Hormone of the heart & adipose tissues
**Natriuretic hormones**

The muscle cells in the **atria** and, to a much lesser extent in the **ventricles**, contains secretory granules.

The granules increase in number when

1. $\uparrow$ NaCl intake
2. $\uparrow$ ECF expanded

 extracts of atrial tissue cause natriuresis.

The types of natriuretic peptide are:

1. **Atrial natriuretic peptide (ANP):**

   Atrial natriuretic peptide is synthesized and secreted by the cardiac atria and much lower in ventricles

<table>
<thead>
<tr>
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<th>amino acids</th>
<th>half-life</th>
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<tbody>
<tr>
<td>Atrial natriuretic peptide (ANP)</td>
<td>28</td>
<td>2 min</td>
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<tr>
<td>Brain natriuretic peptide (BNP)</td>
<td>32</td>
<td>22 minute</td>
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<tr>
<td>C-type natriuretic peptide (CNP)</td>
<td>53 and 22</td>
<td>2.6 min</td>
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<tr>
<td>Dendroaspis natriuretic peptide (DNP)</td>
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2. Brain natriuretic peptide (BNP):
   Brain natriuretic peptide isolated from porcine brain
   Brain natriuretic peptide is also present in the brain in humans, but more is present in the human heart, including the ventricles.

3. C-type natriuretic peptide (CNP):
   C-type natriuretic peptide is present in the brain, the pituitary, the kidneys, and vascular endothelial cells. However, very little is present in the heart and the circulation, and it appears to be primarily a paracrine mediator.

4. Dendroaspis natriuretic peptide (DNP):
   Dendroaspis natriuretic peptide is derived from the venom of the Green Mamba snake
   Dendroaspis natriuretic peptide is found in human plasma and atrial myocardium
   The existence of various natriuretic hormones has characteristic 17-amino-acid ring formed by a disulfide bond between two cysteines.
Natriuretic peptide receptors:

Three different natriuretic peptide receptors have been isolated and characterized.

1. type A natriuretic peptide receptor (NPRA)
2. type B natriuretic peptide receptor (NPRB)
3. type C natriuretic peptide receptor (NPRC)

The natriuretic peptides can stimulate the production of cGMP through the activation of specific receptors: type A natriuretic peptide receptor (NPRA); type B natriuretic peptide receptor (NPRB).

The NPRA receptor is known to have its major role in the clearance of natriuretic peptides from blood circulation.

The NPRC receptor has NO intrinsic ability to generate cGMP although it mediates changes in cAMP and phosphoinositides.

The NPRC (ANP+BNP+CNP with approximately equal affinity) & as well as ring-deleted and truncated linear peptides
Secretion and metabolism

Atrial natriuretic peptide (ANP) is released in response to

a. the atrial stretch: any condition that causes atrial distension. Therefore, elevated levels of ANP are found during hypervolemic states (elevated blood volume), such as occurs in, the ECF volume is increased by

① infusion of isotonic saline or

② heart failure or

③ immersion in water up to the neck (a procedure that counteracts the effect of gravity on the circulation and increases central venous and consequently atrial pressure)

(Note: immersion causes decrease in renin and aldosterone and increase ANP)
A small but measurable decrease in plasma ANP occurs in association with a
1. dehydration
2. decrease in central venous pressure
3. On rising from the supine to the standing position.

b. Blood pressure
c. High NaCl intake
d. Humoral effect:
   i. Rennin-angiotensin-aldosterone system
   ii. endothelin
e. Sympathetic stimulation (beta-adrenoreceptors mediated)

BNP secretion is increased when the ventricles are stretched.
Similarly, BNP secretion is proportional to the degree to which the ventricles are stretched.

BNP expression is increased in 1. heart failure, 2. hypertension and 3. renal failure.

Proteolysis of pro-BNP (108 amino acids) results in BNP (32 amino acids) and the N-terminal piece of pro-BNP (NT-pro-BNP; 76 amino acids). Both BNP and NT-pro-BNP are sensitive, diagnostic markers for heart failure patients.

