Magdalena Borowska
Department of Pharmacology
Pituitary and hypothalamic hormones 2023

I. Hypothalamic hormones and drugs

- GnRH – Gonadotropin-Releasing Hormone (gonadoliberines) and its analogs: goserelin and leuprolide
- Growth hormone–releasing hormone (somatoliberins GHRH), growth hormone inhibitory hormone (somatostatins GHIH) and somatostatin analogs: octreotide and lanreotide
- Prolactin-releasing hormone (prolactoliberins PRH) and prolactin-inhibiting hormone (prolactostatins): dopamin and its analogs - bromocriptine, cabergoline
- Thyrotropin-releasing hormone (TRH)
- Corticotropin-releasing hormone (CRH)

Antagonists of hypothalamic hormones

- Antagonists of Gonadotropin-Releasing Hormone GnRH: ganirelix, cetrorelix

II. Anterior pituitary hormones

- ACTH – Adrenocorticotropin (corticotropin) - controls the secretion of some of the adrenocortical hormones, which affect metabolism of glucose, proteins, and fats,

and analog: tetracosactin

- TSH – Thyroid-Stimulating Hormone (thyrotropin) - controls the secretion rate of thyroxine and triiodothyronine by the thyroid gland, and these hormones control the rates of most intracellular chemical reactions in the body
- GH – Growth Hormone (somatotropin) - promotes growth of the entire body by affecting protein formation, cell multiplication, and cell differentiation.
- Gonadotropes - Luteinizing Hormone (LH) and Follicle-Stimulating Hormone (FSH) - female: LH ovulation and development of the corpus luteum, FSH secretion of estrogen from ovary, male: LH production and secretion of testosterone, FSH production of sperm from testis
- Prolactin (PRL) - stimulates milk secretion and production

III. Posterior pituitary hormones

- Vazopressin and its analogues - desmopressin and terlipressin
- Oxytocin

Gonadoliberyn analogs (GnRH analogs) – Goserelin, Leuprolide

More stable and grater affinity for GnRH receptor than GnRH

Mechanism of action: continuously administered, leads to down-regulation of the GnRH receptor on the pituitary gland and ultimately decreased production of FSH and LH.

Pharmacological effects – chronic exposure:

Male: sustained suppression of pituitary gonadotropins, and serum levels of testosterone, sex organ regression

Female: down-regulation of the pituitary gland, suppression of gonadotropin secretion, and a decrease in serum estradiol, reduction of ovarian size and function, reduction of the size of the uterus and mammary glands

Indications (s.c., i.m.):

- benign prostatic hyperplasia (BPH)
- breast cancer (estrogen-receptor positive)
- endometriosis
- prostate cancer
- uterine leiomyoma (fibroids)
- precociouse puberty (leuprolide)
- hypogonadotropic hypogonadism (pulsatile GnRH administration)

Side effects:

- abdominal pain
- allergic reactions
- spastic states in the bronchial tree
- symptoms associated with hypoestrogenism (hot flushes, vaginal dryness, impotence)
- decreased bone mineral density, osteopenia and osteoporosis (chronic therapy > 6 months)
- increased risk of myocardial infarction

Contraindications: pregnancy, breast-feedeing, undiagnosed abnormal vaginal bleeding
Goserelin – implant s.c
Leuprolide – s.c., i.m.

Therapeutic use of hypothalamic hormones –somatostatin and analogs
Somatostatin:

- inhibits pituitary hormones secretion (GH, thyrotropin)
- inhibits pancreatic hormones secretion (insulin, glucagon, PP – pancreatic polypeptide)

as well as

- inhibits GIP, gastrin, secretin, vasoactive intestinal peptide, cholecystokinin, motilin, argininę, vasopressin, acetylcholine, serotonin secretion
- inhibits gastric acid secretion, gastrointestinal motility

