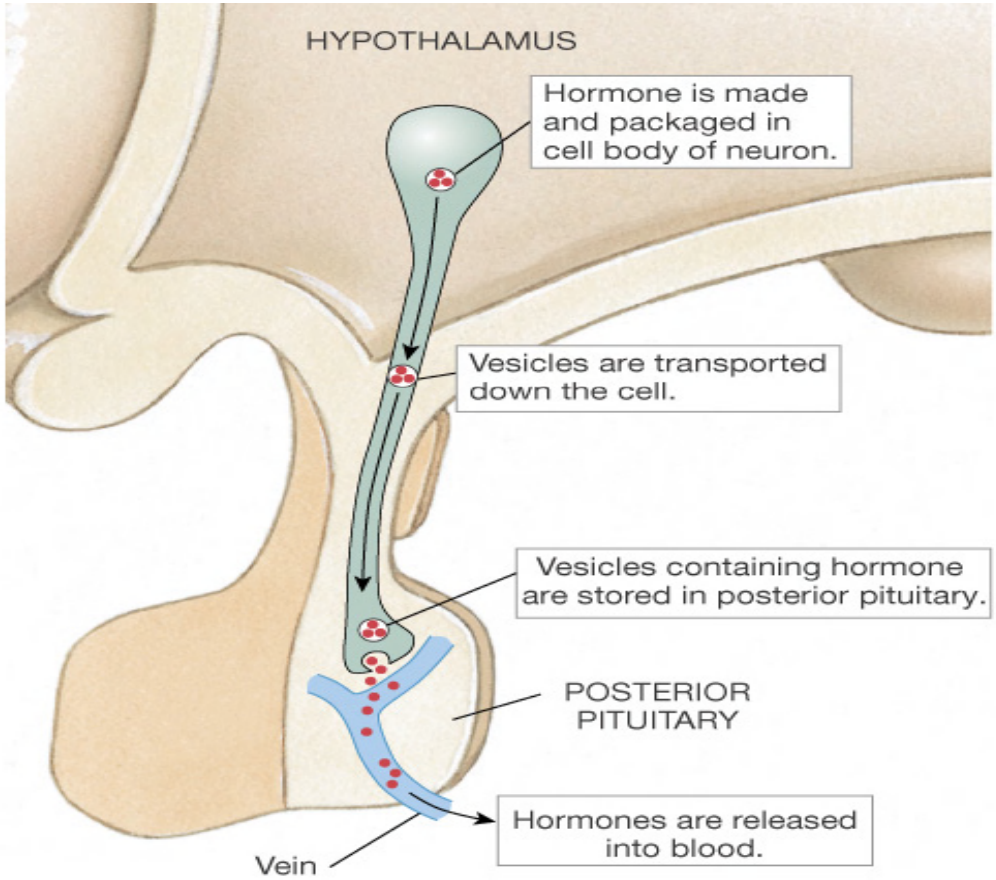
Posterior Pituitary

Hormones synthesized in the hypothalamus are transported down the axons to the endings in the posterior pituitary

Hormones are stored in vesicles in the posterior pituitary until release into the circulation

Principal Hormones: **Vasopressin & Oxytocin**

Secretion of Posterior Pituitary Hormones



Synthesis, storage, and release of posterior pituitary hormones

Vasopressin & Oxytocin

–are nine amino acid peptide hormones

–are synthesized in magnocellular neurons of the paraventricular and supraoptic hypothalamic nuclei.
–are encoded by separate, closely-linked genes that were likely derived from a common ancestral gene.
–are synthesized from larger precursor hormones that also encode a neurophysin, the function of which is critical to processing of AVP and oxytocin
–are released by exocytosis from axon terminals in the posterior pituitary to reach the systemic circulation

Vasopressin (Antidiuretic Hormone)

Overview of Physiology & Pharmacology

• physiological role in regulating fluid volume and plasma osmolality, primarily through its ability to enhance fluid reabsorption from the distal tubule and cortical collecting duct of the kidney.

