HYPOTHALAMO-HYPOPHYSIAL AXIS

2. THE HYPOTHALAMO-NEUROHYPOPHYSIAL SYSTEM

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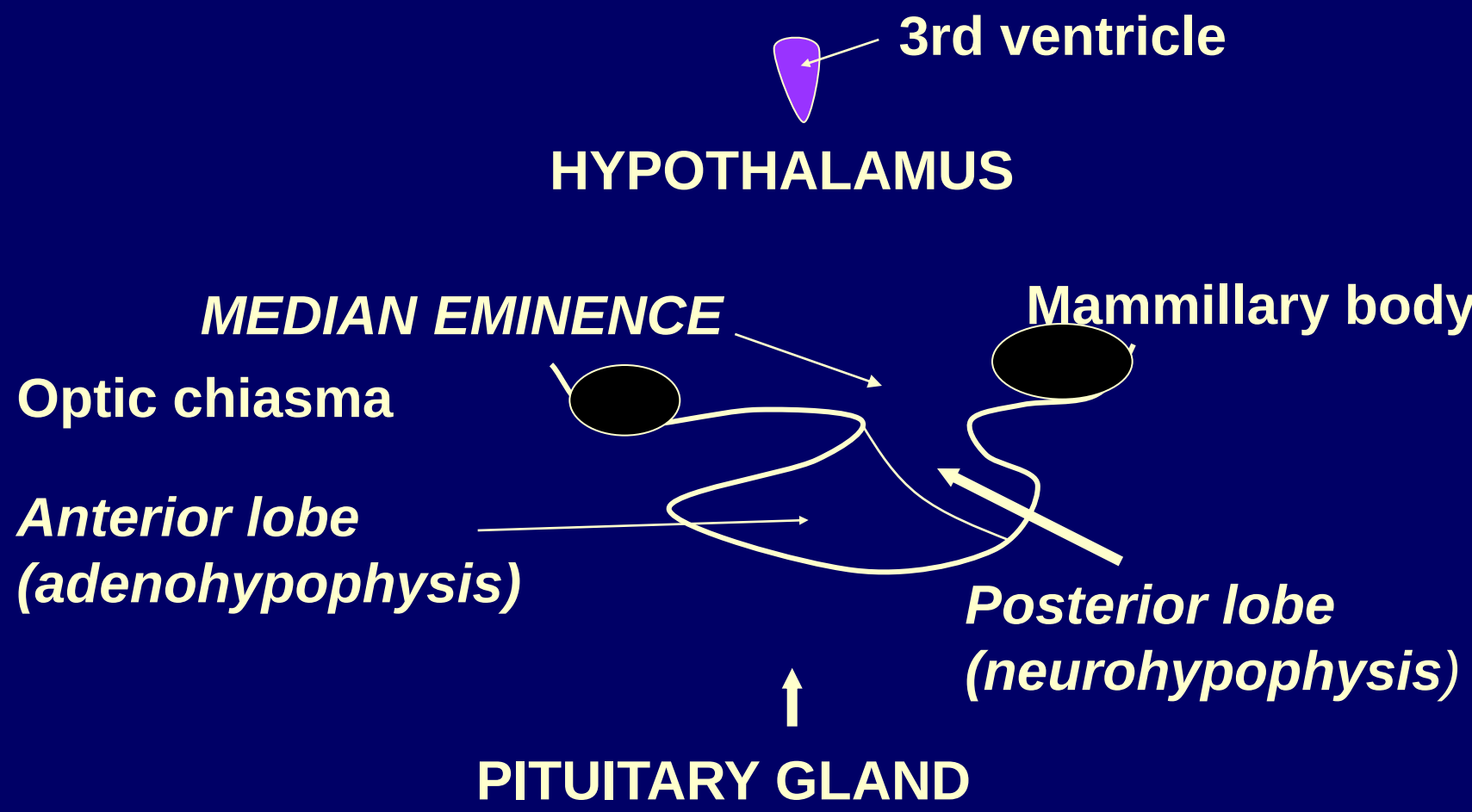
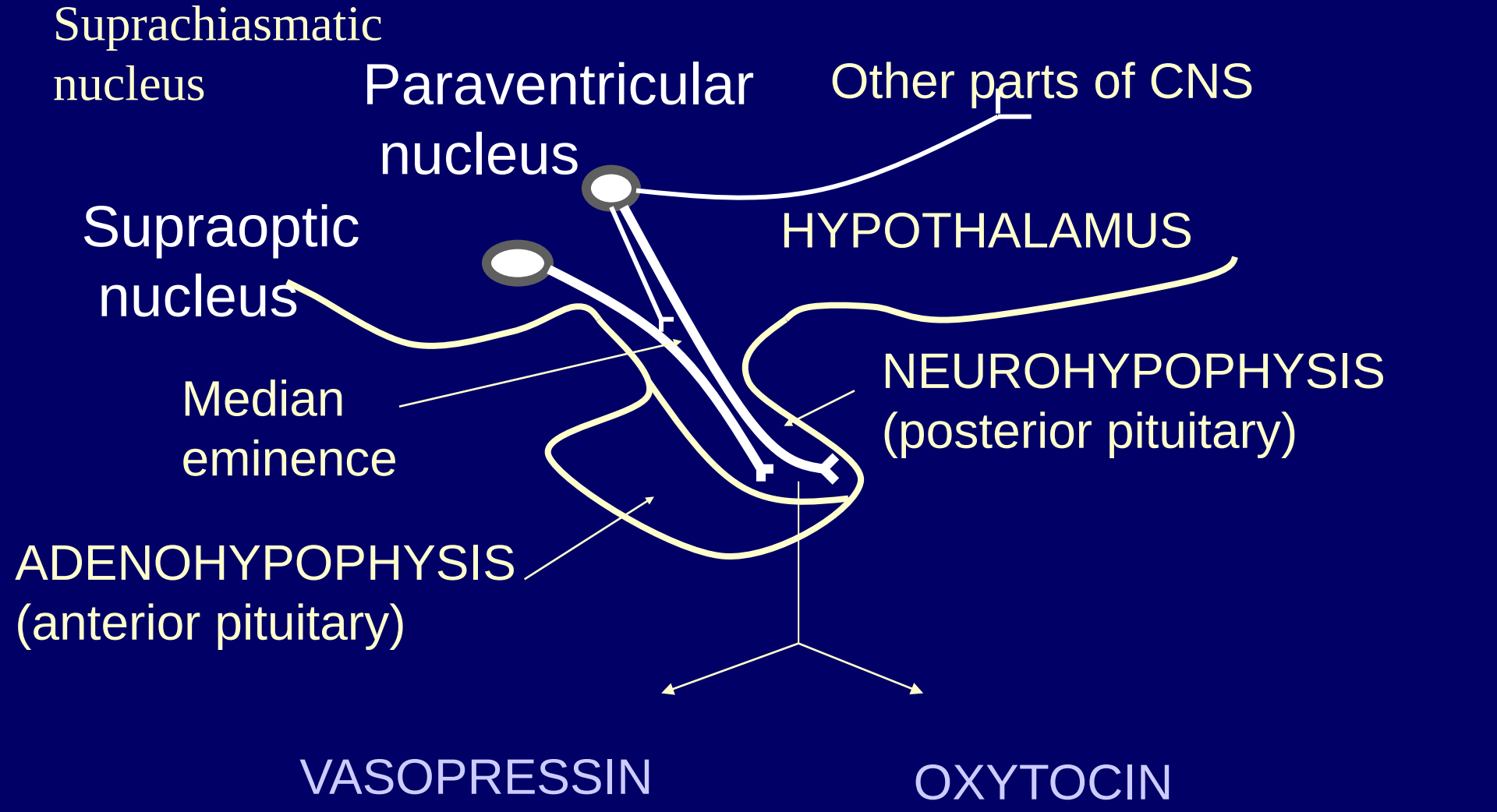

3rd ventricle
HYPOTHALAMUS
MEDIAN EMINENCE
Mammillary body
Optic chiasma
Anterior lobe
(adenohypophysis)
Posterior lobe
(neurohypophysis)
PITUITARY GLAND

THE HYPOTHALAMO-NEUROHYPOPHYSIAL SYSTEM



THE HYPOTHALAMO-NEUROHYPOPHYSIAL SYSTEM

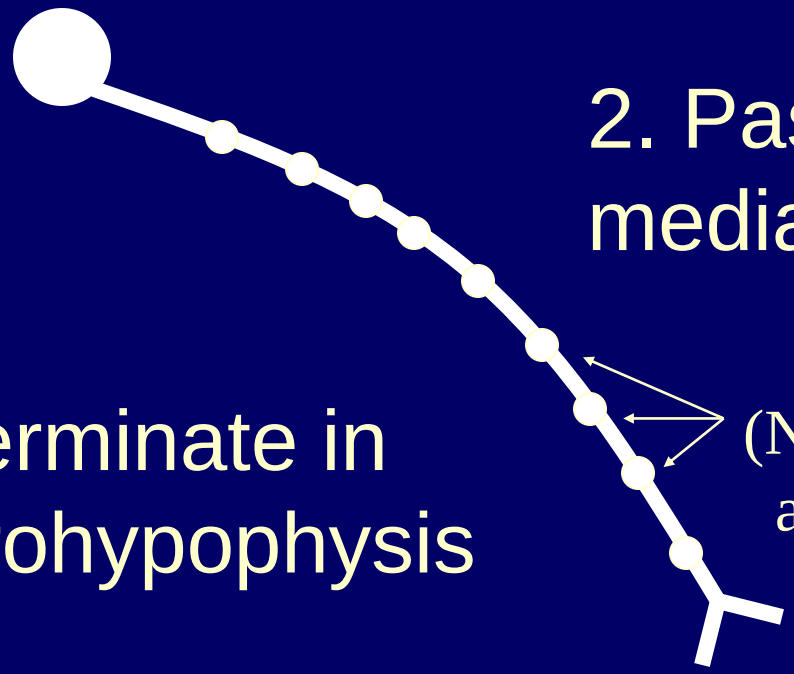
- Cell bodies in the SUPRAOPTIC and PARAVENTRICULAR NUCLEI

- mainly MAGNOCELLULAR NEURONES terminate in the NEUROHYPOPHYSIS

- also some PARVOCELLULAR NEURONES which originate in the PARAVENTRICULAR nuclei terminate either in the median eminence or in other parts of the brain

