# PHARMACOLOGY/THERAPEUTICS II BLOCK III HANDOUTS

# 2015-16

69. ON-LINE ONLY Hypothalamic/pituitary Hormones – Patel

70. & 71 ON-LINE ONLY Estrogens & Progesterone I & II – Patel

72. ON-LINE ONLY Androgens – Patel

73. Diabetes Drugs I – Clipstone

74. Diabetes Drugs II – Clipstone

75. Calcium Metabolism – Clipstone

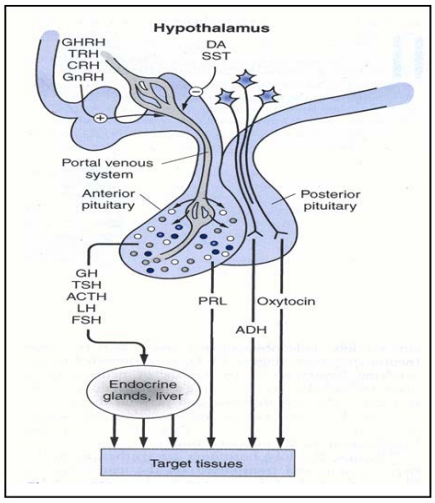
76. Thyroid/Anti-Thyroid Drugs – Clipstone

77. Andrenocorticosteroids & Antagonists - Clipstone

## 1. Overview of Neuroendocrine Systems

The neuroendocrine system controlled by the pituitary and hypothalamus controls major body functions.

- The communication from the hypothalamus to anterior pituitary (AP) is via vascular link: hypothalamic-pituitary-portal-system.
- The hormones of the posterior lobe of pituitary are synthesized in the hypothalamus, transported to the posterior pituitary, and released into circulation in response to specific physiologic signals




## 2. Regulation of Anterior Pituitary (AP) Secretion:

**Key Concepts:**

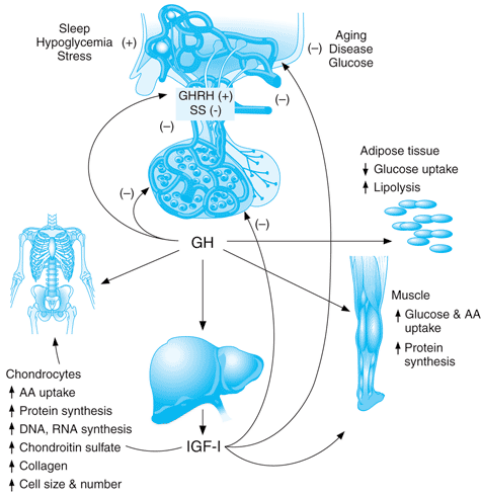
A. Clusters of neurosecretory cells in the hypothalamus synthesize specific "releasing" or "inhibiting" factors or hormones, which are released into the hypothalamic-pituitary-portal-system by action potentials.
B. These hypothalamic (hypophysiotropic) hormones signal release or inhibition of release of AP hormones (except Prolactin)
C. Hormones released from AP stimulate hormone production by a peripheral endocrine gland or the liver (except Prolactin)
D. Each pathway, including a hypothalamic factor(s), pituitary gland factor(s), and the ultimate target gland is referred to as an endocrine axis.
E. There are 5 endocrine axes.

| Anterior Pituitary Hormone | Hypothalamic Hormone | Target Organ | Primary Target Organ Hormone or Mediator |
|---|---|---|---|
| Growth hormone (GH, somatotropin) | Growth hormone-releasing hormone (GHRH) (+) Somatostatin (–) | Liver, muscle, bone, kidney, and others | Insulin-like growth factor-1 (IGF-1) |
| Thyroid-stimulating hormone (TSH) | Thyrotropin-releasing hormone (TRH) (+) | Thyroid | Thyroxine, triiodothyronine |
| Adrenocorticotropin (ACTH) | Corticotropin-releasing hormone (CRH) (+) | Adrenal cortex | Glucocorticoids, mineralo-corticoids, androgens |
| Follicle-stimulating hormone (FSH) Luteinizing hormone (LH) | Gonadotropin-releasing hormone (GnRH) (+)[2] | Gonads | Estrogen, progesterone, testosterone |
| Prolactin (PRL) | Dopamine (–) | Breast | — |

E. All these hormones function through G protein coupled receptors, and GH and prolactin act through JAK/STAT receptors.

F. End-product feedback inhibition tightly controls hormone release from hypothalamus and pituitary gland via Long, Short and Ultra-short loops.

## 3. Hypothalamic-Pituitary-Growth Hormone Axis




## A. Physiological Actions of Growth Hormone (GH)

- **In childhood:** GH promotes linear growth, growth of long bones, cartilage, muscle, organ systems; it is a major determinant of adolescent growth spurt.
- **In adulthood major effects are metabolic:** It increases protein synthesis and bone density; promotes lipolysis and inhibits lipogenesis; promotes gluconeogenesis and glucose release; opposes insulin-induced glucose uptake in adipose tissue, reduces insulin sensitivity.
- GH is released in a pulsatile manner, mostly during sleep. Pulses are generated by interplay of GHRH and Somatostatin.

- GH secretion decreases with age.

- **Mechanism of Action:**
  - Binding of GH to its receptor activates the signaling cascade mediated by receptor associated JAK tyrosine kinases and STATs.
  - The effects of GH are primarily mediated by insulin-like growth factor 1 (IGF-1), released from liver in response to GH.

## B. Disorders of Hypothalamic-Pituitary-Growth Hormone Axis

## Features of Growth Hormone Deficiency

**1. In Children**, results in short stature and adiposity, hypoglycemia. This is most commonly due to a deficiency of GHRH.

**2. In Adults**: This results in
- Changes in body composition: increased generalized adiposity
- Decreased skeletal muscle mass and strength
- Decreased bone density
- Cardiovascular changes; cardiac muscle atrophy, atherogenic blood lipid profile
- Fatigue, weakness, depression, overall malaise

This might be due to a continuation of childhood-onset disease; adult-onset is usually pituitary problem.

## Pharmacology of Growth Hormone Deficiency

**Drugs Used:**
- Synthetic GHRH (Sermorelin)
- **Recombinant human growth hormone** (Somatropin, Somatrem)
- Recombinant IGF1 (Mecasermin)

❖ **Treatment with synthetic GHRH (Sermorelin)**

**Sermorelin** is used if a patient possesses defective hypothalamic release of GHRH but normally functioning anterior pituitary somatotrophs

❖ **Treatment with Recombinant Human Growth Hormone (Somatropin, Somatrem)**

**Drug Description:**

- Most cases of GH deficiency are treated with replacement of recombinant human growth hormone (rhGH). They are:

  **(1) Somatropin** (synthetic growth hormone), which is a 191-amino acid peptide, identical to the native form of hGH

  **(2) Somatrem**, which is a 192-amino acid peptide consisting of 191aa of GH plus an extra methionine residue at the N-terminus

**Mechanism if Action:**

- It replaces GH

**Drug Indications:**

- Documented growth failure in pediatric patients associated with: GH deficiency, chronic renal failure, Prader-Willi syndrome, Turner syndrome
- Small-for-gestational-age condition
- Idiopathic short stature, non GH-deficient (>2.25 S.D. below mean height for age/sex)
- GH deficiency in adults
- Wasting in patients with AIDS
- Short bowel syndrome in patients who are also receiving specialized nutritional support

**Efficacy:**

**Children**

- Increases linear growth, weight gain to low normal range
- Increases muscle mass, organ size, RBCs

**Adults**

- Increases bone mineral density
- Normalizes body composition: decreased central adiposity
- Increases muscle mass and strength
- Improves lipid profile and cardiac function
- Improves psychological symptoms and sense of well being

**Side Effects:**

- Leukemia, rapid growth of melanocytic lesions
- Hypothyroidism
- Insulin resistance
- Arthralgia
- Increase in cytochrome P450 activity

**Contraindications:**

- Pediatric patients with closed epiphyses
- Active underlying intracranial lesion
- Active malignancy
- Proliferative diabetic retinopathy

❖ **Treatment with Recombinant IGF1 (Mecasermin)**

**Mecasermin** is used for children with severe IGF1 deficiency due to mutations in the GH receptor (Laron dwarfism) or development of neutralizing antibodies against GH.

## Features of Growth Hormone Excess

This usually results from benign tumor of the anterior pituitary.

**(1) In children**: It causes **gigantism.**
This occurs before the closure of epiphyses, because excess IGF1 causes excessive longitudinal bone growth

**(2) In adults:** It causes **acromegaly.**
This occurs after epiphyses close, because excess IGF1 although can no longer stimulate long bone growth, can still promote growth of deep organs and cartilaginous tissue. This is characterized by:

- Thickening of bones, esp. face, hands
- Large facial structure, macroglossia and hepatomegaly
- Increased soft tissue growth
- Enlarged, arthritic joints
- Headache, sleep apnea, excessive sweating
- Increased risk of CV disease, GI cancers (esp. colon), reproductive disorders

## Pharmacology of Growth Hormone Excess

Standard treatment for larger pituitary adenoma is transsphenoidal surgery to remove the tumor. Medical options for smaller adenomas are as follows:

**Drugs Used:**

- **Somatostatin analogues** (Octreotide, Lanreotide in Europe)
- **GH receptor antagonist** (Pegvisomant)
- **Dopamine receptor agonist** (Bromocriptine - described under hyperprolactinemia)

❖ **Treatment with Somatostatin Analogue (Octreotide)**

**Drug Description:**

- Somatostatin analogues:
  - **Somatostatin** physiologically inhibits GH secretion, but is rarely used clinically, since it has a very short half-life ( a few minutes)
  - **Octreotide** is a synthetic long-lasting peptide analogue of somatostatin (45 times more potent)

**Mechanism of Action:**

- It inhibits GH secretion

**Drug Indications:**

- Used to control pituitary adenoma growth in acromegalic patients
- Carcinoid crisis- flushing, diarrhea and all symptoms of carcinoid syndrome
- Secretory Diarrhea from vasoactive intestinal peptide-secreting tumors
- To control acute GI bleeding

**Side Effects:**
- Nausea, vomiting, abdominal cramps, GI discomfort
- Cardiac effects include sinus bradycardia and conduction disturbances
- Hypoglycemia
- Gallstone formation

**Contraindications:**
- Hypersensitivity to octreotide

❖ **Treatment with GH Receptor Antagonist (Pegvisomant)**

**Drug Description:**
- **Pegvisomant is** GH receptor antagonist, recombinant protein,191 amino acids
- Has multiple polyethylene glycol (PEG) residues, which prolongs its half-life

**Mechanism of Action:**
- **Pegvisomant** is a competitive antagonist of GH activity
- This can bind to the transmembrane GH receptor but cannot activate subsequent intracellular signaling
- It decreases serum IGF1 levels

**Drug Indications:**
- Used for the treatment of acromegaly that is refractory to other modes of surgical, radiologic, or pharmacologic intervention.

**Side Effects:**
- Increased pituitary adenoma size
- Elevated serum aminotransferase levels

**Contraindications:**
- Hypersensitivity to pegvisoment

## 4. Hypothalamic-Pituitary-Reproductive Axis

## A. Physiological Actions of Gonadotropins

The gonadotroph cells in the pituitary secrete two types of gonadotropins in response to pulsatile GnRH:
- **LH** (Luteinizing hormone)
- **FSH** (Follicle-stimulating hormone)

**In Women:**

The main function of FSH is ovarian follicle development. In the follicular stage of the menstrual cycle, LH stimulates androgen production in the ovary (Thecal cells), whereas FSH stimulates conversion of androgens to estrogens (Granulosa cells). In the luteal phase, estrogen and progesterone production is primarily controlled by LH, and during pregnancy controlled by hCG (human chorionic gonadotropin) produced by the placenta.

**In Men:**

FSH primarily regulates spermatogenesis. LH stimulates production of testosterone by the testicular Leydig cells. In Sertoli cells, FSH produces androgen binding protein, which helps to maintain high testicular levels of testosterone.

## B. Disorders of Hypothalamic-Pituitary-Reproductive Axis

**Key Concepts**:

- In both men and women, **infertility** due to neuroendocrine factors may respond to pharmacological treatment if the gonads are competent to respond in a normal physiologic manner.
- Pharmacological treatments are also used in assisted reproductive technologies in women with genital tract/tubal abnormalities.

## Pharmacology of Female and male Infertility

**Drugs Used:**

**Stimulation**

- **Gonadotropins** (human menopausal gonadotropins or menotropins, human chorionic gonadotropin or hCG, Urofollitropin, Follitropin)
- **Gonadotropin Releasing Hormone (GnRH)** or its analogue **Gonadorelin** with short-half life (4 minutes)- pulsatile form

**Inhibition**

- **Synthetic analogs of GnRH** with longer half-lives – continuous form (Goserelin, Histrelin, Leuprolide, Nafarelin, Triptorelin)
- **GnRH receptor antagonists** (Ganirelix, Cetrorelix, Abarelix)

### ❖ Stimulation of the Gonadal Axis by Gonadotropins

**Drug Description:**

- Menotropins are obtained from the urine of menopausal women and contain FSH and LH
- hCG is a placental hormone and an LH agonist
- Urofollitropin is purified FSH isolated from the urine of postmenopausal women
- Follitropin is a recombinant from of human FSH

**Mechanism of Action:**

- Replaces FSH and LH

**Drug Indications:**

- Ovulation induction (in women) in hypogonadotropic hypogonadism, polycystic ovary syndrome, obesity
- Controlled ovarian hyperstimulation in assisted reproductive technology procedures (example IVF)
- Infertility in male hypogonadotropic hypogonadism

**Side Effects:**

- Ovarian hyperstimulation syndrome (associated with ovarian enlargement, ascites, hydrothorax, hypovolemia, sometimes resulting in shock)
- Increase in multiple pregnancies (15-20% chance)
- Increased risk of gynecomastia in men

- Ovarian cancer
- Ovarian cysts and hypertrophy

**Contraindications:**

- Any endocrine disorder other than anovulation (eg thyroid or adrenal dysfunction)
- Primary gonadal failure
- Pituitary tumors or sex-hormone dependent tumors
- Ovarian cyst or enlargement
- Pregnancy

## ❖ Stimulation of the Gonadal Axis by GnRH Agonist (Pulsatile)

- **Pulsatile** GnRH secretion or short-half life GnRH analogue Gonadorelin (half-life ~4 minutes) can stimulate the gonadotroph cells to produce and release LH and FSH **(Stimulation of gonadal axis)**: mimicking physiology.

- Used mostly in diagnosis of hypogonadism and occasionally to stimulate ovulation or to treat infertility in men.

## ❖ Inhibition of the Gonadal Axis by GnRH Agonist (Sustained)

**Drug Description:**

- Goserelin, Histrelin, Leuprolide, Nafarelin, Triptorelin are synthetic analogs of GnRH
- More potent and longer-lasting than native GnRH or gonadorelin
- Long half-life (~3hours)

**Mechanism of Action:**

- **Sustained**, nonpulsatile administration of GnRH or GnRH analogs **with long half-life** desensitizes the GnRH receptors and inhibits the release of FSH and LH in both men and women - **(Inhibition of gonadal axis).**
- Produces biphasic response:
    1. first there is a transient (7-10 days) increase in gonadal hormone levels **(flare)** – agonist effect
    2. followed by a long-lasting suppression of gonadotropins and gonadal hormones – inhibitory action

**Drug Indication:**

- To keep the LH surge low in controlled ovarian hyperstimulation that provides multiple mature oocytes for assisted reproductive technologies (like IVF)- [leuprolide, nafarelin]
- Endometriosis & Uterine fibroids [leuprolide, nafarelin, goserelin]
- Adjunctive in prostate cancer [leuprolide, goserelin, histrelin, triptorelin]
- Central precocious puberty [leuprolide, nafarelin]
- Others include: advanced breast & ovarian cancer, amenorrhea and infertility in women with polycystic ovary disease

**Side Effects:**

- Hot flashes, sweats, headache (menopausal symptoms)
- Osteoporosis
- Urogenital atrophy
- Temporary worsening of precocious puberty during the initial weeks of treatment

**Contraindications:**
- Hypersensitivity to GnRH or GnRH analogs
- Pregnancy
- Breast feeding

❖ **Inhibition of the Gonadal Axis by GnRH receptor Antagonists**

**Drug Description:**
- Ganirelix, Cetrorelix and Abarelix are used to inhibit gonadal axis
- Ganirelix and Cetrorelix produce immediate antagonistic effect, and so their duration of administration during IVF is shorter compared to GnRH agonists.

