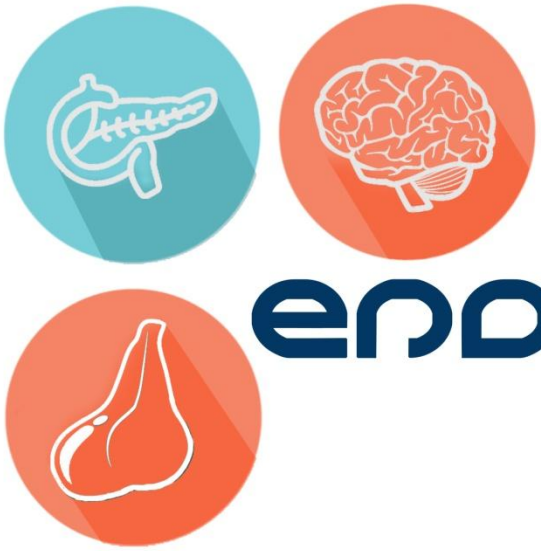

endocrine system

Pharmacology

Sheet Slide

number 2

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Correction

Doctor Munir

Last time we finished talking about Histamine and 5-hydroxytryptamine, which belong to the autacoids family. It's a large family that contains other members such as eicosanoids and vasoactive peptides.

Note: **slide#2 is not required**, the doctor went through the slides quickly mentioning the following points and said we only have to know that **eicosanoids and vasoactive peptides are other constituents of the autacoids family**.

(these points aren't included in the exam, I put them because the doctor mentioned them)

- Eicosanoids: are prostaglandins, thromboxanes and leukotrienes. They are synthesized from arachidonic acid, which is a membrane fatty acid found in phospholipids, by the action of either cyclooxygenase (produces TXs and PGs) or lipooxygenase (produces leukotrienes), these compounds are of great medical importance. For example, misoprostol is a prostaglandin drug used in preventing and treating gastric ulcers caused by analgesics. Also, some prostaglandin drugs are used in relaxing the uterus; others are used in contracting it. We will talk more about them in the urogenital system.

- Vasoactive peptides:

  -Renin-Angiotensin-Aldosterone system (RAAS).
  -Kinins
  -Vasopressin
  -Natriuretic peptides
  -Endothelins
  -Vasoactive intestinal peptide, and many others.

  RAAS is one of the most important autacoids concerning vasoactivity. The story starts with the release of renin from juxtaglomerular apparatus in kidneys, renin converts angiotensinogen to angiotensin I, which in turn is converted to angiotensin II by an enzyme called angiotensin converting enzyme (ACE). Vasoactive peptides generally are used in cardiovascular cases. Angiotensin II effects are: inotropy, hypertrophy, electrical and ventricular remodeling and pathogenesis of atherosclerosis.

  Alternative Pathways Of The Renin: these are alternative enzymatic pathways, which end with angiotensin II production but do not involve ACE enzyme. *Human heart chymase* appears to be the most important of these pathways, particularly in the ventricles.

Pharmacology of hypothalamic and pituitary hormones

As we know, the hypothalamus lies in great proximity to the pituitary gland, which is composed of anterior and posterior lobes. Both, the hypothalamus and the pituitary glands are believed to provide the main guidance to the other endocrine glands. They have great influence over the endocrine system.

Hypothalamic hormones

The hypothalamic hormones are classified according to their activity into release stimulators or release inhibitors. These hormones reach the anterior pituitary gland via the adenohypophyseal portal system, bind to their receptors on the anterior pituitary cells, and stimulate or inhibit the release of the hormones.

A quick view of the hypothalamic hormones:

- GHRH: growth hormone-releasing hormone.
- Somatostatin: inhibits the release of GH.
- GnRH: gonadotropin-releasing hormone stimulates the release of FSH and LH.
- CRH: corticotropin-releasing hormone stimulates the release of ACTH.
- Dopamine: it's a neurotransmitter actually but in these cells it's considered as hormone, it inhibits the release of prolactin.(dopamine agonists are used to stop lactation)
- TRH: thyrotropin-releasing hormone stimulates the release of thyroid-stimulating hormone and prolactin.

  Note: clinically, we don't give GHRH, CRH or TRH; instead, we simply give the related hormone directly, GH, ACTH and thyroxin, respectively. (GnRH is an exception for this rule).

  Now we will talk about the pharmacology of these hormones:

  1-somatostatin: as we said previously, it inhibits the release of GH, and is composed of 14-amino acid peptide, it has a short half life so it's clinically not feasible.
  Octeriotide is a synthetic 8-amino acid analogue of somatostatin that is clinically used to mimic the physiological action of somatostatin. It inhibits the release of many hormones but mainly GHs. Other functions of sandostatin (the trade name of octeriotide) include inhibition of bile flow, inhibition of mesenteric blood flow as well as decreasing the gastrointestinal motility.

  Note: octeriotide is more stable than somatostatin since it is composed of less number of amino acids (8 amino acids).