SUPRAOPTIC NEURONES

1. Leave hypothalamic supraoptic nuclei



2. Pass through median eminence

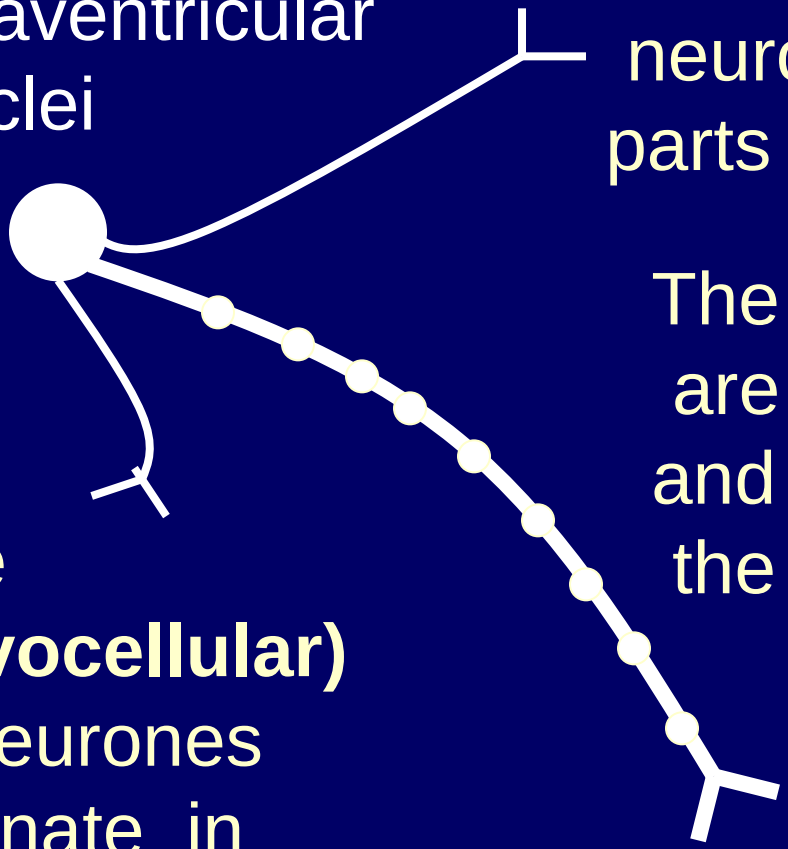
(Note the Herring bodies along axon)

3. Terminate in neurohypophysis

4. They are either **VASOPRESSINERGIC** or **OXYTOCINERGIC**

PARAVENTRICULAR NEURONES

Originate in paraventricular nuclei



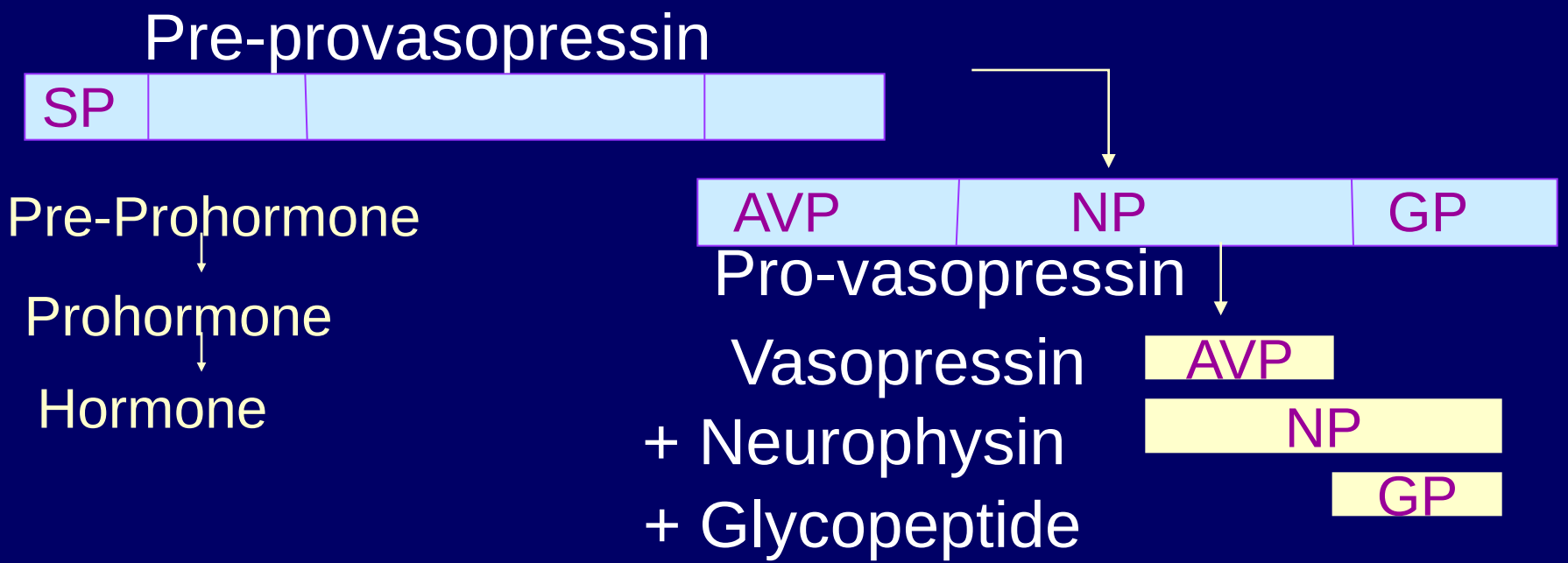
Some **(parvocellular)** neurones pass to other parts of brain

The majority of neurones are **magnocellular**, and these pass down to the neurohypophysis

Some **(parvocellular)** VP neurones terminate in median eminence

They are either vasopressinergic or oxytocinergic

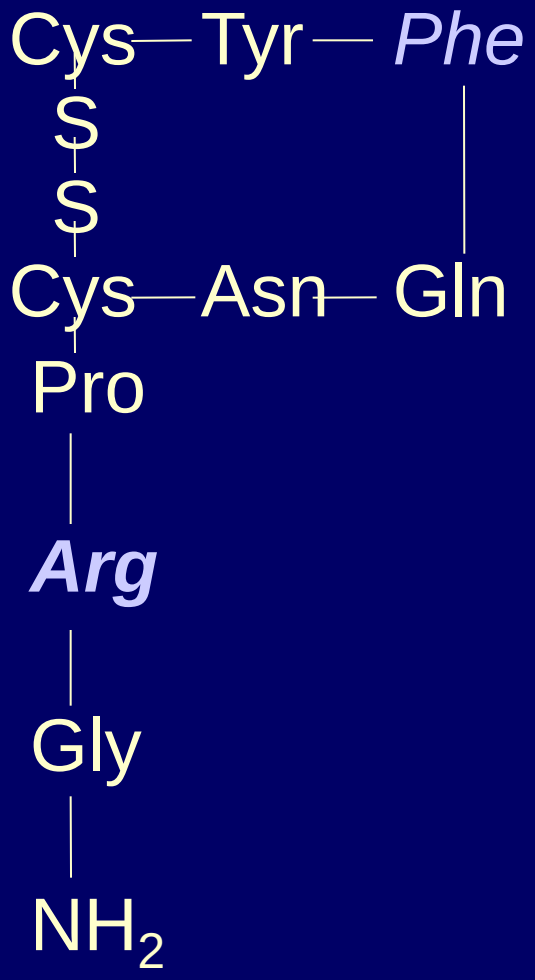
VASOPRESSIN SYNTHESIS

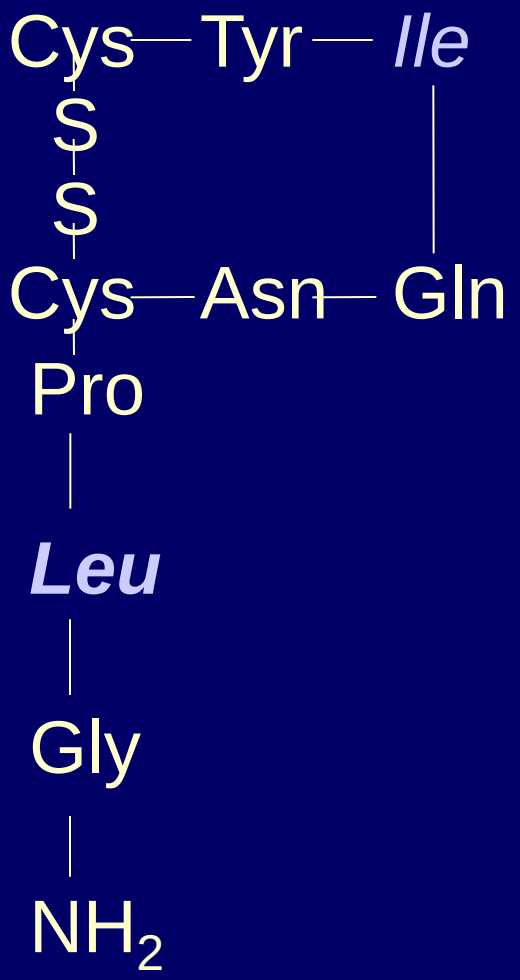


Same sequence for oxytocin synthesis, except that the neurophysin differs slightly and the glycopeptide is absent

AVP = arginine vasopressin

Arginine Vasopressin (AVP)





Oxytocin

VASOPRESSIN AND OXYTOCIN

- Initially synthesized as **Prohormones**
- Cleaved to form hormones and their neurophysin proteins (released together)
- Nonapeptides
- Differ by two amino acids

ACTIONS OF VASOPRESSIN (1)

- Principal physiological action is in the **renal collecting ducts** (principal cells)
- where it **stimulates water reabsorption**
- resulting in its **ANTIDIURETIC** effect

OTHER ACTIONS OF VASOPRESSIN (2)

VASOPRESSIN

vasoconstriction

corticotrophin release (together with CRH)

CNS effects

acting as neurotransmitter e.g. on aspects of behaviour (memory?)

synthesis of blood clotting factors (VIII and Von Willbrandt factor)

Hepatic glycogenolysis

VASOPRESSIN RECEPTORS

V1a

- Arterial/arteriolar smooth muscle (vasoconstriction)
- Hepatocytes (glycogenolysis)
- CNS neurones (behavioural and other effects)

V2

- collecting duct cells (water reabsorption)
- probably other presently unidentified sites (e.g. endothelial cells, depressor effect?)
- (Factor VIII and von Willbrandt factor)

V1b (V3)

adenohypophysial corticotrophs (corticotrophin production)

