Roles of enzymes and hormones produced by the kidneys

The kidneys produce enzymes and hormones involved in:

- Regulation of blood pressure
- Red blood cell development
- Calcium absorption and bone formation
Renin-Angiotensin-Aldosterone system

• System involved in regulation of blood volume / pressure and electrolyte metabolism, through the regulation of aldosterone production.

• Main driving force is angiotensin II which stimulates aldosterone production.

• Production of Angiotensin II depends on the action of the protease enzyme Renin
Renin-Angiotensin-Aldosterone system

Blood vessel

Angiotensinogen → Angiotensins → Aldosterone

Renin produced in response to low BP / low blood volume

Aldosterone action increases BP / blood volume
Renin

- Protease enzyme
- produced by juxtaglomerular cells of the renal afferent arteriole
- cleaves angiotensinogen at the N terminal to release a decapeptide known as angiotensin I
Factors that affect Renin release

**Stimulators**
- decreased BP
- change from supine to erect posture
- salt depletion
- β-adrenergic agents
- prostaglandins

**Inhibitors**
- increased BP
- change from erect to supine posture
- salt loading
- β-adrenergic antagonists
- prostaglandin inhibitors
- potassium
- Vasopressin (Antidiuretic hormone; ADH)
- Angiotensin II
Angiotensinogen

- Inactive
- $\alpha_2$ globulin
- 414 amino acids
- produced by liver
- circulating in plasma

COOH

Renin cleaves at amino end

NH2
Production of Angiotensins

Low blood volume (decreased arterial blood pressure)
Low [Na+]

Kidney

Angiotensinogen (inactive)

Angiotensin I (inactive)

Angiotensin II (active)

Angiotensin III (active)

decapeptide

eptapeptide

ACE

HL

HL

D

Aminopeptidase

Active forms are rapidly degraded by angiotensinases
Production of angiotensins

Angiotensinogen = DRVYIHPFH\(\text{LLVYS + 400aa}\)

\[\text{Angiotensin I} = \text{DRVYIHPFHL}\]

\[\text{Angiotensin II} = \text{DRVYIHPF (ACTIVE)}\]

\[\text{Angiotensin III} = \text{RVYIHPF (ACTIVE)}\]
Angiotensin converting enzyme

- Found in the lungs, endothelial cells and plasma
- removes two amino acids from angiotensin I to produce angiotensin II
- degrades bradykinin (a vasodilator)

This enzyme increases BP via degradation of bradykinin as well as through production of angiotensin II
ACE inhibitors

These are analogues of angiotensin I used as competitive inhibitors of ACE in the treatment of Renin-dependent hypertension.
Aminopeptidase

• Converts angiotensin II to angiotensin III through the removal of a single aminoacid

• Not present in all species
Actions of Angiotensin II

- Vasoconstriction (increases BP)
- Stimulates aldosterone production (aldosterone promotes Na+ retention and so increases BP)
- Stimulates pituitary gland to produce ADH (increases water absorption from collecting ducts)
- Inhibits renin release (feedback regulation of its own production)
Aldosterone is a mineralocorticoid

- Mineralocorticoids are 21-carbon steroids
- Made in zona glomerulosa
- Primary action: **promote Na\(^+\) retention** and **K\(^+\) excretion** (particularly in kidney)

Aldosterone is the most potent mineralocorticoid
Synthesis of aldosterone

- Lipoprotein
- Lipoprotein receptor
- Plasma membrane
- Droplet (cholesterol ester)
- Free cholesterol
- Esterase
- Transport
- *P450 side chain cleavage enzyme complex
- Pregnenolone
- Mitochondrion
- ALDOSTERONE

*Transport & side change cleavage enzyme are rate limiting step.
Stimulation of aldosterone synthesis by angiotensin II

**Angiotensin II receptor on glomerulosa cell**

**Angiotensin II**

**PI cycle**

**Ca^{2+}**

***IP_3** + DAG

Active protein kinase C

**DAG stimulates PKC**

Calcium channel

*IP_3 binds to receptor on ER leading to Ca^{2+} release from ER

**Calcium**

**Calcium channel**

**Actively protein kinase C**

**PI cycle**

**Ca^{2+}**

**Esterase**

**Calcium**

**Transport**

**Cholesterol**

**P450 side chain cleavage enzyme complex**

**Pregnenolone**

**Mitochondrion**

**ALDOSTERONE**

**Stimulation of aldosterone synthesis by angiotensin II**
Regulation of transcription by aldosterone

1. dissociation

2. entry

Bound aldosterone

Free aldosterone

3. Binding & activation

Zinc fingers

4. DNA binding

DNA

nucleus

cytoplasm

5. transcription

mRNA

New proteins

6. translation

Biological response

Target cell
**Actions of aldosterone**

- **Promote Na+ retention and K+ excretion**
- **How?**
  - Increases no. of Na+ channels on luminal side of kidney tubules
  - Increases activity of several mitochondrial enzymes (increased ATP production) which results in increased activity of the Na+/K+ ATPase pump
Renin-angiotensin-aldosterone system

- Angiotensinogen → Angiotensin I → Angiotensin II
- Renin
- Decrease in renal perfusion (juxtaglomerular apparatus)

- Lungs
- Kidney
- Surface of pulmonary and renal endothelium: ACE

- Tubular Na⁺ Cl⁻ reabsorption and K⁺ excretion, H₂O retention
- Adrenal gland: cortex
- Aldosterone secretion

- Arteriolar vasoconstriction. Increase in blood pressure
- ADH secretion
- Pituitary gland: posterior lobe