Neutral endopeptidase (NEP; also called neprilysin) is a circulating enzyme that degrades natriuretic peptides.
Physiological effects:

A. Renal:

1. Increase of glomerular filtration (GFR) and aqueous (water) diuresis
   - dilating afferent arterioles
   - Increases Renal Blood Flow
     - increases glomerular filtration
     - Increases Urine Volume

2. Enhanced urinary excretion of sodium (= natriuresis) and of other electrolytes, phosphate, magnesium, calcium, potassium
   - They appear to produce this effect by
     a. act on the renal tubules to inhibit Na+ reabsorption
        - Increases Sodium Excretion
        - decreases blood flow through the vasa recta,
        - wash the solutes (NaCl and urea) out of the medullary interstitium
        - The lower osmolarity of the medullary interstitium
          - less reabsorption of tubular fluid and increased excretion.
B. Cardiovascular:

1. **Vasodilation** (relax vascular smooth muscle in arterioles and venules)

2. CNP has a greater dilator effect on veins than ANP and BNP.

3. Decrease of vascular reactivity to vasoconstrictive agents (pressor effects of catecholamines and angiotensin II).

4. In the brain, **ANP is present in neurons**, and an **ANP-containing neural pathway** projects from the antero-medial part of the hypothalamus to the areas in the lower brain stem that are concerned with neural regulation of the cardiovascular system.

  **ANP-containing neural circuits** appear to be involved in
  
  a. lowering blood pressure
  b. Promoting natriuresis

In general, the effects of **ANP in the brain** are opposite to those of angiotensin II.
5. ANP reduces sympathetic tone by
①dampening تثبيط of baroreceptors,
②suppressing the release of catecholamines from autonomic nerve endings
③suppressing sympathetic outflow from the CNS.
6. an ↑capillary permeability ► extravasation of fluid

The overall of these effects is decline in blood pressure
C. Cellular effects:
1. **antimitogenic** تقليل انقسام الخلايا effects

D. Hormonal:
1. ↓ **aldosterone** + renin + ADH
2. overall opposite effects to angiotensin II.
3. ↓ the feeling of thirst and appetite for salt.

E. Stimulation of lipolysis.

Natriuretic peptides (NPs) are involved in
1. the long-term regulation of sodium and water balance,
2. blood volume
3. arterial pressure.

There are two major pathways of natriuretic peptide actions:
1) **vasodilator effects**
2) renal effects that leads to natriuresis and diuresis.
The pineal gland is a coned-shaped, pea-sized gland located just beneath the center of the brain; behind the hypothalamus. After the age of 7, the pineal gland undergoes involution (shrinkage), down 75% by the end of puberty and to a tiny mass of shrunk tissue in adulthood.

Involution is accompanied by the appearance of granules of calcium phosphate and calcium carbonate called pineal sand. The pineal gland is innervated by sympathetic neurons.

The pineal gland synthesizes (tryptophan → serotonin → melatonin).

The pineal has a close association with the cerebrospinal fluid of the third ventricle. Evidence suggests that the gland's chief secretory product, melatonin, is released in part directly into the third ventricle.
Melatonin plays an important role in the followings:

1. Regulate the circadian rhythms (daily body cycles)

Melatonin is a hormone produced by the pineal gland of our body at night in response to darkness. The brain may secrete up to 20 times more melatonin at night than in the day time, hence melatonin is nicknamed "the hormone of darkness".

There is a high concentration of melatonin receptors in the SCN because this is where melatonin mediates the majority of its effects on circadian rhythm.

Human infants' melatonin levels become regular in about the third month after birth.

Human melatonin production decreases as a person ages.

For people who sleep "normal hours", natural melatonin production rises sharply in the evening, and peaks between 1 am and 3 am.
Regulate the sleep patterns. This includes the speed of falling asleep, duration and the quality of sleep.

Influence hormones in the body that regulate reproduction, the timing of ovulation; melatonin has the ability to suppress ovulation in humans.

Anti-aging: melatonin is a powerful free-radical scavenger and wide-spectrum antioxidant, a compound that blocks the action of free radicals (activated oxygen molecules) that can damage cells. Therefore some scientists suggest that it has anti-aging functions.

Anti-cancer & anti-inflammatory: Some studies showed that melatonin may suppress the growth of certain types of cancer cells, and may stimulate the natural killer cells (a type of white blood cells) to attack tumors. Melatonin may be useful fighting infectious diseases.

Melatonin is also called "seat of the soul" because of the influence of melatonin on emotions.
Renin-angiotensin-aldosterone system (RAAS)

• is a slow, hormonal mechanism.
• is used in long-term blood pressure regulation by adjustment of blood volume.
• RAAS is a circulatory hormone system (circulating RAAS), all of its components also exist locally in tissues, e.g. in the kidney, blood vessel wall, heart, brain and adrenal cortex (Tissue RAAS). Therefore, RAAS seems to be a regional regulator as well; although the exact function of Tissue RAAS is unsettled.

Renin

• Renin is an enzyme; which is secreted from juxtaglomerular cells of the kidney.

Juxtaglomerular apparatus (JGA): (juxta- means near).