VASOPRESSIN RECEPTORS

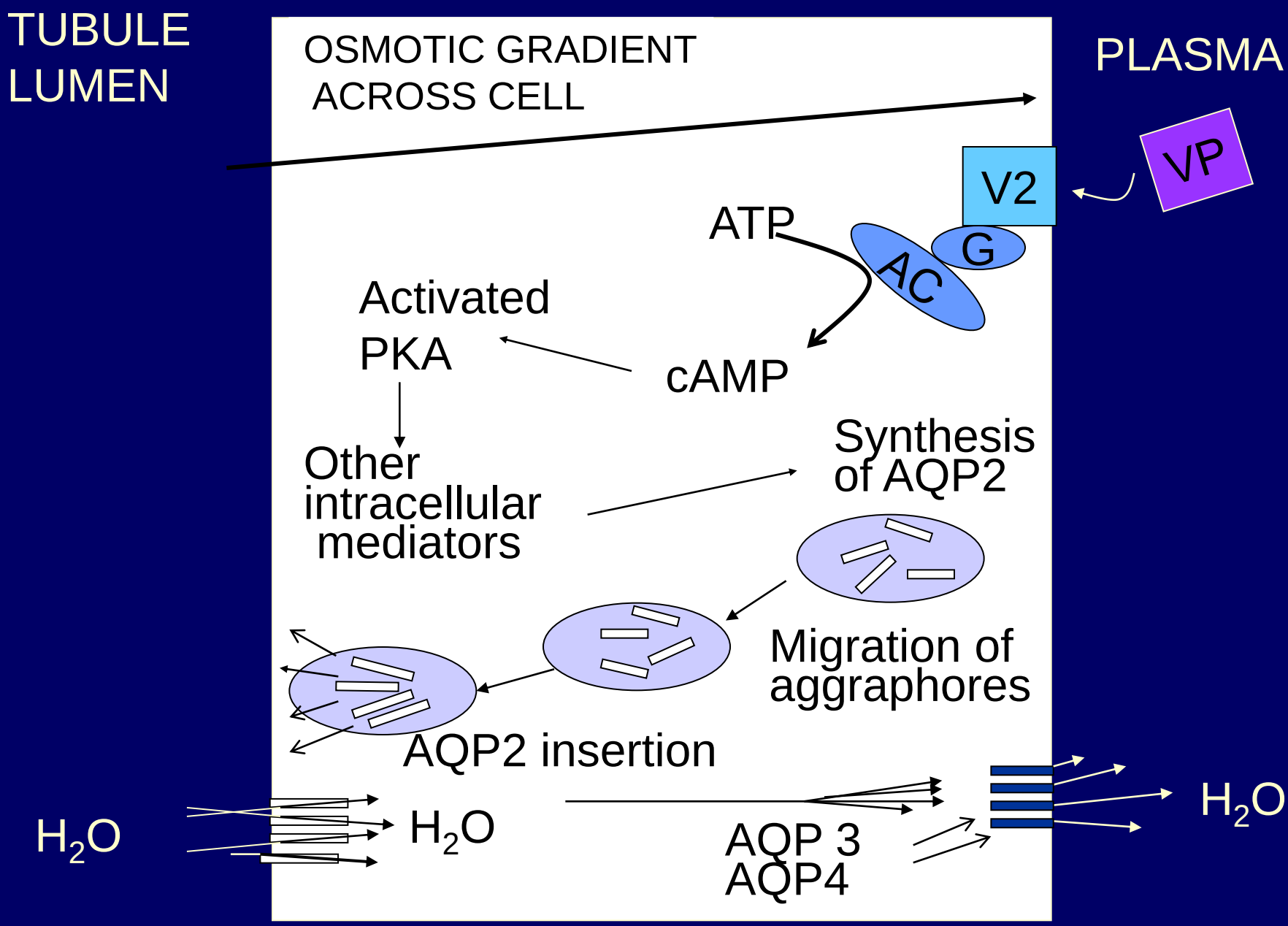
V1 RECEPTORS

- linked via G proteins to phospholipase C
- which acts on membrane phospholipids to produce inositol triphosphate IP_3 (and diacyl glycerol, DAG)
- which increase cytoplasmic $[Ca^{2+}]$ and other intracellular mediators (PKC)
- which produce cellular response

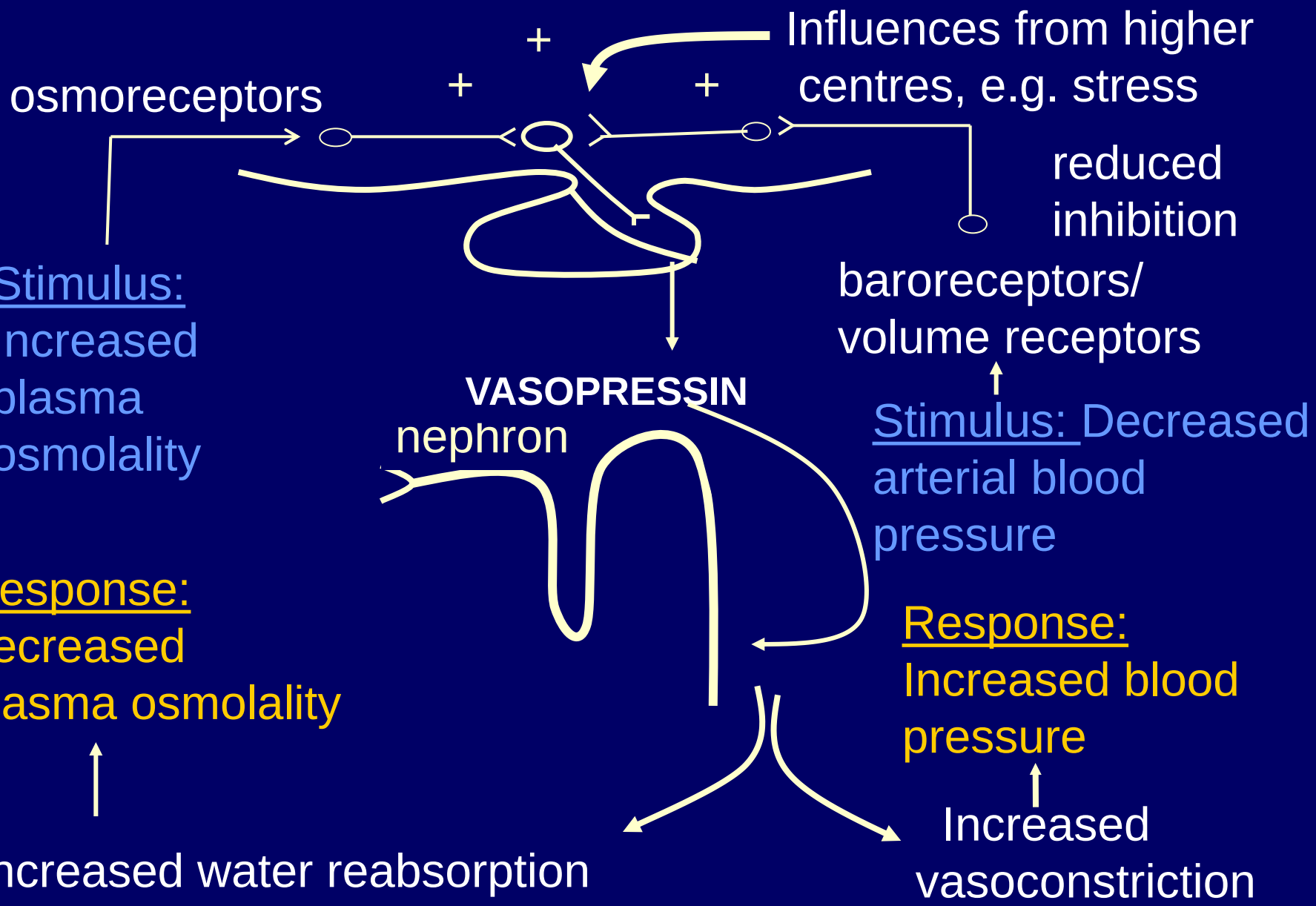
V2 RECEPTORS

- linked via G proteins to adenyl cyclase
- which acts on ATP to form cyclic AMP
- which activates protein kinase A
- which in turn activates other intracellular mediators
- which produce cellular response (aquaporins, AQP2)