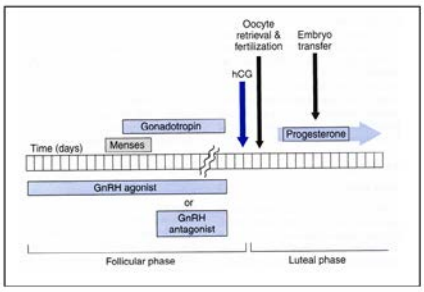
**Mechanism of Action:**
- They function as competitive antagonists of GnRH receptors
- Inhibits the secretion of FSH and LH in a dose dependent manner
- Does not produce the flare effect (increased FSH/LH) as GnRH agonists

**Drug Indications:**
- Ganirelix and Cetrorelix - keeps LH surge low in controlled ovarian hyperstimulation in IVF, resulting in improved rates of implantation and pregnancy
- Abarelix - used in metastatic prostate cancer in patients with extensive metastases or tumor encroaching on the spinal cord

**Side Effects:**
- Ovarian hyperstimulation syndrome
- QT interval prolongation (abarelix)
- Ectopic pregnancy, thrombotic disorder, spontaneous abortion (ganirelix)
- Anaphylaxis (cetrorelix)

**Contraindications:**
- Pregnancy, lactation, ovarian cysts or enlargement not due to polycystic ovarian syndrome
- Primary ovarian failure
- Thyroid or adrenal dysfunction
- Vaginal bleeding of unknown etiology

❖ **Gonadotropin and GnRH in Assisted Reproductive Technology (IVF)**



# 5. Hypothalamic-Pituitary-Prolactin Axis

## A. Regulation of Prolactin Secretion

Lactotrophs of the anterior pituitary produce and secrete prolactin. Prolactin release is inhibited by dopamine**,** secreted by hypothalamus and increased by Thyrotropin-releasing hormone or TRH. Prolactin does-not stimulate hormone secretion in its target organ (mammary gland) and so there is no negative feedback regulation. Increased estrogen levels during pregnancy stimulate prolactin release. Suckling provides a powerful stimulus for prolactin release.

## B. Physiological Actions of Prolactin

Prolactin regulates mammary gland development, milk protein biosynthesis and secretion. Increased prolactin inhibits GnRH release and thus the hypothalamic-pituitary-gonadal axis and estrogen synthesis, thereby suppressing ovulation during lactation.

## C. Disorders of Hypothalamic-Pituitary-Prolactin Axis

## Features of Hyperprolactinemia

Hyperprolactinemia occurs more commonly due to prolactin secreting adenomas. Hyperprolactinemia produces

- A syndrome of amenorrhea and galactorrhea, infertility in women
- Loss of libido and infertility in men
- In large tumors it can cause visual changes due to compression of the optic nerves

## Pharmacology of Hyperprolactinemia

**Drugs Used:**

- **Dopamine Receptor Agonists** Bromocriptine, Cabergoline, Pergolide**;** (Quinagolide is approved in Europe, not available in USA)

**Prolactin Deficiency:**

- No preparation of prolactin is available to treat these patients

❖ **Treatment with Dopamine Receptor Agonists**

**Drug Description:**

- Bromocriptine, Cabergoline, Pergolide, Quinagolide are synthetic dopamine receptor agonists.
- High affinity to dopamine D2 receptors

**Mechanism of Action:**

- They inhibit pituitary prolactin release
- GH release is reduced in patients with acromegaly, although less effectively

**Drug Indication:**

- Amenorrhea, galactorrhea and infertility from hyperprolactinemia, premenstrual syndrome (Bromocriptine, Cabergoline)
- Acromegaly:- requires high doses, and effective only if pituitary tumor secretes both prolactin and GH; otherwise combination therapy with Octreotide is effective (Bromocriptine)
- Parkinson's disease (Bromocriptine, Pergolide, Cabergoline)

**Side Effects:**

- Orthostatic hypotension
- Cerebral vascular accident, seizure, acute myocardial infarction (Bromocriptine)
- Arrhythmia, myocardial infarction, heart failure (Pergolide)
- Pulmonary fibrosis and pleural effusion (Cabergoline)

**Contraindications:**

- Hypersensitivity to ergot derivatives
- Uncontrolled hypertension
- Toxemia of pregnancy (Bromocriptine)

# PHARMACOLOGY OF GONADAL HORMONES: ESTROGENS &PROGESTINS

**Date:** Friday, March 20, 2015 – 9:30 & 10:30 am
**Reading Assignment:** Katzung Chapter 40

## KEY CONCEPTS & LEARNING OBJECTIVES

A. To describe the physiological actions and pharmacological effects of estrogens and progestins those are relevant to their clinical uses.
B. To describe the adverse effects and contraindications to use of estrogens and progestins.
C. To describe the current strategies for the use of estrogens and progestins in oral contraceptives and in hormone replacement therapy in menopause.
D. To describe pharmacological actions and clinical uses of selective Estrogen Receptor Modulators (SERMs).

**Drugs/Hormones Discussed:**

| **Estrogens and related** | **Progestins and related** |
|---|---|
| Estradiol<br>Ethinyl estradiol<br>Conjugated equine estrogens<br>Estradiol Transdermal<br>Diethylstibestrol/DES<br>Tamoxifen, Clomiphene, Raloxifene (SERM)<br>Fulvestrant (ER antagonist)<br>Anastrozole, Letrozole, Exemestane, Formestane (Aromatase inhibitors) | Norgestrel<br>Etonogestrel<br>Medroxyprogesterone<br>Levo-norgestrel<br>Norethindrone<br>Mifepristone (PR antagonist) |

**Gonadal Hormones:**

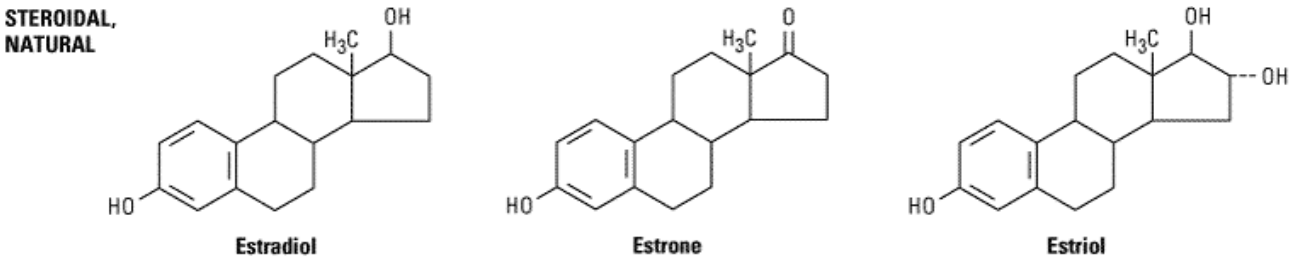
- **Estrogens**
- **Progestins**
- Androgens

**I. ESTROGENS:** Major secretary product of ovary, also formed in the liver from estriol and also produced in peripheral tissue from androgens.
**II. PROGESTINS:** Are synthesized in the ovary, testis and adrenal from circulating cholesterol. It is also synthesized by the placenta during pregnancy.
**III.** ANDROGENS: Are synthesized mainly by testis (95%) and in adrenal glands (5%).

# I. ESTROGENS: PHYSIOLOGY AND PHARMACOLOGY

## Natural Estrogens:

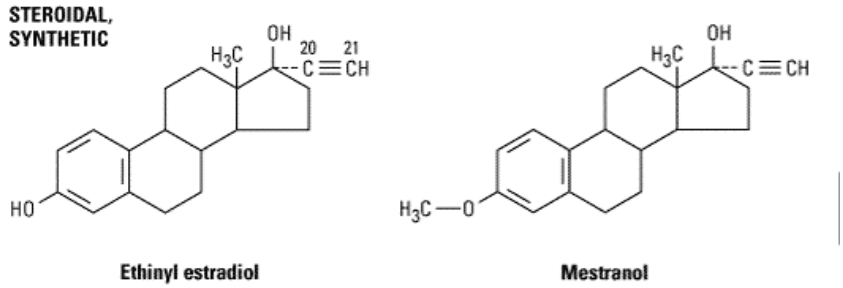
- **Estradiol 17ß (E2);** most estrogenic in action.
- **Estrone (E1);** somewhat less estrogenic.
- **Estriol (E3);** not very active metabolite.




## Synthetic Estrogens:

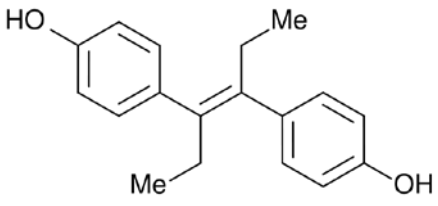
Synthetic Steroidal

- Ethinyl estradiol
- Mestranol
- Quinestrol



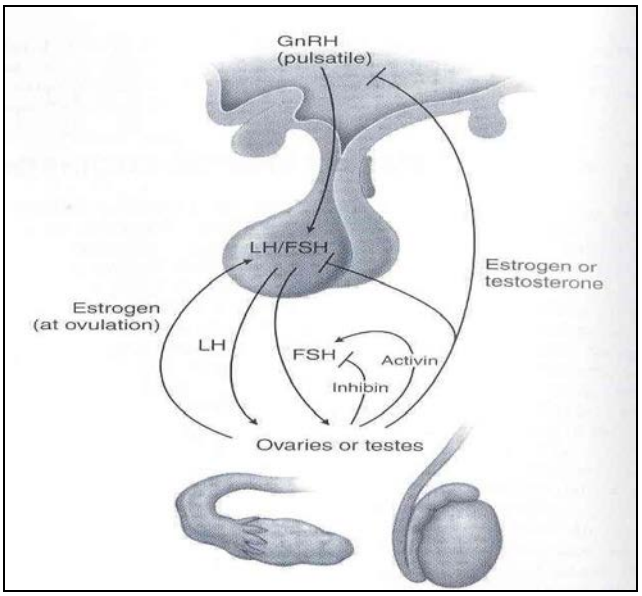

Synthetic Nonsteroidal

- Diethylstilbestrol
- Chlorotrianisene
- Methallenestril



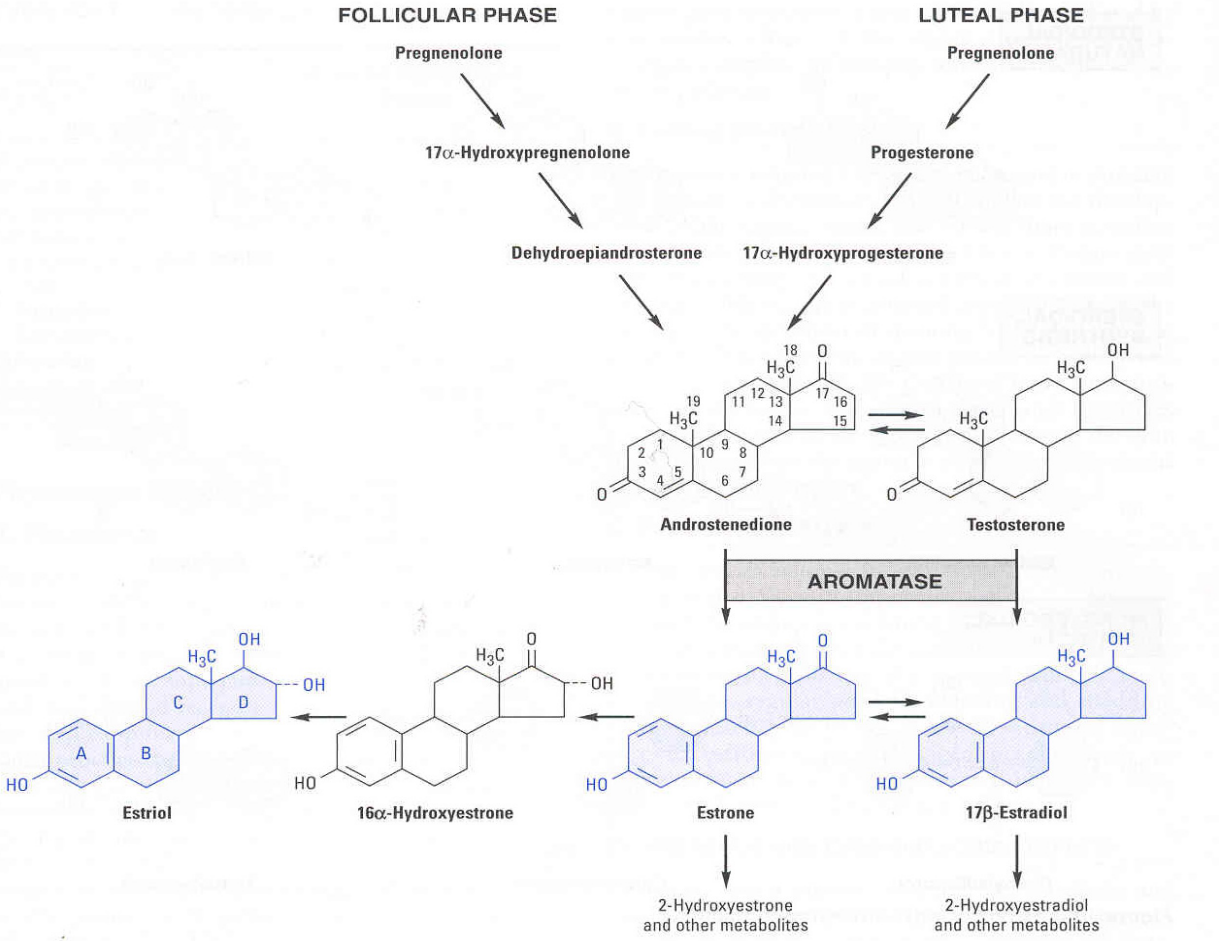

Diethylstilbestrol

## HYPOTHALAMIC-PITUITARY REPRODUCTION AXIS:

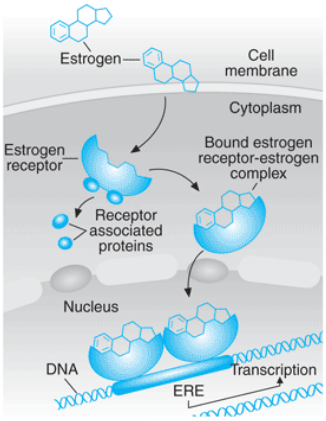



- GnRH (Gonadotropin-Releasing Hormone) is secreted by hypothalamus in **pulses** and travels through hypothalamic-pituitary portal system to stimulate gonadotroph cells of the anterior pituitary gland. These cells increase the synthesis and secretion of LH (Luteinizing Hormone) and FSH (Follicle-stimulating Hormone).
- In female, LH stimulates the Thecal cells to synthesize androgen, which is aromatized to estrone and estradiol in the Granulosa cells via FSH action.
- In male, LH stimulates testicular Leydig cells to increase the synthesis of Testosterone, which diffuses to neighboring Sertoli cells.
- Both Sertoli and Granulosa cells synthesize and secrete, Inhibin A Inhibin B and Activin. Inhibins inhibit the release of FSH, while Activin stimulates FSH release. Inhibins or Activin do not regulate LH release.
- In the male, testosterone works as a negative regulator of pituitary gland and hypothalamic hormone release.
- In female, estrogen's role is more complex and can work as **positive or negative** feedback depending on the prevailing hormonal milieu.

## BIOSYNTHESIS AND METABOLISM OF ESTROGENS:




## BASIC MECHANISM OF STEROID HORMONE ACTION:



a) Hormone diffuses into target cell and binds to receptor in cytoplasm or nucleus.
b) Hormone-receptor complex dimerizes in nucleus and binds to specific regions on DNA; complex w/ co-activators and co-repressors.
c) Complex promotes or inhibits transcription of specific genes.

## D. PHYSIOLOGICAL ACTIONS OF THE ESTROGENS:

1. **Reproductive actions**:
   a. Growth, development, and maintenance of primary and secondary female sex characteristics.
   b. Physiological changes at puberty and adolescence (e.g., growth, epiphyseal closure of bones).
   c. Neuroendocrine regulation of the menstrual cycle; negative feedback and positive feedback regulation of gonadotropin secretion.
   d. Stimulates growth (proliferation) of uterine endometrium.
   e. Stimulates secretion of thin cervical mucus (facilitates sperm transport).

2. **Metabolic actions**:
   a. Increases circulating High Density Lipoproteins (HDL), decreases low density lipoproteins (LDL).
   b. Increases cholesterol saturation of bile (thus lack of E2 leads to gallbladder stone).
   c. Increases blood pressure via increased synthesis of renin substrate.
   d. Increases synthesis of clotting factors, increased # of platelets and platelet aggregation.
   e. Decreases bone resorption; physiological role in bone remodeling.

