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PHARMACOLOGY

18/MHS07/054

PHA 304

Assignment

1. Pharmacology of the pituitary gland

Overview/Background

Master Gland--produces six major hormones, Stores two hormones: Anatomy

Midsagittal section through human pituitary

Midsagittal section of a human pituitary gland; courtesy of Robert H. Parsons, used with permission

Sagittal section of a human pituitary, showing the relationship of its blood supply to the hypothalamic neurosecretory cells in the adenohypophysis

Sagittal section of a human pituitary, showing the relationship of its blood supply to the hypothalamic neurosecretory cells in the adenohypophysis. Neurosecretory neurons are shown secreting releasing factors into the capillary networks giving rise the long and short hypophyseal portal vessels, respectively. The releasing hormones reach the hormone-secreting cells of the anterior lobe via the portal vessels.

courtesy of Robert H. Parsons, Ph.D., Rensselaer Polytechnic Institute, used with permission

Sagittal section of a human pituitary, showing the relationship of its blood supply to the neurosecretory cells of the supraoptic and paraventricular nuclei of the hypothalamus

"Sagittal section of a human pituitary, showing the relationship of its blood supply to the neurosecretory cells of the supraoptic and paraventricular nuclei of the hypothalamus. The neuron labeled N represent a neurosecretory cell releasing ADH (antidiuretic hormone) or oxytocin at its axon terminals into the capillaries giving rise to the venous drainage of the posterior lobe. "

courtesy of Robert H. Parsons, used with permission

Growth hormone (GHRH)-- anterior pituitary synthesis

growth regulation

intermediary metabolism effects

Prolactin (PRL)-- anterior pituitary synthesis

required for lactation

Luteinizing hormone (LH) & Follicle-stimulating hormone (FSH)--anterior pituitary synthesis

male and female gonadal control

Thyroid-stimulating hormone (TSH, thyrotropin)--anterior pituitary synthesis

thyroid function regulation

Adrenocorticotropin (ACTH)--anterior pituitary synthesis

regulation: adrenocortical glucocorticoid functions

Vasopressin (AVP; antidiuretic hormone, ADH) --synthesis site: hypothalamic neurons; storage site: posterior pituitary.

AVP: regulation of renal water conservation

Oxytocin: --synthesis site: hypothalamic neurons; storage site: posterior pituitary.

Oxytocin: required for milk let-down; may assist in parturition

Feedback Relationships:

Feedback between anterior pituitary and its three target glands:

gonads

if gonads fail or removed then LH & FSH increased ­ (primary hypogonadism)

adrenal cortex

with adrenal cortex destruction/removal, primary adrenal-insufficiency occurs (Addison's disease) with increased­ serum ACTH concentration

thyroid

thyroid failure leads to primary hypothyroidism resulting in increased ­ TSH

With removal/destruction of the pituitary gland, trophic hormone is lost:

Secondary hypogonadism

Adrenal-insufficiency

Hypothyroidism

With removal/destruction of the pituitary gland: no effect on vasopressin (AVP) and oxytocin provided intact hypothalamus

Pituitary Control; Hypothalamus- chemical mediation (hormones)

Hypothalamic hormonal synthesis through portal vascular system to the pituitary stalk to the pituitary anterior lobe

Pituitary stalk interruption causes:

decreased release from the anterior pituitary of: GH, LH, FSH, TSH, & ACTH

increased prolactin (hypothalamic influence is normally inhibitory for prolactin secretion)

Hypothalamic ablation:

decreased levels of GH, LH, FSH, TSH, ACTH, AVP & oxytocin

increased prolactin

Secretion Control: hypothalamic factors (peptides)

growth hormone-releasing hormone (GHRH) dominant GH release influence (+)

Somatostatin: inhibitory hormone for GH release (-)

Luteinizing hormone-releasing hormone (LHRH) -- also called gonadotropin-releasing hormone (GnRH): controls LH & FSH

Thyrotropin-releasing hormone (TRH) controls TSH release; influences prolactin release

Corticotropin-releasing hormone (CRH) & other factors control ACTH release

Dopamine: major prolactin inhibitory influence (PIF)

"Action of corticotrophin-releasing hormone (CRH) on cells of the adrenal cortex. CRH binds to membrane receptors (R), which are coupled to adenylate cyclase (AC) by stimulatory G proteins (Gs). Adenylate cyclase is stimulated and cAMP rises in the cell. cAMP activates protein kinase A (PKA), which then phosphorylates proteins (P-Proteins) involved in stimulating ACTH secretion and the expression of the POMC (proopiomelanocortin) gene. The proteolytic processing of POMC occurs in the secretory granules where it is split into several hormones, ACTH (adrenocorticotrophic hormone) and Beta-LPH (Beta-lipotropin). "

courtesy of Robert H. Parsons, Ph.D., Rensselaer Polytechnic Institute, used with permission