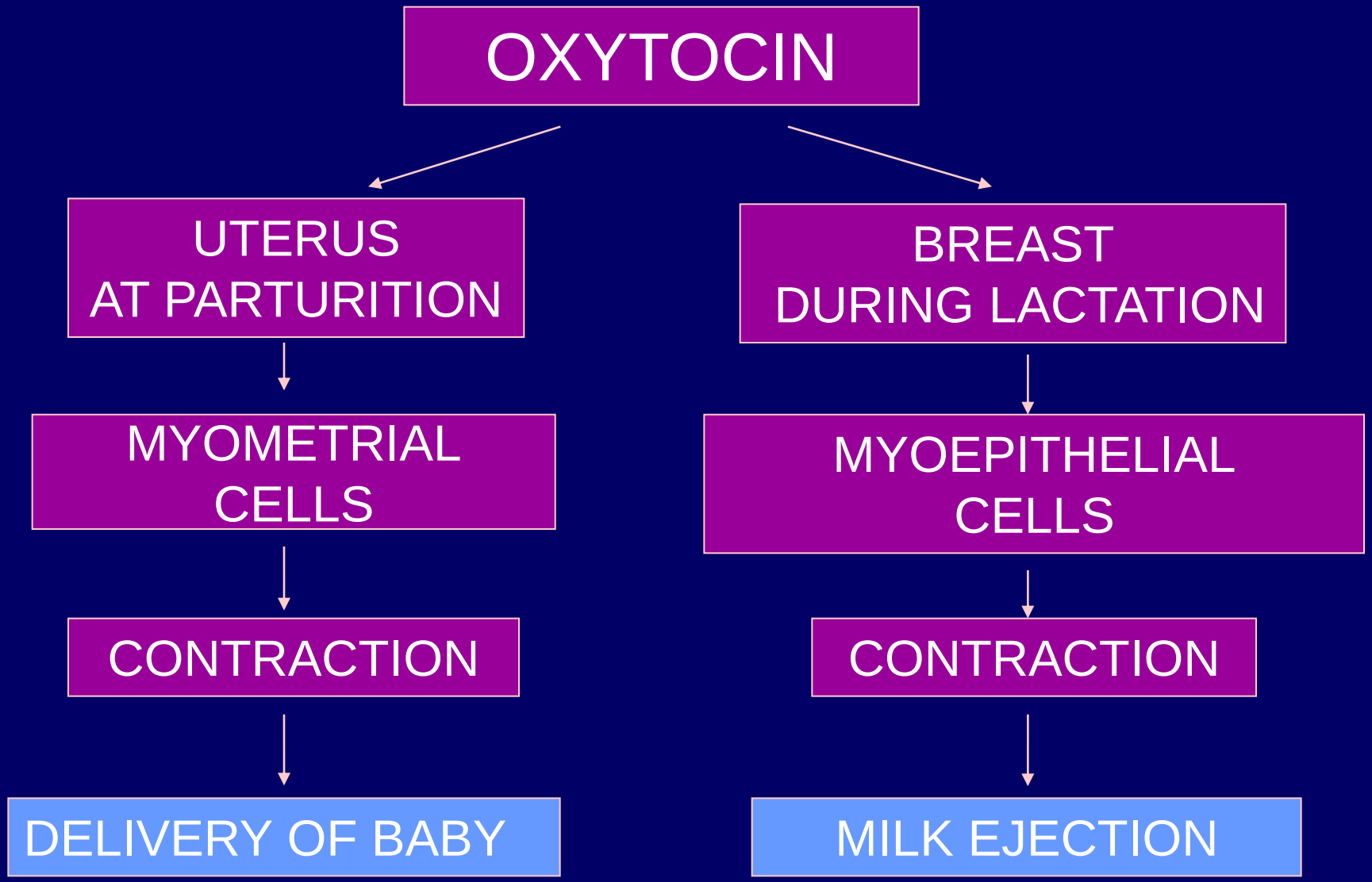
COLLECTING DUCT CELL



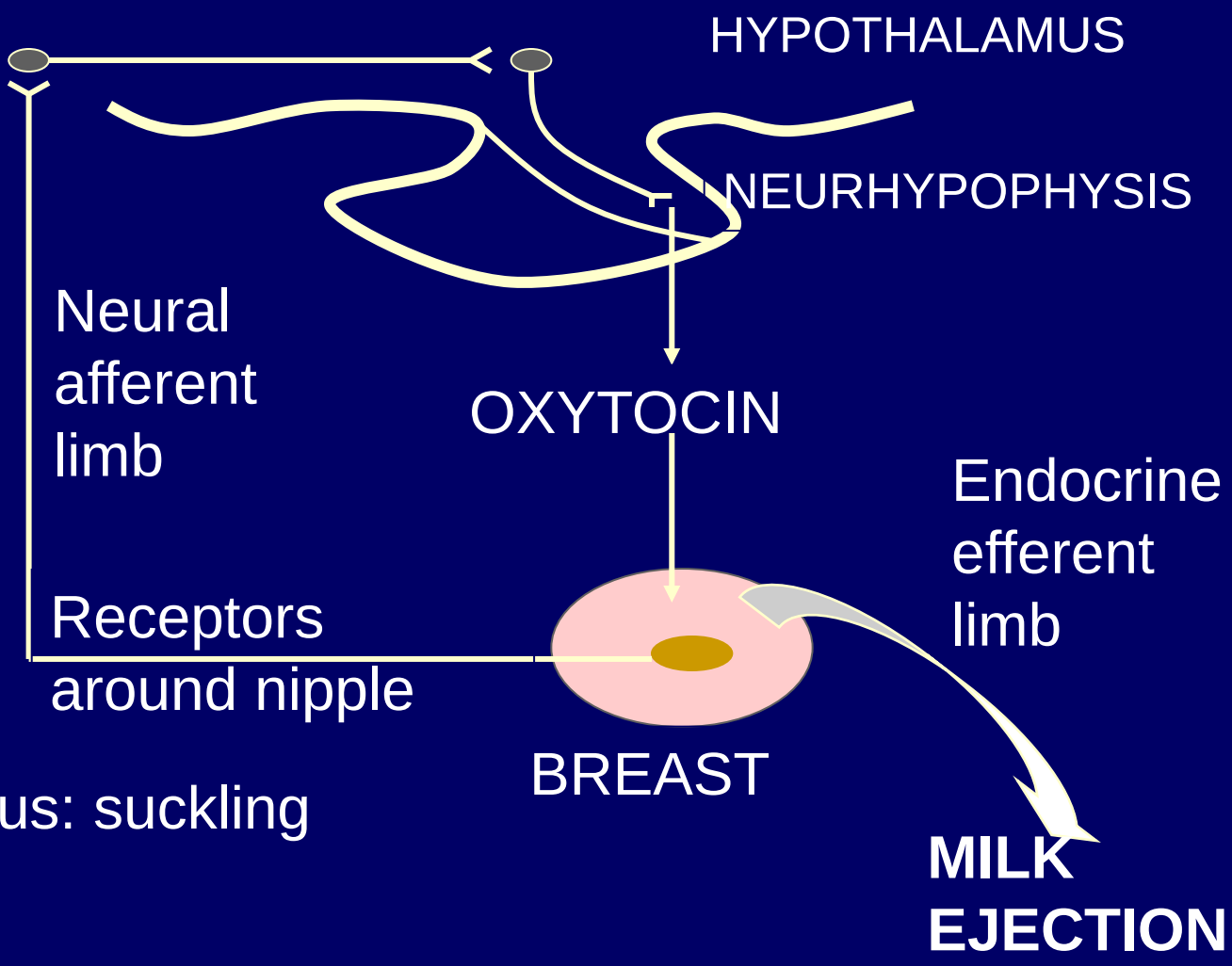
CONTROL OF VASOPRESSIN



ACTIONS OF OXYTOCIN



NEUROENDOCRINE REFLEX ARC



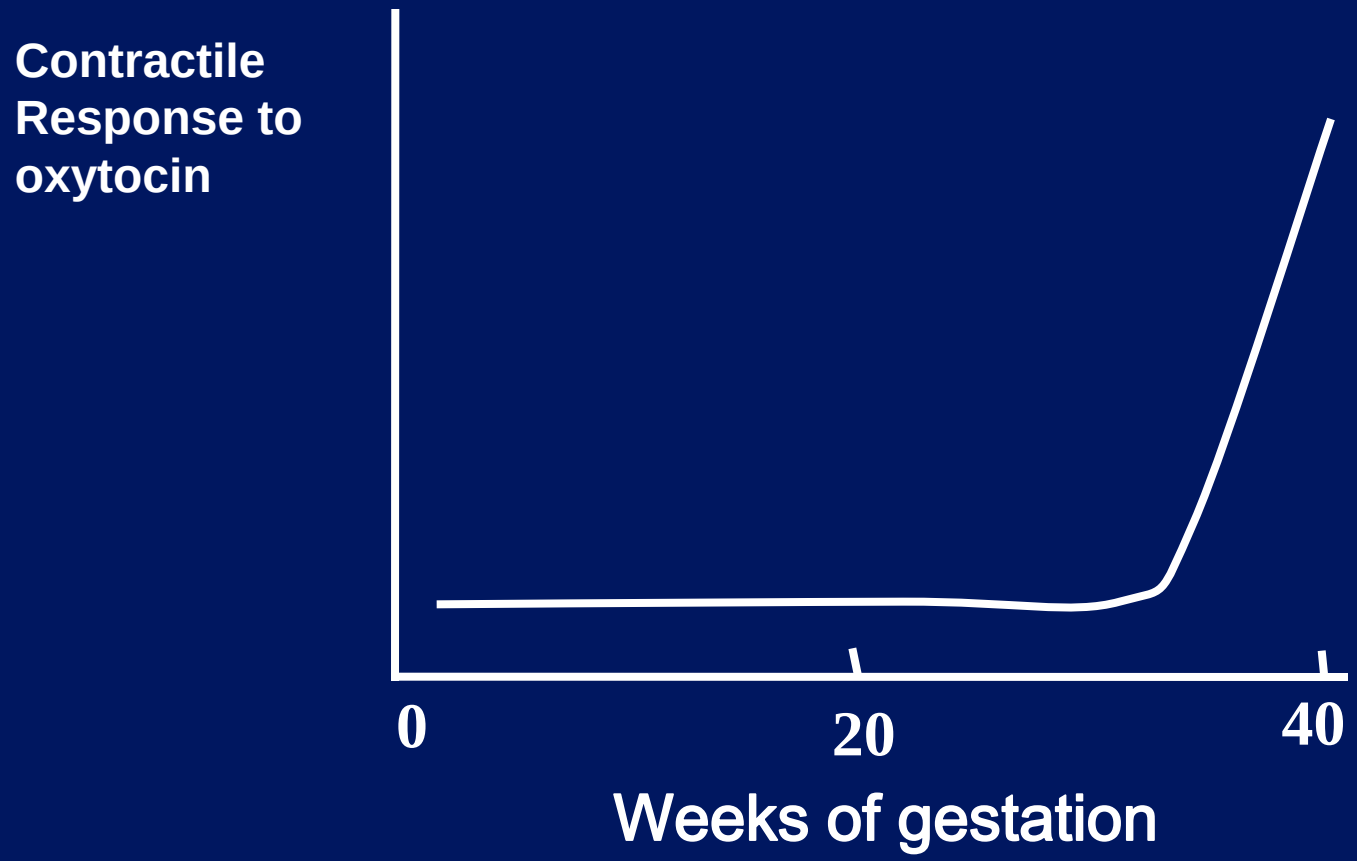
TARGETS FOR OXYTOCIN

- **Major – therapeutic advantage**
  - Uterus
  - Mammary gland – myoepithelial cells
- **Minor – unwanted effects**
  - Cardiovascular system
  - Kidney
- **Additional physiological**
  - CNS

PRINCIPAL ACTIONS OF OXYTOCIN

- **UTERUS**
  - Rhythmic contraction; fundus → cervix
  - Increased local prostanoid production
  - Dilation of cervix
  - *Uterine actions of oxytocin*
    - Suppressed by progesterone
    - Enhanced by oestrogen
    - Most marked in late stages of pregnancy

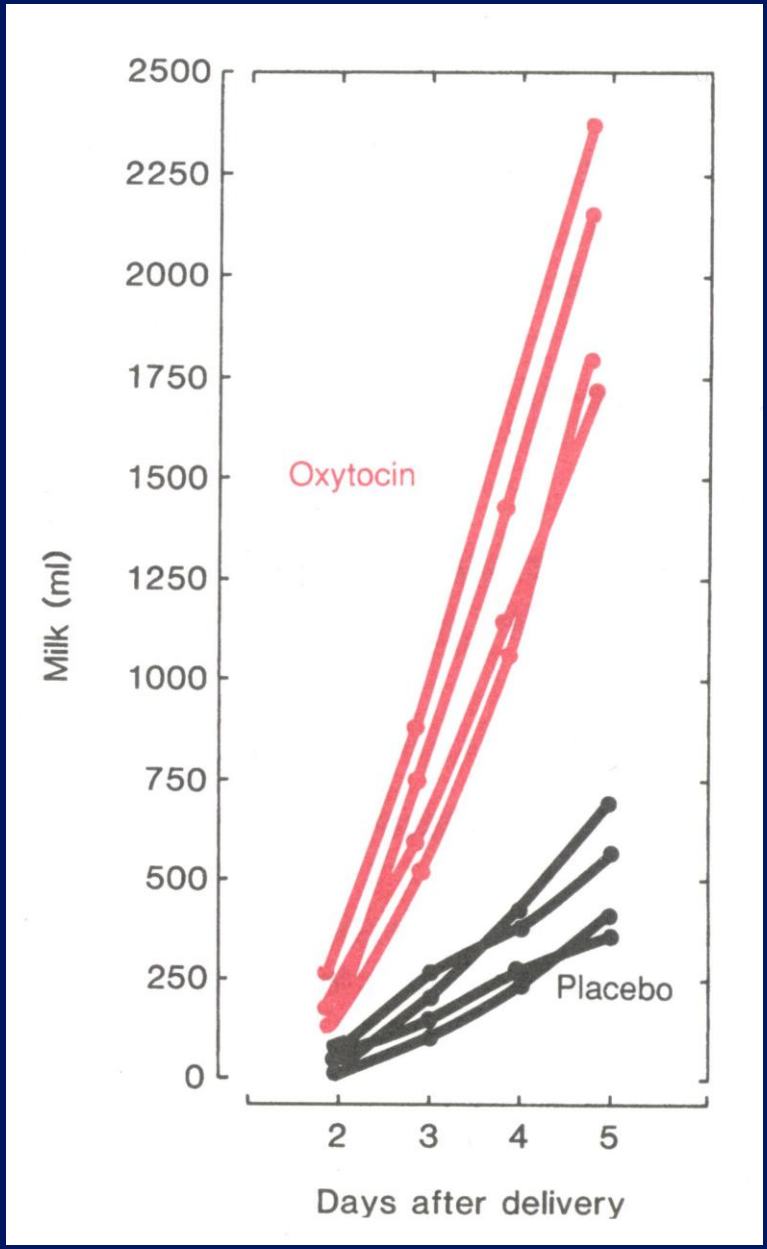
SENSITIVITY OF THE PREGNANT UTERUS TO OXYTOCIN



PRINCIPAL ACTIONS OF OXYTOCIN

- **MAMMARY GLAND**
  - Contraction of myoepithelial cells
  - Milk ejection

EFFECT OF OXYTOCIN TREATMENT ON THE CUMULATIVE AMOUNT OF MILK COLLECTED WITH A BREAST PUMP DURING DAYS 2 –5 AFTER DELIVERY.