• disorders of the vasopressinergic system include:

–neurogenic diabetes insipidus

» treated primarily with ***desmopressin (dDAVP), a synthetic AVP***

–nephrogenic diabetes insipidus

» treated with thiazide diuretics

–Syndrome of Inappropriate ADH secretion (SIADH)

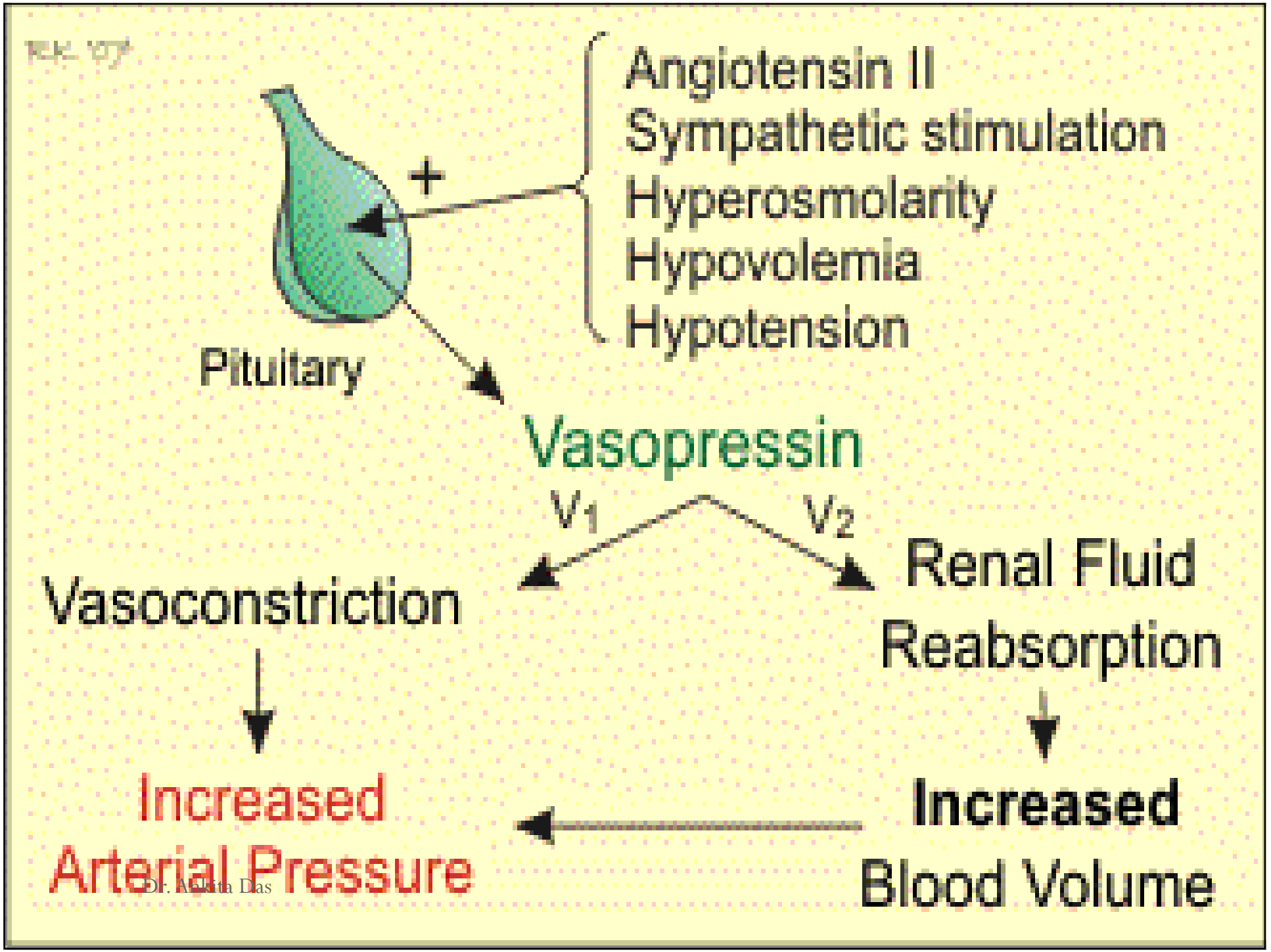
» often asymptomatic, but may be treated with demeclocycline, which interferes with AVP action

