The artist formerly known as Diabetes Insipidus

Miles Levy

Consultant Endocrinologist UHL

RCP Update 2024

Declarations

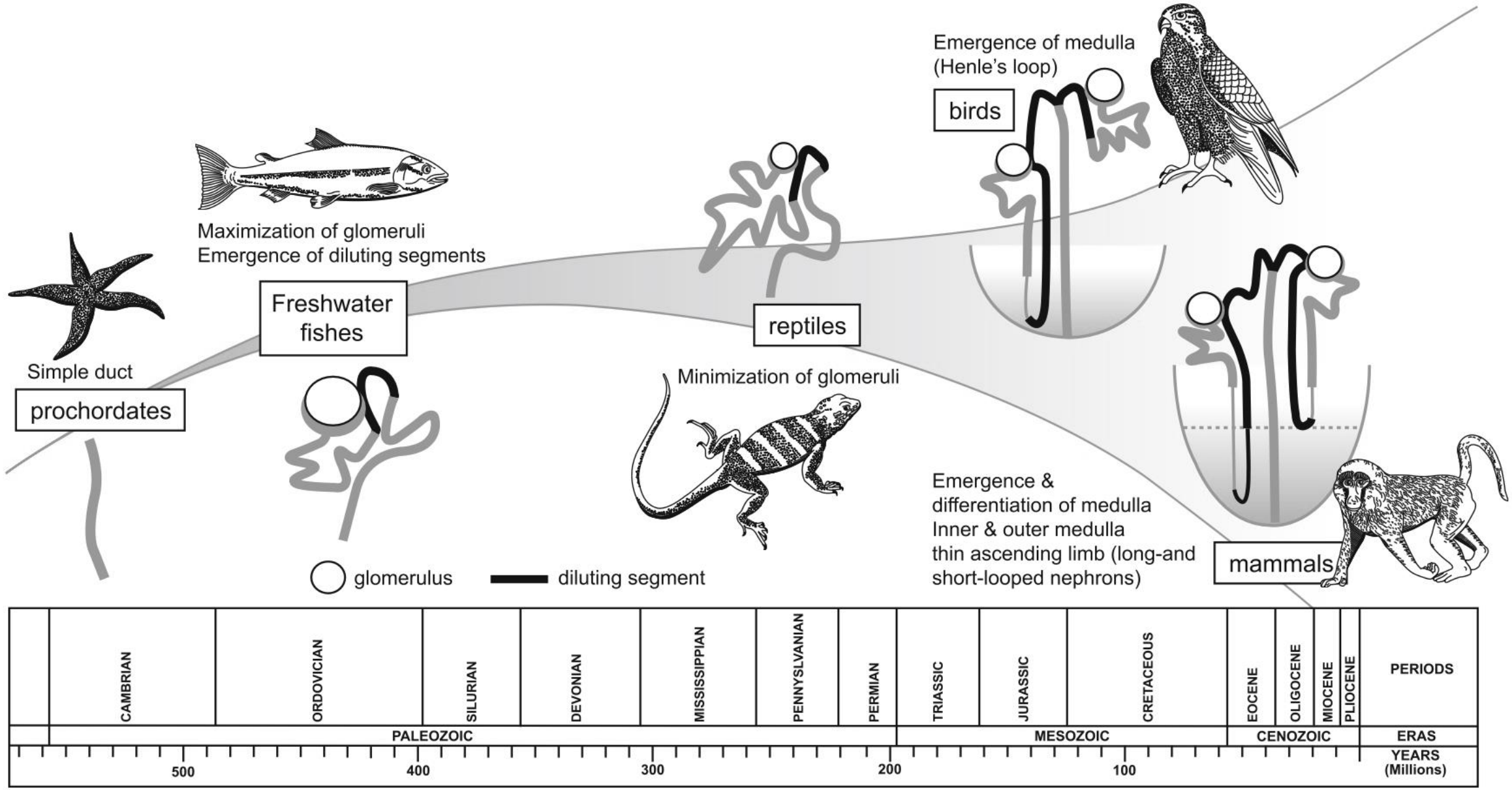
- Nil

Overview of talk

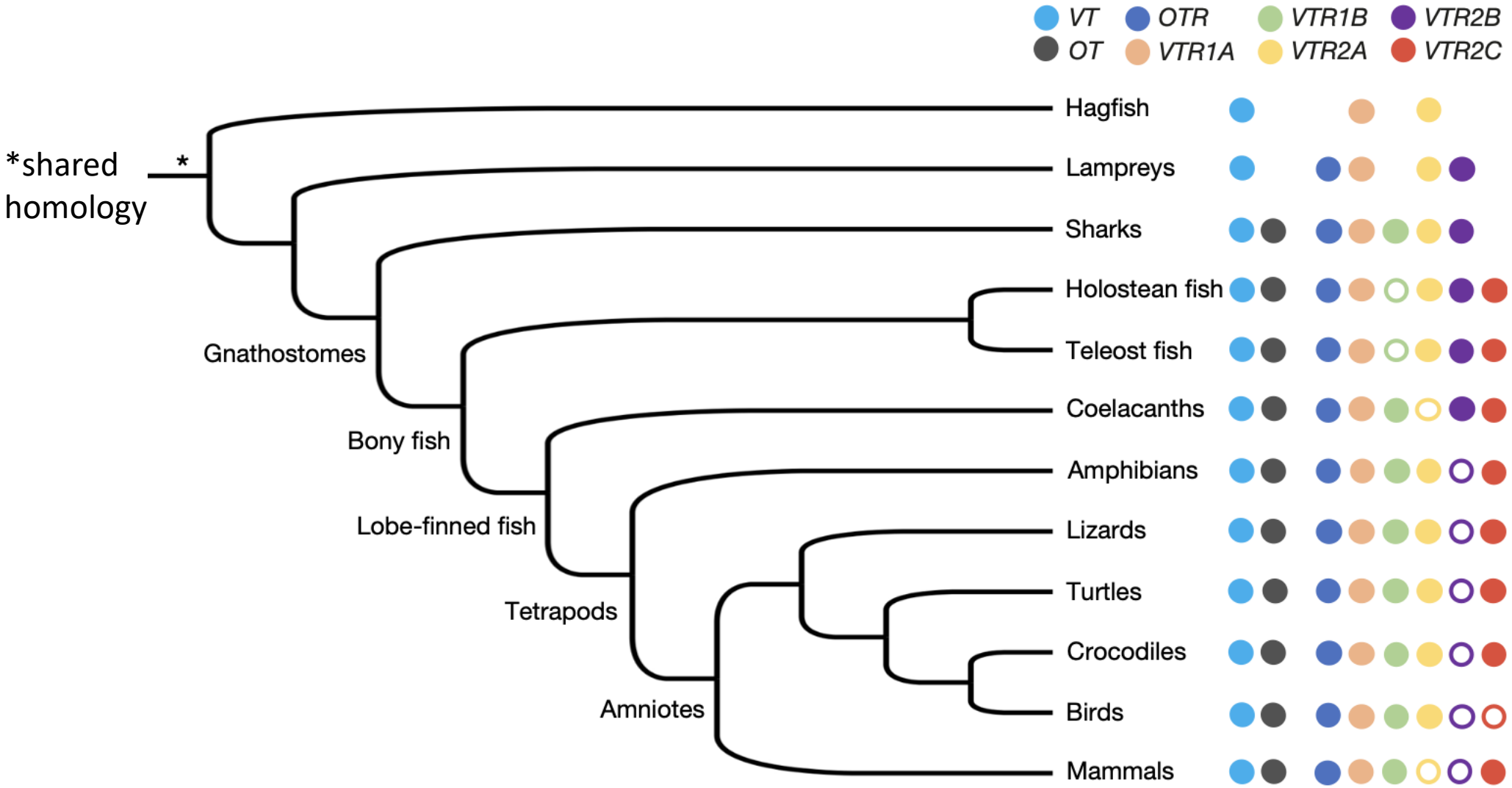
- Mechanism of thirst and water regulation
- Reasons for new terminology
- Test drive with cases
- Update on diagnosis
- A terrible story

Thirst

https://youtu.be/ouYKeeTz7Yw


Emergence of medulla
(Henle's loop)
birds
Maximization of glomeruli
Emergence of diluting segments
Freshwater
fishes
reptiles
Simple duct
prochordates
Minimization of glomeruli
Emergence &
differentiation of medulla
Inner & outer medulla
thin ascending limb (long-and
short-looped nephrons)
mammals
glomerulus
diluting segment
CAMBRIAN
ORDOVICIAN
SILURIAN
DEVONIAN
MISSISSIPPIAN
PENNYSLVANIAN
PERMIAN
TRIASSIC
JURASSIC
CRETACEOUS
EOCENE
OLIGOCENE
MIOCENE
PLIOCENE
PERIODS
PALEOZOIC
MESOZOIC
CENOZOIC
ERAS
500
400
300
200
100
YEARS
(Millions)

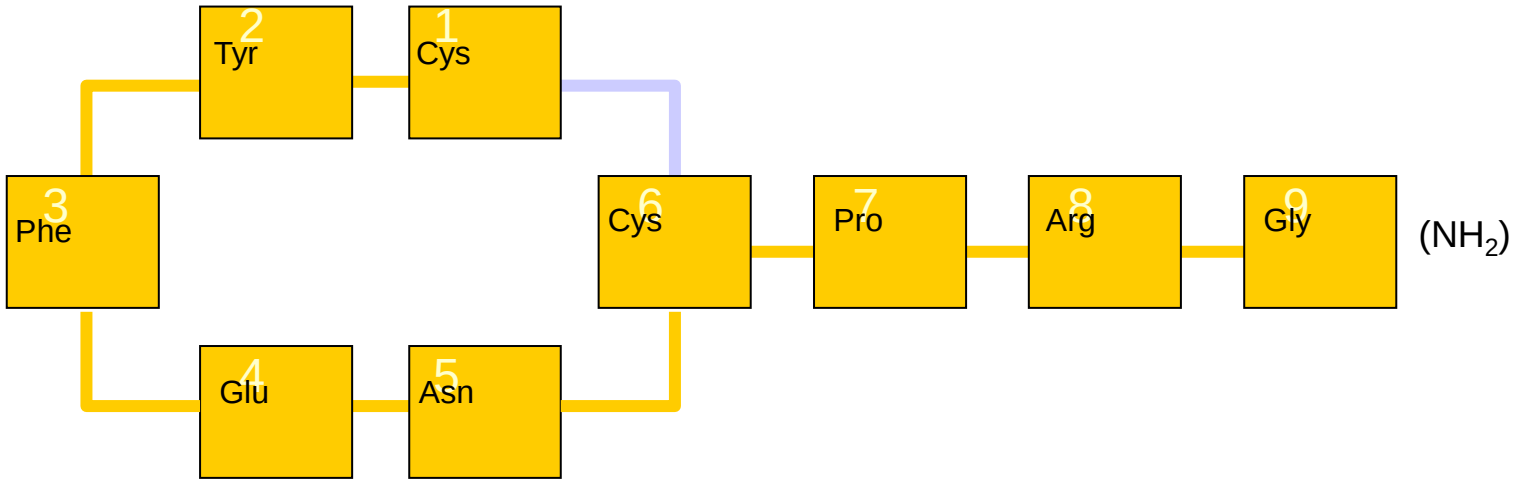
Vasopressin highly conserved



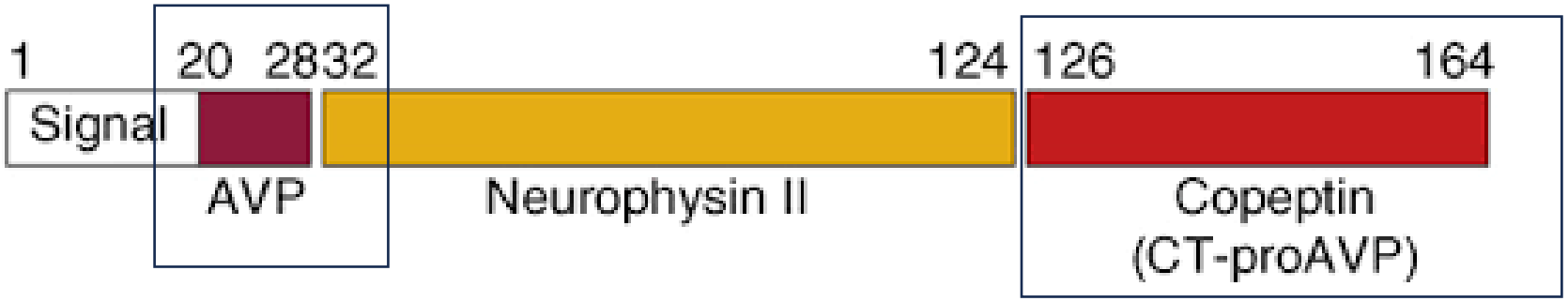
	Hormone	Species
Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Arg-Gly-NH2	Vasopressin	Mammals[a]
Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Lys-Gly-NH2	Lysipressin	Pigs, hippopotamuses, warthogs, some marsupials
Cys-Phe-Phe-Gln-Asn-Cys-Pro-Arg-Gly-NH2	Phenypressin	Some marsupials
Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Arg-Gly-NH2	Vasotocin[b]	Non-mammals

