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Vasopressin

- = function of vasopressin & thirst mechanisms
- total body osmolality \(\propto\) (total Na + total K) / total water
- ↑osmotic pressure in plasma \(\Rightarrow\) ↑vasopressin secretion + ↑thirst
- ↓osmotic plasma \(\Rightarrow\) ↓vasopressin + excretion solute free urine
- \(\therefore\) osmolality kept 280-295 mOsm/kg of H2O

![max inhibition vasopressin seen at <285; stim at higher values]

ADH Molecule

- = 9aa peptide hormone
- aka ADH
- made in magnocellular neurons of supraoptic & paraventricular nuclei of hypothalamus
- transported in their axons to post pituitary where stored
- released via calcium dependant exocytosis

Vasopressin Receptors

- 3 receptors:
  - V1a \(\Rightarrow\) smooth mm sustained vasoC, ↓renin secr, ↓glycogenlysis, platelet aggregation
  - V1b \(\Rightarrow\) ↑ACTH release
  - \(\leftarrow\) Go\textsubscript{Q}-linked \(\Rightarrow\) ↑PLC \(\Rightarrow\) ↑IP3 + DAG \(\Rightarrow\) ↑intracellular [Ca]
  - V2 \(\Rightarrow\) ↑cAMP levels \(\Rightarrow\) ↑protein kinases
    - vasoD, ↑H2O reabsorption, ↑vWF & f8 from endothelial cells
  - V3 = CNS (neurotransmitter)
- All G protein coupled

Effects of Vasopressin

- Vasopressin \(\Rightarrow\) concentrated hypertonic urine & ↓osmolality of plasma
- Without vasopressin \(\Rightarrow\) urine hypotonic & ↑osmolality of plasma

Renal ADH effects

*V impt at physiological concentrations*

- ↑ Water reabsorption (V\textsubscript{2} \(\Rightarrow\) aquaporin-2 from endosome \(\Rightarrow\) luminal membrane of principle cells).
- Synergism with aldosterone:
  - Na reabsorb/K excretion
  - Principal cells of CCDs
- Mesangial contraction \(\Rightarrow\) ↓GFR (V\textsubscript{1a})
- ↑urea reabsorption – inner medullary CDs (aquaporin 3 into basolateral membrane)
- renal afferent vasoC – V1

Non Renal ADH Effects

*Less impt at physiological concentrations*

- Systemic vasoconstriction (V\textsubscript{1a}):
  - effect on bp offset by ↓CO via central affect (area postrema)
  - coronary & cerebral vaosD maintained by NO mediated effect
- ↑ACTH release (V\textsubscript{1b})
- ↑Cortisol release (V\textsubscript{1a})
- Glycogenlysis (V\textsubscript{1a}) + lipolysis (↑ hormone sensitive lipase)
- neurotransmitter _ neuromodulation (V3)
- Coagulation: - ↑ Factor 8 (V2) and ↑ platelet aggregation (V1)

Metabolism

- circulating vasopressin rapid inactivated in liver & kidney
- half life 18mins

Control of Secretion

- ↑ed secretion:
By Adam Hollingworth

- ↑osmotic pressure of plasma –
  - osmoreceptors in anterior hypothalamus (OVLT & SFO ie outside BBB)
  - afferents to ADH secreting neurons
  - osmoreceptor system extremely sensitive mechanism for small ie 1-2% changes
    ⇝ ie when <2% change osmoreceptors activity > baroreceptors
- ↓ECF volume –
  - sensed by low pressure (more imp) & arterial baroreceptors
  - afferent to hypothalamus neurons
  - when >10% change volume: baroreceptor system activity > osmoreceptors
- pain, stress, exercise
- N&V
- Standing
- ATII
- Drugs eg Carbamazepine, morphine, barbituates, nicotine
  - ↓ed secretion
    - ↓osmotic pressure of plasma
    - ↑ECF volume
    - alcohol
    - local negative feedback: ADH ⇒ intramedullary synthesis of PGs which interfere with ADH induced production of cAMP