Pituitary and Hypothalamic Hormones

Pituitary Hormone

Hypophysiotropic Hormone

Thyrotropin (TSH)

Thyrotropin-releasing hormone (TRH) -- tripeptide

Adrenocorticotropin (ACTH)

Corticotropin-releasing hormone (CRH) -- 41 amino acids

Vasopressin (AVP); and other peptides

Luteinizing hormone (LH)

Leutinizing hormone-releasing hormone (LHRH) -- decapeptide

Follicle-stimulating hormone (FSH)

LHRH -- decapeptide

Growth hormone (GH)

Growth hormone-releasing hormone (GHRH) -- 44 amino acids

Growth hormone release-inhibiting hormone (somatostatin, GIH) -- 14 amino acids; somatostatin: also inhibits TRH-stimulated TSH release

Prolactin

Prolactin release-inhibiting factor (PIF) -- dopamine

Prolactin-releasing factor (PRL) -- peptide; TRH stimulates prolactin release

Physiological Consequences of Pituitary Tumors:

hormonal over production/under production

Pituitary tumors: most common syndromes due to:

growth hormone excess

gigantism, acromegaly

prolactin excess

galactorrhea and/or hypogonadism

ACTH-secreting tumors: Cushing's disease

TSH-secreting tumors: hyperthyroidism (rare)

Gonadotropin-secreting tumors: hypogonadism (paradoxical)

Large pituitary tumors:

hypopituitarism (due to gland compression; or pituitary stalk compression) ® visual field disturbances {optic chiasm compression}

Hypothalamic disease:

Hypopituitarism

Prolactin secretion increased

Significant Diagnostic Indication:

Diabetes insipidus (due to vasopressin {AVP} deficiency)

Anatomy: Pituitary

Pituitary gland (hypophysis) resides within Sella turcica of the sphenoid bone at the skull base (weight = between 0.4 and 0.8 grams)

Midsagittal section through human pituitary (above)

Sagittal section of a human pituitary, showing the relationship of its blood supply to the hypothalamic neurosecretory cells in the adenohypophysis (above)

Sagittal section of a human pituitary, showing the relationship of its blood supply to the neurosecretory cells of the supraoptic and paraventricular nuclei of the hypothalamus (above)

Pituitary gland components:

anterior lobe (adenohypophysis)

posterior lobe (neurohypophysis)

Separated from brain by diaphragma sella (dura mater extension) and by thin bone layers from the sphenoid sinus anteriorly and inferiorly

Sella lateral walls abut on the cavernous sinuses (containing internal carotid arteries & cranial nerves III, IV, V, and VI. Recurrent

Optic chiasm located slightly anterior to pituitary stalk -- just above diaphragma sella.

Reason why pituitary tumors result in visual field effects, cranial nerves palsies, sphenoid sinus invasion

Anatomy: Hypothalamus

1. cerebral peduncle

2. mammillary body

3. floor of hypothalamus

4. optic nerve

5. olfactory tract

image source attribution: University of Manitoba Anatomy

Hypothalamus:

anterior extension to optic chiasm margin

posterior extension including mammillary bodies

Separated from pituitary by:

hypothalamic sulcus of the third ventricle

Rounded inferior hypothalamic base: tuber cinereum

Base central portion (median eminence or infundibulum) formed by third ventricle floor, continuing inferiorly to form the pituitary stalk

Hypothalamic releasing factors synthesized in neurons located along third ventricular margins

Fibers from these neurons terminate in the median eminence adjacent to portal capillaries

Neuronal cell bodies of supraoptic and periventricular hypothalamic nuclei produce vasopressin and oxytocin which are transported along nerve axons (supraopticohypophyseal and paraventriculohypophyseal tracts) to the posterior lobe

Hypothalamic-anterior pituitary communication: chemical

Hypothalamic neuronal releasing factors flow through the portal system to stimulate or inhibit anterior pituitary hormone production

Anterior pituitary blood supply: (highest blood flow of any tissue --{0.8mL/g/min})

Blood supplied by way of the hypothalamus

Two derivatives of the internal carotid arteries (superior hypophyseal arteries {SHA} terminate in median eminence {which resides outside the blood-brain barrier} capillary network.

