

PHARMACOLOGY OF HYPOTHALAMIC HORMONES

- Hormones of the anterior and posterior pituitary are administered **intramuscularly (IM)**, **subcutaneously**, or **intranasally** because their **peptidyl nature makes them susceptible to destruction by the proteolytic enzymes of the digestive tract.**

ACTH

- ✓ CRH
- ✓ Corticotropin
- ✓ Cosyntropin

GH

- ✓ Somatropin

GHIH

- ✓ Somatostatin
- ✓ Octreotide
- ✓ Lanreotide
- ✓ Pegvisomant

GNRH

- ✓ Leuprolide
- ✓ Goserelin
- ✓ Nafarelin
- ✓ Histrelin

GONADOTROPINS

- ✓ Menotropins = HMG
 - Both LH & FSH
- ✓ Urofollitropin
 - FSH
- ✓ Follitropin alfa & beta
 - FSH product
- ✓ HCG
 - Identical to LH
- ✓ Choriogonadotropin alfa
 - Identical to LH

PROLACTIN

- ✓ Metoclopramide
 - Dopamine antagonist
- ✓ Risperidone
 - D ant + antipsychotic
- ✓ Bromocriptine
 - D2- R agonist
- ✓ Cabergoline
 - D2- R agonist

VASOPRESSIN

- ✓ & Desmopressin

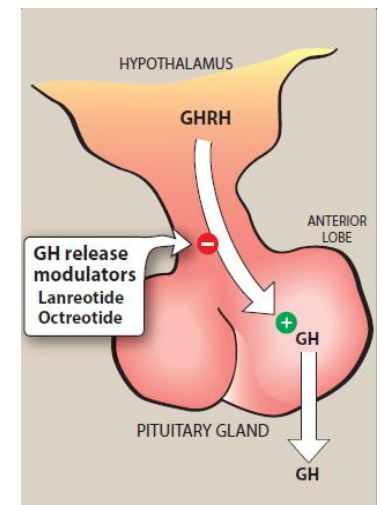
OXYTOCIN

ACTH

- **CRH** is used diagnostically to differentiate between Cushing syndrome and ectopic ACTH-producing cells.
- ACTH release: highest conc @ early morning & lowest @ late evening.
- **Stress stimulates** its secretion;; **Cortisol** acting via *negative feedback suppresses* its release
- **MOA:**
 - **ACTH binds to receptors on the surface** of the adrenal cortex, thereby activating GPCR -> rate-limiting step (cholesterol to pregnenolone)
 - This pathway ends with the synthesis and release of the **adrenocorticosteroids and the adrenal androgens**.
- **Therapeutic uses:**
 - The availability of **synthetic adrenocorticosteroids** with specific properties has limited the use of **CORTICOTROPIN** mainly to serving as a **diagnostic tool for differentiating between primary adrenal insufficiency** (Addison disease, associated with adrenal atrophy) and **secondary adrenal insufficiency** (caused by the inadequate secretion of ACTH by the pituitary).
 - Therapeutic *corticotropin* preparations are extracts from:
 - the anterior **pituitaries of domestic animals**
 - synthetic human ACTH.
 - **COSYNTROPIN** is preferred for the **diagnosis of adrenal insufficiency**.
 - ACTH is also used in the treatment of **infantile spasm** (West syndrome).
- **Adverse effects:**
 - Short-term use of ACTH for diagnostic purposes is usually well tolerated.
 - With longer use, toxicities are similar to those of glucocorticoids and include: hypertension, peripheral oedema, hypokalaemia, emotional disturbances, and increased risk of infection

GROWTH HORMONE

- Synthetic human GH (**SOMATROPIN**) is produced using **recombinant DNA technology**.
- In **acromegaly** IGF-1 levels are consistently high, reflecting elevated GH.
- **Therapeutic uses:**
 - **Somatropin** is used in the treatment of GH deficiency or growth failure in children.
 - GH administered to adults increases lean body mass, bone density, and skin thickness, whereas adipose tissue is decreased.
 - Many consider GH an **“antiaging”** hormone. This has led to off-label use of GH by **older individuals and by athletes** seeking to enhance performance.
 - **Somatropin** is administered by **subcutaneous or IM injection**.
 $T_{1/2}$ = **short** (approximately **25 minutes**), it induces the release of IGF-1 from the liver, which is responsible for subsequent GH-like actions.
- **Adverse effects:**
 - pain at the injection site, oedema, arthralgias, myalgias, flu-like symptoms, and an increased risk of diabetes.
 - Somatropin should **NOT** be used in **paediatric patients with closed epiphyses, patients with diabetic retinopathy.**



SOMATOSTATIN (GHIH)

- In the pituitary, **SOMATOSTATIN** binds to receptors that suppress GH and TSH release; ALSO **insulin, glucagon, and gastrin**.
- Originally isolated from the hypothalamus, also found in neurons throughout the body as well as in the intestine, stomach, and pancreas.
- **OCTREOTIDE** and **LANREOTIDE** are synthetic analogues of somatostatin.
 - Their half-lives are longer than that of the natural compound, and depot formulations are available, allowing for administration once every 4 weeks.
 - They have found use in the treatment of acromegaly.
- An IV infusion of **OCTREOTIDE** is also used for the treatment of bleeding oesophageal varices.
 - Adverse effects: include diarrhoea, abdominal pain, flatulence and nausea.
 - Gallbladder emptying is delayed, and asymptomatic cholesterol gallstones can occur with long-term treatment.
- **Acromegaly** that is refractory to other modes of therapy may be treated with **PEGVISOMANT**, a GH receptor antagonist.