3. **Higher CNS functions**:
   a. Positive effects on mood, cognition, memory.
   b. 'Neuroprotective "effects: protective against damage from ischemia, neurodegenerative disorders.

## E. PHARMACOKINETICS:

1. Biological Activity: E2 > E1 >>> E3.
2. Well absorbed from GI tract and transdermally; substantial first pass metabolism of estrogens in liver after oral administration.
3. E2 is metabolized mainly to E1 and conjugated; E2 is more rapidly metabolized than the analogues used clinically (e.g. ethinyl E2).
4. Pharmacokinetic drug interactions:
   a. Agents that induce cytochrome P450 enzymes can enhance metabolism and Interfere w/ therapeutic actions (e.g., unwanted pregnancies). Examples: rifampin, phenytoin, carbamezepine, phenobarbital, topiramate, St. John's Wort.
   b.Some antibiotics (penicillin, tetracycline) may reduce bioavailability by altering intestinal flora.

## F. CLINICAL USES OF ESTROGENS:

1. As a component of OC; mainly ethinyl estradiol.
2. In HRT during menopause (Premarin ® most widely used).
3. HRT for hypogonadism in women.
4. Rx of dysmenorrhea, dysfunctional uterine bleeding (oligomenorrhea) and some amenorrheic states; perimenopause.
5. Rx of delayed puberty.
6. Rx of acne (Ortho-Tri-Cyclen ®; Estrostep ®).

## F.1 ESTROGEN PREPARATIONS:

- **Drug Description:**
  - Conjugated estrogens (e.g. Premarin).
  - Estradiol (e.g. Estrace and others).
  - Estradiol Transdermal (e.g. Climara, Estraderm, etc.).
  - Ethinyl Estradiol.
  - Diethylstilbestrol/DES (e.g. Stilphostrol).

**Drug Indication:**

- Vasomotor symptoms of menopause.
- Vulvar and vaginal atrophy.
- Female hypoestrogenism secondary to hypogonadism castration or primary ovarian failure.
- In combination with other therapeutic measures to retard bone loss and osteoporosis in post-menopausal women.

**Side Effects:**

- Nausea & vomiting
- Edema
- Headache
- Breast tenderness
- Venous thrombosis
- Breakthrough bleeding
- Estrogen alone (without progesterone) causes endometrial hyperplasia and possible endometrial carcinoma.
- Increased incidence of adenocarcinoma of the vagina in female offsprings of patients who have taken Diethylstilbestrol for advanced prostate cancer.

**Contraindication:**

- Breast & Endometrial cancers.
- Cerebral vascular coronary artery disease.
- Benign or malignant liver tumors.
- Sever hypertension.
- Pregnancy
- Female smokers over 35 years of age.
- Thrombotic disorders.

## F.2 CLINICAL USES OF SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMS):

**SERMS** are Estrogen antagonist in some tissues and estrogen agonist in other tissues. The basis for tissue selectivity may be related to tissue-specific expression of estrogen-receptor subtypes and the differential ability of the ligand-receptor complex to recruit transcriptional co-activators and co-repressors, and differential binding of transcription factors to receptor-ligand-.co-activators /co-repressors complex.

- **Drug Description:**
  Tamoxifen

**Drug Indications:**
Tamoxifen is used for prevention, palliative and as an adjuvant therapy for breast cancer.

**Mechanism of Action:**
It acts as an estrogen receptor antagonist in breast tissue and as a partial agonist in endometrium and bone.

**Side Effects:**
- Malignant neoplasma of endometrium
- Cataract,
- Pulmonary embolism
- Hot flashes
- Abnormal menstruation
- Vaginal discharge

**Contraindication:**
- History of deep vein thrombosis or pulmonary embolism
- Pregnancy

**Therapeutic Considerations:**
- Tamoxifen administration is associated with 4-6 fold increase in the incidence of endometrial cancer.
- Administered for no more than 5 years, to minimize the risk of endometrial cancer.

- **Drug Description:**
  Clomiphene

**Drug Indications:**
Used for female infertility due to ovulatory disorder

**Mechanism of Action:**
An estrogen receptor antagonist in hypothalamus and pituitary gland, and partial agonist in ovaries; disinhibits GnRH release and increases the level of LH and FSH. The increased FSH stimulates follical growth, LH surge and ovulation.

**Side Effects:**
- Thromboembolism
- Ovarian cysts and hypertrophy
- Flushing and vasomotor symptoms
- Abdominal discomfort

**Contraindication:**
- Pregnancy
- Thyroid or adrenal dysfunction
- Liver disease
- Endometrial carcinoma
- Ovarian cysts
- Organic intracranial lesion

**Therapeutic Considerations:**
Unlike exogenous FSH, clomiphene use is rarely associated with the ovarian hyperstimulation syndrome.

- **Drug Description:**
  Raloxifene

**Drug Indications:**
Osteoporosis prevention and treatment

**Mechanism of Action:**
Estrogen receptor agonist in bone and estrogen receptor antagonist in uterus and breast

**Side Effects:**
- Retinal vascular occlusion
- Venous thromboembolism
- Hot flashes
- Leg cramps

**Contraindication:**
- Pregnancy
- History or presence of venous thromboembolism

**Therapeutic Considerations:**
Decreases risk of invasive breast cancer in postmenopausal women with osteoporosis

## F.3 CLINICAL USE OF ESTROGEN RECEPTOR ANTAGONIST:

- **Drug Description:**
  Fulvestrant

**Drug Indications:**
Treatment of estrogen receptor positive metastatic breast cancer in postmenopausal women with disease progression following anti-estrogen therapy.

**Mechanism of Action:**
Competitively inhibit estrogen binding to receptor, blocking the action of estrogen on target tissues.

**Side Effects:**
- Nausea
- Asthenia
- Pain
- Vasodilation (hot flashes)
- Headache

**Contraindication:**
Pregnancy

**Therapeutic Considerations:**
Pure estrogen receptor antagonist with no agonist activity

## F.4 CLINICAL USE OF AROMATASE INHIBITORS:

- **Drug Description:**
  - Anastrozole
  - Letrozole
  - Exemestane
  - Formestane

**Drug Indications:**
Treatment and prevention of estrogen receptor positive early-stage, locally advanced, and metastatic breast cancer

**Mechanism of Action:**
Anastrozole and Letrozole are competitive inhibitors of aromatase, the enzyme that catalyzes the formation of estrogens from androgen precursors (i.e. androstenedione). Exemestane and Formestane are irreversible (covalent) inhibitors of aromatase.

**Side Effects:**

- Osteoporotic fractures
- Thrombophlebitis
- Hypercholesterolemia
- Profuse vaginal bleeding
- Peripheral edema
- Rash
- Nausea
- Arthralgia
- Bone pain
- Headache
- Depression
- Dyspnea

**Contraindication:**

Hypersensitivity to all aromatase inhibitors

**Therapeutic Considerations:**

- Aromatase inhibitors may be more effective than SERMs for the treatment of breast cancer.
- Extreme suppression of estrogen action could lead to high risk of osteoporotic fractures in women taking aromatase inhibitors.

## II. PROGESTINS: PHYSIOLOGY AND PHARMACOLOGY

The naturally occurring progestin is progesterone. There are several synthetic progestins and they are not a uniform group of compounds. A new group of third generation of synthetic progestins has also been introduced principally as components of oral contraceptives (e.g. Desogestrel, Norethynodrel, etc).

### A. PHYSIOLOGICAL ACTIONS OF PROGESTERONE:

1. Neuroendocrine regulation of the menstrual cycle; esp. negative feedback during luteal phase.
2. Transforms estrogen-primed proliferative uterine endometrium to secretory endometrium; essential for implantation of fertilized ovum (nidation).
3. Transforms cervical mucus to thick and viscous (inhibits sperm transport).
4. Increase in body temperature (0.5-1.0° F) at ovulation and during luteal phase.
5. Essential for maintenance of pregnancy; Inhibits uterine contractility during pregnancy, and also suppresses immune responses.
6. Stimulates development of mammary gland in preparation for lactation.
7. Antagonizes some, but enhances other, actions of estrogens.

### B. PHARMACOKINETICS OF PROGESTINS

Similar to the estrogens

### C. CLINICAL USES OF PROGESTINS

1. As OC alone, or a component of OC.
2. In HRT during menopause (mainly medroxyprogesterone) for endometrial protection.
3. Rx of oligomenorrhea or amenorrhea.
4. Rx of polycystic ovary syndrome.
5. Rx of endometriosis.

### D.PHARMACOLOGY OF ORAL CONTRACEPTIVES:

**Three Major Types:**

- Progestin-Only
- Combination (COCs)
- Emergency

### D.1 Clinical use of Progestin-Only Contraceptives:

- **<u>Drug Description:</u>**
- Norgestrel
- Norethindrone
- Medroxyprogesterone acetate (injectable)
- Etonogestrel (implant)

**Drug Indications:**
Contraception

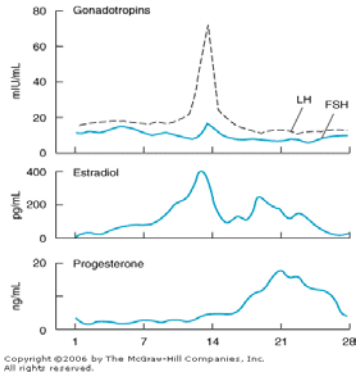
**Mechanism of Action:**
Alter frequency of GnRH pulsing and decrease anterior pituitary gland responsiveness to GnRH. Secondary mechanisms of pregnancy prevention include alterations in tubal peristalsis, endometrial receptivity, and cervical mucus secretions, which together prevent the proper transport of both egg and sperm.

**Side Effects:**
- Irregular periods
- Breast tenderness
- Nausea
- Dizziness
- Headaches

**Contraindication:**
- Acute liver disease
- Benign or malignant liver tumors
- Known or suspected breast cancer
- Pregnancy

**Therapeutic Considerations:**
During spotting, irregular and light menstrual periods: Medroxyprogesterone acetate can be given parenterally every 3 months. Etonogestrel (implant) is effective for 3 years, and Levonorgestrel (orally) can be used in case of emergency contraception.

**KEY CONCEPTS ON COCs**



- COCs consist of an estrogen, usually EE, and a progestin, usually a 19-nortestosterone agent. The classic regimen is 21 days on/7 days placebo.
- Efficacy: approx. 0.1% incidence of accidental pregnancy in 1st year.
- Mechanism: primarily negative feedback on gonadotropin secretion; progestin may thicken cervical mucus.

## D.2 Clinical use of Estrogen-Progestin (combination) Contraception:

- **Drug Description:**
  ***Estrogens:*** Ethinyl estradiol, Mestranol
  ***Progestins:*** Norgestrel, Levonorgestrel, Norethindrone, Norethindrone acetate, Ethynodiol, Norgestimate, Gestodene, Desogestrel, Drospirenone

**Combinatin OC Examples:**
EE + norgestrel (Lo/Ovral 28®)
EE + drospirenone **(**Yasmin ®)

**Drug Indications:**
Contraception

**Mechanism of Action:**
Supress GnRH, LH and FSH secretion and follicular development, thereby inhibiting ovulation; secondary mechanisms of pregnancy prevention include alterations in tubal peristalsis, endometrial receptivity and cervical mucus secretions which together prevent the proper transport of both egg and sperm.

**Side Effects:**
- Arterial and venous thromboembolism
- Pulmonary embolism
- Cerebral thrombosis
- Gallbladder disease
- Hypertension
- Hepatic neoplasm
- Abnormal menstruation
- Breakthrough bleeding
- Breast tenderness
- Bloating symptoms
- Migraine
- Weight change

**Contraindication:**
- Breast cancer
- Endometrial cancer or estrogen-dependent neoplasm.
- Cerebral vascular or coronary artery disease.
- Cholestatic jaundice of pregnancy or jaundice with prior hormonal contraceptive use.
- Benign or malignant liver tumors

- Severe hypertension
- Prolonged immobilization
- Pregnancy
- Female smokers over 35 years of age
- Thrombotic disorders

**Therapeutic Considerations:**

- Progestins vary in their androgenic activity.
- Norgestrel and levonorgestrel have the highest androgenic activity.
- Norethindrone and norethindrone acetate have medium androgenic activity.
- Ethynodiol, norgestimate, gestodene and desogestrel have low androgen receptor cross reactivity.
- Drospirenone is a synthetic progestin which has anti-androgenic activity.
- Combination estrogen-progestin contraceptives are available in various forms in the market, like oral tablets, vaginal rings, transdermal patches.
- Levonorgestrel is used as morning-after contraception.
- Lowest effective dose of ethinyl estradiol is preferred to reduce the risk of deep vein Thrombosis. In a woman with uterus, estrogen is always coadministered with a progestin, to avoid risk of endometrial cancer due to estrogen alone.

### D.3 Clinical use of Progesterone Receptor Antagonist:

- **Drug Description:**
  Mifepristone (RU-486)

**Drug Indications:**
Abortion (through day 49 of pregnancy)

**Mechanism of Action:**
Inhibits progesterone binding to receptor

**Side Effects:**

- Prolonged bleeding time
- Bacterial infections
- Sepsis
- Nausea
- Vomiting
- Diarrhea
- Cramps
- Headache

**Contraindication:**

- Chronic adrenal failure
- Ectopic pregnancy
- Hemorrhagic disorders
- Anticoagulation therapy
- Inherited porphyrias

- Intrauterine device
- Undiagnosed adnexal mass

**Therapeutic Considerations:**

- Commonly administered in conjunction with misoprostol, a prostaglandin analogue that stimulates uterine contractions; co-administration of misoprostol can cause nausea and vomiting.
- Higher concentration of mifepristone also blocks the glucocorticoid receptors.

## D.4 EMERGENCY (morning after) CONTRACEPTION:

- Refers to use of medication to prevent unwanted pregnancy after unprotected intercourse/post-coital.
- Historically estrogen-progestin combination therapy was in practice; which was not approved by FDA.
- FDA has now approved use of two doses of "minipill" (0.75mg of levonorgestrel), separated by 12 hrs.
- Levonorgestrel is a potent progestin that can block the LH surge, disrupting normal ovulation, and produce endometrial changes for implantation.
- The first dose should be taken anytime within 72 hrs after intercourse and second dose after 12 hrs of first dose.

**ADVERSE EFFECTS:**

- Nausea/vomiting
- Headache
- Dizziness
- Mastalgia

**SUGGESTED MECHANISMS:**

- Inhibition of ovulation via strong negative feedback
- Impairment of sperm transport
- Interference w/ endometrial receptivity

## D.5 HORMONE REPLACEMENT THERAPY IN MENOPAUSE:

"Menopause is not a disease, but it does have serious clinical sequel."- R. Lobo, 1999

**Physiology of Menopause**: defined (retrospectively) as the last menstruation; diagnostically if one year since last menses and plasma FSH > 25 mIU/ml. Avg. age in U.S. fitting this definition: 51 yrs w/ large variation; range 40-58 years.

1. Physiological basis: exhaustion of supply of ovarian follicles, loss of cells that secrete estradiol, progesterone; estradiol reduced to castrate levels; less active estrone from conversion of androgens; removal of negative feedback elevates the gonadotropins, no cycles.
2. Perimenopause: transition to menopause, early onset of symptoms, esp. vasomotor, insomnia, mood changes, irregular cyclicity; may begin in late 30's, early 40's.

**KEY CONCEPT**: **Most adverse events in menopause result from estrogen deficiency.**

| **Early symptoms** | **Physical changes (intermediate)** | **Disease development (Longer term)** |
|---|---|---|
| Vasomotor instability (70%) | Urogenital atrophy (60%) | Osteoporosis |
| Insomnia (55%) | Urinary incontinence | Cardiovascular disease (?) |
| Fatigue (90%) | Recurrent genital tract infection | Dementias (?) |
| Mood changes (90-95%) | Skin atrophy, loss of collagen | |

(% reporting)

**Major indications for HRT in menopause:**

1. vasomotor instability (hot flashes or flushes, night sweats)
2. mood changes
3. urogenital atrophy
4. prevention and Rx of osteoporosis

**HRT preparations commonly used:**

1. conjugated equine estrogens (Premarin®, Cenestin ® ), usually 0.625 mg/day, po
2. micronized estradiol (Estrace®), po
3. E2-17ß in skin patch (Vivelle®)
4. Medroxyprogesterone (Provera®, Cycrin®), po
5. Combination products: Prempro®, Premphase ®: Premarin ® plus Cycrin ®, po
   - CombiPatch®: transdermal E2-17ß plus norethindrone

**Effects of HRT:**

1. Relief from vasomotor symptoms; urogenital atrophy and recurrent urinary symptoms
2. Relief from fatigue, depression
3. Maintenance of bone mineral density

**Common adverse effects of HRT:**

**KEY CONCEPTS**: Biological activities of estrogens used in HRT are generally lower than in OCs. The absolute and relative contraindications to estrogen use are similar to those for OCs.