Octeriotide is given as depot injections (monthly) because of its long half-life and mainly used to treat ***acromegaly*** but not gigantism.

"Recall": excessive production of GH before adolescence causes gigantism and acromegaly if it is after adolescence.

Other uses of octeriotide include:

- Diarrhea associated with neuroendocrine tumors such as insulinomas or carcinoid tumors.
- Diarrhea associated with AIDS that doesn't respond to other treatments.

Gastrointestinal discomfort, decreased glucose tolerance and formation of gallstones are the common side effects of octeriotide.

2- Gonadotropin-Releasing Hormone (GnRH) or Gonadorelin: Stimulates the production of Luteinizing hormone (LH) and Follicle stimulating hormone (FSH) from anterior pituitary. It is released in bursts at regular intervals (every 2 hours) and has very short half-life (7 minutes). The response to GnRH (or its analogues) depends on the concentration and mode of administration. Pulsatile administration doesn't have the same effect as continuous (constant) administration:

Drug	Dose/regime	Effect
Agonist	Low, pulsatile (same as the physiologic)	Pituitary and gonadal ***stimulation*** (Used in infertility cases)
Agonist	High, constant	Pituitary and gonadal ***stimulation*** followed by ***suppression for 2 weeks*** (In vitro fertilization)
Antagonist	Constant	Pituitary and gonadal ***suppression*** (in vitro fertilization)

Lutrepulse, GnRH agonist, is used to cause ovulation in women who do not have a period (when FSH and LH are low). It is administered intravenously, in pulses, through a pump. Lutrepulse is used for women who are not producing enough GnRH.

Suppression of gonadotropin:

a) **Goserelin (superagonist of GnRH):** Stable potent derivative of GnRH, it is a long-acting agent that Suppresses gonadotropin production (after initial stimulation), it is Used as *palliative* treatment for reduction of prostate cancer growth.

   How could an agonist cause suppression?

   Giving high doses of an agonist will initially cause stimulation, after that, it causes down regulation and desensitization, thus suppression.

   For your information: prostate cancer is treated by female sex hormones.

b) Ganirelix: is receptor antagonist given by monthly injections and used to *prevent premature ovulation* in women undergoing ovarian stimulation as part of fertility treatment.

Anterior Pituitary hormones

As for the hypothalamic hormones, the anterior pituitary hormones are also released in a pulsatile manner. Secretion of these hormones varies with time of day or physiological conditions such as exercise or sleep.

"Check slide #14 of slide 3 to know all of the anterior pituitary hormones"

- **Growth hormone:** GH is one of the anterior pituitary hormones that plays a major role in the growth and development of all body systems.it is a 191-aminoacid peptide that is required during childhood and adolescence for attainment of normal adult size and has important effects throughout postnatal life on lipid and carbohydrate metabolism, as well as on lean body mass. GHs physiologic effect is mediated via insulin-like growth factor 1 (IGF-1, somatomedin C) and, to a lesser extent, through insulin-like growth factor 2 (IGF-2).

GHs along with many other hormones such as thyroid hormones control the growth and development of our bodies. Deficiency of either of them causes growth suppression but the characteristics of each deficiency are different. GH deficiency causes dwarfism, meanwhile, the mental and metabolic statuses normal. On the other hand, thyroid hormones deficiency causes a condition called cretinism that is characterized by growth suppression as well as mental and metabolic retardations (generally, everything is retarded).

Growth hormone deficiency:

Individuals with congenital or acquired deficiency of GH during childhood or adolescence fail to reach their predicted adult height and have disproportionately increased body fat and decreased muscle mass. Also, these individuals have disproportionate delayed growth of skull and facial skeleton giving them a small facial appearance for their age.

- Somatotropin (Humatrope): is an exact (has the same amino acid sequence) synthetic compound of GH, produced by recombinant DNA and molecular technologies. It is administered subcutaneously in the leg at the evening and used mainly to treat *growth failure in pediatric patients*.

Why pediatric and young patients? Because the epiphyseal plates of the bones are not fused yet, so giving this drug to an adult patient will be of no benefit.

Other effects of humatrope include:

– Improved metabolic state, increased lean body mass, sense of well-being in adults with GH deficiency.

– Increased lean body mass, weight, and physical endurance and wasting in patients with HIV infection.

– Improved gastrointestinal function in short bowel syndrome in patients who are also receiving specialized nutritional support.

As we said earlier, excessive production of GHs causes one of the following:

A) Gigantism: if the production was before adolescence. It is characterized by the general symmetrical overgrowth of all body parts and has no treatment.

b) Acromegaly: if the production was after adolescence.it is a chronic metabolic disorder in which there is too much growth hormone and the body tissues gradually enlarge. Pituitary adenoma (benign tumor) is usually the cause. The treatment involves surgical removal of the tumor and octeriotide administration.

Note: before adolescence→epiphyseal plates aren't closed.

After adolescence→epiphyseal plates are closed.

Good luck