A specialized collection of two cell types

A. Macula densa cells:

Specialized chemoreceptor cells in the wall of the distal convoluted tubule which responds to changes in:

1. Solute concentration (especially sodium levels) in the urine in the distal convoluted tubule
2. Oxygen levels in the blood passing to the glomerulus;

This sensory information is conveyed to the juxta-glo berular cells which will adjust their output of renin accordingly.

B. Juxta-glomerular cells: Specialized smooth muscle cells which act as mechanoreceptors (Intrarenal baro-receptors) which stretch in response to increases in the blood pressure of the afferent arteriole; they also synthesize and secrete the enzyme renin
Renin only known function is to convert angiotensinogen which is derived from the liver to inactive deca-peptide angiotensin I.

The main stimulators of renin release are:
1. Decreased sodium and chloride concentration in the distal tubule across macula densa
2. Decreased in afferent arteriolar blood pressure
3. Increase sympathetic activity via renal nerves,
4. Increase circulating catecholamines through adrenergic $\beta_1$-receptor stimulation,

The main inhibitors of renin release are:
1. Angiotensin II,
2. Plasma Cl, K, Na concentration
3. Antidiuretic hormone
4. Atrial natriuretic peptide
5. Increase sodium and chloride concentration across the distal tubule across macula densa
6. Increase afferent arteriolar pressure
Angiotensin I is inactive.

Angiotensin II is physiologically active.

There are different enzymatic routes of angiotensin II formation from angiotensin I.

1. ACE pathway: Angiotensin I is activated by angiotensin converting enzyme (ACE), which is mainly located on the surface of the vascular endothelium and the lung epithelium.

2. Non-ACE pathway: Other enzymes, including chymase, cathepsin G, Chymostatin-sensitive ANG II generating enzyme (CAGE), can also convert angiotensin I to angiotensin II. In humans, the non-ACE pathways are reported to represent at least 40% of total angiotensin II formation. Some evidence exists that ACE-independent pathways become quantitatively more important under pathological conditions such as diabetes.

Angiotensin II can be formed directly from angiotensinogen directly without converting to angiotensin I by tissue-type plasminogen activator (t-PA), kallikrein, chymotrypsin and trypsin

Angiotensin III

Angiotensin III is one of the peptide fragments of angiotensin II. Angiotensin III has 40% of the presser activity of Angiotensin II, but 100% of the aldosterone-producing activity.
Physiological effects of angiotensin II:

At least two types of angiotensin receptors are present on the surface of the target cells:

1. Angiotensin II type 1 (AT$_1$)

AT$_1$ receptors are serpantin receptor couple by G protein (G$_q$)

AT$_1$ receptors can be further subdivided into subtype A (AT$_{1A}$) and subtype B (AT$_{1B}$) receptors

First: AT$_{1A}$ subtype is found in blood vessel walls, the brain, it mediates most of the known effects of angiotensin II.

Second: AT$_{1B}$ subtype found in the anterior pituitary and adrenal cortex.

An excess of angiotensin II down regulates the vascular receptors (AT$_{1A}$), but it up regulates the adreno-cortical receptors (AT$_{1B}$), making the gland more sensitive to the aldosterone-stimulating effect of the peptide.
AT1A receptor is the major subtype mediating cardiovascular and renal effects of angiotensin II; these include:

1. Contraction of vascular smooth muscle, by enhancement of calcium sensitivity of the contractile apparatus of the smooth muscle,
2. Increased endothelin production,
3. Facilitation of noradrenalin biosynthesis and release and inhibition of its reuptake in sympathetic nerve terminals,
4. Stimulation of catecholamine release from the adrenal medulla,
5. Positive inotropic and chronotropic action on the heart
6. Facilitation of aldosterone biosynthesis and secretion in the adrenal cortex
7. AT1 receptor stimulation augments
   1. Tubular sodium re-absorption in the kidney,
   2. Inhibition of renin release,
   3. Releases vasopressin from the pituitary gland
8. Induces polydipsia (thirst)
9. Angiotensin II leads to contraction alkalosis (Contraction alkalosis refers to the increase in blood pH that occurs as a result of fluid losses (volume contraction). The change in pH is especially pronounced with acidic fluid losses caused by problems like vomiting
10. Stimulate cell growth
2. Angiotensin II type 2 (AT$_2$) receptors:
AT$_2$ receptors it is more plentiful in fetal and neonatal life, but they persist in the brain and other organs in adult.
The stimulation of AT$_2$ receptors is proposed to antagonize the AT$_1$ -mediated blood pressure increase,

Physiological actions of Angiotensin II type 2 (AT$_2$)