**Osmotic Stimuli**
- >285 rate of discharge of neurons ↑s ⇒ ↑secretion
- osmoreceptors in ant hypothalamus:
  - outside bbb, in OVLT
- thirst ?triggered by osmoreceptors also
- delicate feedback system.
- 1% change in osmolality ⇒ big changes in level of vasopressin to keep at 285

**Volume Effects**
- inverse relationship between rate vasopressin secretion & level of stretch in vascular system causing afferent nerve discharge
  - ↑high stretch ⇒ ↓vasopressin
- vascular sensors
  - low pressure – great veins, RA, LA, pulmon vessels
  - high pressure – carotid sinus, aortic arch
- high pressure bp changes ⇒ big change in vasopressin secretion
- low pressure monitor fullness of system
  - mod ↓in blood volume can ↓CVP with no effect on arterial bp
    ⇝: low pressure sensors primary sensors effecting volume related vasopressin
  - afferents vagi to nucleus tractus solitarius (NTS)
  - NTS via inhibitory connection to CVLM
  - CVLM via excitatory to hypothalamus
- ATII reinforces vasc stretch receptors by causing direct ↑vasopressin secretion
• Hypovolaemia and ↓bp ⇒ ↑↑vasopressin
• Hypovolaemia ⇒ L shift with steeper curve

Clinical Implications

• SIADH –
  o Eg post surgery pain & hypovolaemia both ⇒ ↑vasopressin ⇒ ↓plasma osmolality & dilutional hyponatraemia
  o Also cerebral disease, lung disease, vasopressin secreting tumours
  o Vasopressin escape – prolonged ↑vasopressin ⇒ down reg of aquaporin2 production
  o Rx with Demeclocycline = Abx which ↓s renal response to vasopressin

• DI:
  o Central DI = Vasopressin deficiency
    ▪ Tumour of hypothalamus 30%
    ▪ Post traumatic 30%
    ▪ Idiopathic 30%
    ▪ Rest – sarcoid, vasc lesions, infections
  o Nephrogenic DI = kidneys don’t respond to vasopressin
    ▪ V2 receptor X linked recessive mutation
    ▪ Defective gene encoding aquaporin 2 – trapped in intracellular locations
  o Symptoms include polyuria & polydipsia
    ▪ Need this to remain hydrated otherwise potentially fatal
Summary Defence of Volume & Normal Osmolality

- Osmolality = no of osmoles/kg water (not influenced by temp)
- ECF [Na] ~ 140mmol/L:
  - Na & Cl most active & abundant solutes present
  - Cl just follows Na. Na is the most imp
  - Na = 85% ECF osmolality
- Obligatory Water Loss =
  - Minimum UO = 500ml/D
  - Need to excrete daily solute load od ~700mosmoles at max conc 1400mmol/L
    \( \leftarrow \) (Na 100-150, K 70-100, Cl 150, urea 400, creatinine 12 mmol)
- Conditions \( \Rightarrow \) ↓↓osmolality ie max ↓ADH secretion \( \Rightarrow \) dilute urine osmolality ~30mosmoles/kg & UO ~22L/day to secrete daily solute load 70msomoles
- Osmolality feedback mechanism:
  - ↑ osmolality (Small change 1-2% change from 280):
    - Ant HT sensing \( \Rightarrow \) ↑ADH \( \Rightarrow \) ↑AT2, ↑thirst, ↑aldosterone \( \Rightarrow \)
      - ↑Na & water reabsorb
      - afferent arteriole vasC \( \Rightarrow \) ↓GFR\( \Rightarrow \) restore ECF osmolality
  - ↓osmolality:
    - ↓ADH, ↑ANP (↑GFR) \( \Rightarrow \) ↑Na & water excretion
- max urine conc capable = 1400mmol/L
- Volume ECF is determined by
  - total osmotically active solute in ECF
  - Volume control mechanism –
    - mechanism overrides osmotic regulation of vasopressin secretion
    - sensors less sensitive ie >10% changes
    - effect:
      - ↑volume \( \Rightarrow \)
        - ↓vasopressin
        - ↑ANP (atrial ) & ↑BNP (brain) \( \Rightarrow \) diuresis
          \( \leftrightarrow \) ↑Na excretion by kidneys
      - ↓volume \( \Rightarrow \)
        - ↑angiotensin II \( \Rightarrow \)
          - VC
          - ↑aldosterone
          - ↑thirst
          - ↓bp \( \Rightarrow \) ↓glom cap pressure \( \Rightarrow \) ↓GFR \( \Rightarrow \) ↓Na filtered
          - ↓mean intravascular pressure \( \Rightarrow \) ↑aldosterone \( \Rightarrow \) ↑Na reabsorbed
- in dehydration \( \Rightarrow \) moderate ↓ ECF by loss of water from intravascular & extracellular compartments
- disease states can cause marked loss of Na from ECF \( \Rightarrow \) shock:
  - stool - diarrhoea
  - urine – severe acidosis, adrenal insufficiency
  - sweat – heat+
Renin Angiotension System