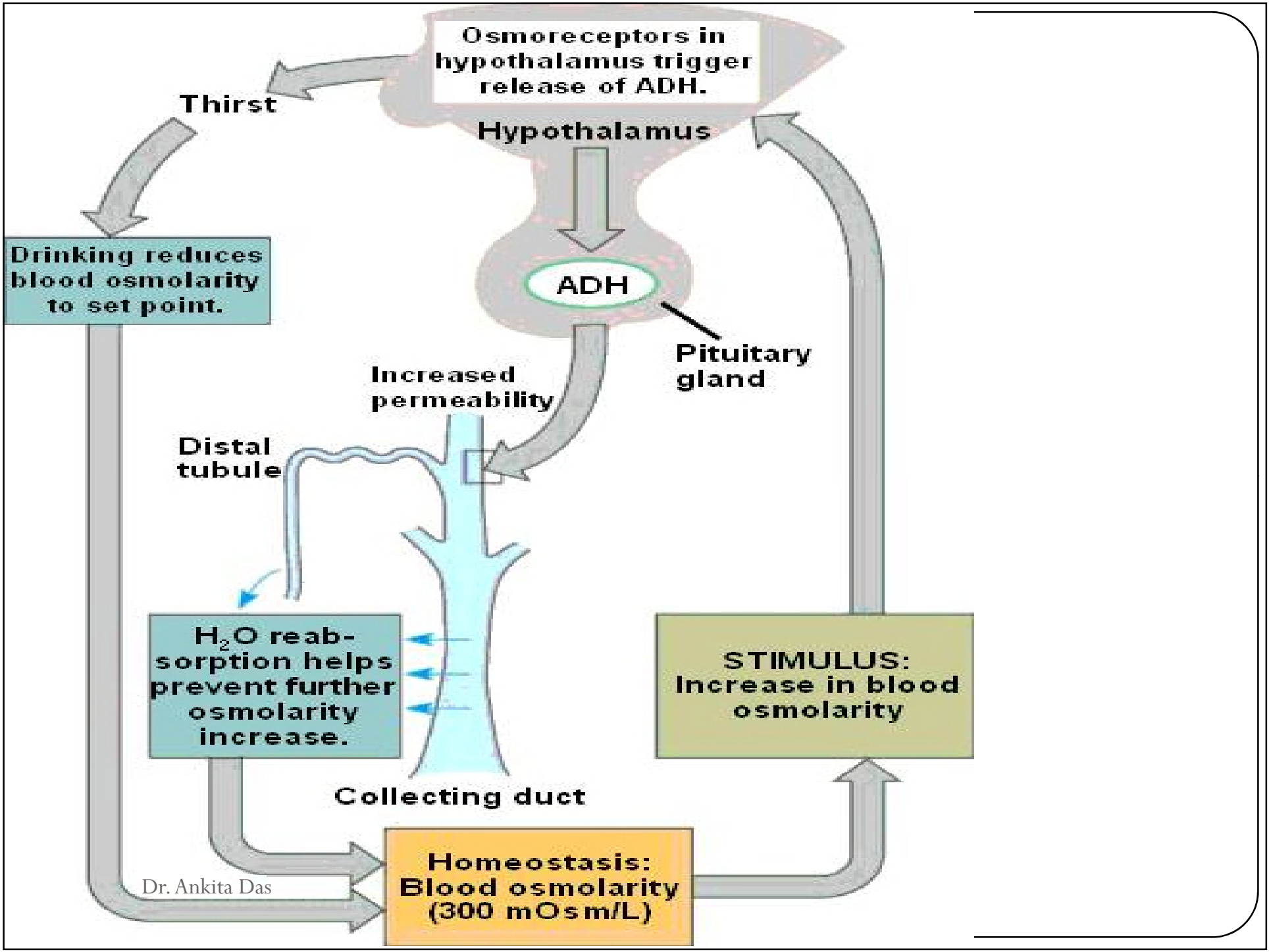
Vasopressin Physiology

• release of AVP from posterior pituitary is:
–increased with increases in plasma osmolality
–inhibited by increases in blood volume and blood pressure
–enhanced by AngII (Angiotensin II) and inhibited by ANP (Atrial natriuretic peptide)
–inhibited by alcohol

• AVP has cardiovascular, pituitary and renal effects
–via V1a receptors, coupled to phospholipases, it causes vasoconstriction
–via V1b receptors, also coupled to phospholipases, it enhances ACTH release (synergistically with CRF)
–via V2 receptors, positively coupled to adenylyl cyclase, it stimulates water reabsorption from the renal distal tubule and collecting duct and causes excretion of a sparse, concentrated urine

- **Vasopressin (Anti Diuretic Hormone)**
  - Some control via anterior hypothalamus
    - Contains separate osmoreceptors which aid in ADH release and thirst regulation
  - Osmotic stimulus
    - Sodium
    - Mannitol
  - Non osmotic factors
    - Blood pressure and volume at extremes
    - Nausea
    - Angiotensin II
    - Insulin induced hypoglycemia
    - Acute hypoxia
    - Acute hypercapnia





Oxytocin

Overview of Physiology & Pharmacology

–endocrine component of neuroendocrine reflex arc that mediates suckling-induced lactation (the milk 'let-down' reflex).

» may be used to assist with breast-feeding

–a potent stimulant of uterine contraction and may be involved physiologically in parturition

» oxytocin is used pharmacologically to induce or augment labor or to reduce post-partum bleeding

• other uterine motility agents

–stimulants of utrine motility include prostaglandins and ergot alkaloids

–inhibitors are ß2-adrenergic agonists, $MgSO_4$, nifedipine & alcohol

Oxytocin Physiology

• Release of oxytocin is triggered by:

–stimulus of the nipples, as in suckling

–distention of the cervix and vagina during delivery

• Effects of oxytocin are

–mediated by G-protein-coupled receptor, acting via phospholipase C and increases in intracellular calcium to stimulate smooth muscle contraction (activation of MLCK)