Mammals produce Arginine Vasopressin (AVP)

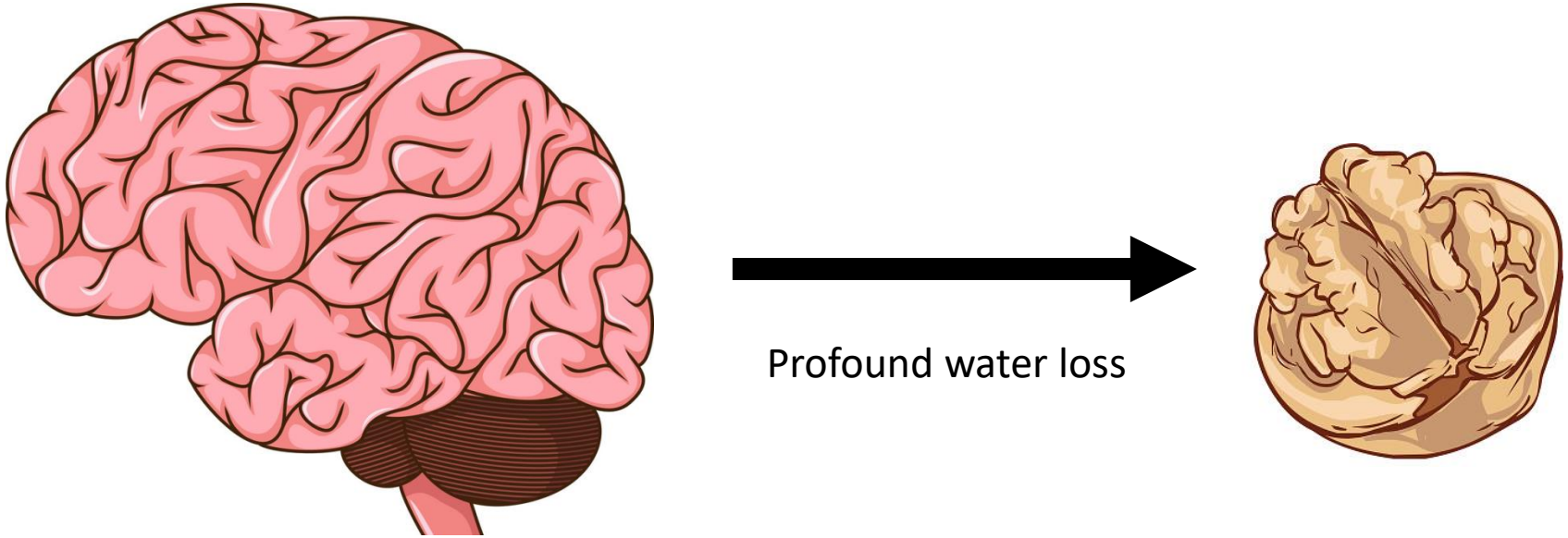
AVP is a small peptide hormone



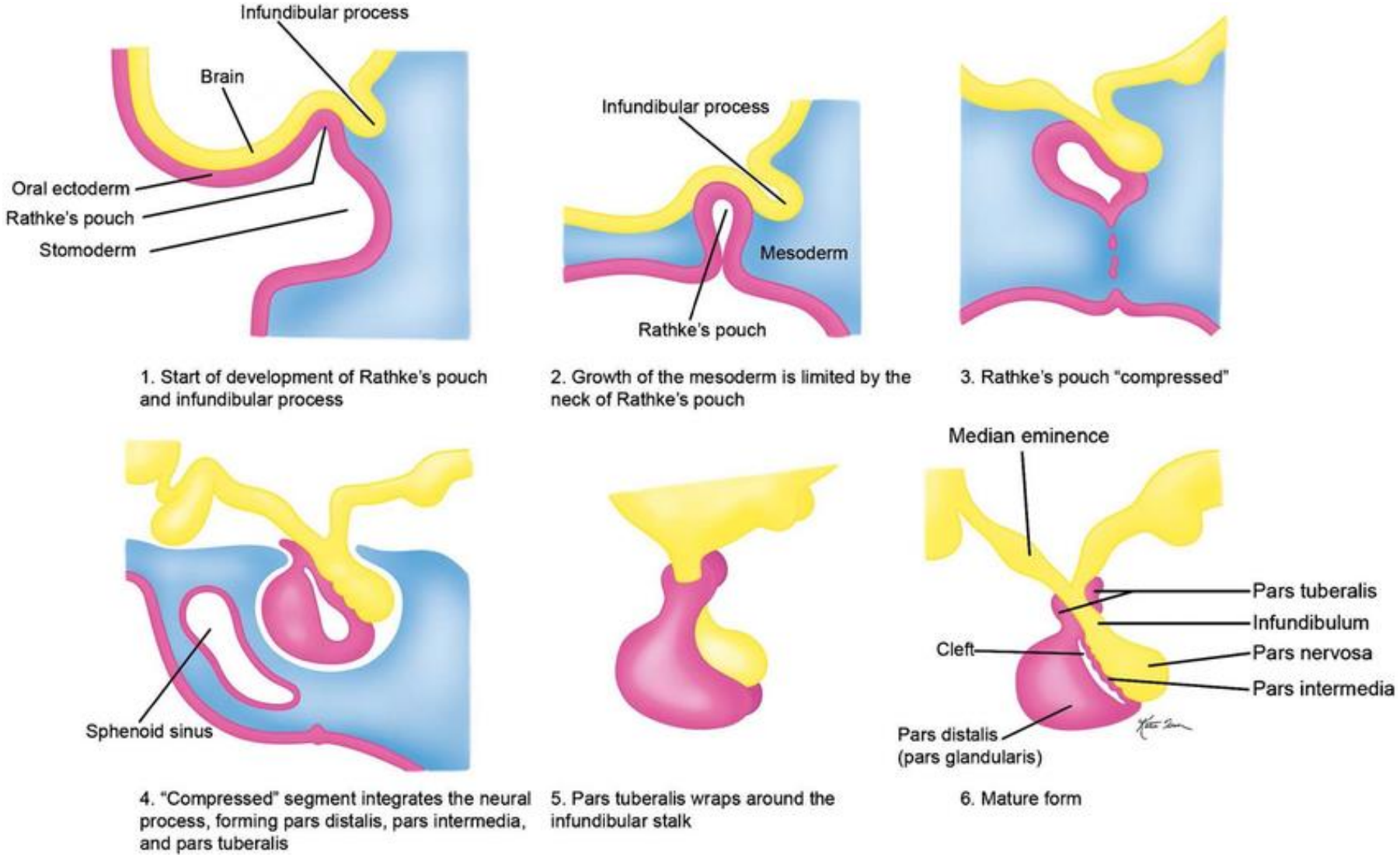
Pre-pro-vasopressin



Whole purpose to preserve water

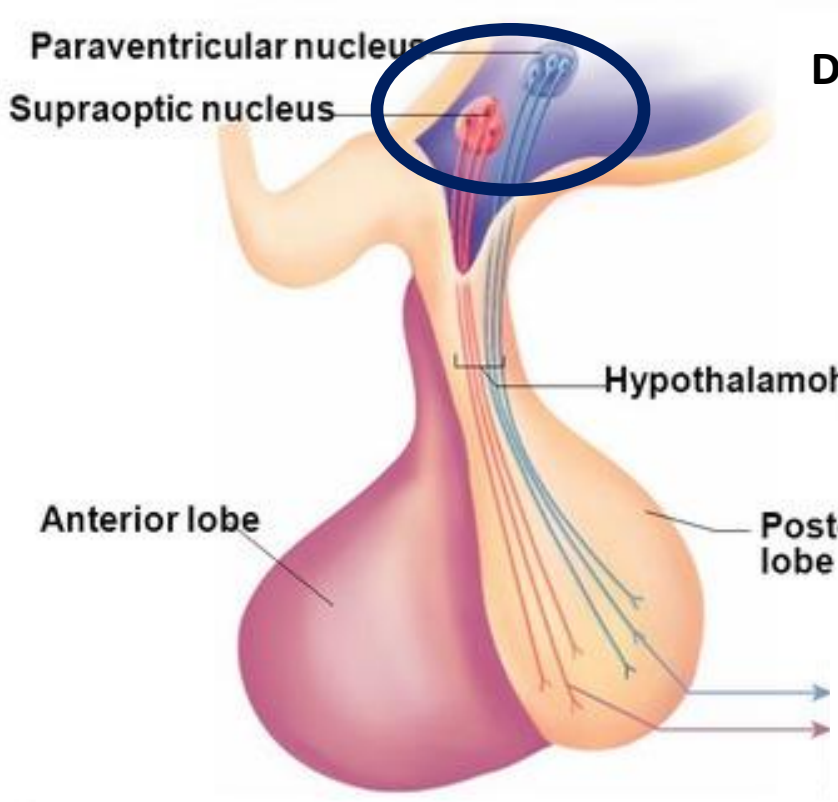


Embryology of posterior pituitary gland



Mechanism of thirst

thirst



Dehydration = high serum osmolality

Vasopressin (AVP)

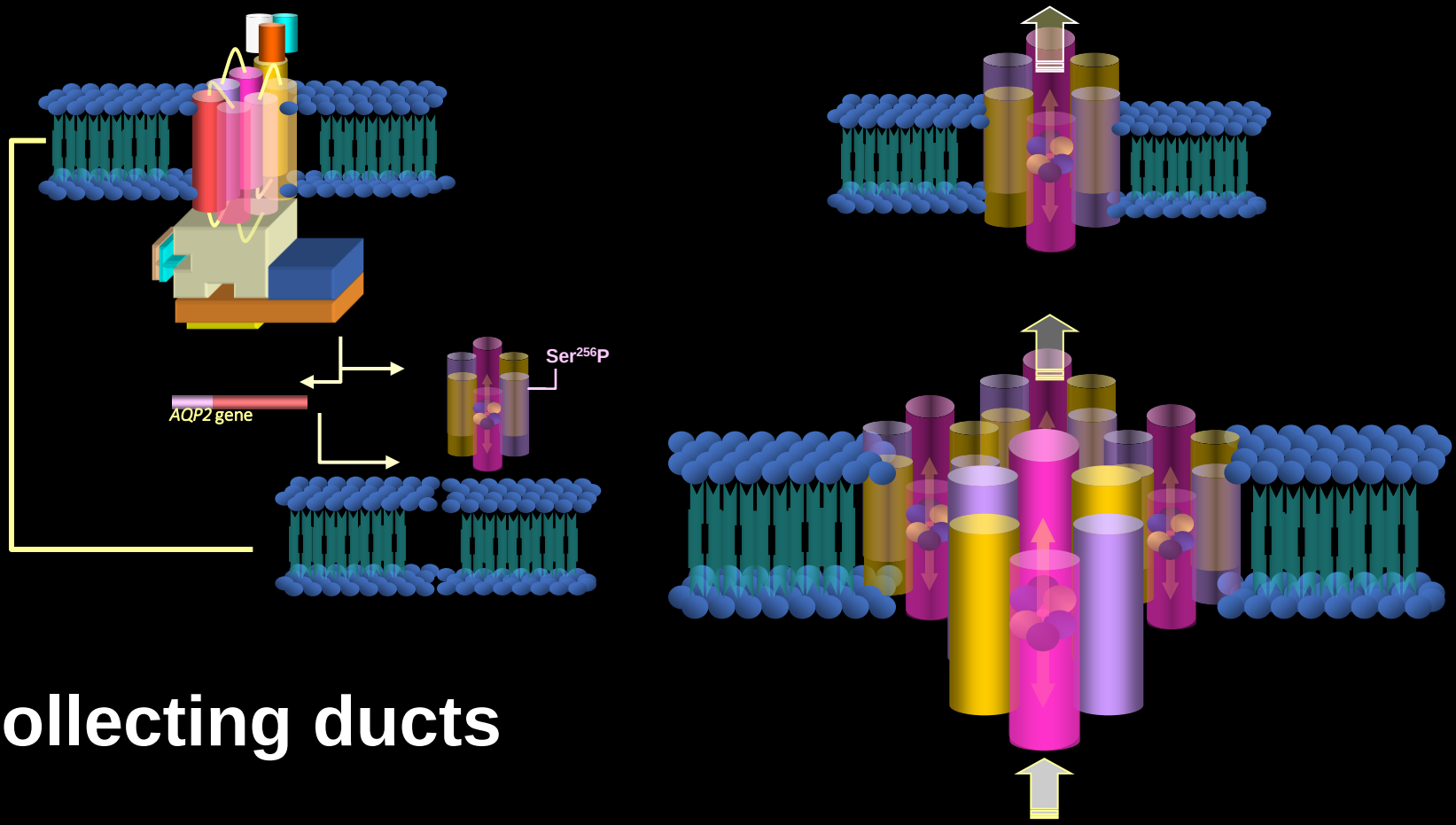
Increased AVP

Action of vasopressin (AVP)