1. estrogen component assoc w/ nausea, mastalgia, headache, fluid retention
2. progestin component assoc w/ weight gain, headache

**HRT and Cancer:**

1. **Endometrial cancer**: Unopposed estrogen taken for 5 years increases the risk of endometrial hyperplasia and cancer by 5-fold , and by 8-fold if taken for longer than 5 years. Risk is nearly eliminated by addition of progestin.
2. **Breast Cancer**:
   a. Little or no increased risk for HRT < 5 yrs
   b. Women's Health Initiative reports relative risk (RR) of 1.26 for approx. 5 years of HRT, and perhaps decreased with ERT
   c. HRT for 10-15 yrs RR ~1.3, from U.S. studies
   d. Results from the Million Women Study (UK) (see Lancet 362: 414-427, 2003):

   1. Overall relative risk for breast cancer incidence in current users vs. never-users was 1.66.
   2. Overall relative risk of breast cancer death was 1.22, same comparison.
   3. Risk increase with duration of use.
   4. No risk for past users.
   5. Risk was higher in estrogen+progestin vs. estrogen alone; Progestin component now believed to contribute significantly.
   6. No differences continuous v. sequential regimens or specific compounds; no difference oral vs. transdermal.

# PHARMACOLOGY OF GONADAL HORMONES: ANDROGENS

**Date:** Tuesday, March 23, 2015 – 10:30 am
**Reading Assignment:** Katzung Chapter 40

## KEY CONCEPTS & LEARNING OBJECTIVES

A. To describe the physiological actions, pharmacological effects, and clinical uses of androgens.
B. To describe the adverse effects and contraindications to use of androgens.
C. To discuss the pharmacology and clinical uses of androgen antagonists.

**Drugs/Hormones Discussed:**

| **Androgens and related** | |
|---|---|
| Testosterone<br>Dihydrotestosterone<br>Methyltestosterone<br>17α-ethinyltestosterone (Danazol)<br>Finasteride (inhibitor of DHT conversion)<br>Flutamide, Spironolactone (AR antagonist) | |

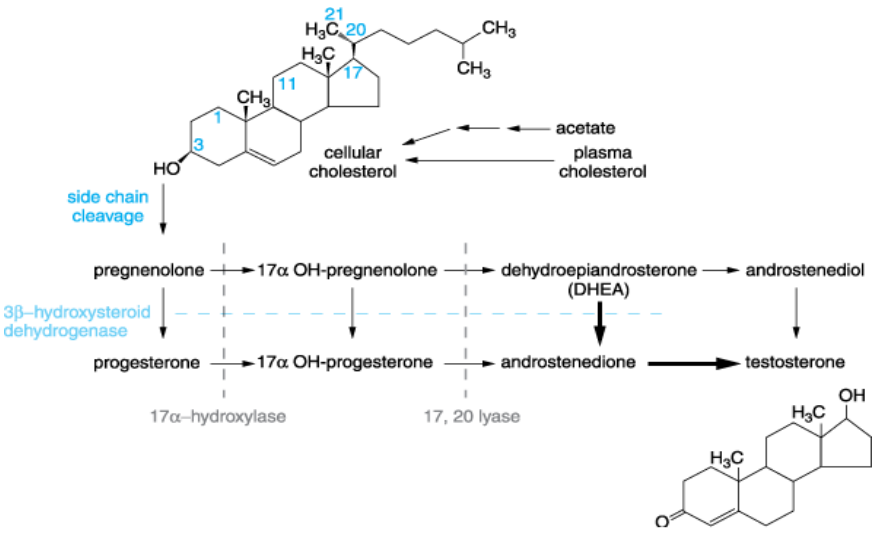
**Gonadal Hormones:**
- Estrogens
- Progestins
- **Androgens**

## III.ANDROGENS: PHYSIOLOGY AND PHARMACOLOGY

**NATURAL ANDROGENS:**
- Testosterone
- Dihydrotestosterone (DHT)
- Androstenedione
- Dehydroepiandrosterone (DHEA)

**SYNTHETIC ANDROGENS: Many**

## A. ANDROGEN SYNTHESIS:






## B. BASIC MECHANISM OF ACTION OF ANDROGENS:

1. Testosterone diffuses into cell and binds to intracellular androgen receptor **OR** is converted to dihydrotestosterone, which binds to androgen receptor, **OR** is converted to estradiol, which binds to estrogen receptor.
2. Hormone-receptor complex dimerizes in cell nucleus and binds to specific hormone-response elements on DNA, along with a complex of co-activator or co-repressor proteins.
3. This promotes or inhibits transcription of specific genes, resulting in physiologic effect.

## C. PHYSIOLOGICAL ACTIONS OF ANDROGENS:

1. **Reproductive actions**:
    a. Growth, development and maintenance of primary (genitalia and genital tract) and secondary sex characteristics in men.
    b. Early stages of breast and pubertal development in girls (adrenarche).
    c. Promote spermatogenesis (with FSH).
    d. Neuroendocrine regulation of gonadotropin secretion.
    e. Stimulate libido.

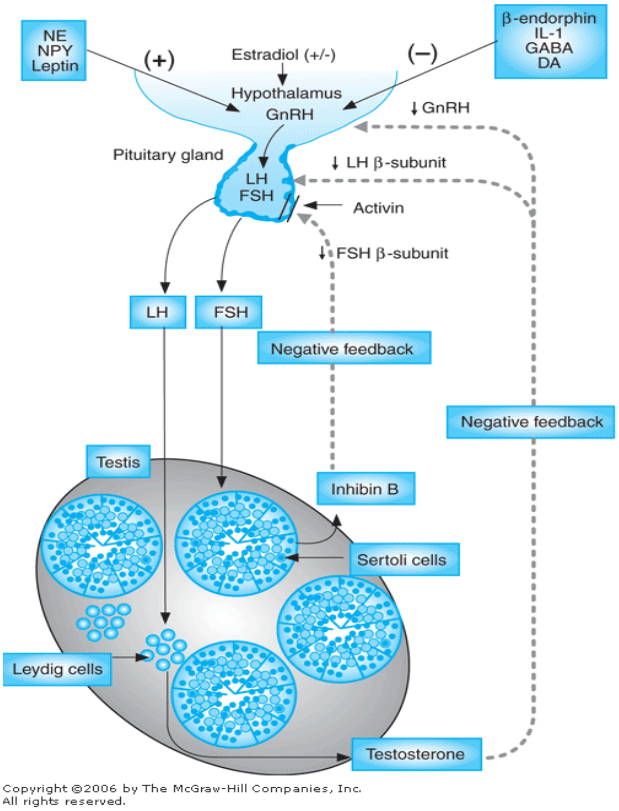
2. **Anabolic actions**:
    a. Increase protein synthesis, increased lean body mass, and body growth.

3. **Effects on growth**:
    a. Skeletal growth and closure of epiphyses of long bones during puberty and adolescence.
    b. Growth of larynx and voice deepening at puberty

4. **Metabolic/hematologic actions**:
    a. Erythropoiesis
    b. Decreased synthesis of several clotting factors
    c. Increased sebum production in skin
    d. Decrease synthesis of HDL cholesterol, increase synthesis of LDL-cholesterol
    e. Androgenic alopecia (male pattern baldness)
    f. Increases bone density

## D. THE HYPOTHALAMIC-PITUITARY-GONADAL AXIS IN MALES:

1. T secreted from interstitial (Leydig) cells exerts negative feedback on hypothalamus and pituitary to inhibit LH secretion.
2. T exerts paracrine effects in the seminiferous tubules along with FSH to promote Spermatogenesis.
3. Inhibin secreted from Sertoli cells (support cells within the tubules for spermatogenesis) exerts selective inhibition over FSH secretion.



## E. CONSEQUENCES OF ANDROGEN DEFICIENCY IN MEN:

1. Decreased libido; erectile dysfunction
2. Decreased lean muscle mass; increased adipose tissue mass
3. Decreased axillary and pubic hair
4. Anemia
5. Osteoporosis
6. Decreased energy, sense of well being

## F. THERAPEUTIC USES OF ANDROGENS:

- HRT in primary or secondary hypogonadism
- Induction of puberty in delayed maturation
- Rx of osteoporosis in males

### F.1 Clinical use of Androgens in HRT:

- **Drug Description:**
- Testosterone enanthate
- Testosterone cypionate

**Drug Indications:**
Hypogonadism

**Mechanism of Action:**

- Replacement of testosterone produces androgenic effects, such as:

a) Growth and maturation of prostate
b) Seminal vesicles
c) Penis & Scrotum
d) Development of male hair distribution
e) Laryngeal enlargement
f) Vocal cord thickening
g) Alterations in body musculature, and
h) Fat distribution

**Side Effects:**

- Cholestatic jaundice sundrome
- Liver carcinoma
- Benign prostatic hyperplasia
- Prostate cancer
- Gynecomastia
- Acne
- Headache

**Contraindication:**

- Breast cancer in men
- Prostate cancer
- Pregnancy when used in women

**Therapeutic Considerations:**

- Various delivery routes and formulations available: intramuscular, transdermal, topical gel and oral. The transdermal is preferred to prevent first-pass hepatic metabolism.
- Androgen HRT for men with consistent symptoms of hypogonadism.

**F.2 Clinical uses of Androgen Receptor Antagonists:**

- **Drug Description:**
  Flutamide

**Drug Indications:**

- Metastatic prostate cancer
- Benign prostatic hypertrophy

**Mechanism of Action:**

Competitive inhibition of dihydrotestosterone & testosterone binding to the receptor.

**Side Effects:**

- Hepatotoxicity
- Hematopoietic disorders
- Diarrhea
- Nausea
- Rash
- Hot Flashes

**Contraindication:**

Severe hepatic impairment

**Therapeutic Considerations:**

- Flutamide is comparatively better than DES and leuprolide in treatment of prostate cancer.
- Excellently effective when combined with medical or surgical castration.

**F.3 Clinical uses of Androgen Receptor Antagonists:**

- **Drug Description:**
  Spironolactone

**Drug Indications:**

- Hirsutism
- Hypertension
- Acne vulgaris
- Edema associated with heart failure
- Cirrhosis or nephrotic syndrome
- Hypokalemia
- Primary aldosteronism

**Mechanism of Action:**
Competitive inhibition of dihydrotestosterone & testosterone binding to the receptor

**Side Effects:**
- Gastrointestinal hemorrhage
- Hyperkalemic metabolic acidosis
- Agranulocytosis systemic lupus erythematosus
- Gynecomastia
- Dyspepsia
- Lethargy
- Abnormal menstruation
- Impotence
- Rash
- Breast cancer – not yet established

**Contraindication:**
- Anuria
- Hyperkalemia
- Acute renal insuffiency

**Therapeutic Considerations:**
An aldosterone receptor antagonist but also acts as an androgen receptor antagonist.

### F.4 Clinical use of Inhibitors of Peripheral Testosterone Conversion to DHT:

- **Drug Description:**
  Finasteride

**Drug Indications:**
- Benign prostatic hyperplasia
- Androgenic alopecia

**Mechanism of Action:**
Selective inhibition of type II 5 α-reductase, the enzyme responsible for conversion of testosterone to dihydrotestosterone in prostate, liver & skin.

**Side Effects:**
- Neoplasm of male breast (rare and not yet investigated)
- Breast tenderness
- Decreased libido
- Erectile dysfunction
- Ejaculatory disorder

**Contraindication:**
- Known or suspected pregnancy

- Women and children

**Therapeutic Considerations:**

- Improves urine flow
- Can be used as alternative to transurethral resection of prostate (TRUP).
- Upto 25% reduction in prostate size when consistently used for one year.
- Most effective in patients with large prostates.
- Women should not be treated with finasteride.

# Drugs used to treat Diabetes I and II

**Date: Diabetes I/II Wednesday March 23rd, 9:30-11:30am**

**Optional reading assignment: Katzung Chapter 41 p743**

## Key Concepts and Learning Objectives

1. Describe the fundamental differences between type 1 and type 2-diabetes.

2. List the current diagnostic criteria and therapeutic goals for the treatment of diabetes.

3. Explain the pharmacological differences between the various insulin formulations used in the treatment of diabetes, especially their duration of action and how this affects their influence on the control of postprandial glucose levels versus fasting glucose levels.

4. Explain the biological effects of insulin therapy on muscle, liver and adipose tissue

5. Discuss the relative benefits and disadvantages between a conventional and intensive insulin therapy regimen.

6. Identify the major adverse effects of insulin therapy and the therapeutic approaches to treat this condition

7. List the indications, contraindications and clinical uses for each of the major classes of hypoglycemic agents used in the treatment of type-2 diabetes.

8. Describe the mechanism of action and physiological effects of each of the major classes of hypoglycemic agents, especially their effects on fasting versus post-prandial glucose levels.

9. List the major adverse effects associated with each of the major classes of hypoglycemic agents

10. Discuss the use of combination hypoglycemic drug therapy including the use of insulin in the treatment of type-2 diabetes

11. Apply your knowledge of the pharmacology of the major classes of hypoglycemic drug agents to select the most appropriate medication for a specific patient based upon patient-specific criteria

## Drugs to be covered in this lecture:

## 1. Insulin Formulations

**Rapid acting insulin**
- Insulin aspart (Novolog®)
- Insulin lispro (Humalog®)
- Insulin glulisine (Apidra®)

**Regular Insulin**
- Regular Insulin (Humulin R®, Novolin R®)

**Intermediate-acting insulin**
- NPH Insulin (Humulin N®, Novolin N®)

**Long-lasting insulin**
- Insulin detmir (Levemir®)
- Insulin glargine (Lantus®)

## 2. INSULIN SECRETAGOGUES

**SULFONYLUREAS**

1st Generation:
- Chlorpropamide (Diabinese®),
- Tolbutamide

2nd Generation:
- Glimepiride (Amaryl®)
- Glyburide (DiaBeta®, Micronase®)
- Glipizide (Glucotrol®)

**MEGLITINIDES**
- Repaglinide (Prandin®)
- Nateglinide (Starlix®)

## 3. INSULIN SENSITIZERS

**BIGUANIDES**
- Metformin (Glucophage®)

**THIAZOLIDINEDIONES**
- Pioglitazone (Actos®)
- Rosiglitazone (Avandia®)

## 4. Incretin mimetics/modulators
- Exenatide (Byetta®)
- Liraglutide (Victoza®)
- Sitagliptin (Januvia®)
- Saxagliptin (Onglyza®)

## 5. INHIBTORS OF CARBOHYDRATE DIGESTION

**ALPHA-GLUCOSIDASE INHIBITORS**
- Acarbose (Precose®)
- Miglitol (Glyset®)

## 6. SGLT2 inhibitors
- Canagliflozin (Invokana®)
- Dapagliflozin (Farxiga®)

## 7. Bromocriptine (Cycloset®)

## 8. Bile acid binding resin
- Colesevelam (Welchol®)

## 9. Amylin homolog
- Pramlintide (Symlin®)

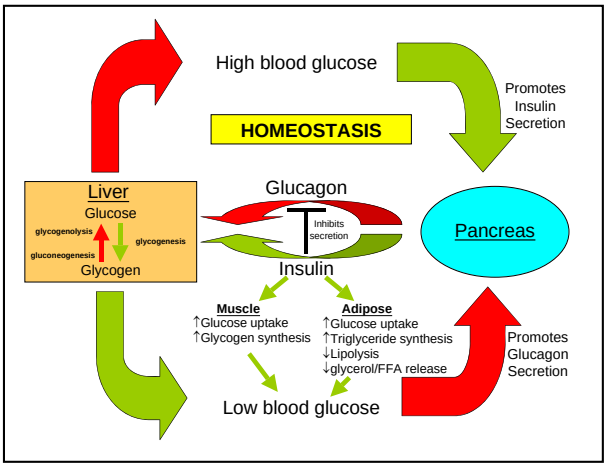
# *1. DIABETES MELLITUS*

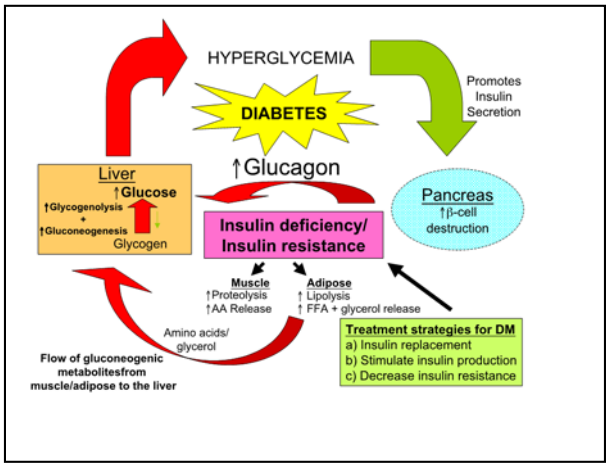
a) Diabetes Mellitus is a metabolic disorder that is characterized by hyperglycemia caused by either a defect in insulin production, insulin action, or a combination of the two.