Octreotide
Lanreotide
Pasireotide
have a longer half-life, greater selectivity for inhibiting glucagon, growth hormone, and insulin release
Mechanism of action: bind to the somatostatin receptor SSTR and inhibit the secretion of both pituitary and gastrointestinal hormones including serotonin, gastrin, vasoactive intestinal peptide (VIP), insulin, glucagon, secretin, motilin, pancreatic polypeptide, growth hormone, and thyrotropin.
Pharmacological effects:

- inhibition of serotonin and other gastroentero-pancreatic peptides release
- increased intestinal absorption of water and electrolytes
- decreased pancreatic and gastric acid secretions

Indications (octreotide - iv., i.m., s.c., lanreotide – s.c., pasireotide i.m.):

- ❑ upper GI and variceal bleeding (symptomatic therapy)
- ❑ prevention of complications after pancreas surgery - octreotide
- ❑ acromegaly - inhibition of growth hormone (GH)
- ❑ symptomatic therapy of neuroendocrine tumors (NETs) – demonstrate antiproliferative, antiangiogenic, and apoptotic effects in neuroendocrine tumors by activation of different intracellular signaling pathways
- ❑ control of diarrhea secondary to AIDS-associated enteropathy

Side effects:

- GI problems, long term use - cholelithiasis (15-30%), fatty stools
- hyperglycemia

Pegvisomant – growth hormone receptor antagonist – used in therapy of acromegaly (s.c.)

Therapy with radiolabeled somatostatin analogs - NETs

NETs – tumors:

- endocrine glands *(hypophysis, adrenal, parathyroid),*
- groups of endocrine cells inside glandular tissues *(thyroid, pancreas)*
- dispersed endocrine cells of the respiratory and digestive system (diffuse endocrine system – DES)

Therapy with ISOTOPES:

- ^{111}In octereotide (In – Ind)
- ^{90}Y DOTA TOC (Y – Itr)
- ^{177}Lu DOTA TATE (Lu – Lutet)
- ^{90}Y /^{177}Lu DOTA TATE – „tandem therapy"– combination of Y and Lu

Therapeutic use of hypothalamic hormones Dopamine - Prolactin PRL

Hyperprolactinemia

- ✓ pituitary tumors – *prolactinoma*
- ✓ damage to the hypothalamus or pituitary pedicle
- ✓ X-ray radiation
- ✓ diseases involving the anterior chest wall or spinal cord injury (chronic afferent stimulation mimicking nipple irritation)
- ✓ hypothyroidism
- ✓ the most common cause of hyperprolactinemia is the intake of medictions (verapamil, MAO inhibitors, estrogens, metoclopramide, neuroleptics, methyldopa, clonidine, cimetidine)

Agent used in the teratment of hyperprolactinemia:

- agonists of dopamine receptor
- ergot alcaloids: bromocriptine
- other rec. D2 agonists - anti-PRL: quinagolide, cabergoline

D2 rec. agonists – indications:

- for stopping unwanted breast milk after pregnancy – drug of choice
- benign breast desease (gynecomastia, mastopathy, recurrent mastitis in women)
- Parkinson's disease and syndrome

- acromegaly (rarely)

Contraindications for bromocriptine:
hypersensitivity to ergot alcaloids, uncontrolled hypertension, coronary artery desease and other serious cardiovascular deseases, history of severe mental disorder.

Adverse effects of dopamine agonists (anti-PRL):
- orthostatic hypotension
- nasal congestion
- mental disorders - high doses - hallucinations, confusion, psychotic, paranoid and manic states
- dry mouth

Vasopressin
- increases the resorption of water at the renal collecting ducts
- induces the release of adrenocorticotropic hormone, increases plasma cortisol concentrations, and exhibits vasopressive and contractile action on visceral smooth muscle
- stimulates the contraction of vascular smooth muscle in coronary, splanchnic, GI, pancreatic, skin, and muscular vascular beds

Vasopressin analogs:

1) Desmopressin
- is more potent and much longer acting than vasopressin (8-12 h)
- is a strong V2 agonist and has no effect on V1
- in contrast to vasopressin, desmopressin does not induce the release of adrenocorticotropic hormone or increase plasma cortisol concentrations

Indications:
- central diabetes insipidus
- nocturia in patients over 5 year of age
- hemophilia A and von Willebrand's disease - providing homeostasis

Side effects:
- skin allergic reactions
- swelling of the nasal mucosa, epistaxis (intranasal preparations)
- vomiting, stomach ache
- water retention, water poisoning
- bleeding, peripheral vasoconstriction

Desmopressin - injectable administration (i.v., s.c.), intranasal inhalation (nasal spray), oral administration (sublingual tablets).