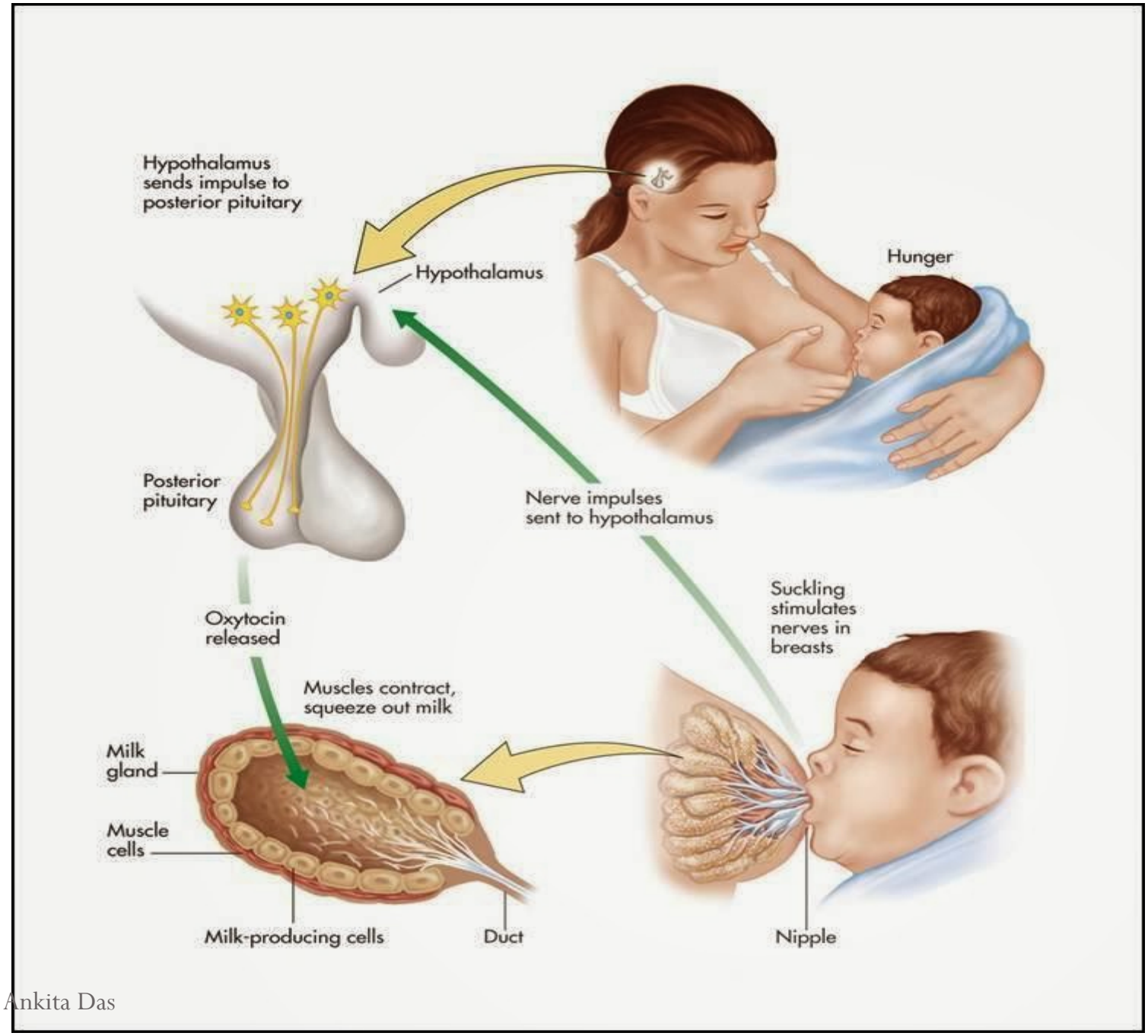
» stimulates contraction of breast myoepithelial cells

» increases force & frequency of uterine contractions

» constricts umbilical arteries and veins

LET-DOWN REFLEX

- By sucking at the breast, the baby triggers tiny nerves in the nipple.
- These nerves cause hormones to be released into your bloodstream.
- One of these hormones (prolactin) acts on the milk-making tissues.
- The other hormone (oxytocin) causes the breast to push out or 'let down' the milk.
- The let-down reflex makes the milk in your breasts available to your baby.
- Cells around the alveoli contract and squeeze out the milk, pushing it down the ducts towards the nipple.
- Oxytocin also makes the milk ducts widen, making it easier for the milk to flow down them.
- The let-down may happen if you see or hear your baby or even just think about him.
- The let-down can also be triggered by touching your breast and nipple area with your fingers or by using a breast pump.
- People often say that let-down may not work as well if you are very anxious, extremely tired, upset or in pain. The truth is that breastfeeding is a powerful process. With support and encouragement, mothers cope with many different stresses and still breastfeed successfully.