PRINCIPAL ACTIONS OF OXYTOCIN

- **CARDIOVASCULAR - *pharmacological***
  - Transient vasodilation & tachycardia
  - Constriction of umbilical arteries and veins
- **RENAL - *pharmacological***
  - Anti-diuresis and secondary hyponatraemia, i.e. vasopressin-like
- **CNS - *physiological***
  - Maternal behaviour, social recognition

CLINICAL USES OF OXTOCIN

- **INDUCTION OF LABOUR AT TERM**
  - controlled i.v. infusion
- **PREVENTION TREATMENT OF POST-PARTUM HAEMORRHAGE**
  - Slow i.v. injection/infusion
  - Local pressor action in uterus suppresses bleeding
- **FACILITATION OF MILK LET-DOWN**
  - Intranasal spray

Neurohypophysial disorders

LACK OF NEUROHYPOPHYSIAL HORMONES

OXYTOCIN: parturition and milk ejection effects induced/replaced by other means

VASOPRESSIN: DIABETES INSIPIDUS

DIABETES INDIPIDUS (DI)

Absence or lack of circulating vasopressin

CENTRAL (or CRANIAL)

Diabetes Insipidus

NEPHROGENIC

End-organ (kidneys) resistance to vasopressin

DIABETES INSIPIDUS: AETIOLOGY

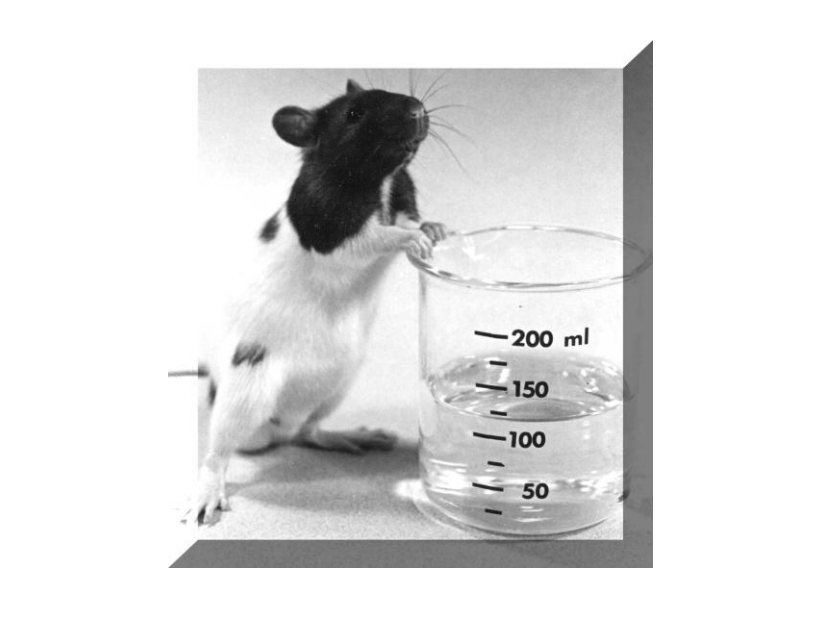
A. CENTRAL (CRANIAL)

1. Damage to Neurohypophysial system

- injury to neurohypophysis
- surgery
- cerebral thrombosis
- tumours (intrasellar and suprasellar)
- granulomatous infiltrations of median eminence

DIABETES INSIPIDUS: AETIOLOGY

2. Idiopathic
3. Familial rare (cf. Brattleboro rats)



DIABETES INSIPIDUS: AETIOLOGY (cont'd)

B. NEPHROGENIC

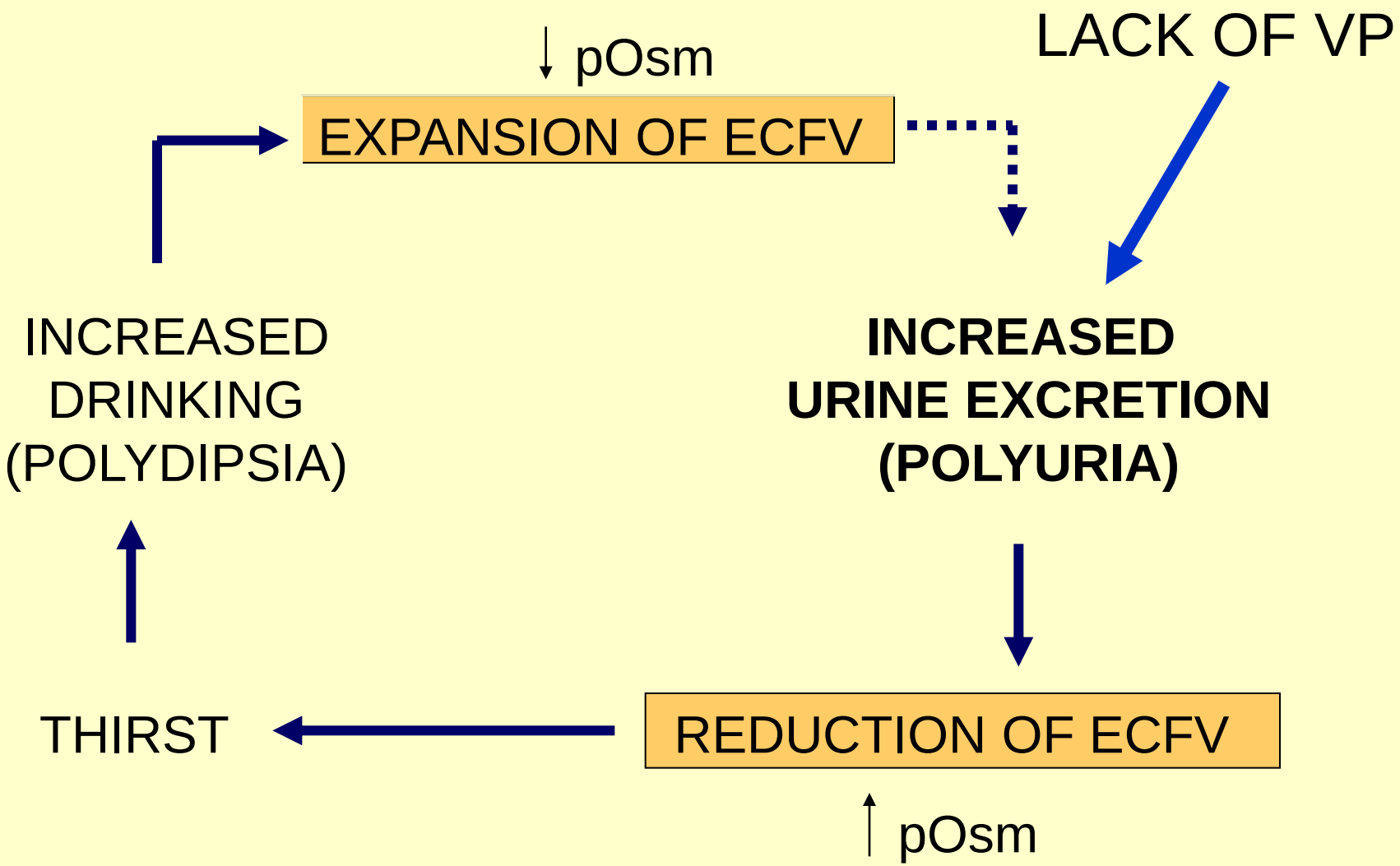
1. Familial rare (e.g. receptor defects)

2. Drugs (e.g. lithium, demeclocycline, dimethyl chlortetracycline DMCT)

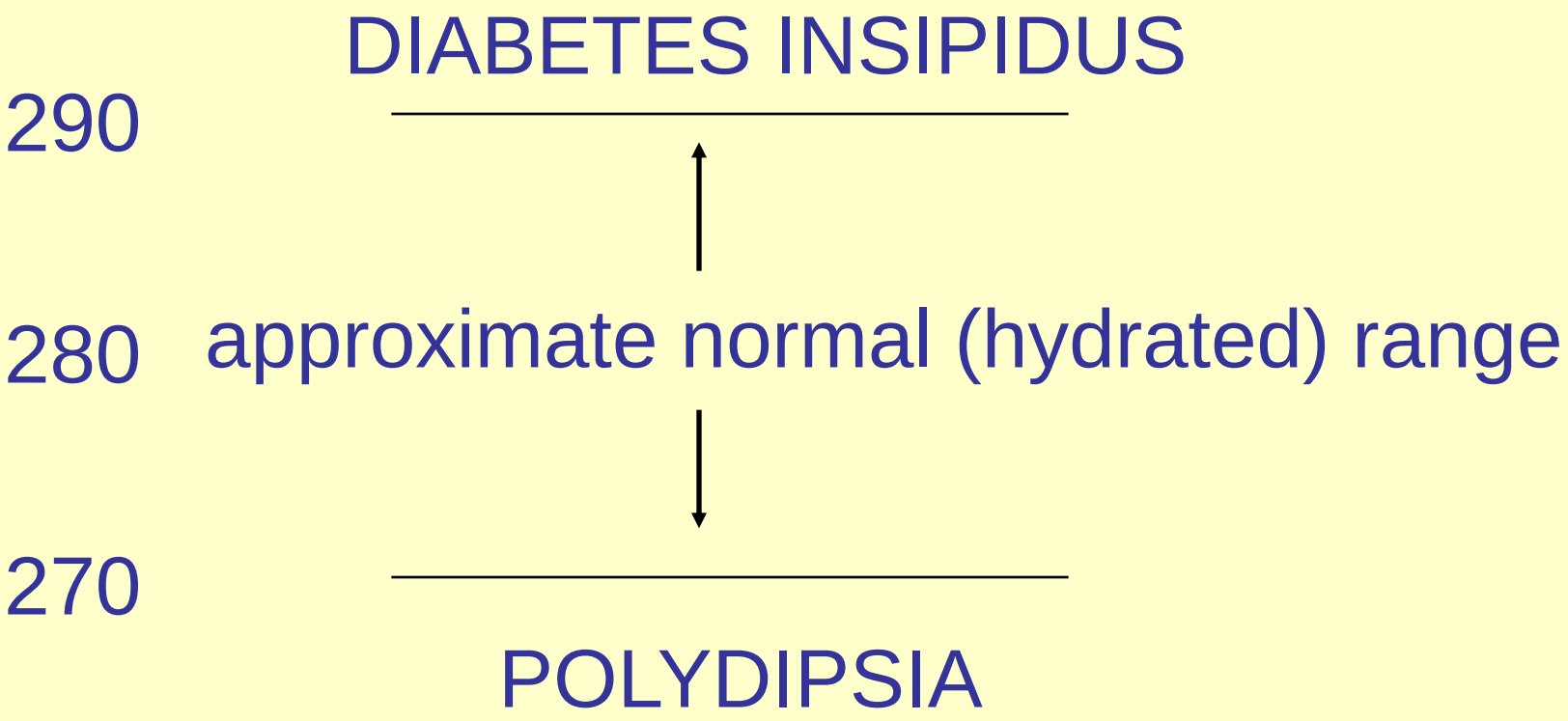
DIABETES INSIPIDUS SIGNS AND SYMPTOMS

- Large volumes of urine (polyuria)
- Urine very dilute (hypo-osmolar)
- Thirst and increased drinking (polydipsia)
- Dehydration (and consequences) if fluid intake not maintained
- Possible disruption to sleep with associated problems
- Possible electrolyte imbalance