1. Vasodilatation
2. Inhibition of angiogenesis and cell growth
3. Increase endothelial nitric oxide (NO) production
4. Apoptosis of cells

Factors inhibits release of angiotensin II

1. Increase renal artery mean pressure
2. Decrease discharge of renal nerve
3. Increase fluid volume
Adipose tissue as endocrinal gland:
The classic function of the adipocyte is to store and release lipid fuel.
Most recent data emphasize the role of adipose tissue as a
1. hormonally active system,
2. influencing inflammation,
3. lipid and glucose metabolism
4. body weight, feeding behavior, energy balance
5. Hemostasis
6. vascular tone
7. insulin sensitivity and insulin resistance
Endocrine function of the adipocyte can be divided into proteins and enzymes involved in steroid metabolism.
A. adipocytokines (or adipokines or Protein):

Good adipokines

1. Leptin

Leptin is secreted not only from white adipocytes, but also from placenta and stomach. Leptin is found more in subcutaneous than visceral fat.

Leptin identification in 1994

Leptin endocrine effects include

1. regulation of immune function,
2. hematopoiesis,
3. angiogenesis, and
4. bone development.

Leptin has been known for its role in

1. controlling body weight,
2. food intake through hypothalamic pathways,
3. glucose homeostasis
Leptin primary function is to
① increase satiety
② energy expenditure through action on the hypothalamus.

Leptin action in the muscle, ↑ glucose uptake and metabolism.
Leptin action in the liver ↑ glucose production
Leptin action in the pancreases, ↑insulin
Leptin activates the hypothalamic-pituitary-adrenal axis
Leptin suppresses
①the hypothalamic-pituitary - thyroid axis
②the hypothalamic -pituitary-gonadal axis

Leptin is involved in the regulation of reproductive development and function by indirectly influencing GnRH neuron activity.
Adiponectin:

Adiponectin is exclusively secreted by adipocytes.
Adiponectin has higher serum concentration in females.
Adiponectin is found more in the subcutaneous adipose deposits than in the visceral deposits.

- Adiponectin in the liver: downregulate glucose + free fatty acid.
- Adiponectin in the muscle: upregulate free fatty acid oxidation + downregulate triglyceride production.

Adiponectin has anti-atherogenic activity because it acts through:

A. upregulate nitric oxide (NO) by the insulin receptor of the vascular endothelium.
B. Positive correlation to HDL and inverse correlations to LDL, triglycerides, insulin resistance, and diastolic blood pressure.
A strong and consistent inverse association between

A. Adiponectin and insulin resistance

① Adiponectin activity ↑ during insulin sensitivity
② Adiponectin activity ↓ during insulin resistance

B. Adiponectin and an inflammatory state

Adiponectin seems to have anti-inflammatory

Taken together, these studies suggest that adiponectin is a unique adipocyte-derived hormone with

① anti-diabetic,
② anti-inflammatory and
③ anti-atherogenic effects
Bad adipokines

3. Adipsin & Acylation Stimulating Protein

Adipsin is found more in the subcutaneous adipose deposits than in the visceral deposits. Adipsin is the enzyme required for the production of Acylation Stimulating Protein (ASP). Both adipsin and Acylation Stimulating Protein positively correlate with:

1. Adipocyte,
2. Insulin resistance,
3. Dyslipidemia
4. Cardiovascular disease

Acylation Stimulating Protein increases insulin secretion.

Acylation Stimulating Protein in the adipose tissue

↑ glucose transport + ↑ Triglycerides synthesis by

1. Increasing the activity of diacylglycerol acyltransferase
2. Decreases lipolysis
3. Decreases release of Non-esterified ("free" or unsaturated) fatty acid from adipocytes
Resistin is 15 times greater in the visceral adipose deposits than in the subcutaneous deposits. Resistin↑in insulin resistance and type 2 diabetes mellitus. Resistin potentially linking obesity with insulin resistance.

Tumor necrosis factor-alpha (TNP-α)
TNP-α is secreted more from the subcutaneous adipose deposits than from the visceral deposits and may be dependent on regional fat mass. TNP-α increases insulin resistance in liver, muscle and adipose tissue.

TNP-α in liver increased:
1. Free fatty acid (FFA) production
2. Cholesterol synthesis

TNP-α in liver decreased:
1. Glucose uptake
2. Free fatty acid storage
Protein from the renin angiotensin system

Renin angiotensin system proteins are found more in visceral adipose deposits than subcutaneous deposits.

RAS proteins include: rennin, angiotensinogen, angiotensin I, angiotensin II, angiotensin converting enzyme

Similar to the renin-angiotensin system in the kidney, these proteins affect the same target organs.