GNRH

- **continuous administration of GnRH inhibits gonadotropin release** through down-regulation of the GnRH receptors on the pituitary.
- Continuous administration of **synthetic GnRH analogues**, such as **LEUPROLIDE, GOSERELIN, NAFARELIN**, and **HISTRELIN**, is effective in **suppressing production of the gonadotropins**.
- Several of these agents are available as **implantable formulations** that provide **convenient continuous delivery of the drug**. Suppression of gonadotropins → reduced production of androgens and oestrogens.
- effective in the treatment of **prostate cancer, endometriosis, and precocious puberty**.
- **AE:**
 - In women, may cause **hot flushes and sweating, as well as diminished libido, depression, and ovarian cysts**.
 - In men, they **initially cause a rise in testosterone** that can result in **bone pain**.
 - **Hot flushes, oedema, gynecomastia, and diminished libido** may also occur.
- **Contraindicated:**
 - In pregnancy and breast-feeding.

GONADOTROPINS

- treatment of infertility.
- **MENOTROPINS** (also known as *human menopausal gonadotropins* or *hMG*) are obtained from the urine of postmenopausal women and contain both FSH and LH.
- **UROFOLLITROPIN** is FSH obtained from postmenopausal women and is devoid of LH.
- **FOLLITROPIN alfa** and **FOLLITROPIN beta** are human FSH products manufactured using recombinant DNA technology.
- **HUMAN CHORIONIC GONADOTROPIN (HCG)** is a placental hormone that is excreted in the urine of pregnant women.
- The effects of **hCG** and **choriogonadotropin alfa** (made using recombinant DNA technology) are essentially identical to those of LH.
- All: IM or subcutaneous route.
- Injection of **hMG** or **FSH products** over a period of 5 to 12 days causes → ovarian follicular growth and maturation, and with subsequent injection of hCG → ovulation occurs.
- **Adverse effects:** *ovarian* enlargement and possible ovarian hyperstimulation syndrome, which may be life threatening.
- Multiple births are not uncommon.

PROLACTIN

- Drugs that act as **DOPAMINE ANTAGONISTS** (for example, **METOCLOPRAMIDE** and antipsychotics such as **RISPERIDONE**) can increase the secretion of prolactin.
- Treatment of:
 - **Hyperprolactinaemia** → **D2 RECEPTOR AGONISTS**, such as **BROMOCRIPTINE** and **CABERGOLINE**.
 - **pituitary microadenomas** → **BROMOCRIPTINE** and **CABERGOLINE**
 - **type 2 diabetes** → **BROMOCRIPTINE**
- **adverse effects**: nausea, headache and, sometimes, psychiatric problems.

hormones of the posterior pituitary: both administered **IV** & have v short $t_{1/2}$

OXYTOCIN

- **Oxytocin** is used in obstetrics to stimulate uterine contraction and induce labor.
- Oxytocin also causes **milk ejection** by contracting the myoepithelial cells around the mammary alveoli.
- Although toxicities are uncommon when the drug is used properly, hypertension, uterine rupture, water retention, and foetal death have been reported.
- Its antidiuretic and pressor activities are much less pronounced than those of **vasopressin**.

VASOPRESSIN

- Binds to:
 - V2 receptor @ kidney -> increase water permeability and reabsorption in the collecting tubules.
 - V1 receptor @ liver, vasc. SM, other tiss. -> constriction
- **Uses:**
 - Majorly: **diabetes insipidus**.
 - management of cardiac arrest
 - controlling bleeding due to oesophageal varices.
- **AE:**
 - **major toxicities:** water intoxication and hyponatraemia.
 - **Abdominal pain, tremor, and vertigo** can also occur.
- **DESMOPRESSIN**, an analogue of vasopressin
 - has minimal activity at the V1 receptor, making it largely free of pressor effects.
 - longer acting
 - preferred for the treatment of **diabetes insipidus and nocturnal enuresis**.
 - may be administered **intranasally** or **orally**.
 - The **nasal spray** should **NOT** be used for enuresis due to reports of **seizures** in children.
 - **Local irritation** may occur with the nasal spray.

Nocturnal enuresis =
involuntary urinating when
sleeping