b) Chronic hyperglycemia is associated with long-term damage, dysfunction and failure of various organs including the eyes, kidneys, nerves, heart and blood vessels.

| | **Type 1** | **Type 2** |
|---|---|---|
| **Defect** | Autoimmune destruction of pancreatic beta cells | Insulin resistance with progressive loss of pancreatic beta cell function |
| **Insulin levels** | zero | Typically higher than normal |
| **Insulin resistance** | No | Yes |
| **Age of onset** | Typically < 30yrs | Typically > 40yrs |
| **Nutritional status at time of onset** | Undernourished | Typically obese |
| **Frequency** | 10-20% | 80-90% |
| **Genetic predisposition** | moderate | strong |
| **Acute complications** | Ketoacidosis/wasting | Hyperglycemia |
| **Chronic complications** | Neuropathy, Retinopathy Nephropathy, CVD, Peripheral vascular disease, Lower extremity amputations | Same as type 1 |
| **Treatment** | Insulin replacement | Oral hypoglycemics/insulin |

## Regulation of glucose levels during homeostasis and Diabetes



## 2. DIAGNOSIS AND GOALS OF DIABETES THERAPY

***Symptoms of diabetes:*** polyuria, polydipsia, unexplained weight loss + polyphagia, blurred vision, and a causal plasma glucose concentration > 200mg/dL or FPG of > 126mg/dL.

| | Normal | Pre-diabetes IFG/IGT | Diabetes | Treatment Goal |
|---|---|---|---|---|
| **Fasting plasma glucose** | **<100 mg/dL** | 100-125 mg/dL | **>126 mg/dL** | **90-130 mg/dL** |
| **2hr Peak postprandial plasma glucose** | **<140 mg/dL** | 140-199 mg/dL | **>200 mg/dL** | **<180 mg/dL** |
| **Glycated hemoglobin (HbA1c)** | **<6.0%** | | **>6.5%** | **<6.5%** |

***Treatment Goals:*** To achieve and maintain glycemic levels as close to the non-diabetic range as possible in order to prevent the development of complications of chronic diabetes.

## *3. DRUGS TO TREAT TYPE 1 DIABETES*

### Insulin

a) Insulin replacement therapy is the only treatment available for patients with type 1-diabetes.
b) Commercially available insulin preparations are available in a variety of formulations that differ based upon their time of onset, peak activity and duration of action.

| | Formulation | Onset | Peak | Duration | Usage |
|---|---|---|---|---|---|
| **Rapid-acting**<br>Insulin aspart<br>Insulin lispro<br>Insulin glulisine | Amino acid substituted insulin variants that are monomeric for faster absorption | 5-15 mins | 45-75mins | 2-4 hrs | For meals or acute Hyperglycemia; Can be injected immediately before meals |
| **Regular Insulin** | Zinc ions added for stability; forms hexamers that dissociate into monomers prior to absorption | 30-60 mins | 2-4 hrs | 6-8 hrs | For meals or acute Hyperglycemia; Needs to be injected 30-45 mins prior to meal |
| **Intermediate acting**<br>NPH Insulin | Conjugated with protamine peptide which delays absorption until it is proteolytically cleaved by endogenous tissue proteases | 1.5-2 hrs | 6-10 hrs | 16-24 hrs | Provides basal insulin And overnight coverage |
| **Long acting**<br>Insulin glargine | Amino acid substituted insulin variant that forms large ppt at body pH and is slow to be absorbed | ~2 hrs | No Peak | 20->24 hrs | Provides basal insulin And overnight coverage |
| Insulin detmir | Insulin with fatty acid side chain that associates with tissue bound albumin that slows its absorption | ~2 hrs | No Peak | 6-24 hrs | |

**Mechanism of Action.**

a) Insulin acts through its plasma membrane cell surface receptor
b) Insulin corrects hyperglycemia by:
(i) promoting glucose uptake in muscle, liver and adipose
(ii) inhibiting hepatic glucose production (gluconeogenesis/glycogenolysis)
(iii) inhibiting the flow of gluconeogenic precursors from muscle/adipose to the liver
(iv) inhibiting the secretion of the counter-regulatory hormone glucagon

**Insulin Administration**

a) Subcutaneous injection with syringe: upper arms, upper legs, abdomen (most effective), and buttocks-sites of injection should be rotated to avoid injection site lipodystrophy
   - Initial dose 0.2-0.6 units/kg/day in divided doses
   - Typically 50-75% of dose is given as intermediate/long-acting insulin and the remainder is administered as rapid-acting or short acting insulin at meal times
b) Continuous subcutaneous insulin pump (regular insulin or rapid-acting insulin)
c) Inhaled Insulin (Exubera®; powder formulation of rapid-acting insulin)
   - As effective as regular insulin in type 1 and type 2 diabetes
   - NOW DISCONTINUED due to poor patient adoption

**Adverse reactions**

Hypoglycemia, tachycardia, fatigue, mental confusion, Injection site lipodystrophy, diapheresis, and hypersensitivity (less common with human insulin).

**Drug Interactions.**

a) Drugs which DECREASE hypoglycemic effect of insulin: oral contraceptives, corticosteroids, dlitiazem, niacin, ephinephrine, thiazide diuretics, Ca2+ channel blocker, beta2-adrenergic agonists and HIV protease inhibitors.
b) Drugs that INCREASE hypoglycemic effect of insulin: alcohol, beta-blockers, salicylates, lithium, sulfonamides and tetracylines

**<u>Hypoglycemia</u>**

a) Blood glucose levels < 60 mg/dL
b) Potentially fatal if not promptly treated
c) Caused by lack of glucose availability to the brain and CNS

<u>Symptoms</u>

*Mild Hypoglycemia:* Tremor, palpitations, sweating and intense hunger

*Moderate hypoglycemia:* Headache, mood changes and irritability, decreased attention, drowsiness, Patients may require assistance to help themselves

*Treatment*- oral dose of a simple carbohydrate

*Severe hypoglycemia:* Unresponsiveness, Unconciousness, convulsions, prolonged severe hypoglycemia can result in death, patients require assistance.

*Treatment.* Either IV glucose or IV/IM GLUCAGON (stimulates release of glucose from liver.

## Insulin Therapy Regimens

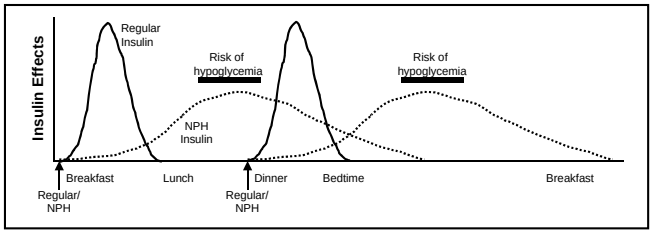
**Goal -** To achieve near normaoglycemia, which has been demonstrated in clinical trials to prevent and/or slow the onset of diabetic complications
- Achieving normoglycemia requires the administration of multiple doses of insulin every day

| **Glycemic Goals:** | | |
|---|---|---|
| | Fasting blood glucose | 90-120 mg/dL |
| | 2hr Postprandial BG | <180 mg/dL |
| | HA1c | <6.5% (higher value in those with significant hypoglycemia risk) |

**Typical Insulin dose:** 0.5-0.8 units/kg/day in a divided dose split between a basla insulin (50-75% of total) and pre-prandial insulin

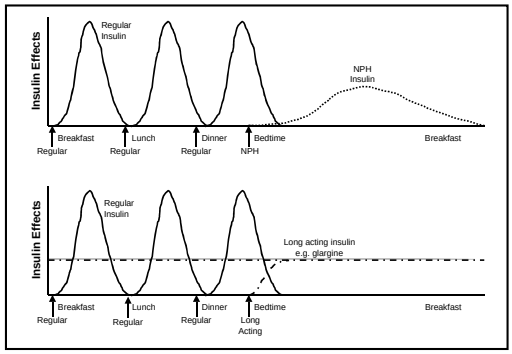
### (A) Conventional Insulin Therapy

a) A simple non-physiological insulin regime consisting of either a single or two daily injections of insulin usually a mixture of regular or rapid acting insulin together with intermediate (i.e. NPH) insulin given in fixed amounts in the same syringe before breakfast and dinner
b) Convenient, but will not adequately control glycemia
c) NOT recommended unless patient cannot or will not comply with an intensive insulin regime




### (B) Intensive Insulin Therapy/Standard insulin therapy

a) Aims to provide a more physiological profile of insulin by administration of a basal level of insulin to lower fasting glucose (provided by daily or twice daily injections of long-acting insulin preparations e.g. NPH or glargine) together with pre-meal boluses of a rapid or very rapid acting insulin to control postprandial glucose elevations
b) The dose of the pre-meal bolus is determined by the ambient blood glucose level before the meal, the size and composition of the meal and anticipated activity levels.
c) Essentially near normal glycemia can be achieved using an intensive insulin regime
d) Significantly reduces the risk of diabetic complications
e) Recommended for the majority of type-1 patients




### *Drawbacks to intensive insulin therapy*

a) Greater effort required by patient
b) Incidence of hypoglycemia/coma is higher
c) Weight gain more likely
d) Cost (~3x conventional therapy)

# *4. DRUGS TO TREAT TYPE 2 DIABETES*

## 4.1 ORAL ANTI-DIABETIC DRUGS- INSULIN SENSITIZERS

### 4.1.1 BIGUANIDES

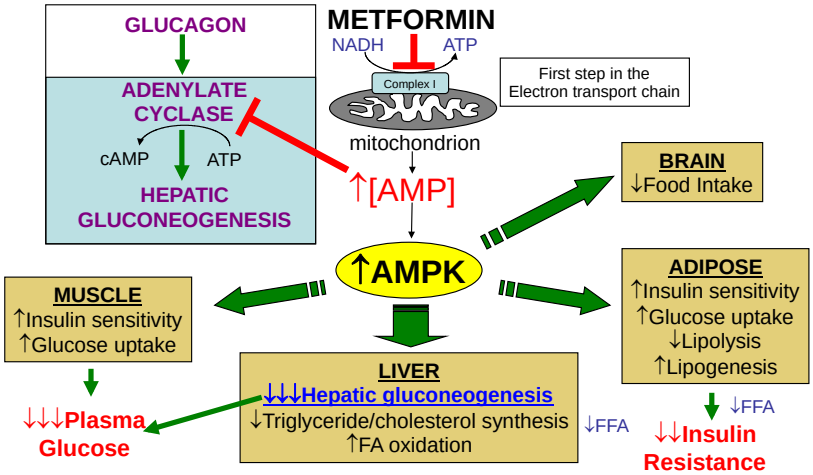
Metformin (Glucophage®)

#### 4.1.1A DESCRIPTION

a) An oral anti-hyperglycemic medication that acts to lower plasma glucose levels primarily by reducing hepatic glucose production.
b) Does NOT act by promoting insulin production
c) **Recommended** by ADA and EASD as **first line treatment** for type 2 diabetes concurrent with lifestyle changes, diet and exercise

#### 4.1.1B MECHANISM OF ACTION

a) Reduces hepatic glucose production by inhibiting both gluconeogenesis and glycogenolysis
b) Increases peripheral glucose uptake and utilization in muscle and fat tissues
c) Effective only in the presence of insulin
d) Acts by inhibiting complex I in the electron transfer chain of mitochondrion resulting in an increase in the cellular concentration of AMP that in turn:
    (i) Inhibits GLUCAGON-induced hepatogluconeogenesis by inhibiting the glucagons-induced activation of adenylate cyclase
    (ii) activates the AMP-dependent protein kinase (AMPK), an important metabolic enzyme involved in cellular and systemic energy homeostasis.
        - Activation of AMPK in muscle and adipose tissue promotes glucose uptake
        - Activation of AMPK in the liver inhibits hepatic glucose production, as well as inhibiting hepatic cholesterol and triglyceride biosynthesis (potentially explains favorable effects of metformin on lipid profiles and the development of CVD- see below).
        - AMPK activation promotes fatty acid oxidation, thereby reducing FFA stores that contribute towards the development of insulin resistance
        - AMPK activity inhibits the activity of inhibitors of the insulin signaling pathway thereby enhancing insulin signaling and preventing insulin resistance.



### 4.1.1C INDICATIONS AND CLINICAL USE

b) Approved for either monotherapy, or in combination with other oral hypoglycemic drugs, for the treatment/prevention of hyperglycemia in type 2-diabetes.
c) Metformin is rapidly absorbed from the small intestine, it is not metabolized and is secreted in the urine with a half life of 1.5-5 hrs. Peak plasma concentration is achieved in 2 hrs & the duration of its biological effect is ~ 6hrs
d) Primarily affects fasting blood glucose levels (i.e. inhibition of hepatic gluconeogenesis) rather than postprandial glucose increases.
e) Lowers fasting blood glucose by 20% and HbA1c by ~1.5% points
f) Does NOT cause WEIGHT GAIN and can even promote WEIGHT LOSS
g) Does NOT cause HYPOGLYCEMIA
h) Multiple clinical trials show that metformin treatment DECREASES the frequency of MI, diabetes-related death and all-cause mortality in type-2 obese patients compared to other oral hypoglycemic agents
i) Potential beneficial effect on CVD outcomes likely due to the effects of metformin on improving lipid profiles- decreased TG and FFA, small decrease in LDL, modest increase in HDL

### 4.1.1D ADVERSE EFFECTS

a) Generally well tolerated - only ~5% of patients discontinue due to adverse effects
b) Most common adverse effect is on the GI tract- metallic taste, nausea, diarrhea and abdominal pain, which are minimized by taking the drug with food.
c) Decreases absorption of Vitamin B12, although rarely causes megalobalstic anemia
d) Lactic Acidosis is a rare (<1:100,000), but potentially fatal complication
    - Most associated with use in high risk patients- esp RENAL INSUFFICIENCY
    - Symptoms- deep/rapid breathing, vomiting, abdominal pain, muscle weakness
    - Caused by a build up of lactate in the blood due to the fact that lactate is a substrate for hepatic gluconeogenesis, which is inhibited by metformin.
    - In normal circumstances lactate is cleared by the kidney, but in renal insufficiency the lactate levels increase causing acidification of the blood

N.B. phenformin an earlier biguanide was removed from the market because of increased frequency of lactic acidosis

### 4.1.1E CONTRAINDICATIONS

a) Women who are pregnant or that are lactating (insulin is the preferred treatment)
b) Impaired renal function, since both metformin and lactate are entirely cleared by the kidney and patients with decreased renal function are more susceptible to drug accumulation and lactic acidosis
c) Not to be given to the elderly >80 yrs due to renal insufficiency
d) Should be discontinued in patients injected with iodinated contrast agents for radiographic studies and not started until 48hrs later to avoid contrast-induced acute renal failure which can increase metformin levels- insulin used during this time period to control hyperglycemia
e) Conditions pre-disposing to lactic acidosis:
    - Congestive heart failure requiring drug therapy
    - Myocardial Infarction- immediate withdrawal
    - Impaired liver function/excessive alcohol consumption

- Impaired renal function
- Shock/septicemia
- Serious acute illness or hypoxic condition
- Hypoxic or ischemic states i.e. lung disease

## 4.1.2 THIAZOLIDINEDIONES

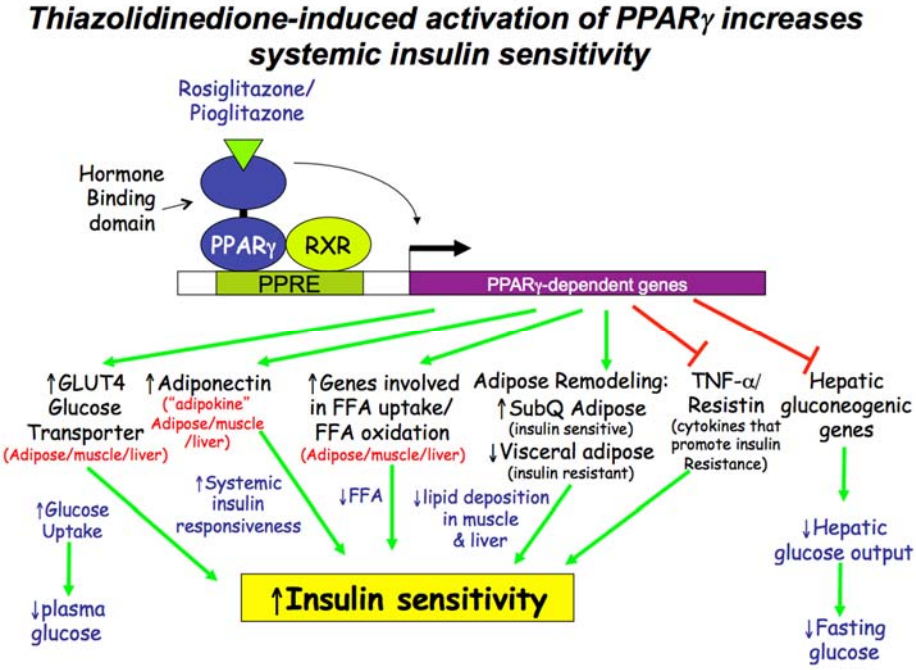
Pioglitazone (Actos®)
Rosiglitazone (Avandia®)

### 4.1.2A DESCRIPTION

"Insulin Sensitizers" that increase the sensitivity of adipose tissue, skeletal muscle and liver to endogenous insulin

### 4.1.2B MECHANISM OF ACTION

Thiazolidinediones act as agonists of the peroxisome proliferators-activated receptor gamma (PPARγ) transcription factor, which influences the expression of multiple genes involved in the regulation of insulin sensitivity.