stops water leaking out

Action of AVP

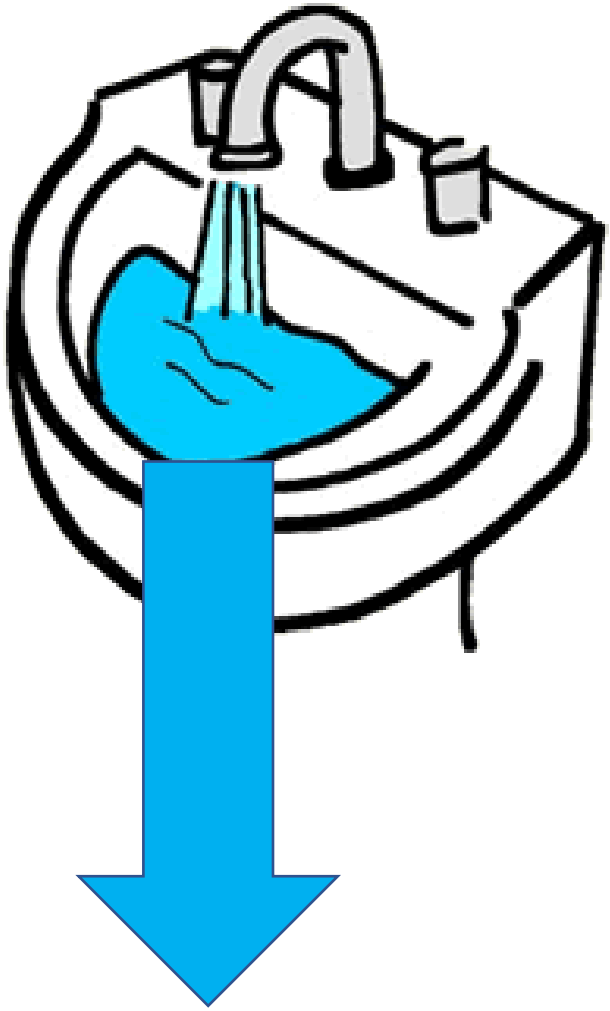
Renal interstitium



Collecting ducts

AVP-related polyuria

AVP-related polyuria



stops water leaking out

‘Diabetes Insipidus’

Unquenchable thirst

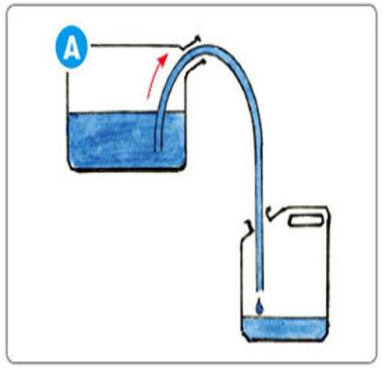
Large quantities pale urine

‘I recall leaning over the running cold tap, letting the water just run though my parched mouth. I was desperate to quench my thirst but couldn’t’

‘The only fluid in sight was the water in my flower vase, so with one final effort I grabbed the rim and gulped’

Change in terminology

Diabetes

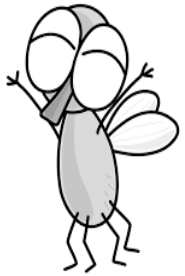


diabetes

“passing water like a siphon” *(Greek)*

mellitus

“sweetened with honey”

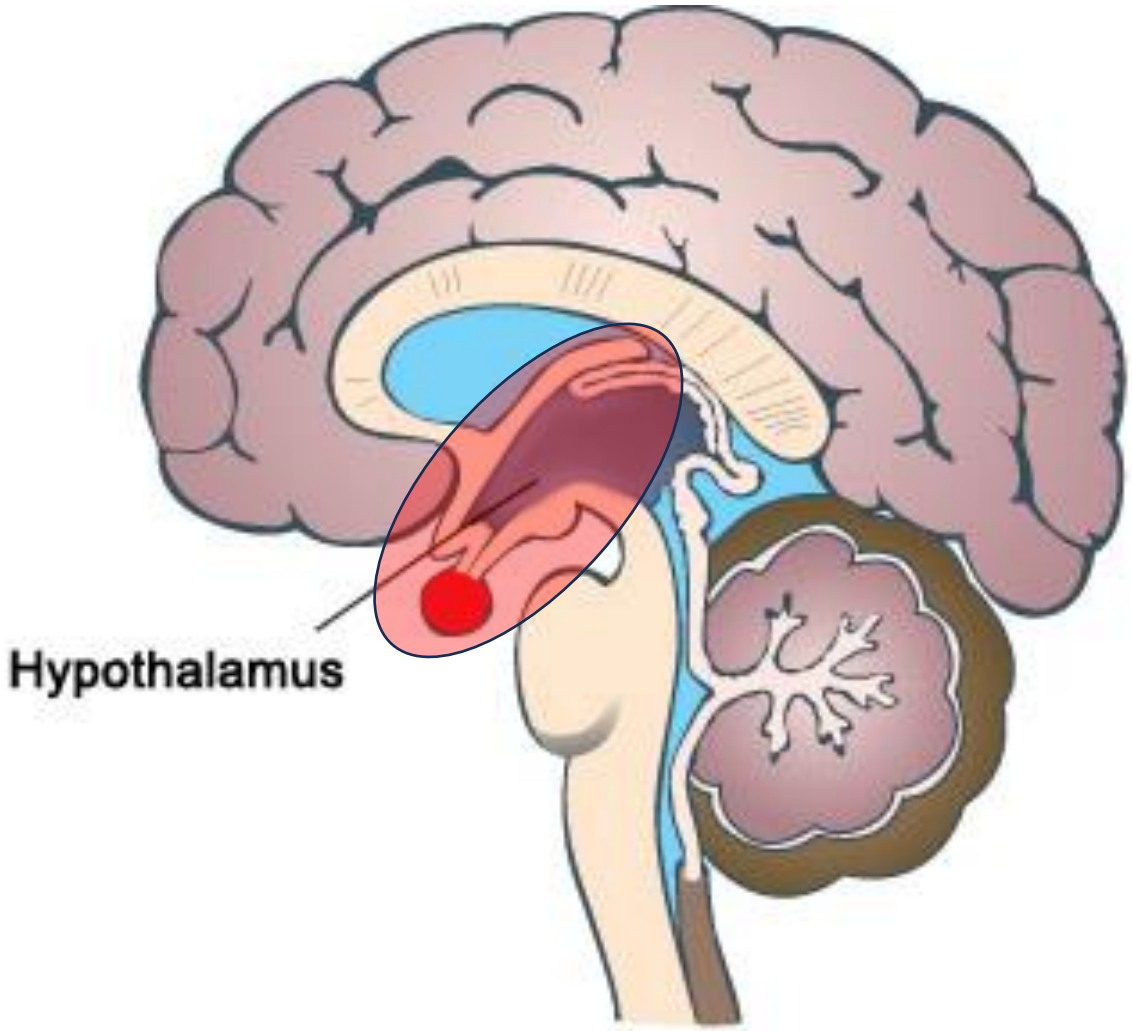


insipidus

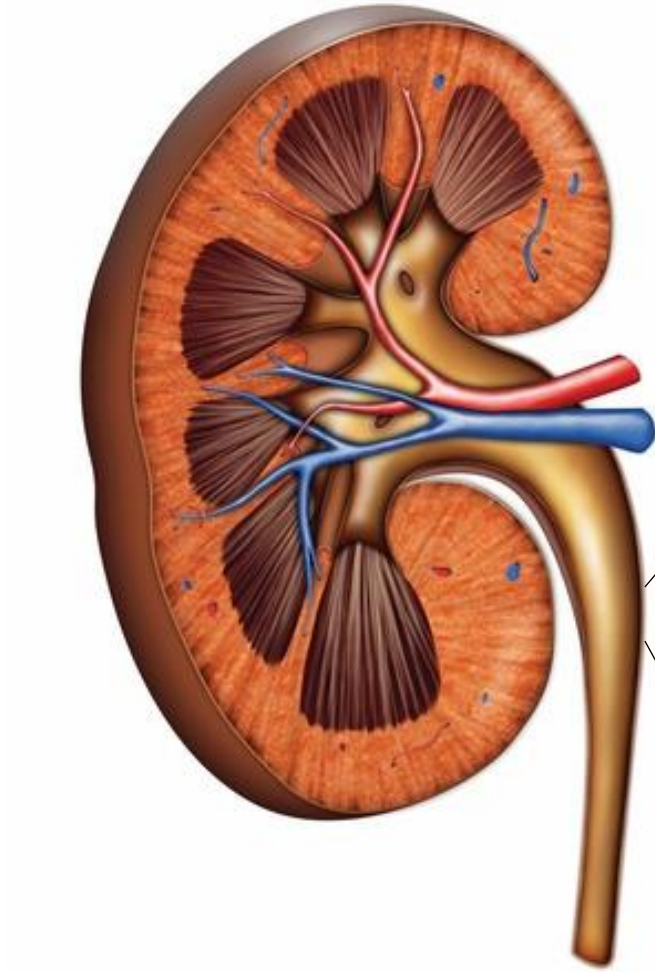
“without taste”

‘Central Diabetes Insipidus’

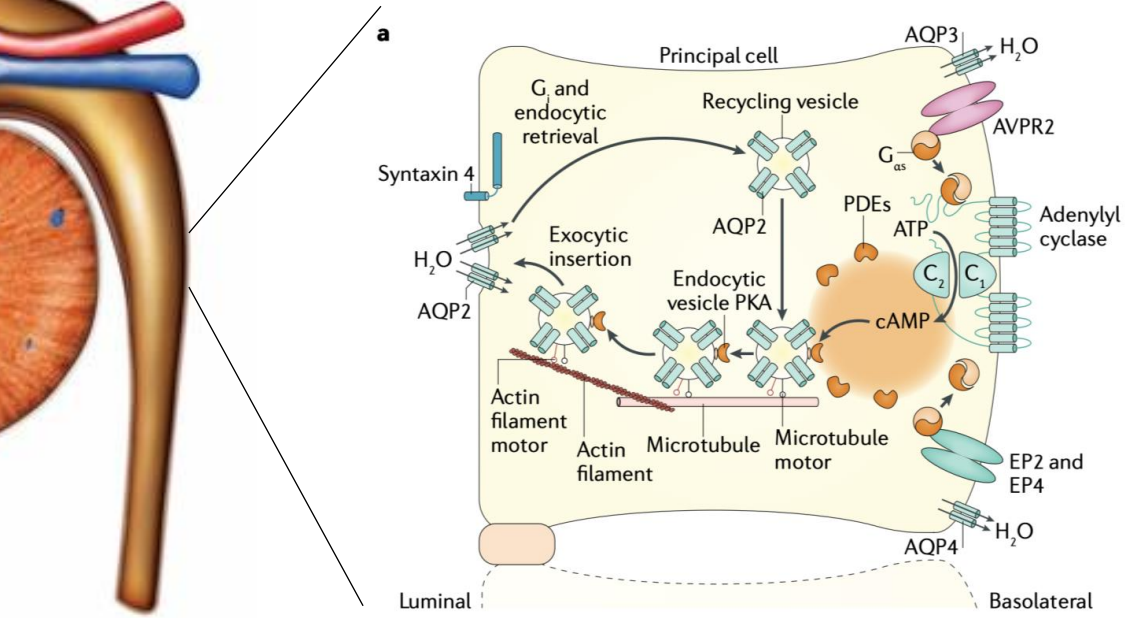
AVP not produced



‘Nephrogenic Diabetes Insipidus’



