15.6.1.10: Hormones of Kidney, Skin and Heart

Kidney

The human kidney secretes two hormones:

- **Erythropoietin (EPO)**
- **Calcitriol (1,25(OH)2 Vitamin D3)**

as well as the enzyme **renin**.

Erythropoietin (EPO)

Erythropoietin is a glycoprotein that acts on the bone marrow to increase the production of red blood cells. Stimuli such as bleeding or moving to high altitudes (where oxygen is scarcer) trigger the release of EPO. People with failing kidneys can be kept alive by dialysis, which only cleanses the blood of wastes. Without a source of EPO, these patients suffer from anemia. Now, thanks to recombinant DNA technology, **recombinant human EPO** is available to treat these patients.

Some other uses for recombinant EPO:

- Some of the drugs used to treat AIDS, zidovudine (AZT) for example, cause anemia as a side effect. Recombinant EPO helps AIDS patients cope with this one of the many problems that the disease creates.
- Recombinant EPO improves the anemia that is such a frequent side effect of cancer chemotherapy.
- Severe blood loss in Jehovah’s Witnesses, whose religion forbids them to receive blood transfusions, can also be helped with recombinant EPO.
Because EPO increases the hematocrit, it enables more oxygen to flow to the skeletal muscles. Some cyclists (and
distance runners) have used recombinant EPO to enhance their performance. Although recombinant EPO has exactly
the same sequence of amino acids as the natural hormone, the sugars attached by the cells used in the pharmaceutical
industry differ from those attached by the cells of the human kidney. This difference can be detected by a test of the
athlete’s urine.

Another problem: since recombinant EPO became available, over two dozen young competitive cyclists have died
unexpectedly (usually during the night). Perhaps an EPO-induced increase in their hematocrit — leading to a reduction
in heart rate — is responsible. Prolonged exposure to reduced oxygen levels (e.g., living at high altitude) leads to
increased synthesis of EPO. In mice, and perhaps in humans, this effect is mediated by the skin. Mouse skin cells can
detect low levels of oxygen ("hypoxia") and if this persists, blood flow to the kidneys diminishes leading to increased
synthesis of EPO by them.

EPO is also synthesized by osteoblasts in mice that have been made anemic and in the brain when oxygen becomes
scarce there (e.g., following a stroke), and helps protect neurons from damage. Perhaps recombinant human EPO will
turn out to be useful for stroke victims as well.

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### Calcitriol

Calcitriol is 1,25(OH)₂ Vitamin D₃, the active form of vitamin D. It is derived from

- calciferol (vitamin D₃) which is synthesized in skin exposed to the ultraviolet rays of the sun
- precursors ("vitamin D") ingested in the diet.

Calciferol in the blood is converted into the active vitamin in two steps:

- calciferol is converted in the liver into 25(OH) vitamin D₃
- this is carried to the kidneys (bound to a serum globulin) where it is converted into calcitriol. This final step is
  promoted by the parathyroid hormone (PTH).

### Calcitriol Action

Calcitriol acts on

- the cells of the intestine to promote the absorption of calcium and phosphate from food
- bone to mobilize calcium from the bone to the blood

Calcitriol enters cells and, if they contain receptors for it (intestine cells do), it binds to them. The calcitriol receptors are
zinc-finger transcription factors. The receptor-ligand complex bind to its response element, the DNA sequence:

5' AGGTCAnnnAGGTCA 3'

This sequence of nucleotides (n can be any nucleotide) is found in the promoters of genes that are turned on by
calcitriol. Once the hormone-receptor complex is bound to its response element, other transcription factors are recruited
to the promoter and transcription of the gene(s) begins.
Deficiency disorders

Insufficient calcitriol prevents normal deposition of calcium in bone.

- In childhood, this produces the deformed bones characteristic of rickets.
- In adults, it produces weakened bones causing osteomalacia.

The most common causes are inadequate amounts of the vitamin in the diet or insufficient exposure to the sun. However, some rare inherited cases turn out to be caused by inheriting two mutant genes for the kidney enzyme that converts 25(OH) vitamin D3 into calcitriol. Other cases of inherited rickets (also very rare) are caused by inheriting two defective genes for the calcitriol receptor. Mutations that change the amino acids in one or another of the zinc fingers interfere with binding to the DNA of the response element.

Renin

One of the functions of the kidney is to monitor blood pressure and take corrective action if it should drop. The kidney does this by secreting the proteolytic enzyme renin. Renin acts on angiotensinogen, a plasma peptide, splitting off a fragment containing 10 amino acids called angiotensin I. Angiotensin I is cleaved by a peptidase secreted by blood vessels called angiotensin converting enzyme (ACE) producing angiotensin II, which contains 8 amino acids.

Figure 15.6.1.10.1 Angiotensin

Angiotensin II modulates all of the below actions to increase in blood pressure:

- constricts the walls of arterioles closing down capillary beds
- stimulates the proximal tubules in the kidney to reabsorb sodium ions
- stimulates the adrenal cortex to release aldosterone. Aldosterone causes the kidneys to reclaim still more sodium and thus water.
- increases the strength of the heartbeat
- stimulates the pituitary to release the vasopressin
Skin

When ultraviolet radiation strikes the skin, it triggers the conversion of dehydrocholesterol (a cholesterol derivative) into calciferol (vitamin D3). Calciferol travels in the blood to the liver where it is converted into 25[OH] vitamin D3. This compound travels to the kidneys where it is converted into calcitriol (1,25 [OH]2 vitamin D3). This final step is promoted by the parathyroid hormone (PTH). Although called a vitamin, calciferol and its products fully qualify as hormones because they are

- made in certain cells
- carried in the blood
- affect gene transcription in target cells

Heart

Natriuretic Peptides

In response to a rise in blood pressure, the heart releases two peptides:

- **A-type Natriuretic Peptide** (ANP)
  
  This hormone of 28 amino acids is released from stretched atria (hence the "A").

- **B-type Natriuretic Peptide** (BNP)
  
  This hormone (29 amino acids) is released from the ventricles. (It was first discovered in brain tissue; hence the "B").

Both hormones lower blood pressure by

- relaxing arterioles
- inhibiting the secretion of renin and aldosterone
- inhibiting the reabsorption of sodium ions by the kidneys.

The latter two effects reduce the reabsorption of water by the kidneys. So the volume of urine increases as does the amount of sodium excreted in it. The net effect of these actions is to reduce blood pressure by reducing the volume of blood in the circulatory system. These effects give ANP and BNP their name (natrium = sodium; uresis = urinate).

Contributors

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