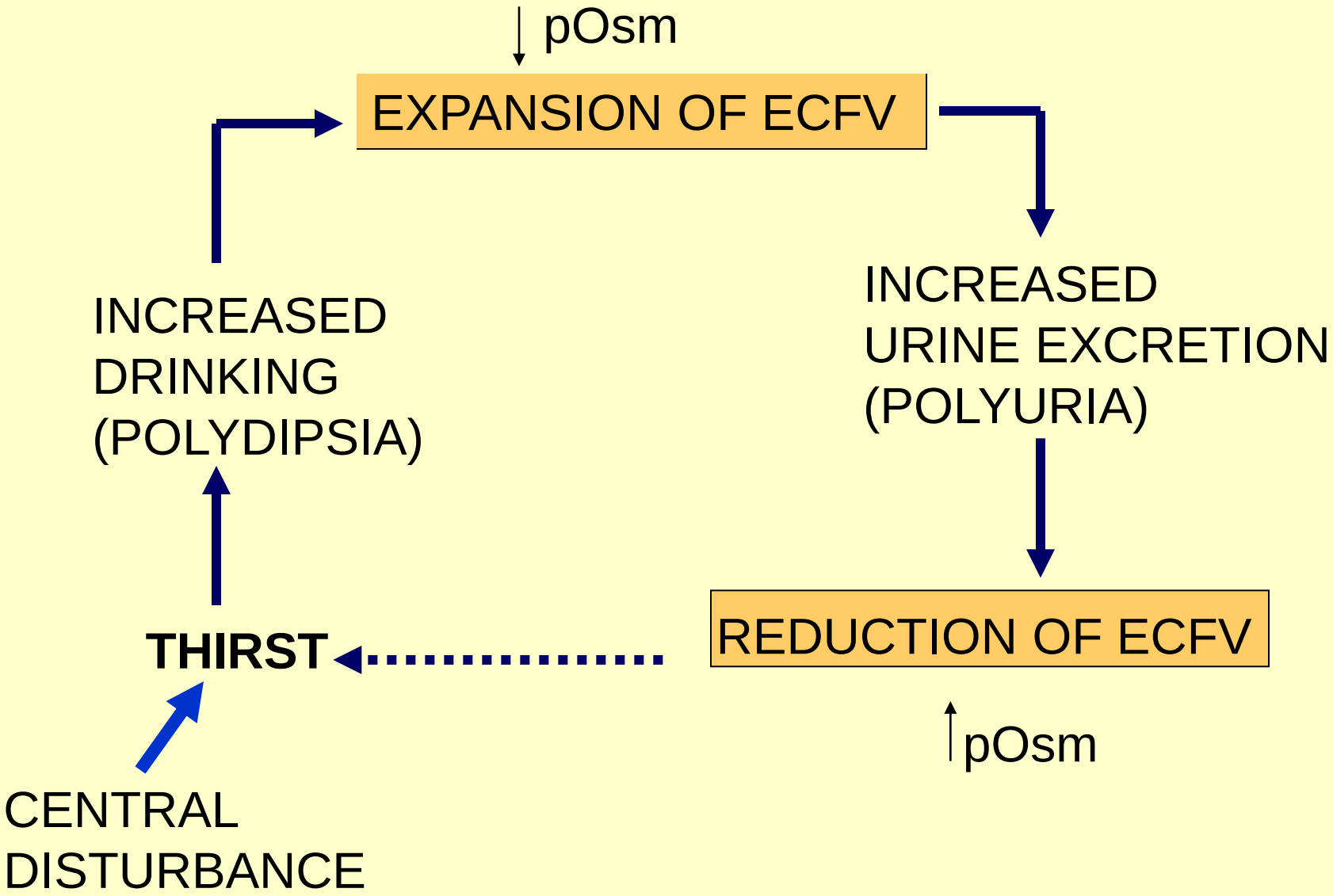
DIABETES INSIPIDUS

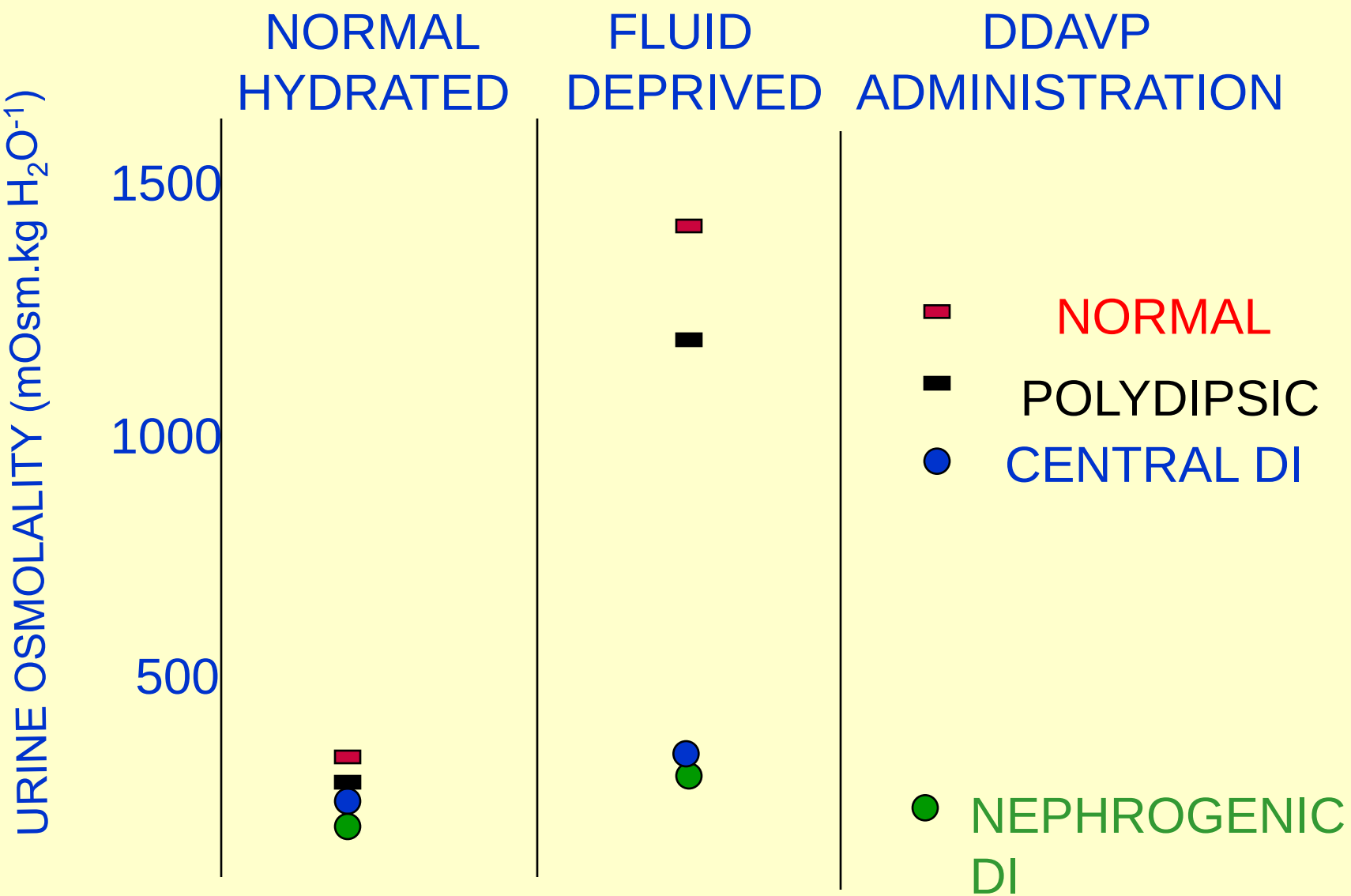


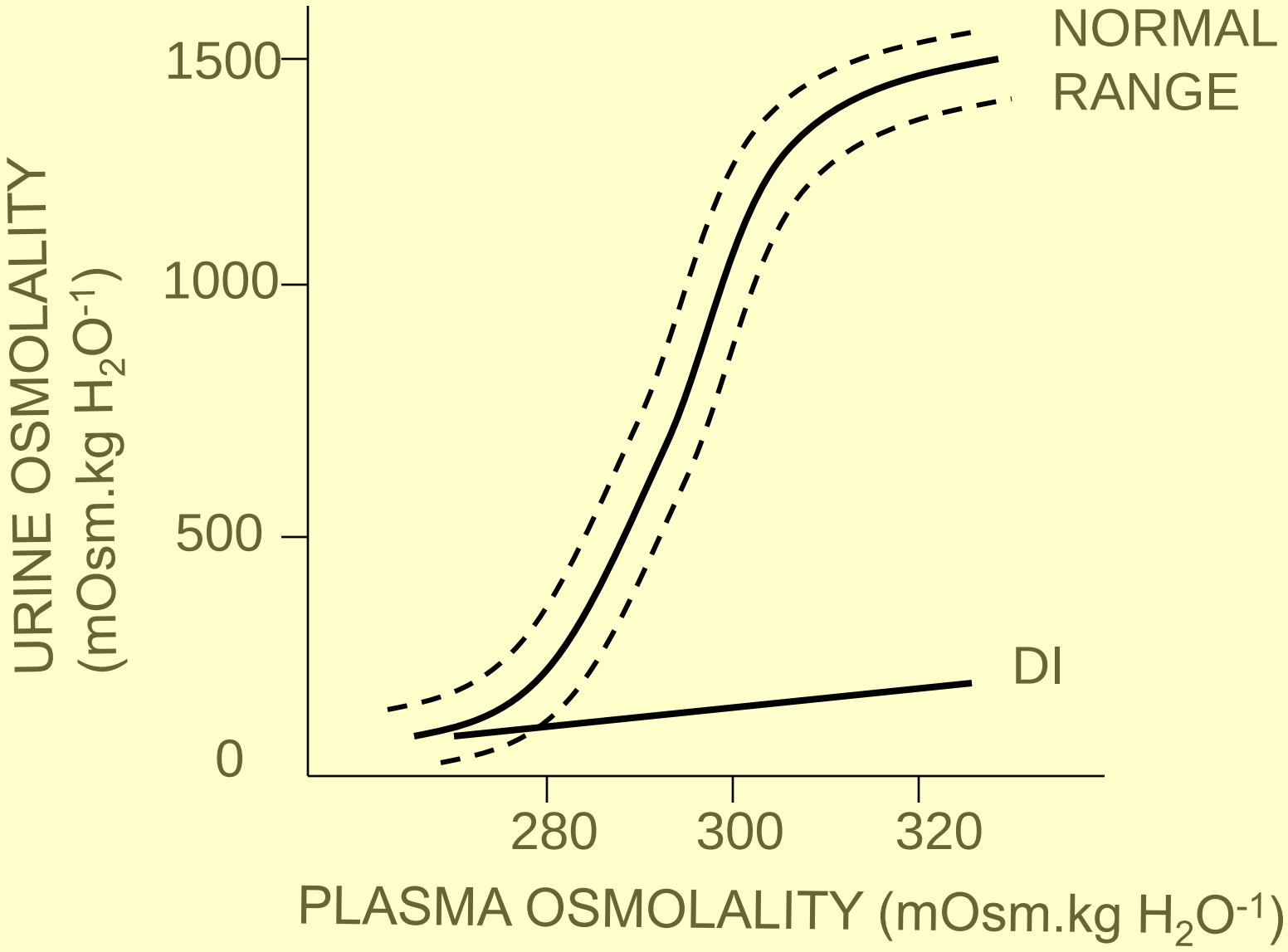
Plasma osmolality
(mOsm.kg H_2O^{-1})