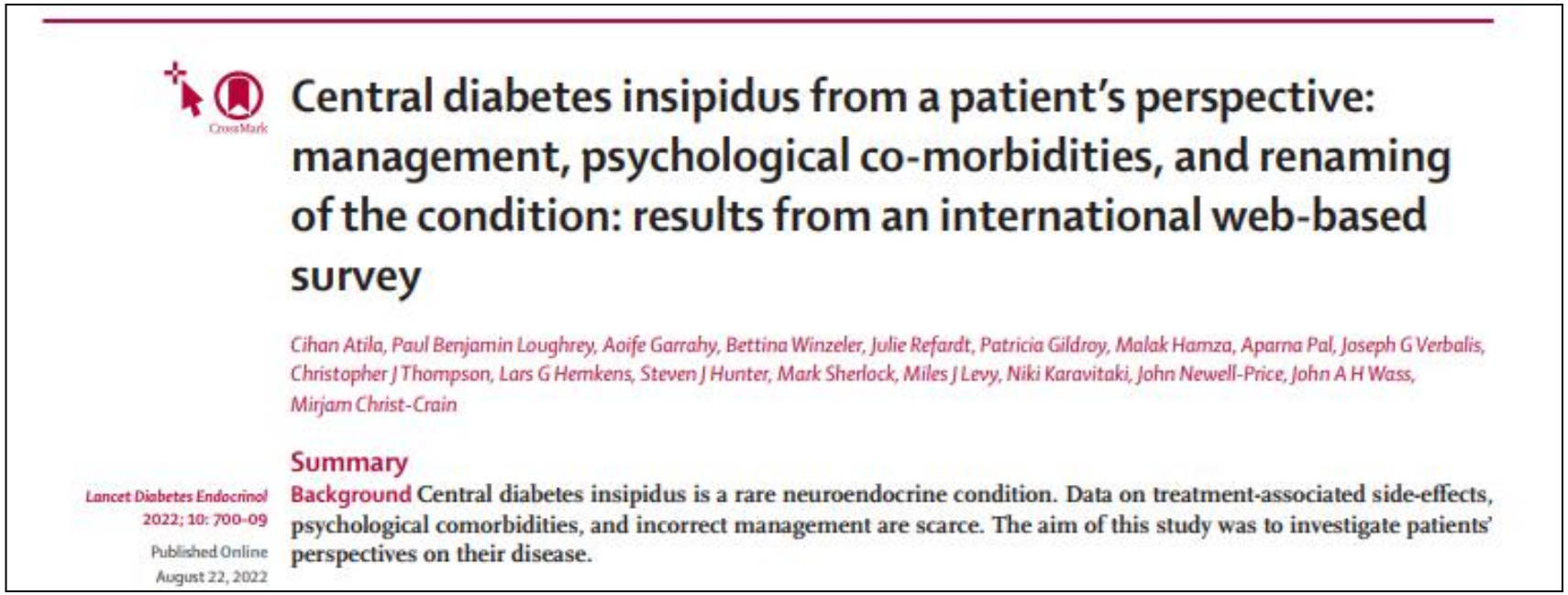
AVP doesn’t work



‘Diabetes Insipidus’

- An old-fashioned term for passing large amounts pale urine
- Indicates nothing of pathology or treatment
- Commonly confused with sugar diabetes
- Patients are not happy about it
- We can do better in 2024

Evidence that patients want change



Central diabetes insipidus from a patient's perspective: management, psychological co-morbidities, and renaming of the condition: results from an international web-based survey

Cihan Atila, Paul Benjamin Loughrey, Aoife Garrahy, Bettina Winzeler, Julie Refardt, Patricia Gildroy, Malak Hamza, Aparna Pal, Joseph G Verbalis, Christopher J Thompson, Lars G Hemkens, Steven J Hunter, Mark Sherlock, Miles J Levy, Niki Karavitaki, John Newell-Price, John A H Wass, Mirjam Christ-Crain

Lancet Diabetes Endocrinol 2022; 10: 700–09

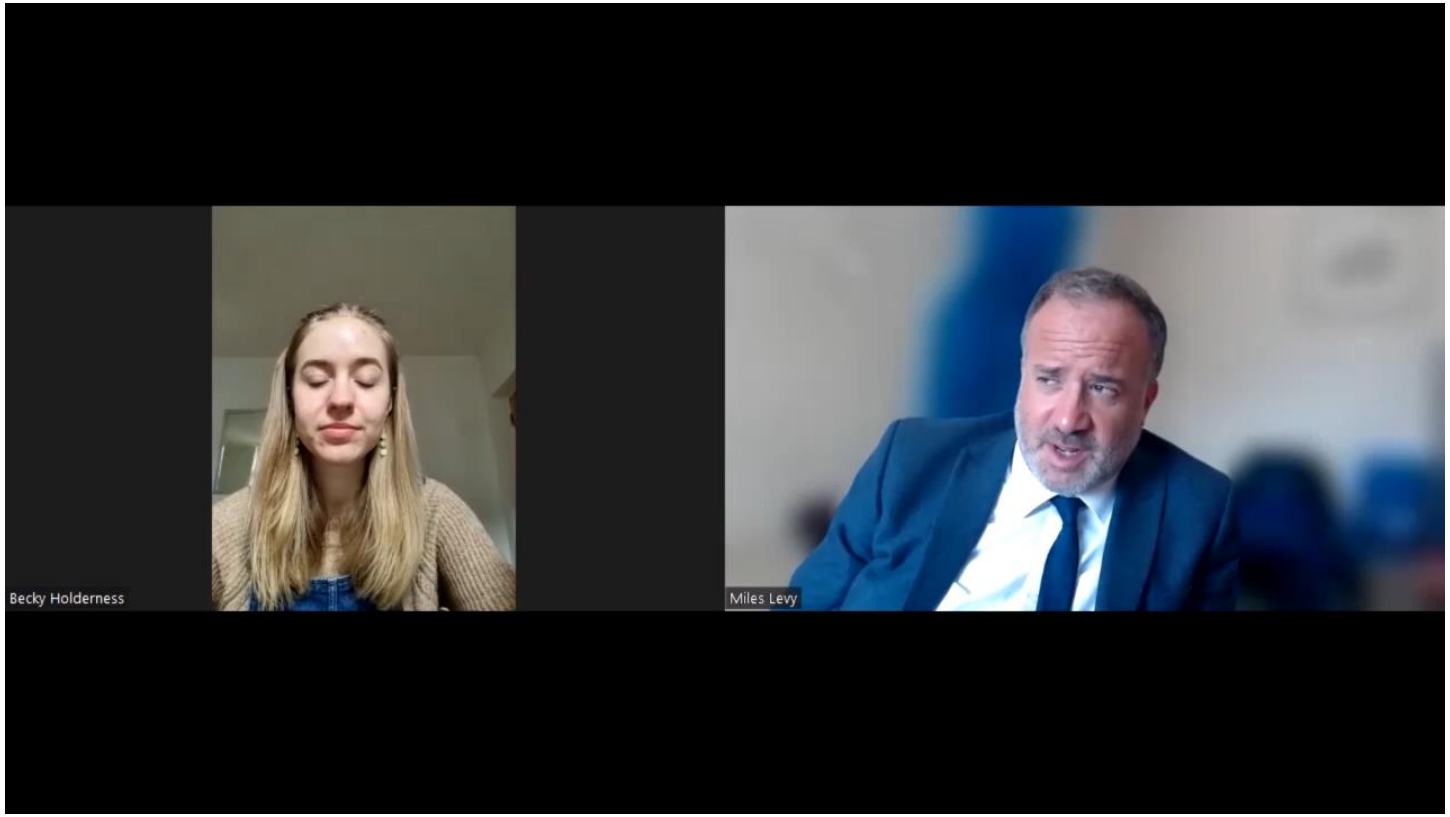
Published Online August 22, 2022

Summary

Background Central diabetes insipidus is a rare neuroendocrine condition. Data on treatment-associated side-effects, psychological comorbidities, and incorrect management are scarce. The aim of this study was to investigate patients' perspectives on their disease.

> 1000 patients with 'Diabetes Insipidus'
80% were confused with Diabetes Mellitus
85% want name change

Becky



https://youtu.be/2E4CMjGyEpA

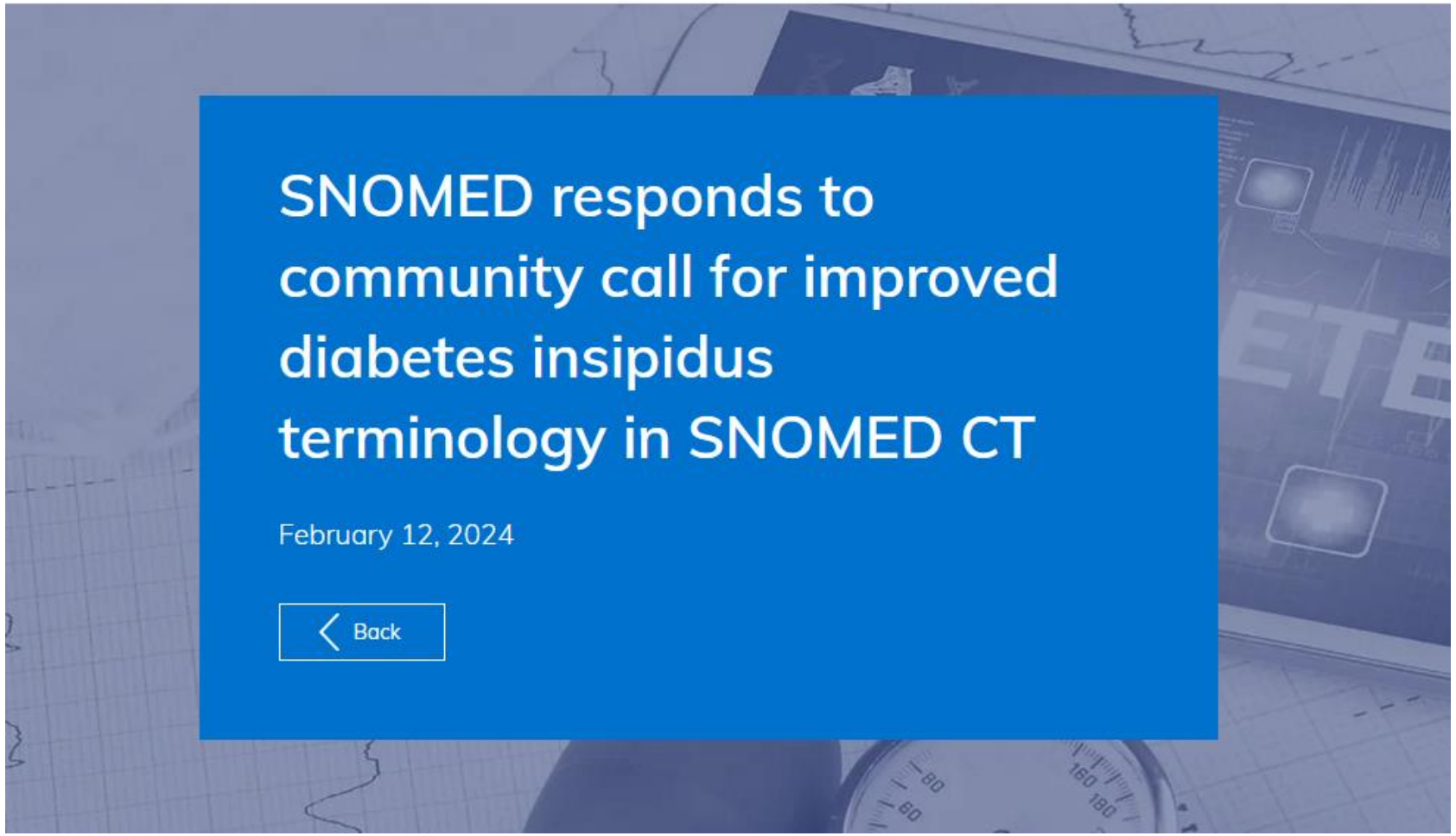
Changing the name of diabetes insipidus: a position statement of The Working Group for Renaming Diabetes Insipidus

The Working Group for Renaming Diabetes Insipidus, Hiroshi Arima[1,2], Timothy Cheetham[3,4], Mirjam Christ-Crain[5,6], Deborah Cooper[7], Mark Gurnell[6,8], Juliana B Drummond[9,10], Miles Levy[11,12], Ann I McCormack[13,14], Joseph Verbalis[15,16], John Newell-Price[16,17] and John A H Wass[18,19]