In the adrenal gland, aldosterone is increased, increasing the reabsorption of sodium and water in the kidneys.

In the vasculature, vasoconstriction is primary activity from adipocyte renin angiotensin system.

In the liver, results in

1. decreased lipolysis
2. increased lipogenesis, gluconeogenesis, glycogenolysis, and insulin resistance
Interleukin-6

Interleukin-6 is found more in visceral adipose deposits than in subcutaneous deposits.

Approximately 1/3rd of the circulating Interleukin-6 originates from the adipose tissue.

Interleukin-6 primary function is to increase

1. insulin resistance in hepatic, muscle and adipose tissue.
2. hepatic hyperlipidemia
3. hepatic glucose production.

↓ Interleukin-6 In the CNS
   ↓
   ↓ energy expenditure
Plasminogen activator inhibitor-1 is found more in visceral adipose deposits than in subcutaneous deposits.

Fibrinolysis is the breaking down of blood clots.

Plasminogen activator inhibitor-1 inhibits tissue plasminogen activator which initiates the fibrinolysis cascade: thus, Plasminogen activator inhibitor-1 inhibits fibrinolysis.

TNP-α ➤ Plasminogen activator inhibitor-1 in adipose tissue
B. Steroidgenic enzymes:
Several enzymes from the adipose tissue are involved in steroid metabolism; activation, inter-conversion and inactivation. The steroid activity can be divided into sex steroids and glucocorticoid activity the enzymes involved in sex steroids convert androgens to estrogens. convert specific sex steroids to their more active form
1 androstenedione to testosterone
2 estrone to estrodiol.
In glucocorticoid activity, steroidogenic enzymes
1 increase insulin sensitivity
2 control visceral adipose tissue deposition
Hunger & satiety:
There are several levels of energy balance in metabolism.
The obvious balance is that of food intake and energy expenditure.
In the balance of caloric intake and energy expenditure,
the factors affecting caloric intake include:
1. Hunger is a physiological urge to consume food.
2. Satiety is the signal for cessation of food intake.
3. Appetite is a physiological preference for specific foods.
How much of these factors can be modified by psychological factors in the control of food intake for humans?
The feelings of hunger and satiety are stimulated by the “gut-brain axis”, where a crucial role is played by gastrointestinal hormones:
glucagon-like peptide 1, glucose-dependent insulinotropic polypeptide, pancreatic polypeptide, peptide YY, oxyntomodulin, cholecystokinin and ghrelin.
These hormones affect
1. the functioning of the digestive tract
2. insulin secretion
3. mediators which affect brain areas involved in the regulation of food intake.
Ghrelin

Ghrelin is an endogenous peptide with 28 amino acid peptide.

Ghrelin is the substance found to be associated with meal initiation in humans.

Ghrelin is secreted by the stomach and intestine.

Ghrelin has been found to increase before meals.

Ghrelin believed that glucose concentrations and energy balance lead to ghrelin production and release.

Ghrelin fall to its lowest point within one hour following the meal.

Functions of Ghrelin

1. Ghrelin increases growth hormone.

Ghrelin acts as an antagonist of somatostatin that inhibits the secretion but not the synthesis of GH.

GHRH+ ghrelin acts synergistically to stimulate the release of GH from the somatotrophic cells of the hypophysis.

Ghrelin actions of feeding are independent from the growth hormone actions.
Ghrelin is adipogenic by lowering the catabolism of fat participates in
a. the regulation of energy homeostasis,
b. increases food intake, and
c. decreases energy expenditure.

orexigenic (appetite-stimulating) and

Ghrelin increases food intake + weight gain in experimental animals

Ghrelin induces hunger in humans.

Ghrelin is part of a complex neuroendocrine network involved in the regulation of appetite and energy homeostasis.

Several studies suggested that the orexigenic signal of ghrelin secreted from the stomach is transmitted to the brain via the vagal afferent nerve.

Peripheral ghrelin may exert its effects on the CNS by crossing the blood brain barrier (BBB) although the rate at which it passes the BBB is very low.

Areas in the brain that are implicated in the regulation of feeding behavior express receptors for ghrelin.
Obestatin is 23 amino acid peptide.

Obestatin was initially considered to oppose the orexigenic effects of ghrelin. Later studies, however, cast doubt on the initial findings as subsequent studies failed to confirm the anorexigenic effects (appetite suppressant) of obestatin.

Obestatin has been reported to have additional roles such as:

1. the inhibition of thirst
2. the regulation of memory, anxiety, and sleep
3. stimulate the proliferation of human retinal cells
4. promote the survival of pancreatic β-cells and human islets
5. the regulation of adipocyte metabolism and adipogenesis