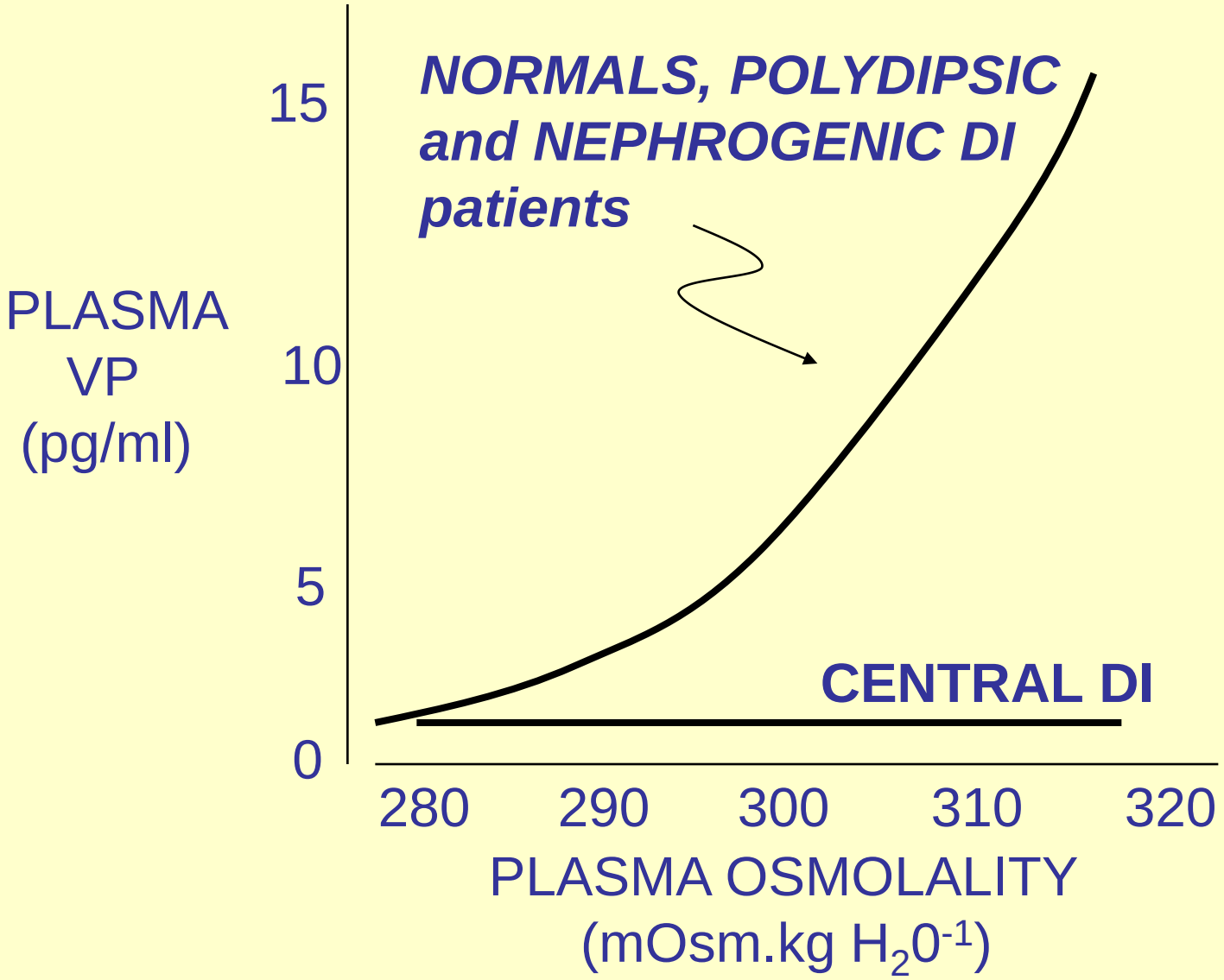
PSYCHOGENIC POLYDIPSIA




NORMAL HYDRATED
FLUID DEPRIVED
DDAVP ADMINISTRATION
URINE OSMOLALITY (mOsm.kg H_2O^{-1})
1500
1000
500
NORMAL
POLYDIPSIC
CENTRAL DI
NEPHROGENIC DI


NORMAL
RANGE
DI
1500
1000
500
0
280
300
320
URINE OSMOLALITY
(mOsm.kg H_2O^{-1})
PLASMA OSMOLALITY (mOsm.kg H_2O^{-1})

STIMULATION WITH HYPERTONIC SALINE iv



Neurohypophysial hormone excess: the Syndrome of Inappropriate ADH (SIADH)

The Syndrome of Inappropriate ADH (SIADH)

By definition

the plasma vasopressin concentration

is ***inappropriate*** for

the existing plasma osmolality

INCREASED VP

↓

INCREASED WATER REABSORPTION

↓

DECREASED PLASMA OSMOLALITY
= HYPONATRAEMIA

↓

COMPENSATORY “ESCAPE” PHENOMENON
(**NATRIURESIS** AND RESTORATION OF URINE OUTPUT?)

SIADH

Signs:

- raised urine osmolality, decreased urine volume (initially)
- decreased p[Na^+] (HYPONATRAEMIA) mainly due to increased water reabsorption

SIADH

Symptoms:

- can be symptomless
- however if p[Na^+] <120 mM: generalised weakness, poor mental function, nausea
- if p[Na+] <110 mM: CONFUSION leading to COMA and ultimately DEATH

SIADH

CAUSES:

- *Tumours (ectopic secretion)*
- *Neurohypophysial malfunction (e.g. meningitis, cerebrovascular disease)*
- *Thoracic disease (e.g. pneumonia)*
- *Endocrine disease (e.g. Addison's disease)*
- ***Physiological** i.e. non-osmotic stimuli (e.g. hypovolaemia, pain, surgery)*
- *Drugs (e.g. chlorpropamide)*
- *Idiopathic*

SIADH

TREATMENT

- *Once cause identified (e.g. tumour), then appropriate treatment (e.g. surgery) applied.*
- *To reduce immediate concern, i.e. hyponatraemia*

  1. Immediate: fluid restriction

  2. Longer-term: use drugs which prevent vasopressin action in kidneys e.g. lithium, demeclocycline (and V_2 receptor antagonists - vaptans)

PHARMACOLOGY OF VASOPRESSIN AND ITS ANALOGUES

RESPONSES TO EXOGENOUS VASOPRESSIN

All vasopressin receptors will be activated

V1

- Vascular smooth muscle
- Non-vascular smooth muscle
- Anterior pituitary
- Liver
- Platelets
- CNS

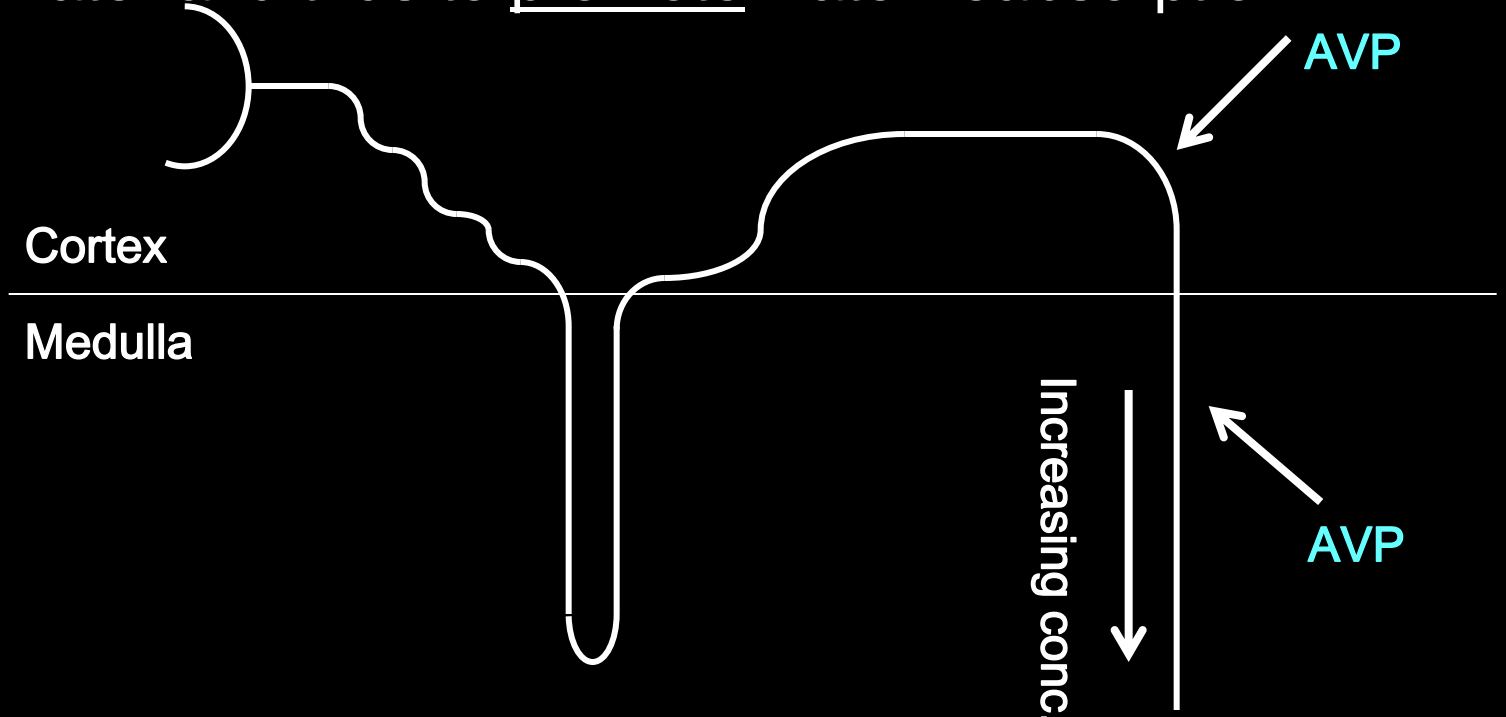
V2

- Kidney
- CNS

PHARMACOLOGICAL ACTIONS OF VASOPRESSIN 1.

Anti-diuresis - V2-mediated

AVP acts on the collecting duct and possibly the distal renal tubule to increase the permeability of the cells to water and thus to promote water reabsorption.



PHARMACOLOGICAL ACTIONS OF VASOPRESSIN - 2

- Natriuresis
  - V2-mediated renal action
  - Evident with high doses only
  - May lead to hyponatraemia

PHARMACOLOGICAL ACTIONS OF VASOPRESSIN - 3

- Pressor action
  - V1-mediated
  - Effect on vascular smooth muscle
  - Not all beds are equally sensitive
  - Effect on coronary vessels important as may cause cardiac ischaemia or anginal attacks

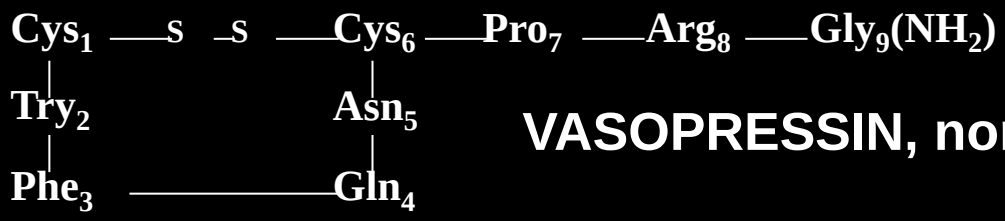
PHARMACOLOGICAL ACTIONS OF VASOPRESSIN - 4

- **Contraction of non-vascular smooth muscle (V1)**
- **Increased ACTH secretion (V1)**
- **Increased Factor VIII and von Willbrand factor production (V2)**