This article is CC-BY and has been published in the following titles: *Archives of Endocrinology and Metabolism, Clinical Endocrinology, Endocrine Connections, Endocrine Journal, European Journal of Endocrinology, Hormone Research in Pediatrics, Pituitary* and *The Journal of Clinical Endocrinology and Metabolism*. The articles are identical except for

Central D.I becomes AVP-Deficiency

Nephrogenic D.I becomes AVP-Resistance



SNOMED responds to community call for improved diabetes insipidus terminology in SNOMED CT

February 12, 2024

Back

Central diabetes insipidus (CDI)

MedGen UID: 146919 • Concept ID: C0687720 • Disease or Syndrome

Synonym:	Arginine vasopressin deficiency
SNOMED CT:	Diabetes insipidus - pituitary (45369008); Vasopressin deficiency (45369008); Central diabetes insipidus (45369008); Diabetes insipidus secondary to vasopressin deficiency (45369008); Vasopressin deficiency syndrome (45369008); Neurohypophyseal diabetes insipidus (45369008); Pituitary diabetes insipidus (45369008); Primary central diabetes insipidus (45369008); Neurogenic diabetes insipidus (45369008); Cranial diabetes insipidus (45369008)
Modes of inheritance:	Autosomal recessive inheritance (Orphanet) Autosomal dominant inheritance (Orphanet) X-linked dominant inheritance (Orphanet)
Related gene:	AVP
HPO:	HP:0000863
Monarch Initiative:	MONDO:0015790
OMIM®:	125700; 192340
Orphanet:	ORPHA178029

Definition

Go to:

A form of diabetes insipidus related to a failure of vasopressin (AVP) release from the hypothalamus. [from HPO]

Test-driving some cases

Polyuria polydipsia syndrome

- Primary polydipsia Behavioural drive to drink
- AVP-related polyuria AVP-deficiency or resistance

There is no substitute for taking a good history and sound clinical judgement

Case 1

Urinary frequency

Case 1

- 53-year-old female
- Always needing to pass urine
- Feeling tired and has low libido
- Computer says ‘Diabetes Insipidus’

Case 1

- 70 kg in weight
- No clinical signs
- Euvolaemic

Home 24h urine volume

- 2100 ml
- 30 ml/kg

Urine volume < 50ml/kg unlikely to be pathological

Basic biochemistry

- Serum sodium 143 mmol/L
- Serum osmolality 290 mOmol/Kg
- Urine osmolality 850 mOsmol/Kg

Good ability to concentrate urine
Suggests AVP produced and working OK

Summary of case

- Urine volumes not high
- Urine osmolality > 800 mosmol/kg

Diagnosis

- This is not AVP-related polyuria
- Computer gets the sack
- Investigate bladder

Suspected hypotonic polyuria

Urine Volume
< 50ml/kg/day

Urine Osmolality
> 800 mosmol/Kg

AVP Related polyuria excluded

Case 2

Primary Polydipsia

Case 2

- 36-year-old female
- Constantly feeling thirsty
- High volumes of pale urine

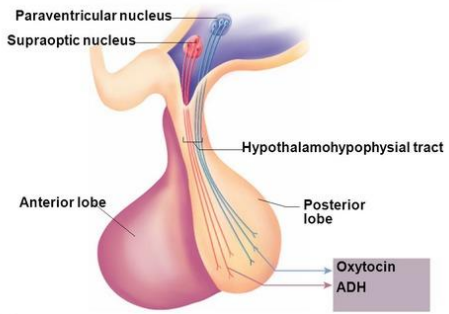
Case 2

- 60 kg in weight
- Psychological issues
- Always has bottle of water

Home 24h urine volume

- 6000 ml
- 100 ml/kg

Case 2



- Serum sodium 129 mmol/L
- Serum osmolality 275 mOsmol/Kg Dilute blood
- Urine osmolality 90 mOsmol/Kg

Dilute urine

Diagnosis

- Primary Polydipsia
- AVP suppression due to water intake
- She cannot compensate and sodium low

Suspected hypotonic polyuria

Urine Volume
> 50ml/kg/day

Urine Osmolality
< 800 mosmol/Kg

Plasma Osmolality
< 285 mosmol/Kg

Serum sodium
< 135 mmol/L

Primary Polydipsia

Case 3

AVP-Resistance

Case 3

- 50-year-old female
- Constantly feeling thirsty
- Large volumes of pale urine

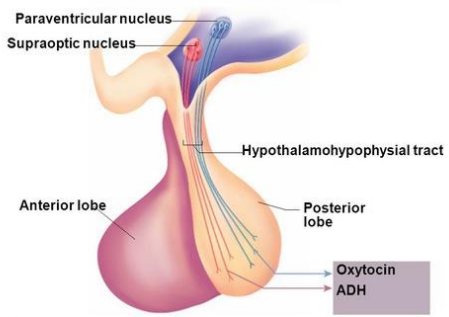
Case 3

- 90 kg in weight
- Long-standing bipolarity
- On lithium for for years
- No symptoms before drug

Home 24h urine volume

- 4950 ml
- 55 ml/kg

Case 3



- Serum sodium 147 mmol/L
- Serum osmolality 301 mOsmol/Kg
- Urine osmolality 95 mOsmol/Kg

Concentrated blood

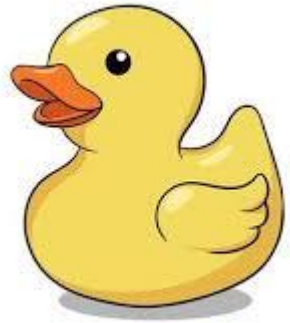
Dilute urine

Case 3

- Calcium 2.95 mmol/L Slightly high
- Phosphate 0.5 mmol/L
- PTH 20.4 pmol/L

Diagnosis

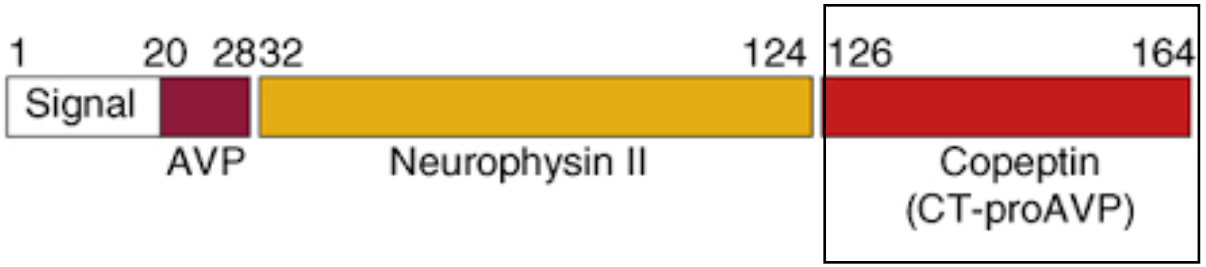
- AVP Resistance (nephrogenic Diabetes Insipidus)



Confirmatory tests

- If you are someone who likes certainty
- Copeptin is a good new surrogate marker of AVP

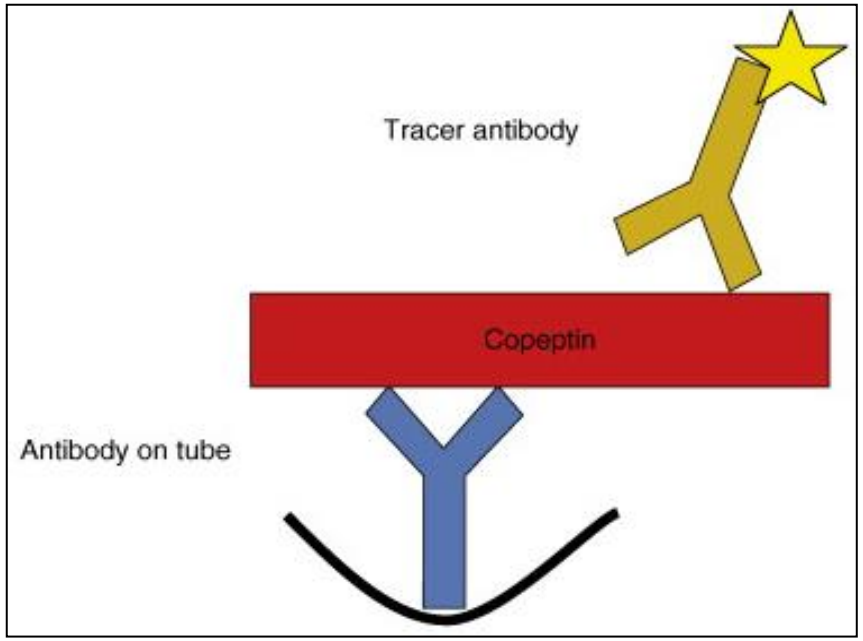
Pre-pro AVP



It is technically difficult to assay AVP

Copeptin is a stable immuno-assay

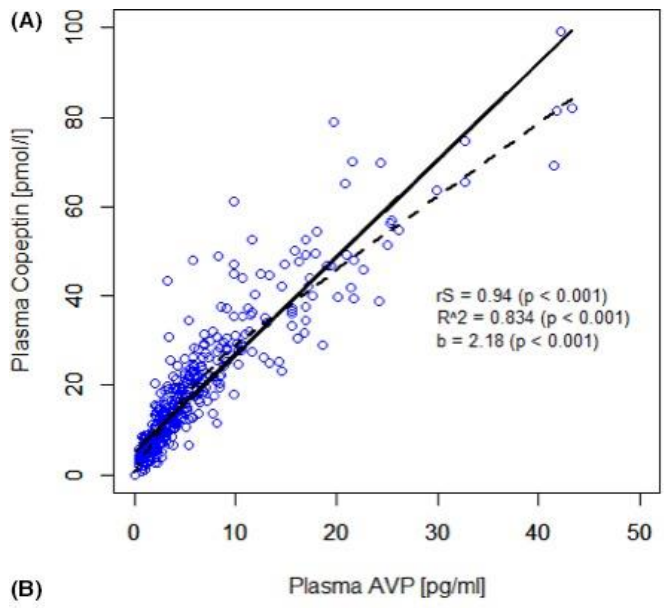
Copeptin immuno-assay



Copeptin based tests

- Surrogate marker circulating AVP
- High basal levels suggest resistance
- Low basal levels suggest deficiency