**Renin**
- = acid protease (glycoprotein hormone)
- mw 37326
- secreted by kidney into bloodstream
- synthesised as preprorenin ⇒ prorenin ⇒ rennin
- active renin half life 80 mins
- kidney:
  - active renin secreted by specialized cells (granular cells) = JG cells
  - found in media of afferent arterioles as enter glomerulus
  - renin found in membrane lined secretory granules
  - cells also convert some prorenin to renin
  - only place to do this
  - secretes some prorenin – none converted systemically
- Renin also found in lacis cells
  - Found junction between afferent/efferent arterioles
  - Agranular
  - significance of renin here
- prorenin also made in other organs eg ovaries
  - after nephrectomy prorenin level normal BUT active renin zero

**Note:**
- Macula densa is close proximity to JG cells
- Juxtaglomerular apparatus =
  - Macula densa
  - Lacis cells
  - JG cells

**Regulation of Renin Secretion**
- Main regulatory mechanisms:
  - Factors ↑ renin secretion (and opposite of factors which ↓ renin release):
    - ↑ SNS outflow
      - ↑ circulating catecholamines
        - β_1_ receptors on JG cells ⇒ ↑ cAMP ⇒ ↑ renin release
      - any cause of ↑ post-ganglionic symp activity on kidney via renal nerves
Regulation of ECF

MOA of BBs on controlling volume status & bp
- Factors ↓renin secretion (opposite of above and…):
  - ↑Na & Cl reabsorb across macula densa
    - renin secretion inv∝ amount of Na & Cl entering distal tubule
    - enter mac densa via Na-K-2Cl transporter in apical membrane
    - ⇒ ↓renin secretion from adjacent JG cells
      → mediated by NO
    - ↑Na this is diff to TG Feedback (ie ↑Na ⇒ vasod of afferent arteriole)
  - Baroreflex ie ↑afferent arteriolar pressure:
    - ↑MAP at JG cells ⇒ ↓renin release
      → via ↓post ganglionic symp activity via renal nerves
  - AT II – direct action in JG cells ie -ve feedback loop

Secondary mechanisms:
- ↑renin release:
  - prostaglandins
  - ↑plasma K level
    - linked to Ks effect on delivery of Na & Cl to macula densa
- ↓renin release:
  - Vasopressin - ?direct or indirect effect
  - ↑ANP

Conditions which ↑renin secretion ie anything which ↓ECF, ↓MAP, ↑SNS
- Na depletion
- Diuretics
- ↓bp
- haemorrhage
- upright posture
- dehydration
- heart failure
- cirrhosis
- constriction of renal artery
- psych stimuli