Hypothalamus sends impulse to posterior pituitary
Hypothalamus
Hunger
Posterior pituitary
Nerve impulses sent to hypothalamus
Suckling stimulates nerves in breasts
Oxytocin released
Muscles contract, squeeze out milk
Milk gland
Muscle cells
Milk-producing cells
Duct
Nipple

Posterior Pituitary: Regulation of Osmolality

- Plasma osmolality is monitored by osmoreceptors in the hypothalamus
- Increases in plasma osmolality stimulates secretion of vasopressin
- Small changes above the normal plasma osmotic pressure (285 mosm/kg) stimulate release of vasopressin

Osmolality

- Refers to the amount of solutes in a solution (litres)

- Loss or gain of water without solutes (free water gain or loss) changes the osmolality of ECF

- Must be regulated to maintain normal cell activity

CLINICAL MANIFESTATIONS

Dr. Ankita Das

Diabetes Insipidus

- Etiology
  - Deficient AVP can be primary or secondary
    - The **primary form**
      - Deficiency in secretion
        - Agenesis or irreversible destruction of the neurohypophysis
        - Malformation or destruction of the neurohypophysis by a variety of diseases or toxins
        - *Neurohypophyseal DI*, *Pituitary DI*, or *Central DI*
      - Deficiency in action
        - Can be genetic, acquired, or caused by exposure to various drugs
        - *Nephrogenic DI*
      - It can be caused by a variety of congenital, acquired, or genetic disorders
        - 50% idiopathic

Diabetes Insipidus

- Gestational DI
  - Primary deficiency of plasma AVP
  - Result from increased metabolism by an N-terminal aminopeptidase produced by the placenta
  - Signs and symptoms manifest during pregnancy and usually remit several weeks after delivery

Diabetes Insipidus

- Secondary deficiencies of AVP
  - Results from **inhibition of secretion** by **excessive intake of fluids**
    - *Primary polydipsia*
      - *Dipsogenic DI*
        - characterized by an inappropriate increase in thirst
        - caused by a reduction in the "set" of the osmoregulatory mechanism.
        - association with multifocal diseases of the brain such as neurosarcoid, tuberculous meningitis, or multiple sclerosis but is often idiopathic.
      - *Psychogenic polydipsia*
        - is not associated with thirst
        - polydipsia seems to be a feature of psychosis
      - *Iatrogenic polydipsia*
        - results from recommendations of health professionals or the popular media to increase fluid intake for its presumed preventive or therapeutic benefits for other disorders

Diabetes Insipidus

- Pathophysiology
  - When secretion or action of AVP is reduced to <80 to 85% of normal
    - urine concentration ceases and the rate of output increases to symptomatic levels
  - Primary defect (pituitary, gestational, or nephrogenic DI)
    - Polyuria results in a small (1 to 2%) decrease in body water and a commensurate increase in plasma osmolarity and sodium concentration that stimulate thirst and a compensatory increase in water intake
    - Overt signs of dehydration do not develop unless the patient also has a defect in thirst or fails to drink for some other reason

Diabetes Insipidus

- Pathophysiology
  - Primary polydipsia
    - Pathogenesis of the polydipsia and polyuria is the reverse of that in pituitary, nephrogenic, and gestational DI
      - Excessive intake of fluids slightly increases body water, thereby reducing plasma osmolarity, AVP secretion, and urinary concentration.
      - Results in a compensatory increase in urinary free-water excretion that varies in direct proportion to intake
      - Clinically appreciable overhydration uncommon
        - unless the compensatory water diuresis is impaired by a drug or disease that stimulates or mimics endogenous AVP

Diabetes Insipidus

- Clinical Presentation
  - Production of abnormally large volumes of dilute urine
    - The 24-h urine volume is >50 mL/kg body weight and the osmolarity is <300 mosmol/L.
  - The polyuria produces symptoms of urinary frequency, enuresis, and/or nocturia, which may disturb sleep and cause mild daytime fatigue or somnolence.
  - It is also associated with thirst and a commensurate increase in fluid intake (polydipsia).
  - Clinical signs of dehydration are uncommon unless fluid intake is impaired.