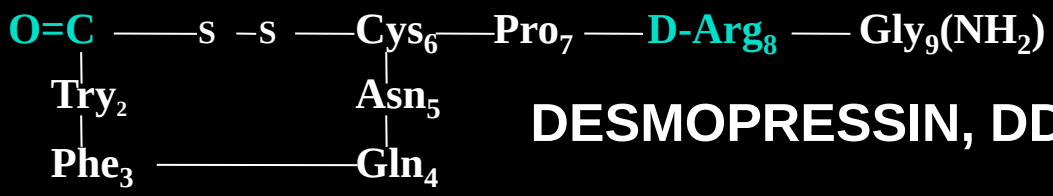
SELECTIVE VASOPRESSIN RECEPTOR AGONISTS

- V1 –TERLIPRESSIN
- V2 – DESMOPRESSIN (DDAVP)

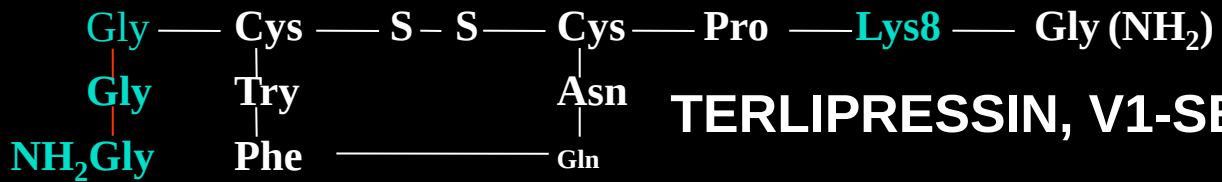
AGONISTS AT VASOPRESSIN RECEPTORS



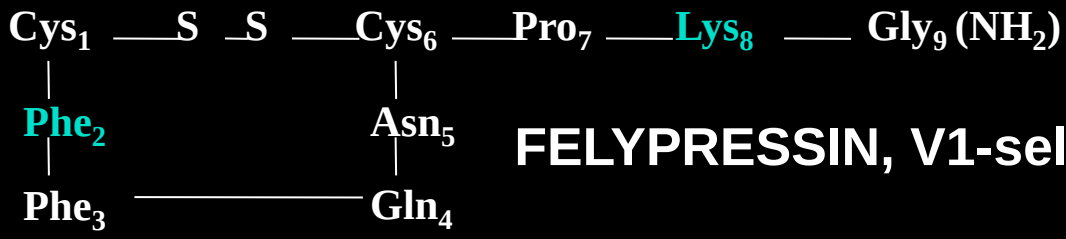
VASOPRESSIN, non-selective



DESMOPRESSIN, DDAVP, V2-selective



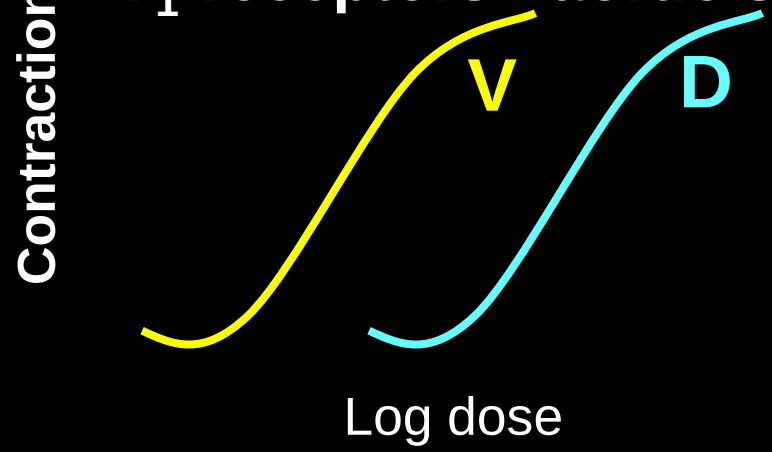
TERLIPRESSIN, V1-SELECTIVE



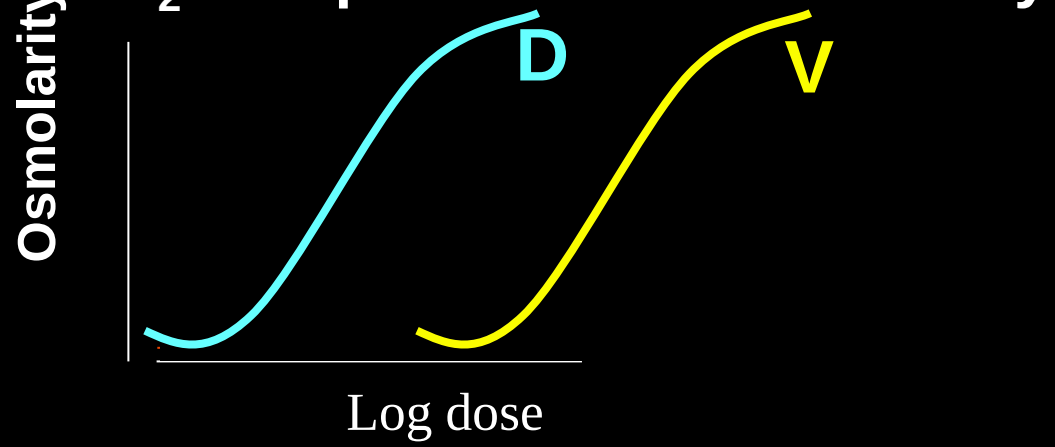
FELYPRESSIN, V1-selective

COMPARISON OF THE ACTIVITIES OF VASOPRESSIN AND DESMOPRESSIN AT V_1 AND V_2-RECEPTORS

- V_1-receptors - aortic strip



- V_2-receptors - urine osmolarity



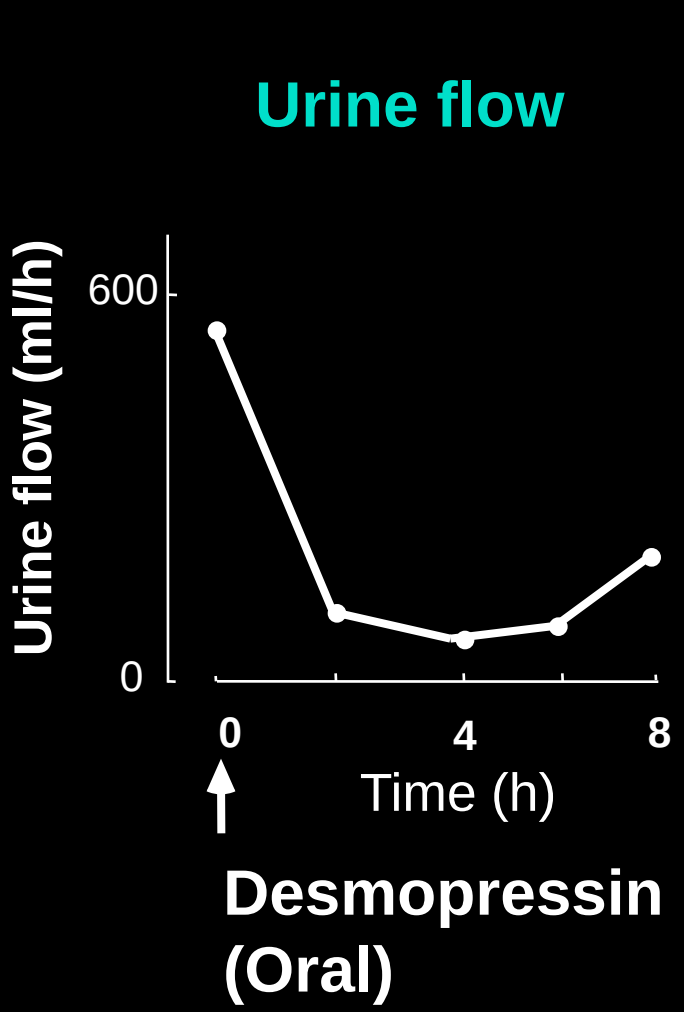
DESMOPRESSIN – CLINICAL USES

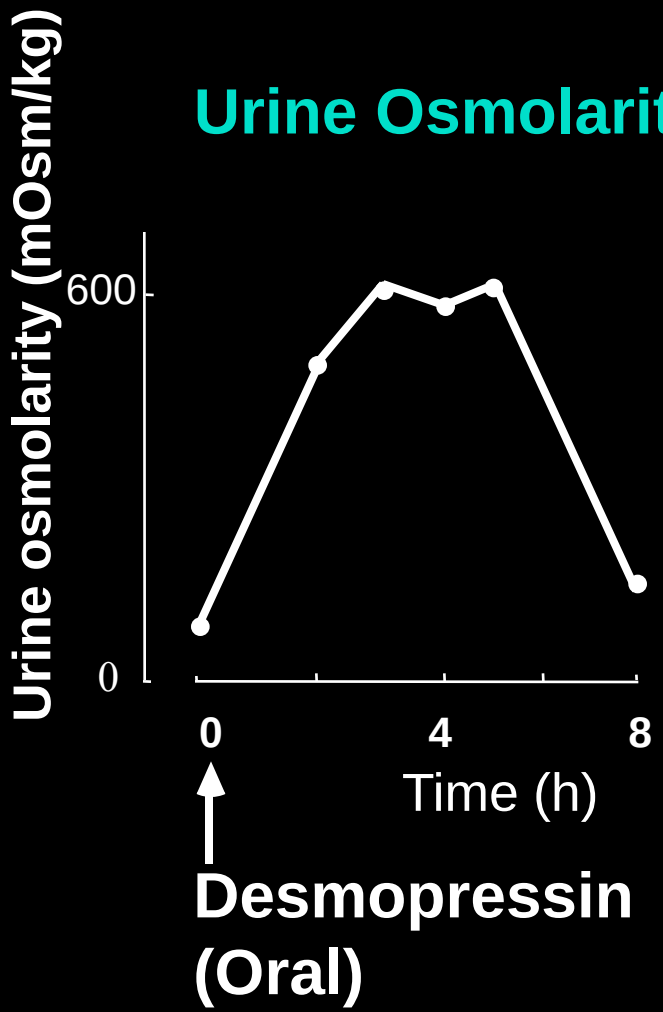
- Cranial diabetes insipidus
- Nocturnal enuresis
- Haemophilia

DESMOPRESSIN
PHARMACOKINETICS - 1

- **Administration**
  - **Nasally**
  - **Orally**

Oral desmopressin produces a prompt sustained decrease in urine volume and increase in urine osmolarity.





DESMOPRESSIN
PHARMACOKINETICS - 2

- **Distribution**
  - **Retained in extracellular fluid**
- **Metabolism**
  - **Hepatic/renal – t1/2 about 5h**

UNWANTED EFFECTS OF DESMOPRESSIN

- Fluid retention and hyponatraemia
- Abdominal pain
- Headaches
- Nausea

DRUGS AFFECTING VASOPRESSIN SECRETION

Increasing

Nicotine

Decreasing

Alcohol

Glucocorticoids

CLINICAL USES OF V1 RECPTOR AGONISTS

- **TERLIPRESSIN**
  - **OESOPHAGEAL VARICES**
- **FELYPRESSIN**
  - **TO PROLONG THE ACTION OF LOCAL ANAESTHETICS**

TREATMENT OF NEPHROGENIC DIABETES INSIPIDUS

- Thiazides, e.g bendroflumethiazide
- Possible mechanism
  - Natriuretic action depletes extracellular Na+ →
  - Compensatory increase in Na+ reaborption from the proximal tubule
  - Water follows Na+ →
  - Reduced urine volume

THIAZIDES – UNWANTED EFFECTS

- K+ loss → hypokalaemia
- Hypercalcaemia
- Diabetogenic
- For further details see Pharmacology and Therapeutics