Activation of PPARγ results in the:

(i) Increased expression of GLUT4- the insulin-sensitive glucose transporter
(ii) Increased expression of Adiponectin- an adipocytokine involved in promoting systemic insulin sensitivity
(iii) Increased expression of genes involved in FFA uptake and FFA oxidation, which acts to decrease serum FFA that has been implicated in promoting insulin resistance.
(iv) Decreased expression of the TNF-alpha cytokine involved in promoting insulin resistance

(v) Decreased expression of Resistin an adipocytokine involved in inhibiting systemic insulin sensitivity
(vi) Remodels adipose tissue: Reduces insulin-resistant visceral adipose tissue and increases the appearance of newly differentiated insulin-sensitive subcutaneous adipocytes.
(vii) Inhibits hepatic genes involved in gluconeogenesis
***Overall these effects act to improve systemic insulin sensitivity and lower plasma glucose levels.***

**4.1.2C INDICATIONS AND CLINICAL USE**

a) Approved for monotherapy or in combination with either metformin, sulfonylureas or insulin in the treatment of hyperglycemia in type 2-diabetes.
b) Typically decreases FPG with moderate effect on postprandial glucose
c) Decrease Hb1Ac by 0.5-1.4% points
d) Takes 6-14 weeks to achieve maximum effect

**4.1.2D ADVERSE EFFECTS**

a) Weight gain – mainly subcutaneous not visceral
b) Fluid retention resulting in peripheral edema
- Fluid retention is more common with concurrent insulin use
- Fluid retention caused by increased expression of gamma subunit of Na+ channel in the collecting tubule cells of the nephron leading to increased Na+ reabsorption
- Maybe related to increased risk of heart failure – BLACK BOX WARNING
c) Increased risk of bone fractures in women

**4.1.2E CONTRAINDICATIONS**

a) Should be used cautiously in patients with underlying liver disease- 1st Thiazolidinedione drug Troglitazone was removed from market due to increased fatalities due to liver failure
b) Heart Failure- should not be given to patients with Class III/Class IV cardiac disease
**c)** Not recommended for pregnancy (Insulin is preferred therapy)

## 4.2 ORAL ANTI-DIABETIC DRUGS: INSULIN SECRETAGOGUES

## 4.2.1 SULFONYLUREAS- INSULIN SECRETAGOGUES

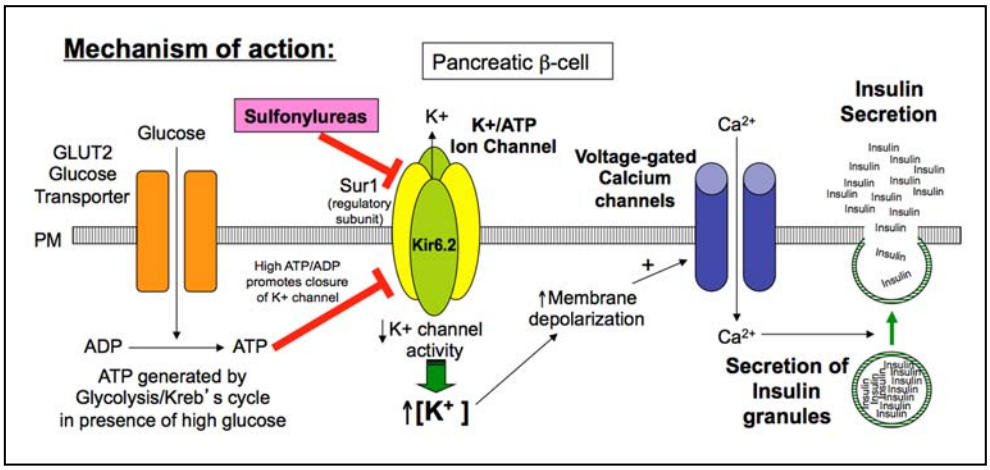
| 1st Generation: | 2nd Generation: |
|---|---|
| Chlorpropamide (Diabinese®), | Glimepiride (Amaryl®) |
| Tolbutamide | Glipizide (Glucotrol®) |
| | Glyburide (DiaBeta®, Micronase®) |

**4.2.1A DESCRIPTION**

Insulin secretagogues that rapidly lower blood glucose levels by promoting insulin secretion from the beta cells of the pancreas.

**4.2.1B MECHANISM OF ACTION**

Sulfonylureas act by interacting with the SUR1 subunit of ATP-sensitive K+ channels (Kir6.2) expressed on pancreatic beta cells, this inhibits channel activity resulting in cell depolarization that triggers voltage-gated Ca2+-channels leading to Ca2+ influx and the secretion of insulin.




## 4.2.1C INDICATIONS AND CLINICAL USE

a) For control of blood glucose levels in type 2 diabetes
b) Primarily reduce FPG, with little effect on postprandial glucose increases
c) Decreases blood glucose by ~20% and HbA1c by ~1.5% points
d) Approved for either monotherapy or in combination with other oral hypoglycemic drugs
e) Typically given once per day
f) Most effective in patients who have had diabetes for less than 10 years, whose weight is normal or slightly elevated and that can still secrete considerable amounts of insulin
g) During the chronic progression of diabetes, as the total number of beta cells decrease, the sulfonylureas become less effective.
h) 2nd generation drugs are more potent than 1st generation drugs, are associated with a lower frequency of inducing hypoglycemia and have fewer drug interactions.
i) 2nd generation drugs are similar to each other in efficacy, but differ in dosage and duration of action

| | Duration of Biological Effect |
|---|---|
| **First Generation** | |
| Chlorpropamide | 24-72 hrs |
| Tolbutamide | 14-16 hrs |
| **Second Generation** | |
| Glipizide | 14-16 hrs |
| Glyburide | 20-24+hrs |
| Glimepiride | 24+ hrs |

## 4.2.1D ADVERSE EFFECTS

a) Modest weight gain (~2 kg) – primarily subcutaneous adipose tissue not visceral
b) Can cause hypoglycemia- especially in elderly patients with impaired RENAL and/or HEPATIC function- all drugs metabolized in liver and secreted in urine
c) Severe hypoglycemia is rare

## 4.2.1E CONTRAINDICATIONS

a) Elderly Patients – lack of awareness of hypoglycemia
b) Patients with sulfa allergies
c) Patients with type 1-diabetes
d) Pregnant or lactating patients (Insulin is the preferred medication)
e) Impaired RENAL/LIVER function – all sulfonylureas metabolized in the liver and metabolites are excreted in the urine.

Note: Glipizide is a short acting sulfonylurea that is metabolized in the liver and is excreted in the urine as inactive metabolites- it is therefore the drug of choice in the elderly or patients with chronic renal failure

### 4.2.1F DRUG INTERACTIONS

Sulfonylureas are highly protein bound and therefore interact with many drugs e.g. salicylates, beta-blockers, warfarin & phenylbutazone, which compete for binding and act to increase serum concentrations of sulfonylureas thereby resulting in increased potential for hypoglycemia

## 4.2.2 MEGLITINIDES: NON-SULFONYLUREA INSULIN SECRETAGOGUES

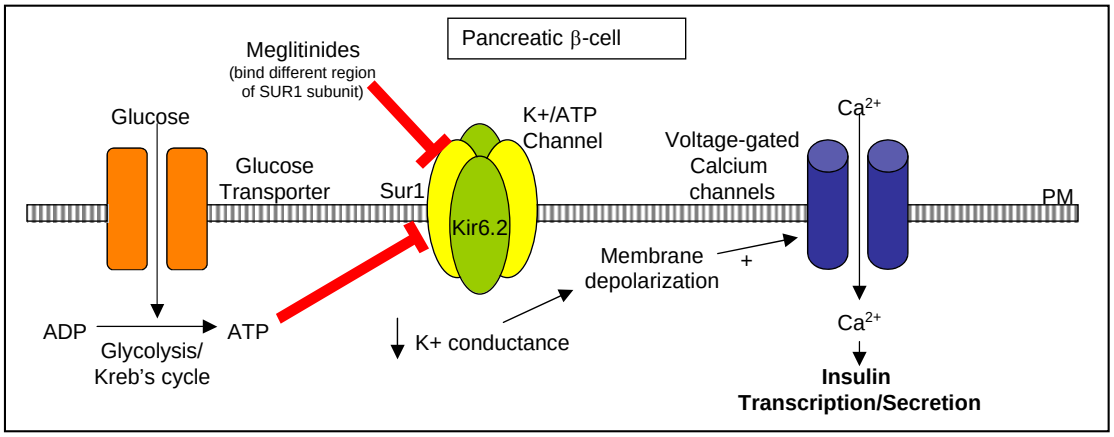
Repaglinide (Prandin®) and Nateglinide (Starlix®)

### 4.2.2A DESCRIPTION

Short acting glucose-lowering drugs that are structurally distinct from the sulfonylureas, but act similarly to lower blood glucose levels by promoting insulin secretion.

### 4.2.2B MECHANISM OF ACTION

Meglitinides trigger insulin secretion by a similar mechanism to the sulfonylureas, but interact with a different region of the SUR1 subunit of the beta cell ATP-sensitive K+ channel.




### 4.2.2C INDICATIONS AND CLINICAL USE

a) Meglitinides are short acting glucose-lowering drugs used for the treatment of hyperglycemia in type 2-diabetes.
b) Both drugs are rapidly absorbed and their peak action is at 1 hr and lasts for 4 hrs, they must therefore be given frequently, typically three times per day with meals. If meal is missed drug should be omitted
c) Primarily affect postprandial glucose elevations with less effect on FPG
d) Likely to be beneficial to patients with barely elevated FPG but prominent postprandial hyperglycemia
e) Monotherapy is indicated early in type-2 diabetes when FPG is not greatly elevated
f) They decrease Hb1Ac by ~1-1.5% points
g) Approved for either monotherapy, or together with metformin and/or a thiazolidinedione.
h) Nateglinide is less effective than repaglinide, which is as effective as sulfonylureas or metaformin at lowering Hb1Ac
i) Considerably more expensive than sulfonylureas (~5-8X)

j) Useful as a replacement for sulfonylureas in patients with sulfa allergies
k) Repaglinide is metabolized to inactive metabolites and is therefore safe to use in patients with renal insufficiency

### 4.2.2D ADVERSE EFFECTS

a) Weight gain – similar to sulfonylureas
b) Hypoglycemia – although less frequent than with sulfonylureas

### 4.2.2E CONTRAINDICATIONS

a) Liver disease- both drugs are metabolized primarily in the liver and excreted in the bile – increased risk of hypoglycemia
b) Not to be used during pregnancy

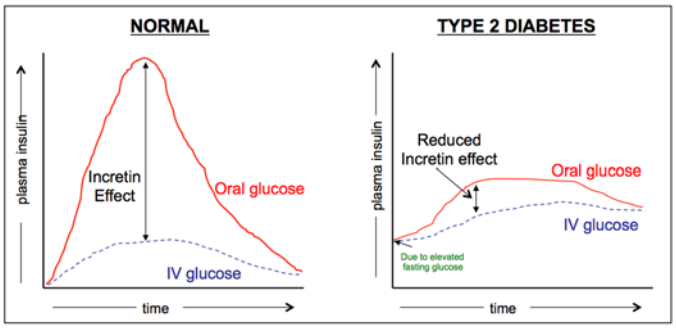
## 4.3 INCRETIN MIMETICS AND MODULATORS

### 4.3.1 GLP-1 ANALOGS

Exenatide (Byetta®); Liraglutide (Victoza®)

### 4.3.1A DESCRIPTION

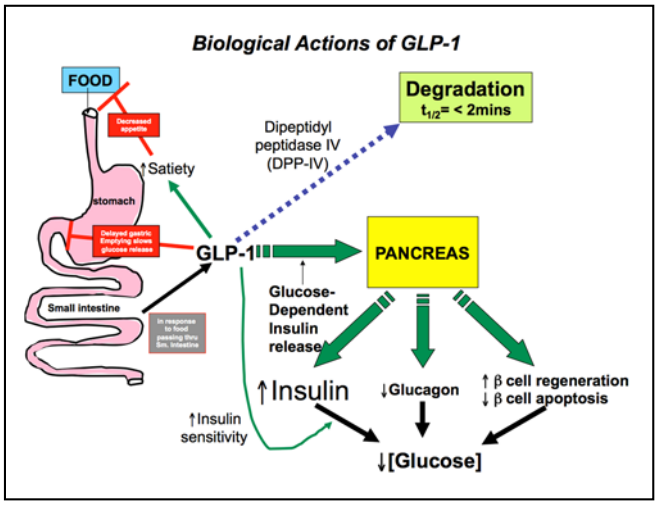
a) Exenatide is a stable analog of Glucagon-like peptide-1 (GLP-1) that binds to the GLP-1 receptor on the pancreatic beta cells and potentiates glucose-mediated insulin secretion
b) GLP-1 is produced by the L-cells of the small intestine and helps mediates the INCRETIN EFFECT on plasma insulin levels




c) Incretin Effect: Observation that plasma insulin levels are higher in response to oral glucose compared to intravenous glucose- indicating that factors produced in the GI tract (i.e. GLP-1) influence insulin secretion.

### 4.3.1B MECHANISM OF ACTION

a) Exenatide potentiates glucose-induced insulin secretion when glucose levels are high.
b) As glucose levels fall, the enhancing effects of exenatide on insulin secretion diminishes.
c) Suppresses pancreatic production of glucagon
d) Suppresses glucose release from liver
e) Slows stomach emptying
f) Increases satiety
g) Acts to maintain beta cell mass



#### 4.3.1C INDICATIONS AND CLINICAL USE

a) Exenatide and Liraglutide are approved as an alternative to starting insulin therapy in type 2 diabetic patients who have not achieved adequate glycemic control with either metformin, a sulfonylurea, or both.
b) Need to be injected once or twice daily
c) Mainly acts by reducing postparandial glucose concentrations
d) Decreases Hb1Ac by ~0.5-1% point
e) Little risk of hypoglycemia as the enhancing effects of exenatide on insulin secretion diminish as glucose levels fall
f) Do NOT cause WEIGHT GAIN and may cause WEIGHT LOSS

#### 4.3.1D ADVERSE EFFECTS

a) Frequent (30-45%) Nausea vomiting, diarrhea
b) Increased risk of mild to moderate hypoglycemia when used with a sulfonylurea

#### 4.3.1E DRUG INTERACTIONS

Due to the slowing of gastric emptying it can affect the absorption of other orally administered drugs (e.g. contraceptives & antibiotics), which should be taken 1 hr before or 2 hrs after.