Angiotensinogen
- synthesized in liver
- alpha glycoprotein (453 aa’s) (13% CHO)
- circulating level is ↑ed by:
  - glucocorticoids
  - thyroid hormones
  - oestrogens
  - cytokines
  - AT II

AT1
- Decapeptide (10aas)
- Splited from N-terimal of angiotensinogen by renin’s action
- Sole function is as a precursor of AT2

ACE
- ACE:
  - AT I to AT II
  - Inactivates bradykinin
- ↑ tissue bradykinin produced when ACE is inhibited
  ← this acts on B2 receptors ⇒ cough in 20% of people on ACEI
• most ACE found in endothelial cells
• Most converting in lungs but other parts of body contribute
• ACE exists in 2 forms:
  o Somatic – throughout body
  o Germinal – spermatogenic cells & spermatozoa
• Kidneys do not contain angiotensionogen & ACE
  \( \leftrightarrow \) AT2 can be fully produced in kidneys by itself
  \( \leftrightarrow \) kidneys influenced by blood borne & intrarenally produced AT2

**AT2 & It's Metabolism**
• octapeptide
• Half life 1-2mins
• Removed from circulation by:
  o Metabolised by various peptidases:
    ▪ angiotensinase (Aminopeptidase) – removes aspartic acid residue \( \Rightarrow \) AT III
    ▪ AT III can be converted to AT IV
      \( \leftrightarrow \) both AT III & AT IV have some activity; other peptide fragments inactive
    ▪ occurs in rbcs & many tissues
  o trapping system in vascular beds of non-lung tissue

**Actions of AT’s**
• AT1 – precursor of AT2 ie no action
• ATII – actions (via Go-linked receptors\( \rightarrow \) phospholipase C/IP3\( \rightarrow \) \( \uparrow \) Ca)
  o Arteriolar VC \( \Rightarrow \) \( \uparrow \) systolic & diastolic bp
    ▪ X4 more powerful vasoC than NA
    ▪ VasoC activity decreased in:
      • Hyponatraemic patients
      • Cirrhosis
      \( \leftrightarrow \) because \( \uparrow \) AT II found circulating \( \Rightarrow \) downregulate ATII receptors on smooth mm
  o \( \uparrow \) aldosterone – direct action on Z Glomerulosa of adrenal cortex
  o \( \downarrow \) renin release: -ve feedback control
  o blockade of NA re-uptake (uptake 1) \( \Rightarrow \) \( \uparrow \) active NA
    ▪ direct action on postganglionic symp neurons
    ▪ central effect on area postrema
  o \( \downarrow \) GFR – contraction of mesangial cells
  o arteriolar effects:
    ▪ [low concs] \( \Rightarrow \) selective afferent arteriolar constriction ie defend volume by \( \downarrow \)ing GFR
    ▪ [higher concs] \( \Rightarrow \) efferent constriction
  o \( \uparrow \) Na & HCO3 reabsorb –
    ▪ direct effect on PCT
    ▪ indirect by \( \downarrow \)interstitial hydrostatic pressure
  o \( \downarrow \) sensitivity of baroreflex \( \Rightarrow \) \( \uparrow \)pressor effect
  o activation of circumventricular organs on brain (not cross bbb)
    ▪ thirst
    ▪ \( \uparrow \)ADH release
    ▪ \( \uparrow \)ACTH release
      \( \leftrightarrow \) remember:
      o area postraema \( \Rightarrow \) VC
      o SFO & OVLT \( \Rightarrow \) polydipsia
      o ??organ \( \Rightarrow \) \( \uparrow \)vasopressin & \( \uparrow \)ACTH

• AT III – same actions as AT2 but:
  o VasoC – 40%
  o \( \uparrow \)aldosterone – 100% action ATII

**Summary AT2 actions always results in:**
• \( \downarrow \)RBF – afferent +/- efferent vasoC
• effect on GFR dependant on conc of AT2:
  o low: same or slightly ↓ed
  o high: ↓↓↓ (via mesangial & afferent arteriolar contraction)