Copeptin and AVP correlation



Suspected hypotonic polyuria

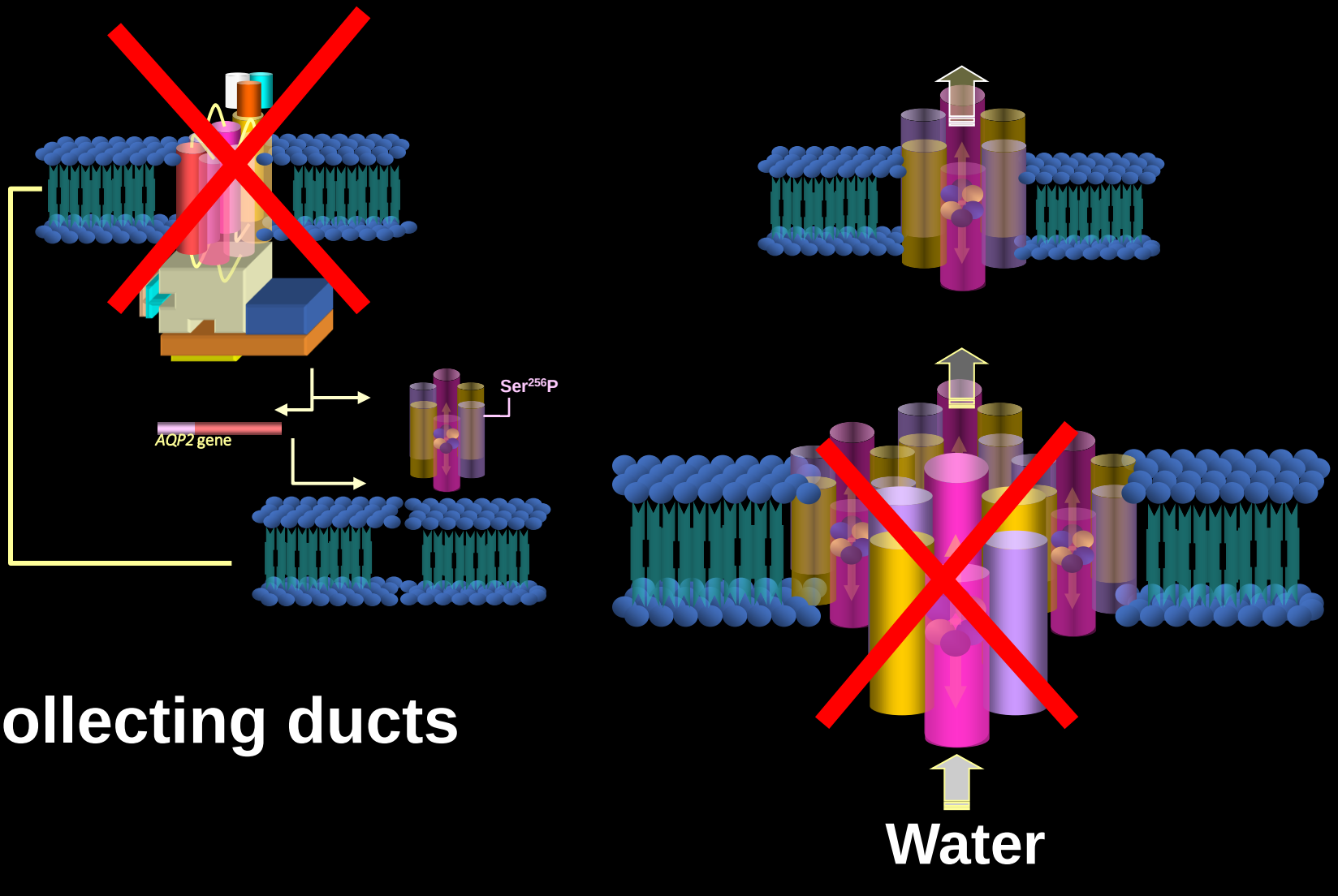
Urine Volume
> 50ml/kg/day

Urine Osmolality
< 800 mosmol/Kg

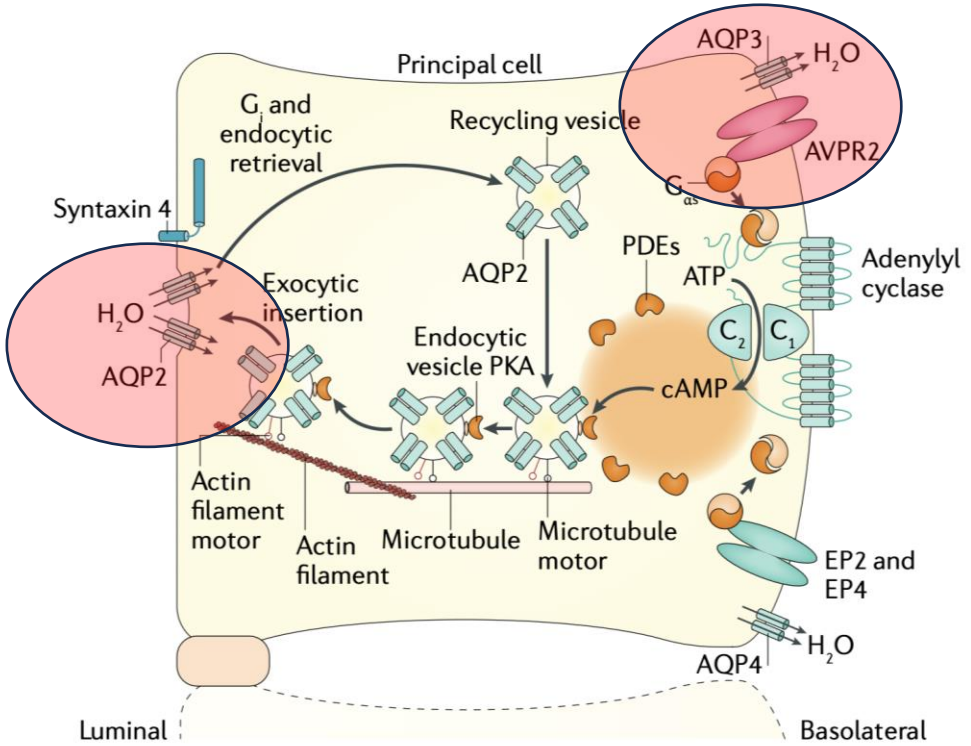
Plasma Copeptin
> 21.4 pmol/L

AVP Resistance

Action of AVP



AVP action


Principal cell
AQP3
H_2O
AVPR2
G_{as}
G_i and endocytic retrieval
Recycling vesicle
Syntaxin 4
AQP2
PDEs
ATP
Adenylyl cyclase
C_2
C_1
H_2O
AQP2
Exocytic insertion
Endocytic vesicle PKA
cAMP
Actin filament motor
Actin filament
Microtubule
Microtubule motor
EP2 and EP4
AQP4
H_2O
Luminal
Basolateral

Case 3

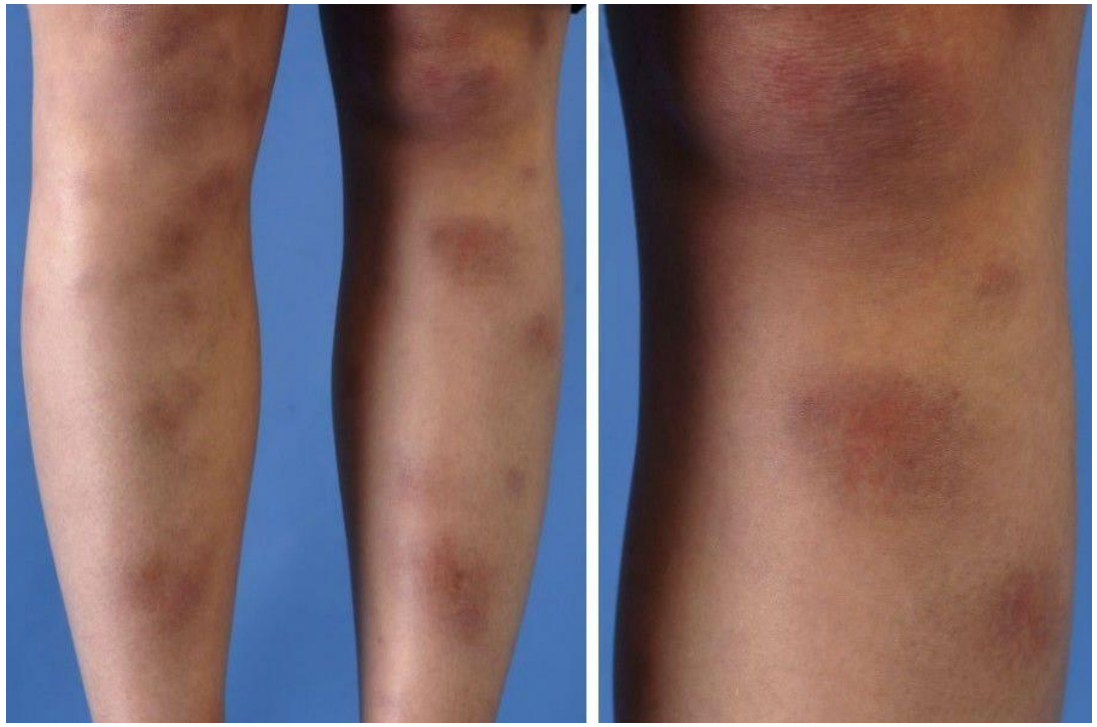
AVP-Deficiency

Case 4

- 31-year-old female
- Always feeling tired
- Constantly feeling thirsty
- High volumes of pale urine
- Getting up a lot at night

Case 4

- Abrupt onset about 8 weeks ago
- Recently put on steroids by rheumatologists
- Painful rash on shins and joint pains
- Energy better but new onset polyuria



Erythema Nodosum

Endocrine tests

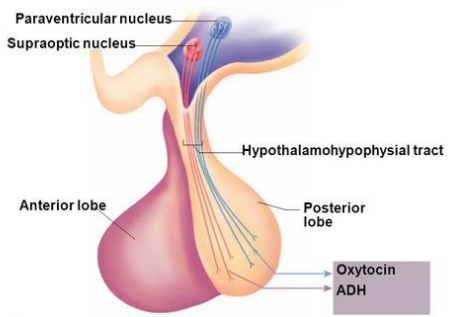
• fT4	8.5 pmol/L	TSH deficiency
• TSH	1.2 miU/L	
• Prolactin	1195 miU/L	Hyperprolactinaemia
• Cortisol	< 25nmol/L	Likely ACTH deficiency

More than a whiff of pituitary pathology

Home 24h urine volume

- 4200 ml
- 60 ml/kg

Case 3



- Serum sodium 145 mmol/L
- Serum osmolality 299 mOsmol/Kg

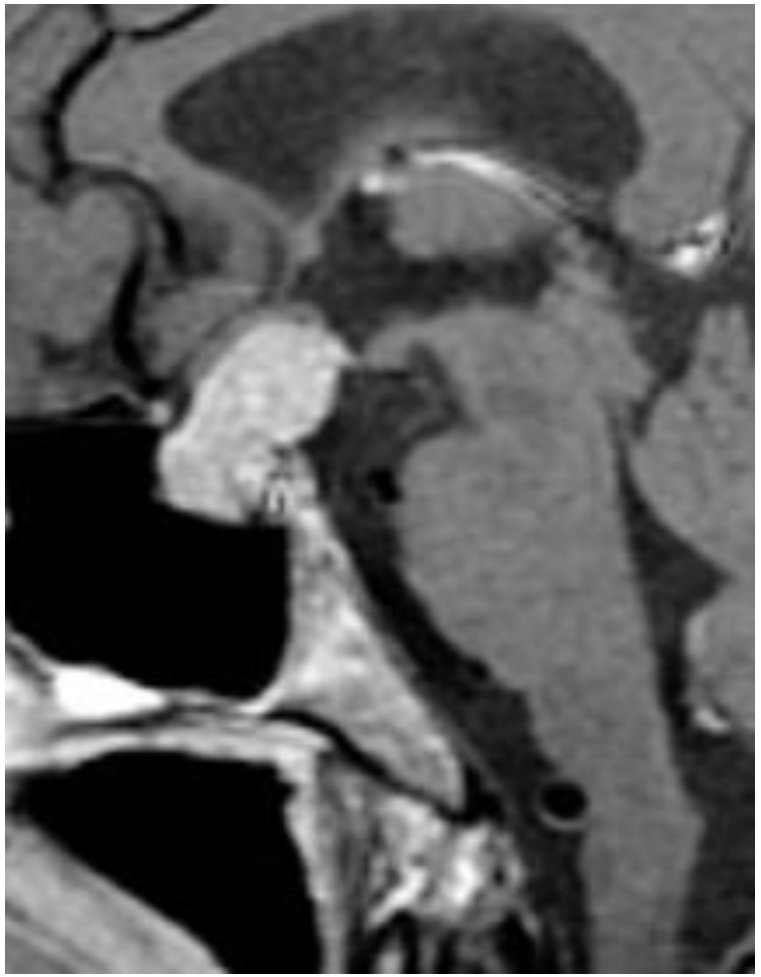
Concentrated blood

- Urine osmolality 86 mOsmol/Kg

Dilute urine

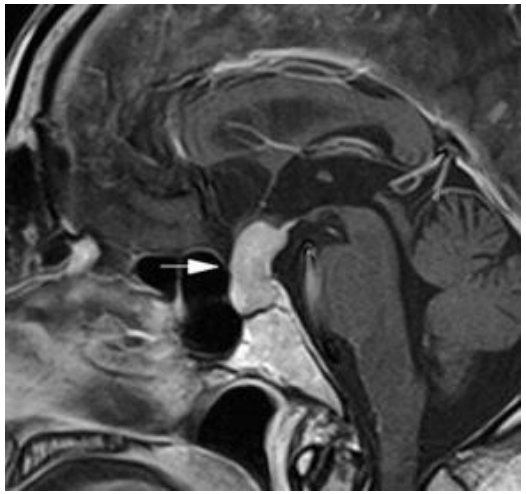
Bilateral hilar lymph nodes

Thickened pituitary stalk

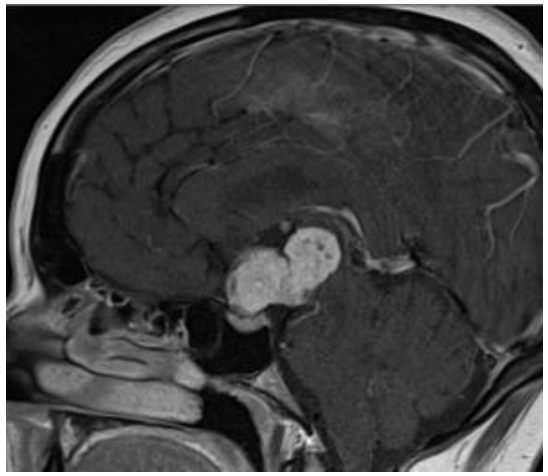


Causes of AVP-D

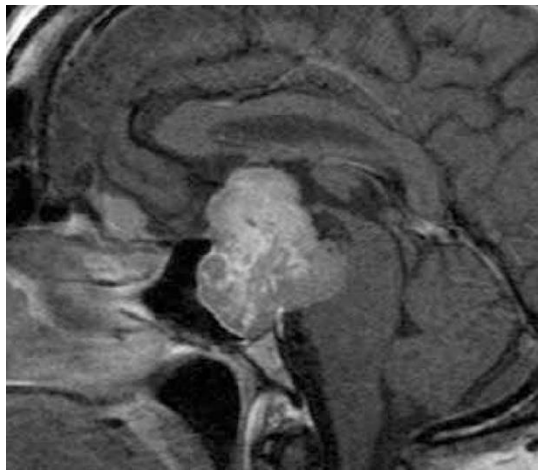
Surgery or trauma



Stalk thickening



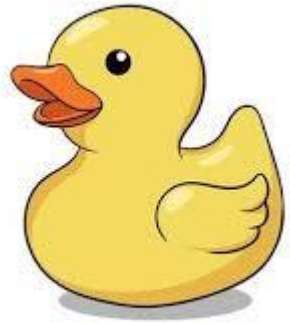
Supra-sellar mass



Weird looking mass

Diagnosis

- AVP Deficiency (cranial Diabetes Insipidus)