### 4.3.2 DIPEPTIDYL PEPTIDASE-IV (DPP-IV) INHIBITORS

Sitagliptin (Januvia®); Saxagliptin (Onglyza®)

#### DESCRIPTION

a) Sitagliptin is an inhibitor of DPP-IV, the peptidase that cleaves and inactivates GLP-1
b) Sitagliptin therefore promotes the action of endogenous GLP-1 by increasing its half-life
c) Sitagliptin is an oral medication that is taken once daily.
d) It is rapidly absorbed, reaches a peak 1-4 hrs after ingestion and is effective over 24hrs.
e) Sitagliptin can decrease both FPG and postprandial glucose elevations, although is less effective than either pramlintide or exenatide in limiting postprandial hyperglycemia
f) Stagliptin is approved for adjunct therapy of type-2 diabetes in combination with either metformin or a thiazolidinedione
g) It reduce Hb1Ac almost as effectively as exenatide i.e. 0.6-0.8%
h) There is no effect on weight loss
i) It is not associated with hypoglycemia

## 4.4 ORAL ANTI-DIABETIC DRUGS: INHIBTORS OF CARBOHYDRATE DIGESTION

### 4.4.1 ALPHA-GLUCOSIDASE INHIBITORS

Acarbose (Precose®) and Miglitol (Glyset®)

#### 4.4.1A DESCRIPTION

Drugs that reduce postprandial blood glucose levels by inhibiting the rate of digestion of polysaccharides in the small intestine

#### 4.4.1B MECHANISM OF ACTION

Acarbose and Miglitol inhibit the alpha-glucosidase enzyme that lines the brush border of the small intestine and is responsible for the hydrolysis of carbohydrates thereby delaying the absorption of glucose and other monosaccharides.

### 4.4.1C INDICATIONS AND CLINICAL USE

a) The control of postprandial hyperglycemia- should be taken with each meal
b) Acarbose and Miglitol do NOT cause HYPOGLYCEMIA
c) Acarbose and Miglitol are less potent than sulfonylureas or metformin – they decrease Hb1Ac by 0.5-0.8% points
**d)** Because different mechanism of action Acarbose and Miglitol have an additive effect on reducing glycemia together with either a sulfonylurea, metformin or insulin
**e)** Acarbose and Miglitol are not considered to be first line anti-diabetic drugs because of their reduced efficacy and poor tolerance due to side effects (see below)

### 4.4.1D ADVERSE EFFECTS

a) Unabsorbed carbohydrate causes abdominal pain, diarrheas and flatulence due to osmotic effect and bacterial fermentation
b) Many patients (25-45%) stop taking the drugs due to side effects
c) Do not cause hypoglycemia by themselves, but can increase the risk when given with a sulfonylurea or insulin
d) In event of hypoglycemia patients should be treated with oral administration of glucose not sucrose due to inhibitory effects of drug on the breakdown of sucrose

### 4.4.1E CONTRAINDICATIONS

a) Chronic intestinal disease
b) Inflammatory bowel disease
c) Colonic ulceration or any degree of intestinal obstruction

## 4.5 ORAL ANTI-DIABETIC DRUGS: SODIUM GLUCOSE LINKED TRANSPORTER 2 PROTEIN INHIBITORS

### 4.5.1 SGLT2 INHIBITORS

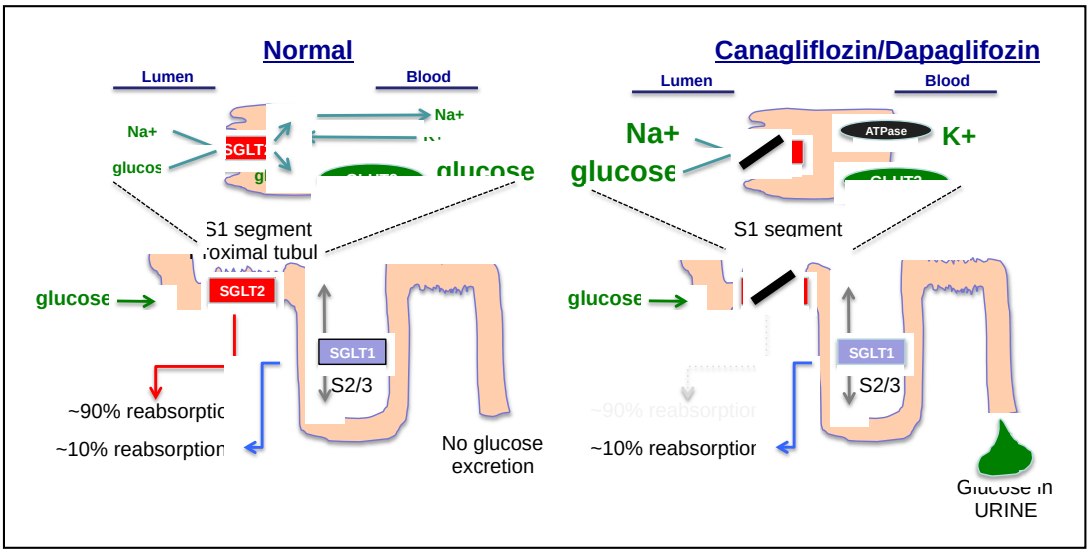
Canagliflozin (Invokana®) & Dapagliflozin (Farxiga®)

### 4.5.1A DESCRIPTION

Drugs that reduce hyperglycemia by promoting glucose excretion in the urine

### 4.5.1B MECHANISM OF ACTION

a) Inhibition of Sodium-Glucose Linked Transporter 2 protein (SGLT2) activity in the S1 segment of the proximal renal tubule prevents the normal process of glucose reabsorption leading to excretion of glucose in the urine




**4.5.1C**

**INDICATIONS AND CLINICAL USE**

a) Improving glycemic control in Type 2 Diabetes- monotherapy or in combination
b) Decreases HbA1c by **0.5-0.9%**- low risk hypoglycemia when used as monotherapy
c) ↓Body weight- ~ 80g of glucose (200-300 kCal) eliminated each day
d) ↓BP- $H_20$ eliminated by increased Osomotic diuresis

**4.5.1D ADVERSE EFFECTS**

a) Urinary Tract Infections- genital mycotic infections
b) Thirst/Dehydration
c) Hypotension
d) ↑LDL-Cholesterol
e) Hypoglycemia **when given with other** anti-hyperglycemia medications
f) Hyperkalemia- especially patients taking Meds that interfere with K+ excretion (e.g. K+ sparing diuretics)

**4.5.1E CONTRAINDICATIONS**

a) Renal impairment

# 4.6 ORAL ANTI-DIABETIC DRUGS: BROMOCRIPTINE

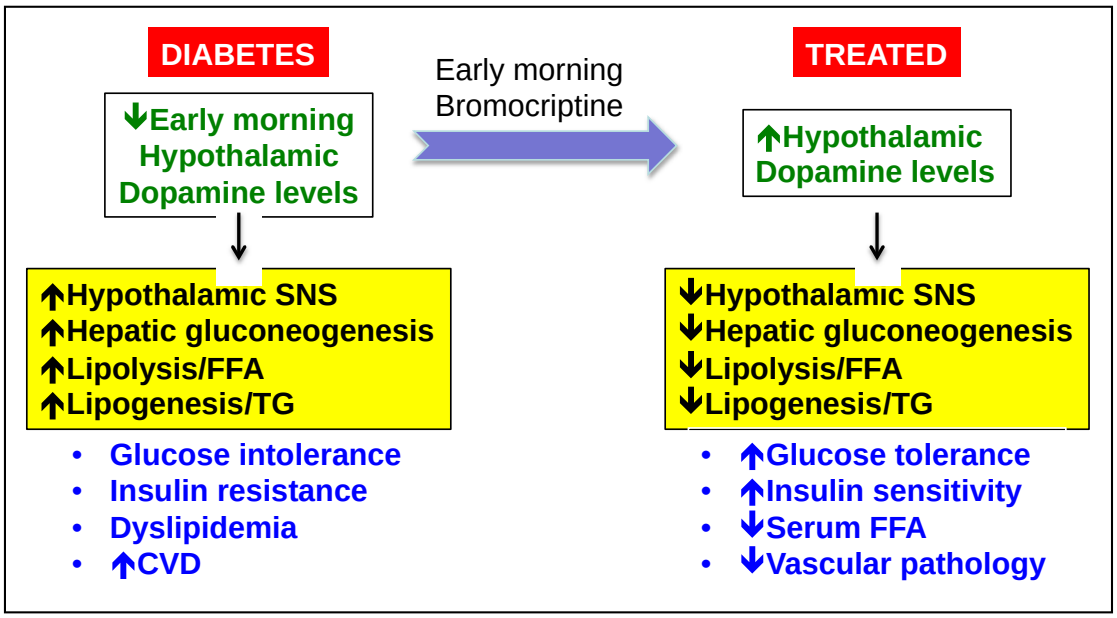
## 4.6.1 Bromocriptine (Cycloset)

**4.6.1A DESCRIPTION**

a) Sympatholytic Dopamine D2 receptor agonist
b) Quick Release formulation- taken within 2 hrs of waking
c) decreases HbA1c by ~ 0.5%
d) Dosage much lower than that used in Parkinson's

**4.6.1B MECHANISM OF ACTION**

a) Exact MOA in diabetes is unknown
b) thought to act on the CNS to normalize the decreased AM dopamine levels present in Type 2 patients
c) Increased morning dopamine signaling antagonizes hypothalamic sympathetic nervous system leading to a decrease in hepatic gluconeogenesis, reduced lipolysis and lipogenesis, which in turn results in an increase in insulin sensitivity and glucose tolerance.




4.7

# ORAL ANTI-DIABETIC DRUGS: COVELESELAM (Bile Acid-Binding resin)

## 4.7.1 Coveleselam

### 4.7.1A DESCRIPTION:

a) A lipid-lowering drug used in the treatment of hypercholesterolemia
b) Serendipitously found to have beneficial effects in diabetes
c) Used as an **Adjunct "Add On"** anti-diabetic therapy to reduce blood glucose levels by indirectly increasing expression of **GLP-1**

### 4.7.1B MECHANISM OF ACTION

a) Colesevelam binds bile acids in the small intestine forming insoluble complexes that are excreted in the feces
b) Prevents reabsorption of bile acids
c) Allows bile acids to enter the colon
d) Bile acids bind to the TGR5 GPCR expressed on intestinal cells in the colon to stimulate GLP-1 secretion

### 4.7.1C INDICATIONS AND CLINICAL USE

a) Add on therapy to metformin, sulfonylureas or insulin
b) Decreases HbA1c by ~ 0.5%
c) NOT considered FIRST LINE anti-diabetic drugs
d) Useful in patients that also exhibit elevated LDL-cholesterol levels

## 4.8 INSULIN THERAPY THE TREATMENT OF TYPE 2 DIABETES

a) As type 2 diabetes progresses beta cell function gradually declines and insulin therapy is often required to achieve satisfactory glycemic control. Insulin is the most effective medication at lowering glycemia.

b) Insulin can be considered a first-line therapy for all patients with type-2 diabetes and should be the initial therapy for patients HbA1c>10%, fasting plasma glucose >250 mg/dL and random glucose consistently >300 mg/dL, Insulin is also the preferred 2nd line agent in patients with HbA1c > 8.5%.

c) Insulin is indicated in patients presenting with a sudden onset of diabetes, significant recent weight loss, and polyuria accompanied by polydipsia- some of these patients may have late onset type 1 diabetes.

d) Initial therapy is aimed at providing basal insulin with either intermediate (NPH) or long-term insulin (glargine) given once/twice daily before breakfast/dinner. The primary goal of basal insulin is to lower fasting glucose by inhibiting hepatic gluconeogenesis. Note that because of increased obesity and insulin resistance in type 2 diabetics considerably more insulin is required to treat these patients compared to those with type 1 diabetes.

e) If necessary, insulin therapy can be intensified by the addition of regular- or rapid-acting insulin before selected meals in order to reduce postprandial glucose elevations. In this case, any insulin secretagogue medications should be eliminated.

f) Disadvantages of insulin therapy: hypoglycemia, weight gain, and injection site lipodystrophy.

## 4.9 AMYLIN HOMOLOGS

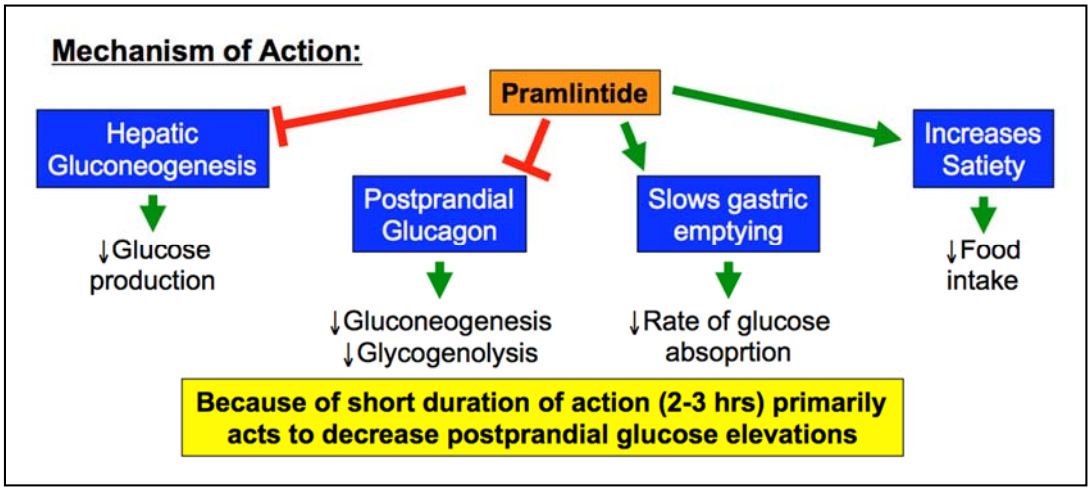
Pramlintide (Symlin®)

### 4.9A DESCRIPTION

a) Pramlinitide is a synthetic analog of human Amylin, an endogenous neuroendocrine hormone that is synthesized by pancreatic beta cells and co-secreted with insulin, which contributes to glucose control in the postparandial period
b) Amylin production is absent in patients with diabetes

### 4.9B MECHANISM OF ACTION

a) Decreases hepatic gluconeogenesis
b) Decreases postprandial glucagon levels – i.e. resulting in a decrease in gluconeogenesis, glycogenolysis and lipolysis
c) Slow gastric emptying - this slows the rate of delivery of glucose to the circulation thereby helping prevent excessive increases in the postprandial glucose concentration N.B. gastric emptying is often increased in type1 and type 2 diabetic patients and contributes to rapid rises in postprandial glucose seen in these patients
d) Increases Satiety – i.e. reduces food intake




### 4.9 INDICATIONS AND CLINICAL USE

a) Pramlinitide is indicated as an ADJUNCT therapy in patients with either TYPE 1 or TYPE 2 diabetes who are using mealtime insulin therapy and who have not achieved adequate glycemic control.
b) The effects of pramlinitide are additive to insulin
c) Provides postprandial control of glucose levels and limits glucose fluctuations
d) Pramlinitide needs to be injected subcutaneously before each meal
e) Pramlinitide therapy decreases Hb1Ac by 0.5-0.7% points
f) Decreases amount of short acting insulin required
g) Can promote WEIGHT LOSS ~1-1.5kg over 6 months (may be due to GI side effects)
h) Most appropriate for highly motivated patients who can tolerate nausea and are willing to add 2-4 more injections per day and more frequent glucose monitoring
i) Most likely to have greatest benefit in type 1 patients who are obese

### 4.9D ADVERSE EFFECTS

a) Nausea, vomiting, anorexia, headache
b) Together with insulin it increases the risk of severe hypoglycemia- the dose of insulin should be reduced ~50%.

### 4.9E DRUG INTERACTIONS

Due to the slowing of gastric emptying it can affect the absorption of other orally administered drugs (e.g. contraceptives & antibiotics), which should be taken 1 hr before or 2 hrs after

## 5. CURRENT RECOMMENDATIONS OF THE ADA/EASD FOR THE MANAGEMENT OF TYPE 2 DIABETES

a) Patients should initially undergo life style changes including diet and exercise to improve glycemia, blood pressure and lipid profile.
b) However, continuous treatment with oral anti-diabetic mediations will typically be required to maintain normal or near normal glycemia.
c) Metformin therapy should be the first drug of choice in most patients. The Metformin dose should be titrated over a two-month period to the maximally effective dose (typically 850 mg twice a day). Advantages: Efficacy, Safety, Weight Loss, no risk of hypoglycemia and beneficial effects on CVD mortality.

d) In cases where metformin is specifically contraindicated (e.g. elderly patients, renal hepatic, or cardiac disease, excess alcohol) another oral agent should be used (i.e. a sulfonylurea or thiazolidinedione).
e) If after 2-3 months adequate glycemic control is NOT achieved (i.e. HbA1c remains >7%), another medication should be added e.g. a sulfonylurea (least expensive), thiazolidinedione (no hypoglycemia), exenatide (maybe useful in overweight patients), or insulin (most effective; especially if HbA1c is > 8.5%).
f) Further adjustments to therapy should be made no less frequently than every three months.
g) In those patients that fail to achieve adequate control of glycemia on a combination of two drugs a third drug or insulin can be added, or the insulin therapy regimen can be intensified.