2) Terlipressin
- is V1 rec. agonist (3-6 h)
- is potent vasoconstrictor (in the vessels of the visceral area and the skin)
- promotes intestinal peristalsis and causes uterine smooth muscle spasms, even when not pregnant

Indications:
- gastrointestinal bleeding in the course of esophageal varices, peptic ulcer, gastritis
- during procedure complicated by bleeding in the abdomen, pelvis as well as gynecological operations

Side effects:
- facial pallor

- GI problems
- rarely – heart attack, stroke (when hypertension coexists)

Terlipressin - i.v.

Therapeutic use of pituitary hormones - Oxytocin

- the pharmacologic and clinical properties of exogenous oxytocin are identical with those of naturally occurring oxytocin
- potency of its action depends on the ratio of gestagens to estrogens
- it indirectly stimulates contraction of uterine smooth muscle during gestation
- causes milk ejection after milk has been produced in the breast
- at hihgher doses has antiduretic effects

Indications:

- labor induction and augmentation
- incomplete abortion
- postpartum bleeding due to uterine atony
- insufficient postpartum uterine contraction
- breastfeeding difficulties - impaired milk secretion, prevention and treatment of mastitis in lactating women
- uterine curettage (minimizing blood loss)

Side effects:

- hypotension and reflex tachycardia

Contraindications:

- abnormal fetal position
- placenta previa
- risk of uterine rapture – cesarean section
- severe pregnancy intoxication
- increased uterine tone

Oxytocin - i.v. (half-life = 3 min.)

Therapeutic use of pituitary hormones – Somatotropin STH (GH – growth hormon)

STH, GH:

- is secreted in a pulsatile manner
- pulse frequency and intensity depends on age and gender
- secretion reflects the interplay of two hypothalamic regulatory peptides, growth hormone–releasing hormone (GHRH) and somatostatin (somatotropin release–inhibiting factor SRIF)

Somatotropin effects:

- **indirect effects mediated by somatomedin (IGF-1 and IGF-2):**

- stimulates growth resulting from stimulatory effects on osteoblast and chondrocyte activity to promote bone growth, stimulates the growth of muscle tissue.

- **direct effects on target tissue:**

- promotes glycogenolysis and increased hepatic glucose release; prolonged use of GH leads to increased insulin secretion by pancreatic beta cells
- promotes lipolysis and decreases lipogenesis leading to increased FFA level in plasma

Indications

- hypopituitarism due to somatotropin deficiency or polyhormonal hypopituitarism
- congenital growth hormon deficiency

- disorders of growth associated with chronic renal failure
- Turner syndrome
- Prader-Willi syndrome
- growth hormone deficiency with diagnosed hypothalamic-pituitary disease in adults

Side effects:

- syndroms releated to fluid retention (edema, tingling, joint stiffness, muscle pain)
- skin reactions at the site of injection
- diabetes and increased intracranial pressure
- low risk of leukemia

Somatotropin – s.c.

Gonadotropin-releasing hormone (GnRH) antagonists Ganirelix, cetrorelix

- prevent premature LH surge, supress LH production by competitively blocking GnRH receptors
- rapid and reversible supression of gonadotropin release
- indicated in women undergoing controlled ovarian hyperstimulation with FSH and HCG, followed by subsequent assisted insemination
- the main advantage is the reduction in the required fertility drug therapy per cycle from several weeks (i.e., 3 weeks) to several days, thereby increasing patient convenience
- rapid onset of action and the effects reverse rapidly
- Side effects: hot flashes, headache, injection site reaction, abdominal pain
- S.c. once a day