**Tissue Renin-Angiotensin Systems**
• many tissues contain local indep renin-AT systems which generate ATII for local use
  - eg blood vessel walls, uterus, placenta, foetal membranes, eyes, heart, sex organs
• tissue renin contributes little/nothing to circulating renin pool
• local ATII role in:
  o growth factor in heart & blood vessels

**AT II Receptors**
• are 2 classes of ATII receptors:
  o AT$_1$
  o AT$_2$
    - ATII has stronger affinity for AT$_1$

**AT$_1$ Receptors**
• = 7 transmembrane domains
• found on chromosome 3
• couple by G protein to phospholipase C
• ATII ⇒ (on AT$_1$)
  o ↑free cytosolic Ca
  o activates numerous tyrosine kinases
  o in smooth mm: ↑caveolin-1
• regulation of AT$_1$ receptor depends on location:
  o in arterioles - ↑ATII ⇒ ↓AT$_1$ receptor predominance
  o in adrenal cortex - ↑ATII ⇒ ↑AT$_1$ receptor ⇒ ↑sensitivity of gland ⇒ ↑aldosterone release

**AT$_2$ Receptors**
• = 7 transmembrane domains
• found on chromosome X
• couple by G protein to various phosphatases
• AT II ⇒ (on AT$_2$)
  o Antagonise growth effects
  o Open K channels
  o ↑production of NO ⇒ ↑ing cGMP
  - overall effects unsure but more receptors found in fetal & neonatal life

**Hormones of Heart & Other Natriuretic Factors**

**Structure**
• atria & ventricles contain secretory granules
• granules ↑in number when
  o ↑NaCl intake
  o ↑ECF volume

**Types**
• from heart:
  o ANP – also found in other tissues
  o BNP – brain or beta NP
    - More present in heart (esp ventricles) than brain
  o CNP –
    - Found in brain, kidney, pituitary, vascular endothelial cells
• Very little in heart & circulation
  \(\rightarrow\): paracrine regulator

**Actions**

- **ANP & BNP act on kidney** \(\Rightarrow\) overall \(\uparrow\) in Na excretion
- **Done by:**
  - Dilation afferent arterioles \(\Rightarrow\) \(\uparrow\) GFR
  - Relax mesangial cells
  - Act on tubules \(\Rightarrow\) \(\downarrow\) Na reabsorb
  - \(\uparrow\) cap permeability \(\Rightarrow\) extravasation of fluid into ECF \(\Rightarrow\) \(\downarrow\) bp
  - \(\uparrow\) of arterioles & venules
    \(\leftarrow\) CNP greater VD effect on veins than ANP/BNP
  - \(\downarrow\) renin secretion
  - counteract pressor effects of catecholamines & ATII
- **ANP in brain:**
  \(\leftarrow\) BNP/CNP prob similar functions but unknown
  - General effects opposite to ATII
  - Found in neurons connecting hypothalamus to brainstem concerned with regulation of CV system
  \(\leftarrow\) ANP \(\Rightarrow\) \(\downarrow\) bp & excretion of Na

**Receptors**

- 3 natriuretic peptide receptors:
  - NPR A
    - Guanylyl cyclase cytoplasmic domain
    - ANP greatest affinity
  - NPR B
    - Guanylyl cyclase cytoplasmic domain
    - CNP greatest affinity
  - NPR C
    - Binds all peptides
    - Truncated Guanylyl cyclase cytoplasmic domain
    - ?function
- All span cell membrane