# SUMMARY: INSULIN PREPARATIONS

## *Properties of commercially-available Insulin Preparations*

| | Formulation | Onset | Peak | Duration | Usage |
|---|---|---|---|---|---|
| **Rapid-acting**<br>Insulin aspart<br>Insulin lispro<br>Insulin glulisine | Amino acid substituted insulin variants that are monomeric for faster absorption | 5-15 mins | 45-75mins | 2-4 hrs | For meals or acute Hyperglycemia; Can be injected immediately before meals |
| **Regular Insulin** | Zinc ions added for stability; forms hexamers that dissociate into monomers prior to absorption | 30-60 mins | 2-4 hrs | 6-8 hrs | For meals or acute Hyperglycemia; Needs to be injected 30-45 mins prior to meal |
| **Intermediate acting**<br>NPH Insulin<br>(Isophane) | Conjugated with protamine peptide which delays absorption until it is proteolytically cleaved by endogenous tissue proteases | 1.5-2 hrs | 6-10 hrs | 16-24 hrs | Provides basal insulin and overnight coverage |
| **Long acting**<br>Insulin glargine | Amino acid substituted insulin variant that forms large ppt at body pH and is slow to be absorbed | ~2 hrs | No Peak | 20->24 hrs | Provides basal insulin and overnight coverage |
| Insulin detmir | Insulin with fatty acid side chain that associates with tissue bound albumin that slows its absorption | ~2 hrs | No Peak | 6-24 hrs | |

# SUMMARY DRUGS TO TREAT TYPE 2 DIABETES

| | HbA1c Decrease | Duration of Effect | Mechanism | Advantage | Adverse Effects | Contraindications |
|---|---|---|---|---|---|---|
| **Metformin** | ~1.5% | 6 hrs | Inhibits mito complex I<br>⇒↑AMP<br>↓Adenylate cyclase/↑AMPK<br>Opposes GLUCAGON<br>**↓Hepatic gluconeogenesis**<br>↑Glucose utilization<br>↑Insulin sensitivity | **Lowers fasting glucose**<br>Weight loss,<br>Improved lipid profile,<br>No hypoglycemia<br>↓ Frequency MI/Death | **Lactic Acidosis**,<br>GI side effects,<br>↓absorption B12 | Elderly >80 yrs<br>pregnancy<br>**Renal failure, MI**<br>**Congestive heart failure,**<br>Liver disease/alcohol abuse,<br>Hypoxia/Shock/septicemia,<br>Iodinated contrast agent |
| **Sulfonylureas**<br>Chlorpropamide/Tolbutamide<br>Glimepiride/Glipizide/<br>Glyburide | ~1.5% | Tol/Glip<br>14-16 hrs<br>Chlor/Gly/Glim<br>24+ hrs | Inhibits β-cell K+ channel<br>(Kir6.2/Sur1) resulting in<br>**↑Insulin secretion** | **Slow onset**<br>**Long duration**<br>**Lowers fasting glucose** | **↑ Hypoglycemia risk**<br>Weight gain | Pregnancy<br>**Renal/Liver disease**<br>Sulfa allergies<br>Type-1 diabetes<br>Elderly |
| **Meglitinides**<br>Repaglinide/nateglinide | 1-1.5% | 2-4 hrs | Inhibits β-cell K+ channel<br>(Kir6.2/Sur1) resulting in<br>↑glucose-dependent<br>Insulin secretion | **Fast acting**<br>**Short duration**<br>↓Postprandial glucose | Hypoglycemia<br>Weight gain | Pregnancy<br>Liver disease |
| **Thiazolidinediones**<br>Pioglitazone/Rosiglitazone | 0.5-1.4% | weeks | Agonist of PPARγ<br>Transcription Factor<br>**↑Insulin sensitivity**<br>**↑Glucose utilization**<br>**↓Insulin resistance** | Lowers fasting glucose<br>↓triglycerides | **Weight gain (subQ)**<br>**Fluid retention**<br>**↑HF risk**<br>**↑Bone fractures in women**<br>Increased risk bladder cancer | **Liver disease**<br>**Stage III/stage IV**<br>**Congestive Heart Failure**<br>**CVD**<br>Pregnancy |
| **Alpha-glucosidase Inhibitor**<br>Acarbose/Miglitol | 0.5-0.8% | 3-4 hrs | Inhibits carbohydrate<br>Digestion in GI tract<br>**↓Glucose absorption** | ↓Postprandial glucose<br>No risk hypoglycemia | Significant GI side effects | Chronic intestinal Disease<br>Inflammatory bowl disease<br>Colonic ulceration |
| **Incretin Mimetics**<br>Exenatide/Liraglutide | 0.5-1.0% | Ex ~6-8 hrs<br>L ~11-15 hrs | GLP-1 analog<br>**Potentiates glucose-induced Insulin release**<br>**↓Pancreatic glucagon**<br>**↓Hepatic gluconeogenesis**<br>Slows gastric emptying<br>↑Satiety | **↓Fasting glucose**<br>**↓ Postprandial glucose**<br>Little risk hypoglycemia<br>Weight loss | Requires Injections<br>Nausea | |
| **DPP-IV inhibitors**<br>Sitagliptin/Saxagliptin | 0.48-0.61% | ~24 hrs | Inactivates DPP-IV<br>the GLP-1 peptidase<br>(potentiates GLP-1 action) | **↓ Fasting glucose**<br>**↓Postprandial glucose**<br>Little risk hypoglycemia | | |

| | HbA1c Decrease | Duration of Effect | Mechanism | Advantage | Adverse Effects | Contraindications |
|---|---|---|---|---|---|---|
| **Pramlintide**<br>(Used as adjunct therapy with insulin in both Type 1 and Type 2 -reduce insulin by 50%) | 0.5-0.7% | 2-3 hrs | Amylin mimetic<br>Adjunct to insulin therapy<br><br>↓Postprandial glucagon<br>↓Hepatic gluconeogenesis<br>Slows gastric emptying<br>↑Satiety | ↓Postprandial glucose<br>Weight loss | Requires injections<br>Nausea<br>Hypoglycemia<br>(especially with insulin<br>-need to reduce insulin by 50%) | |
| **SGLT2 inhibitors**<br>Canagliflozin<br>dapagliflozin | 0.5-0.9% | >24 hrs | Inhibits glucose renal reabsorption by inhibiting SGLT2 promotes increased glucose excretion in urine | ↓Blood pressure<br>Weight loss | Urinary tract infections<br>Thirst/Dehydration<br>Hypotension<br>↑LDL Cholesterol<br>Risk of hyperkalemia | Renal impairment<br>Type 1 diabetes |
| **Bromocriptine**<br>(Cycloset) | ~0.5% | | Dopamine D2 agonist acts on the CNS to normalize hypothalamic dopamine levels thereby decreasing Sympathetic tone resulting in:<br>↓Hepatic glucogenogenesis<br>↓Lipolysis/FFA<br>↓Lipogenesis/TG<br>↑Glucose tolerance<br>↑Insulin sensitivity | | | |
| **Bile acid-binding resin**<br>Covelesalam | ~0.5% | | Prevent Bile acid reabsorption<br><br>Allow bile acids to enter the colon<br><br>Bile acids bind TGR5 GPCR expressed on intestinal cells and induce GLP-1 secretion | | | |

# Agents to treat Mineral Ion and Bone Disorders

**Date: Monday March 29th, 2016, 10:30am -11:30am**

**Reading assignments:** Basic and Clinical Pharmacology. B.G. Katzung, 12th Edition. Chapter 42, p747

## Key Concepts and Learning Objectives

1. Describe the hormonal pathways regulating daily calcium and phosphate homeostasis

2. Describe the mechanisms regulating bone remodeling

3. Describe the principal functions of parathyroid hormone and the negative feedback mechanisms that regulate its synthesis

4. Describe the synthesis of active Vitamin D3 and its principal effects on mineral ion and bone homeostasis

5. Discuss the regulation and function of calcitonin

6. Describe the indications, mechanisms of action, major adverse effects and contraindications of the principal drug classes used in the treatment of mineral ion and bone disorders

7. Compare and contrast the recommended treatment options for the treatment of the major mineral ion and bone disorders

## Drugs covered in this lecture:

Vitamin D and its analogues
Bisphosphonates
Denosumab
Teriparitide
Raloxifene
Calcitonin
Cincalcet
Sevelamer

| Drug Class | Indications | Mechanism of Action | Adverse Effects | Miscellaneous |
|---|---|---|---|---|
| **Vitamin D**<br>Calcitriol<br>Doxercalciferol<br>Ergocholecalciferol<br>Cholecalciferol | Nutritional Supplements<br>Rickets & Osteomalacia<br>Prevention of Osteoporosis<br>Hypoparathyroidism<br>Secondary Hyperparathyroidism | Agonists of VitD receptor<br>↑Ca2+/PO4 intestinal absorption<br>↑Ca2+/PO4 renal absorption<br>↓PTH expression | Hypercalcemia | Not to be administered in presence of hyperphosphatemia due to risk of malignant calcification |
| **Bisphosphonates**<br>Alendronate<br>Pamidronate<br>Risendronate<br>Zoledronate | Osteoporosis<br>Hypercalcemia<br>Paget's Disease | Inhibit Farensyl Pyrophosphate Synthase<br>↓ Protein farnesylation<br>↓ Osteoclast activity<br>↓ Bone resorption | Esophageal Irritation<br>Occular side effects<br>Osteonecrosis of the Jaw<br>Renal impairment | Contrainindications:<br>Esophageal disease<br>Chronic kidney disease |
| **Denosumab** | Osteoporosis<br>Hypercalcemia<br>Giant Cell tumor of the bone | Anti-RANKL mAb<br>RANKL antagonist<br>↓ Osteoclast bone resorption | Hypocalcemia<br>Osteonecrosis of the Jaw | Contrainindications:<br>Hypocalcemia |
| **Teriparitide** | Osteoporosis | PTH receptor agonist<br>Intermittent activity<br>Stimulates osteoblasts<br>Promotes bone growth<br>↑ Renal 1a-hydroxylase activity<br>↑ Renal calcium reabsorption | Transient Hypercalcemia<br>Hyperuricemia<br>↑ Risk of osteosaarcoma | Contraindications:<br>History of gout<br>Risk of osteosarcoma<br>Active malignancy of the bone<br>Radiation therapy of the bone<br>Unexplained ↑ Alk Phosphatase<br>Paget's Disease of the bone<br>Children /adolescents |

| Drug Class | Indications | Mechanism of Action | Adverse Effects | Miscellaneous |
|---|---|---|---|---|
| **Raloxifene** | Osteoporosis (post menopausal women) | SERM<br>ER agonist in bone<br>Anti-estrogen in breast & uterus<br>↓ Genes involved in osteoclast activation<br>↓ Osteoclast activity | ↑ Risk venous thromboembolism<br>Worsening vasomotor symptoms | |
| **Calcitonin** | Severe hypercalcemia<br>Paget's Disease<br>Osteoporosis | Calcitonin Receptor agonist | Nausa<br>Hand swelling, intestinal cramping<br>Concern regarding ↑rates of cancer | Rapidly reduces serum Ca2+ In 4-6 hrs |
| **Cinacalcet** | CKD/secondary hyperparathyroidism<br>Hypercalcemia<br>Primary hyperparathyroidism | Calcimimetic<br>Allosterically enhances affinity of CaSR for Ca2+ | Hypocalcemia<br>Seizure risk | Contraindicated if serum Ca2+ is < 8.4 mg/dL |

# Thyroid and Anti-Thyroid Drugs

**Date: Tuesday, March 29th, 2016, 10:30am -11:30am**

**Reading assignments:** Basic and Clinical Pharmacology. B.G. Katzung, 12th Edition. Chapter 38, p681

## Key Concepts and Learning Objectives

1. Describe the role of the Hypothalamus-Pituitary-Thyroid axis in the regulation of thyroid hormone production and the feedback mechanisms involved in the regulation of this pathway.

2. Describe the steps in the biosynthesis of the thyroid hormones: Tetraiodothyronine (T4) and triiodothyronine (T3), and identify the steps that are targeted by anti-thyroid drugs

3. Compare and contrast the pharmacological properties of tetraiodothyronine (T4) and triiodothyronine (T3) and discuss how these properties influence their use in the treatment of thyroid disease.

4. Describe the indications, contrainindications, mechanism of action, and major adverse effects of the major drug classes used in the treatment of hyperthyroidism

5. Discuss the role of surgery in the treatment of thyroid disorders and the role of thyroid and antithyroid drugs used in pre/postoperative care

6. Discuss the use of drugs in the medical management of thyroid storm

7. Describe the role of thyroid hormone and antithyroid drugs used in the postoperative therapy of a patient with thyroid carcinoma

| | Indications | MOA | Major Adverse Effects | Misc. |
|---|---|---|---|---|
| **Levothyroxine/ Tetraiodothyronine (T4)** | Hypothyroidism | Pro-hormone converted in vivo to the active T3 form, which acts as an agonists of the VDR transcription factor | Hyperthyroidism with overdose<br>↑ risk atrial fibrillation<br>↑Bone loss in premenopausal women | Slow onset 3-5 days<br>Peak effect 4-6 weeks<br>Half life ~7 days<br>Smooth dosing |
| **Liothyronine/ Triiodothyronine (T3)** | Hypothyroidism when rapid onset of action is required<br>e.g. myxedema coma<br><br>Preparation of thyroid cancer Patient for radioiodine therapy<br>To avoid extended period of thyroid hormone withdrawal | Active hormone acts as an agonists of the VDR transcription factor | Risk of thyrotoxicosis with over dose | Fast onset 2-4 hrs<br>Half life ~19 hrs<br>Extreme troughs and peaks |
| **Beta blockers e.g. propanolol or esmolol** | To ameliorate adrenergic symptoms associated with hyperthyroidism | Antagonists at beta-adrenergic receptors<br><br>Propanolol also inhibits peripheral conversion of T4 to T3 (small effect) | Exacerbation of HF<br><br>↑Airway resistance<br><br>Exacerbation of peripheral artery disease | Contraindicated in Asthma, COPD or HF<br><br>Alternative drug choices:<br>Diltiazem (Ca2+ blocker)<br>Metropolol/atenolol (cardiac-selective beta blocker) |

| | Indications | MOA | Major Adverse Effects | Misc. |
|---|---|---|---|---|
| **Thionamides/ Thiourylenes**<br>Propylthiouracil (PTU)<br>Methimazole (MMI) | Hyperthyroidism<br>e.g. Grave's Disease | Inhibit Thyroid Peroxidase<br>Organification<br>Coupling<br><br>Do not inhibit release of<br>Preformed thyroid hormone<br><br>PTU (not MMI) partially inibits<br>Peripheral deiodination of T4 to T3 | Common: Skin rash/joint pain<br><br>Rare but serious:<br>Hepatotoxicity PTU>>>>MMI<br>ANCA-positive vasculitis PTU>>>>MMI<br>Agranulocytosis PTU=MMI<br>Teratogenicity MMI>>>>PTU | MMI is preferred agent in<br>Non-pregnant patients<br><br>PTU preferred for<br>1st trimester<br>in pregnant patients |
| **Iodide** | Severe Hyperthyroidism<br>e.g. Thyroid storm<br>Preoperative prep of<br>Patients for thyroidectomy<br>After major nuclear accidents<br>To prevent radioiodine uptake | Acutely inhibits hormone secretion<br><br>Inhibits hormone synthesis via<br>Wolff-Chaikoff effect (Transient)<br><br>Decreases thyroid organ vascularity | | Wolff-Chaikoff effect is<br>Transient lasts ~ 10 days |
| **Radioactive Iodine** | Hyperthyroidism<br>e.g. Grave's Disease<br>Toxic nodular goiter | Emission of beta particles cause<br>Necrosis of follicular cells | Radiation Thyroiditis<br><br>Exacerbation of<br>Grave's Ophthalmopathy | Contraindications:<br>Pregnancy, breast feeding,<br>Severe ophthalmopathy<br><br>Takes 2-3 months for effect |
| **Bile acid sequestrant**<br>e.g. cholestyramine | Thyroid Storm | Prevents reabsorption of<br>Thyroid hormone | | |