- Collecting duct: H₂O absorption

Legend:
- Secretion from an organ
- Stimulatory signal
- Inhibitory signal
- Reaction
- Active transport
- Passive transport

Water and salt retention. Effective circulating volume increases. Perfusion of the juxtaglomerular apparatus increases.
The kidney and red blood cell formation

The kidney produces erythropoietin (Epo) which stimulates erythropoiesis (red blood cell formation) in humans.
Human Erythropoietin (Epo)

- Glycoprotein 166aa (MW ~ 34000)
- Produced by kidney in response to low O₂ tension
- Travels to bone marrow
- Acts on progenitors of RBC via a specific receptor (EpoR)
- EpoR is a dimeric transmembrane protein; affects gene expression via the JAK-STAT pathway

BFU = burst forming unit
CFU = colony forming unit

BFU-E

CFU-E

Mature erythrocyte

Proliferation & differentiation

Proliferation & differentiation
“EPO has a history of usage as a blood doping agent in endurance sports such as cycling, distance running, cross country skiing, biathlon, triathlons and most recently billiards”

Should it be allowed? There are other legal means of increasing rbc count...
Erythropoietin receptor (EpoR) - activation influences gene expression in RBC precursors

- Binding of Epo causes EpoR subunits to dimerise and bind JAK
- JAK phosphorylates EpoR
- STAT-5 binds phosphate group on EpoR via SH2 domain
- STAT-5 is phosphorylated by JAK
- Phosphorylated STAT-5 dimerises and nuclear localisation signal (NLS) is exposed
- STAT-5 dimer is transported into nucleus and activates genes associated with erythrocyte maturation
- JAK also activates MAPK cascade

**JAK** = Janus kinase; soluble tyrosine kinase

**STAT** = signal transducers and activators of transcription
The Kidneys and Calcium Metabolism

- The kidney produces enzymes involved in the conversion of Vitamin D₃ (cholecalciferol) to 1,25-dihydrovitamin D₃ (1,25-dihydrocholecalciferol)

- 1,25-dihydrocholecalciferol effects increased Ca²⁺ uptake in the gut
Formation of 1,25-dihydroxycholecalciferol

7-dehydrocholesterol (in skin)
Provitamin D₃

UV light

UV light

25-hydroxycholecalciferol (25-hydroxyvitamin D₃)

25-hydroxylase
Liver

24-hydroxylase
Renal, bone, placental, intestinal or cartilage

24, 25-hydroxycholecalciferol (24, 25-dihydroxyvitamin D₃)

1α-hydroxylase
Renal, bone or placental

1, 25-dihydroxycholecalciferol
(1,25-dihydroxyvitamin D₃)
CALCITRIOL
Calcitriol

Hormone of the steroid / thyroid class

Also known as:

- $1,25$-dihydroxycholecalciferol
- $1,25$-dihydroxyvitamin $D_3$
- $1,25(OH)_2D_3$
Calcitriol

Binds intracellular receptor and stimulates expression of genes involved in:

- transfer of Ca\(^{2+}\) and PO\(_4\)\(^{3-}\) across the intestinal mucosa (increases absorption).
- excretion of calcium (reduces excretion by stimulating reabsorption in the distal renal tubules)

*Provides the proper balance of calcium and phosphorus to support mineralization of bone*
Figure 1. Overview of the metabolic systems that maintain calcium homeostasis. PTH, parathyroid hormone.
Ricketts

• **May be caused by:**
  – Vitamin D deficiency
  – Defect in conversion of 25-hydrocholecalciferol to calcitriol
  – Non-functional calcitriol receptor

• **Characterised by:**
  – low plasma calcium and phosphorus levels
  – poorly mineralised bones
  – skeletal deformities
Renal stones

- **Kidney stones (renal stones/renal calculi)**
  - gravel-like collections of chemicals that may appear in any area of the urinary system, from the kidney to the bladder.

- **They may be small or large, single or multiple.**

- **Four main types:**
  - Calcium stones
  - Uric acid stones
  - Struvite stones
  - Cystine stones

Check [http://www.herringlab.com/photos/](http://www.herringlab.com/photos/) for other photos including stone from a Mummy (800AD)!
Calcium stones

- Most common type; 95% of all renal stones are calcium
- Caused by:
  - Defective kidney function which allows too much calcium in the urine, or excessive calcium absorbed from the stomach and intestines.
  - an excess of oxalate, present in many foods; binds easily with calcium to form a stone.
- Risk of calcium stone formation is increased in hyperparathyroidism and inflammatory bowel disease
Other less common types of renal stones

- **Uric acid stones**
  - common in people with gout
  - may be pure uric acid, calcium containing or a mixture

- **Struvite stones**
  - Also called “infection stones”
  - Composed of ammoniomagnesium phosphate
  - Bacteria convert to ammonium which complex with magnesium and phosphate in the urine to form stones. As the stones form bacteria are trapped within them.
  - More common in women than men

- **Cystine stones**
  - very rare; almost always diagnosed during childhood
  - Genetic defect (autosomal recessive); kidneys do not adequately reabsorb cystine (cystinuria).
Diet and kidney stones

• Change in diet can reduce risk of forming stones in patients
• **Recommendations depend on cause of kidney stones**
• Recommendations may include:
  – Increased
    • fluid intake
    • Magnesium intake
  – Reduced
    • calcium (e.g. milk and other dairy products)
    • sodium
    • oxalate (e.g. nuts, chocolate, green leafy vegetables, Vitamin C [excess converted to oxalate])
    • Foods high in purines (degraded to uric acid) eg. meats