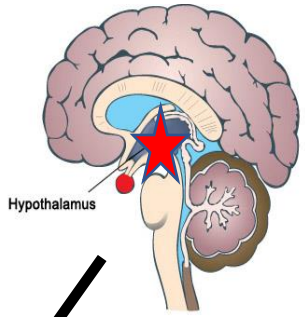


Confirmatory tests

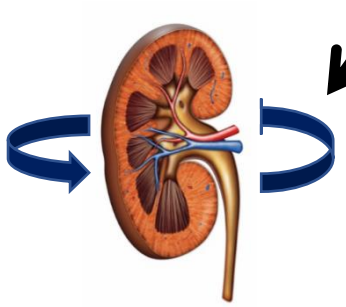
- If you are someone who likes certainty
- Water deprivation indirect test of AVP action
- Copeptin is a direct marker of AVP reserve

Water deprivation and AVP

AVP release and action

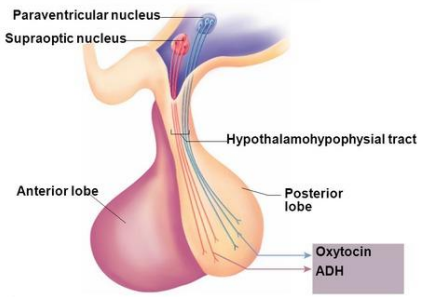


Water deprivation



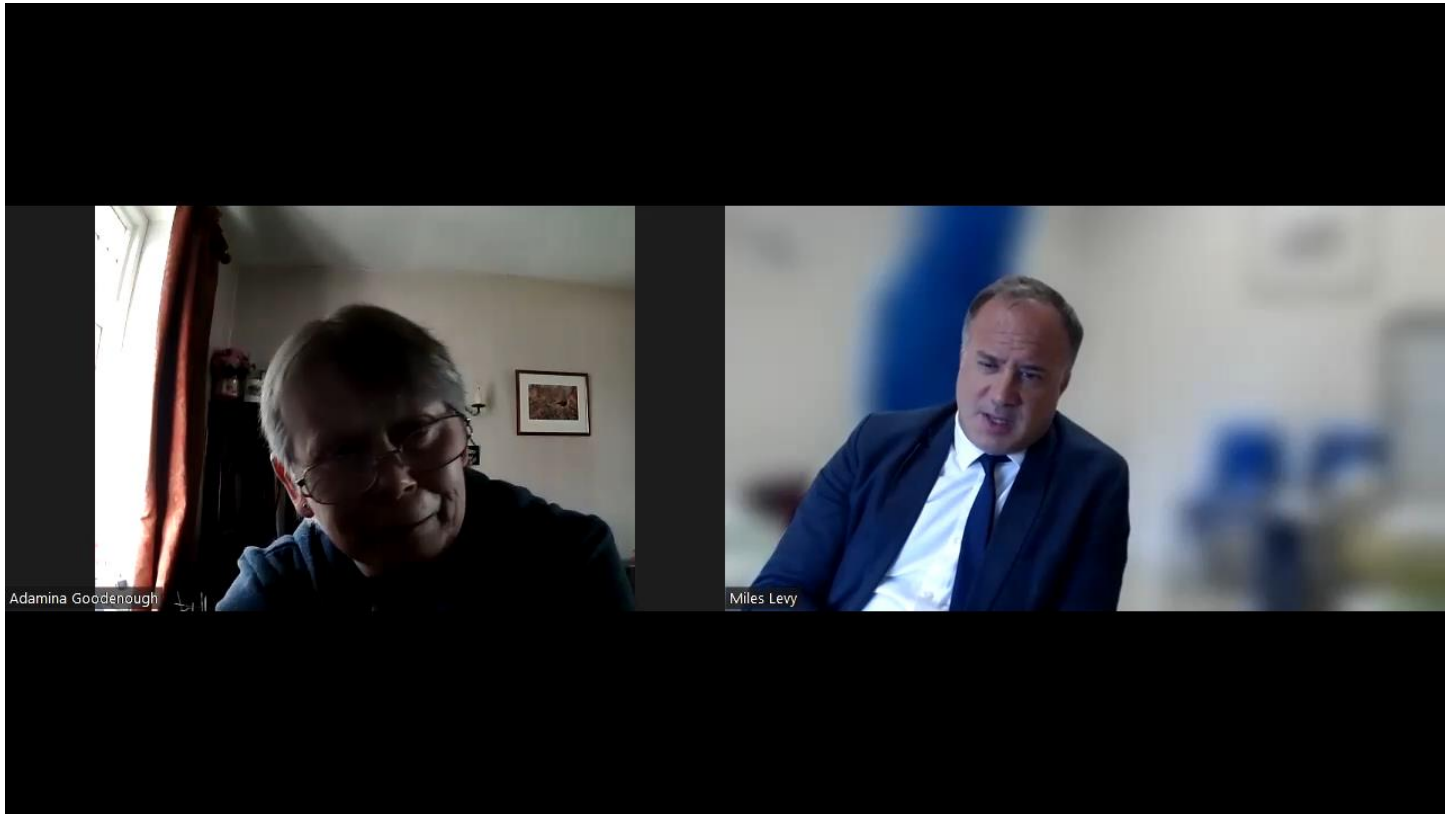
AVP-mediated
H_20 reabsorption
via aquaporin

Water deprivation tests



- Water deprivation should increase serum osmolality
- Leading to increased thirst and AVP release
- Water reabsorption stops further rise osmolality
- Appropriate reduction in urine volume
- Absolute torture for patient with severe AVP-D

Mina



https://youtu.be/3EdQTgzRKkE

Water deprivation test

Part 1

- No fluid intake allowed 08:30 – 16:30
- Serial measurements of urine volume and urine osmolality
- Serial measurements of plasma sodium and osmolality (stop if > 300)
- Hourly weight measurement – stop if lose > 3% weight

Part 2

- At 1630 drink freely, give DDAVP (20ug nasal spray or 2ug IM)
- In AVP-D the urine volume drops and urine osmolality rises

Normal Water Deprivation Test

- Plasma osmolality < 300 mosmol/Kg Not high
- Urine osmolality > 750 mosmol/Kg Good concentrating ability
- Urine volume reduces

AVP-Deficiency

- Plasma osmolality > 300 mosmol/Kg Abnormally high after water deprivation
- Urine osmolality < 300mosmol/Kg No rise after water deprivation
- Urine volume remains high

- <u>After desmopressin</u>
- Urine osmolality > 750mosmol/Kg
- Urine volumes fall as DDAVP works

AVP-Resistance

- Plasma osmolality > 300 mosmol/Kg — Abnormally high after water deprivation
- Urine osmolality < 300mosmol/Kg — No rise after water deprivation
- Urine volume remains high

- <u>After desmopressin</u>
- No response

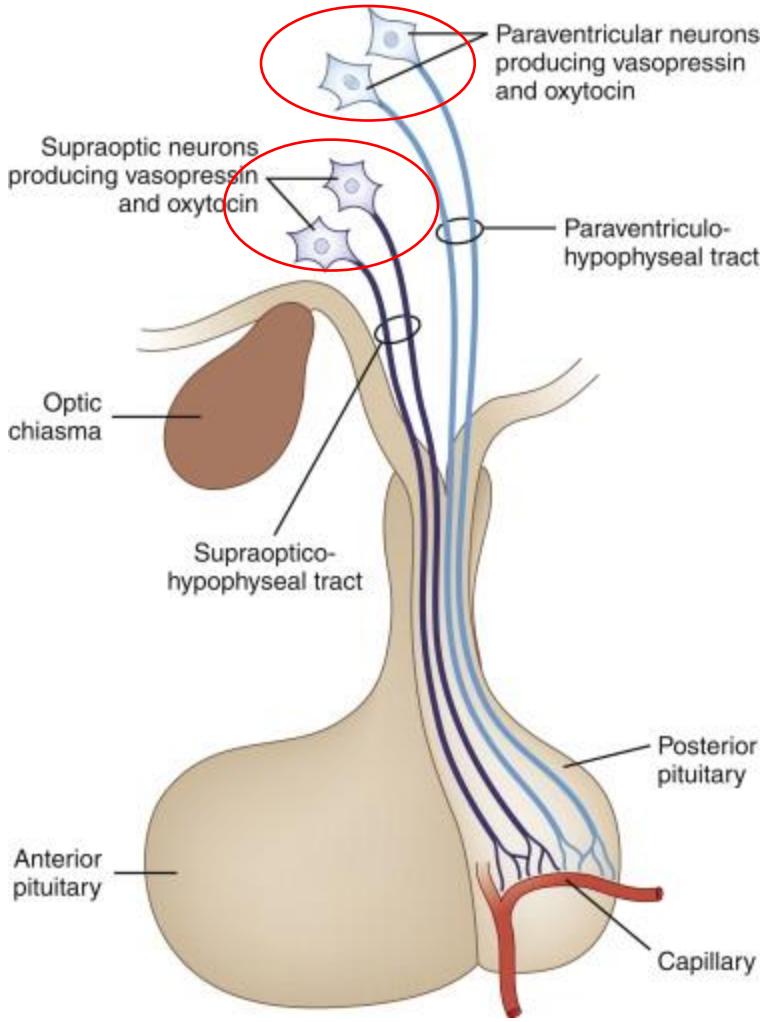
Problems with WDT

- Diagnostic accuracy only 70% as indirect test
- Particularly bad with Primary Polydipsia (41%)
- PP washes out medullary concentrating gradient
- Impaired concentration and response to DDAVP

JCEM, 2011

Copeptin stimulation tests

A new alternative to Water Deprivation tests



Arginine*
Hypertonic Saline*

Arginine stimulated copeptin

Arginine-stimulated copeptin measurements in the differential diagnosis of diabetes insipidus: a prospective diagnostic study

Bettina Winzeler, Nicole Cesana-Nigro, Julie Refardt, Deborah R Vogt, Cornelia Imber, Benedict Morin, Milica Popovic, Michelle Steinmetz, Clara O Sailer, Gabor Szinnai, Irina Chifu, Martin Fassnacht, Mirjam Christ-Crain