**Secretion & Metabolism**

- **ANP norm conc in plasma 5fmol/ml**
- **ANP**
  - half life short
  - metabolised by neutral endopeptidase (NEP)
  - \(\uparrow\) ANP secretion:
    - \(\uparrow\) ECF volume
    - atrial stretch
  \(\leftarrow\) also water immersion up to neck: removes gravity \(\Rightarrow\) \(\uparrow\) CVP \(\Rightarrow\) \(\uparrow\) atrial stretch
  - \(\downarrow\) ANP secretion:
    - lie to stand \(\Rightarrow\) \(\downarrow\) CVP
- **\(\uparrow\) BNP secretion:**
  - ventricle stretch
  \(\leftarrow\) ANP & BNP secretion \(\propto\) to degree of stretch

**Na,K ATPase-Inhibiting Factor**

- = another natriuretic factor
- It inhibits Na,K ATPase \(\Rightarrow\) \(\uparrow\) bp
- May be ouabain from adrenal glands
**Defence of Specific Ionic Composition**

- certain ions in ECF under close control:
  - Ca – parathyroids, calcitonin secreting cells
  - Mg – mechanism incompletely understood
- Control of Na & K also depend on:
  - H+ conc
  - pH
Endocrine Functions of Kidney

- **Hormones produced by kidney:**
  - 1,25 dihydroxycholecalciferol (active Vit D, aka calcitriol)
  - Erythropoietin
  - Prostaglandins

- **Hormones produced in circulation as result of enzymes released by kidney:**
  - Angiotensin-2 + aldosterone production, initiated by **renin** released by kidneys
  - Production of bradykinin in circulation, due to **kallikrein** from kidneys

- **Hormones which have site of action on kidney:**
  - ADH
  - Aldosterone
  - Calcitriol
  - PTH
  - ANP

**Calcitriol**

- **Creation of active form of vit D**
- **final step of activation**
  - 1-alpha hydroxylation occurs in cells of prox tubule
  - reaction ↑ed by:
    - catalysed by 1-alpha hydroxlase (mitochondrial enzyme)
    - ↑ed by PTH
    - ↑gonadal steroids
  - reaction ↓ed by:
    - ↓ s-calcium or phosphate
    - ↑ed calcitriol ie –ve feedback loop

- **function:**
  - ↑intestinal absorption of calcium & phosphate
  - ↑tubular reabsorption of Ca
  - ↑bone reabsorption of Ca & phosphate ie ↑serum Ca & PO4

**EPO**

- **EPO = circulating glycoprotein**
- **Half life 5 hours**
- **Takes 2-3 days for ↑ circulating rbcs**

**Sources**

- mRNA found in liver & kidney
  - →EPO also found in spleen & salivary glands but no mRNA ′. not made there
- source from:
  - 85% - interstitial cells in peritubular cap bed of kidney
  - 15% - perivenous hepatocytes in liver
    - (↔ in fetus main production is the liver ie not from kidney)
  - trace – brain- protective effect from hypoxia
  - trace – uterus & oviducts – ↑oestrogen ⇒ ↑EPO ⇒ oestrogen dependant angiogenesis

- **liver has little compensatory ability if kidneys removed ⇒ anaemia**
- recombinant EPO made and can be injected
  - o autologous transfusions for surgery
Regulation of Secretion

• ↑EPO:
  o hypoxia:
    ▪ main stimulus
    ▪ O2 sensor in kidney & liver
  • Heme protein:
    o Deoxy form ⇒ ↑EPO
    o Oxy form ⇒ inhibit transcription forming EPO mRNA
  o ↓rbc volume eg anaemia/haemorrhage
  o ↑androgens
  o alkalosis eg high altititude
  o catecholamines via β-adrenergic system
• ↓EPO:
  o ↑red cell volume eg transfusion/polycythaemia

Function

• EPO marrow effects:
  o committed stem cells ⇒ rbc precursors ⇒ mature erythrocytes
• EPO acts via membrane receptor =
  o Linear protein
  o Single transmembrane domain
  o Cytokine receptor family
  o Activates Tyrosine kinase ⇒ activates cytoplasmic transcription factors ⇒ nucleus ⇒ activate new m-RNA synthesis ⇒ inhibited apoptosis of red cells ⇒ ↑growth & development