Diabetes Insipidus

- Diagnosis
  - Verify polyuria
    - a 24-h urine output collection
    - > 50 mL/kg per day (>3500 mL in a 70-kg man).
  - Check osmolarity
    - >300 mosmol/L
      - due to a solute diuresis and the patient should be evaluated for uncontrolled diabetes mellitus or other less common causes of excessive solute excretion
    - <300 mosmol/L
      - Due to water diuresis and should be evaluated further to determine which type of DI is present

Diabetes Insipidus

- Diagnosis
  - Water deprivation test
    - If does not result in urine concentration before body weight decreases by 5% or plasma osmolarity/sodium exceed the upper limit of normal
      - (osmolarity **>300** mosmol/L, specific gravity >1.010)
      - Primary polydipsia or a partial defect in AVP secretion or action are largely excluded
  - Severe pituitary or nephrogenic DI are the only remaining possibilities

Diabetes Insipidus

Diagnosis: Neurogenic vs Nephrogenic

- Administer Desmopressin
  - 1 µg
  - 0.03 ug/kg
  - subcutaneously or intravenously
- Measure urine osmolality
  - (30,60,120 min)
  - 1 to 2 h later
- An increase of >50% indicates severe pituitary DI
- Smaller or absent response is strongly suggestive of nephrogenic DI

Diabetes Insipidus

- Treatment
  - Neurogenic DI
    - DDAVP (Desmopressin)
    - Chlorpropamide (Diabinese)
      - Antidiuretic effect can be enhanced by cotreatment with a thiazide diuretic
      - SE: hypoglycemia, disulfiram like reaction to ethanol
      - Contraindicated in Gestional DI
  - Nephrogenic DI
    - Not affected by treatment with DDAVP or chlorpropamide
    - May be reduced by treatment with a thiazide diuretic and/or amiloride in conjunction with a low-sodium diet
    - Inhibitors of prostaglandin synthesis (e.g., indomethacin) are also effective in some patients
  - Psychogenic or dipsogenic DI
    - there is no effective treatment

Syndrome of Inappropriate ADH secretion (SIADH)

- Etiology
  - CNS
    - Lesions, Inflammatory disease
    - Trauma, psychosis
  - Drugs
    - Stimulate AVP release
      - Nicotine, phenothiazines
    - Chlorpropamide, clofibrate, carbamazepine, cyclophosphamide, vincristine
  - Pulmonary
    - Infection
    - Mechanical/ventilatory issue

Syndrome of Inappropriate ADH secretion

- Pathophysiology
  - Excessive AVP production resulting in decreased volume of highly concentrated urine
  - Water retention
  - Decreased plasma osmolarity
  - Decreased plasma Na

Syndrome of Inappropriate ADH secretion

- Clinical Presentation
  - Acute
    - Water intoxication
    - Headache, confusion
    - Nausea, vomiting
    - Anorexia
    - Coma, convulsions
  - Chronic
    - May be asymptomatic

Syndrome of Inappropriate ADH secretion

- Diagnosis
  - Diagnosis of exclusion
  - AVP level inappropriately elevated relative to plasma osmolality

Syndrome of Inappropriate ADH secretion

- Treatment
  - Acute
    - Fluid restriction
    - Hypertonic saline
      - Central myelinolysis
  - Chronic
    - Demeclocyline 150-300mg
      - Reversible Nephrogenic DI

Books to refer:

1. **Medical Physiology, Guyton and Hall**
2. **Medical Physiology, Ganong**
3. **General Physiology, A.K. Jain**

Practice Questions:

1. Why posterior pituitary is called neurohypophysis?
2. Briefly describe the mechanism of synthesis and release of posterior pituitary hormones.
3. Why vasopressin is also called ADH?
4. What is diuresis?
5. What is SIADH? Describe its pathophysiology.
6. How ADH maintains the blood osmolarity?
7. Briefly describe the let-down reflex and role of oxytocin in it.
8. Write about the clinical manifestations of diabetes insipidus.