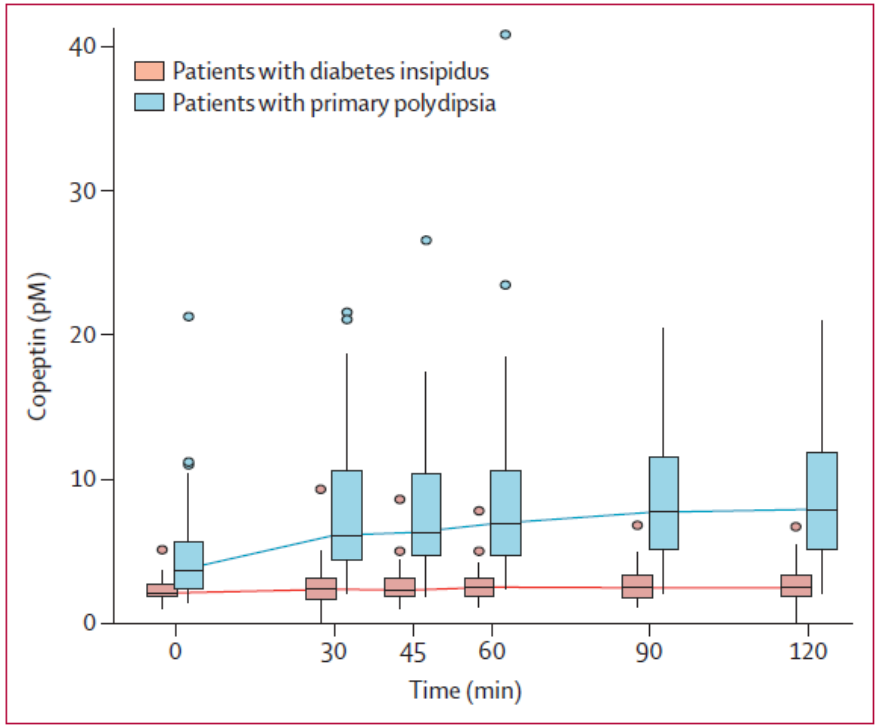


Figure 1: Copeptin concentrations after arginine stimulation in patients with diabetes insipidus (complete and partial) and primary polydipsia, in the pooled patient dataset

Winzeler et al. The Lancet 2019

Hypertonic saline better than WDT

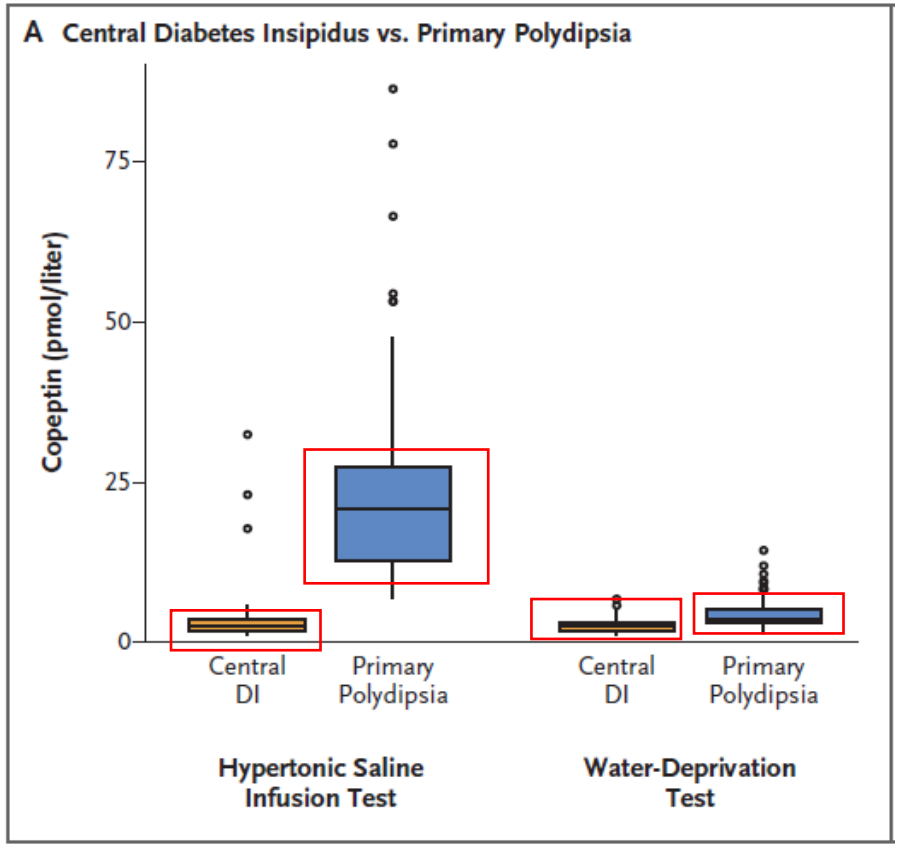


Figure 1. Stimulated Copeptin Levels in Response to the Hypertonic Sa Polyuria.

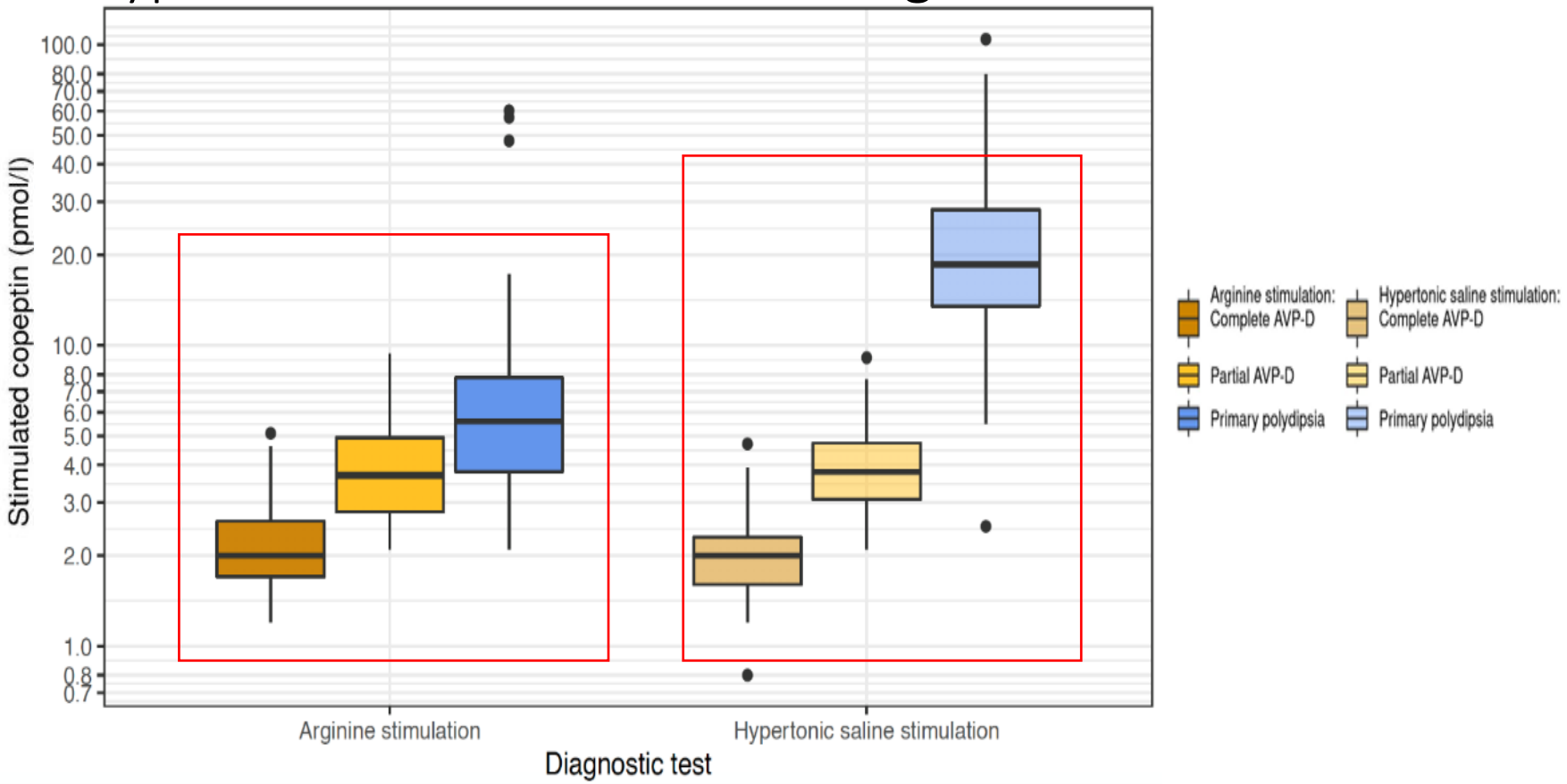
Fenske, Refardt et al. NEJM 2018

Close sodium monitoring and constant surveillance needed due to risk of overstimulation and possible side effects

Diagnostic accuracy:

- Hypertonic saline 96.5%
- Water deprivation test 76.6%

Hypertonic saline better than arginine stimulation



Diagnostic accuracy:

74.4%

Diagnostic accuracy:

95.6%

Refardt J et al NEJM Jan 2024

Preventing catastrophe

Kane’s story

Why this matters for all doctors

Died on his 22nd Birthday

Daily Mail

2 for 1 SPA BREAKS

GOOD Health

The bunion operations that could cripple you

40 REASONS YOUR DIET IS DOOMED

Inquest hears of mother's fury at nurses who neglected son

PATIENT DYING OF THIRST RANG 999

Airmiles Andy and a huge new travel bill

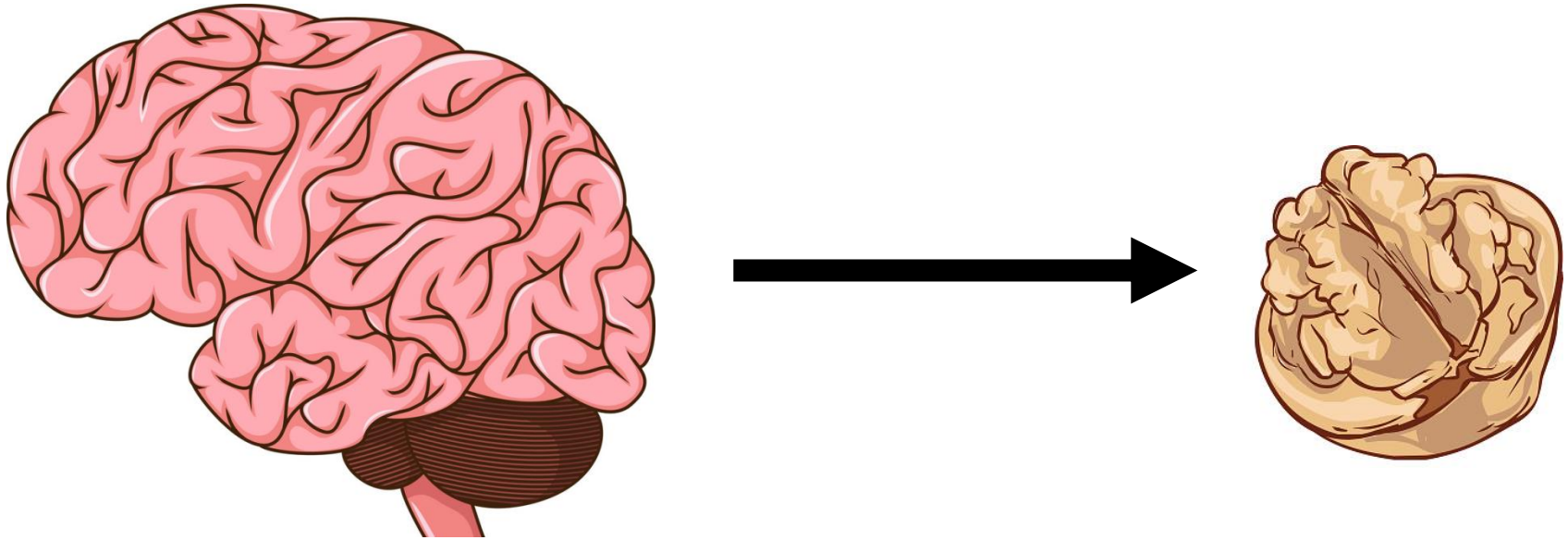
New Labour is dragged into bank rate scandal

Rita


https://www.loom.com/share/136b8632021944dca02a8ca1fa186347
ADRENALINE
a runner

The tragedy of this case

- All Kane needed was water and desmopressin
- He was becoming increasingly hypernatrameic



Endocrine CONNECTIONS

S E Baldeweg *et al.* | Management of cranial diabetes insipidus | 7:7 | G8–G11

GUIDELINES AND GUIDANCE

SOCIETY FOR ENDOCRINOLOGY CLINICAL GUIDANCE

Inpatient management of cranial diabetes insipidus

S E Baldeweg[1], S Ball[2], A Brooke[3], H K Gleeson[4], M J Levy[5], M Prentice[6] and J Wass[7] on behalf of the Society for Endocrinology Clinical Committee[8]

Things you can get involved with if you like

- Name change might help
- Animated video roll out
- Social media education
- Life sustaining medication
- NCEPOD hospital audit
- UK AVP-D registry

miles.j.levy@uhl-tr.nhs.uk

Overview of talk

- Mechanism of thirst and water regulation
- Reasons for new terminology
- Test drive with cases
- Update on diagnosis
- A terrible story

The end

Nearly time to go home