These capillaries exhibit a fenestrated endothelium which results in easy access to hypothalamic releasing hormones (regulation: vasoactive intestinal peptide)

Capillaries form 6-10 straight veins: the hypothalamic pituitary portal circulation -- main blood supply to anterior lobe (supply nutrients and hypothalamic factors)

Mechanisms of Hormone Action

Overview: hormone action mechanisms

Hypothalamic/Pituitary hormones: all peptides; bind to target cell surface receptors

Human Growth hormone highlighted (left); Human Growth hormone binding protein highlighted GHRH, Somatostatin, PRH, TSH, CRH, ACTH, GnRH, FSH, LH, and Dopamine receptors:

Seven-transmembrane-domain serpentine peptides

Ligand binding: conformational change (activating)

G protein coupling

G14 protein: GnRH & TRH

Gi protein: dopamine receptor

Gs protein: other receptors noted above

GHRH, CRH, GnRH, TSH, ACTH, FSH, LH, and Dopamine receptors associated G protein-GTP complex: adenylyl cyclase activation: ­cAMP production: protein kinase activation: ­intracellular protein phosphorylation: ­hormonal effects

Dopamine receptor -- Gi protein coupling (lactotroph receptor system): decreased adenylyl cyclase activity: decreased prolactin secretion

Growth hormone: a-GTP complex related to somatostatin receptors: potassium channels: inhibit growth hormone (GH) secretion

Thyrotropin-releasing hormone: G protein complexes related to thyrotrophs' TRH receptors: phosphoinositide-specific phospholipase C: cytoplasmic free calcium: stimulating TSH secretion

Growth hormone & Prolactin receptors:

single peptides

extracellular amino-terminal hormone-binding domains

intracellular carboxyl terminal sequence activates JAK2 (tyrosine kinase) leading to intracellular protein tyrosine phosphorylation and gene regulation

GH receptor fragments (GH binding protein, GHBP): bind 50% of circulating growth hormone

Growth hormone-releasing hormone (GHRH, Sermorelin) & Growth hormone-releasing peptides (GHRPs)

Overview: GHRH; GHRPs

Hypothalamic growth hormone-releasing hormone (GHRH): pituitary growth hormone (GH) secretion

GHRH belongs to a family of molecules including:

secretin, VIP, gastric inhibitory peptide (GIP), glucagon

Major site of GHRH production: arcuate nucleus hypothalamus;

GHRH receptor:

G protein-coupled transmembrane receptor

Activation: ­GH gene transcription, ­synthesis & ­GH release (cAMP mediated)

Chemistry, Pharmacokinetics, & Pharmacodynamics: GHRH & GHRP

Chemistry: GHRH & GHRP

Growth hormone-releasing hormone:

40-amino acid peptide; 44-amino acid peptide ® GH release stimulation

Activity: first 29-amino acids

Growth hormone-releasing peptides

groups of small, synthetic peptides

stimulate GH secretion (similar to GHRH)

Pharmacokinetics: GHRH & GHRP

GHRH: Routes of administration:

IV

subcutaneous

intranasal

Pharmacodynamics: GHRH & GHRP

Stimulation: growth hormone secretion only (anterior pituitary)

Clinical use: GHRH & GHRP

GHRH: evaluation of short children with subnormal GH response to:

insulin-induced hypoglycemia, oral L-DOPA, IV arginine

Normal response in this group: GH deficiency secondary to hypothalamic dysfunction

Subnormal response in this group: pituitary or hypothalamic dysfunction

Growth hormone level increase following GHRH: favorable clinical response to GHRH treatment

Toxicity: GHRH & GHRP:

facial flushing; injection site discomfort (nasal GHRP- 2-- well tolerated)

Somatostatin (Growth hormone-inhibiting hormone, Somatotropin release-inhibiting hormone)

Overview: somatostatin

14- and 28-amino acid peptide forms, most widely distributed of the hypothalamic releasing hormones

14-amino acid peptide form: more abundant, less bioactive in GH inhibition (compared to 28-of the glass of form)

Localization: hypothalamus & other CNS locations

periventricular & medial pre-optic areas of anterior hypothalamus

neurosecretory granules at nerve terminals in the median eminence

serves as neurotransmitter in the spinal cord, cerebral cortex, brain stem -- in addition to hormonal action

also gastrointestinal & pancreatic location

Pancreatic D cells (somatostatin-secreting) -- insulin & glucagon regulation {paracrine action}

Inhibits growth hormone release

also decreases GH responds to secretagogues without altering GH mRNA levels

somatostatin lowers serum TSH in response to TRH

Precursor: Prosomatostatin

Pharmacokinetics: somatostatin

half-life-- 1-3 minutes

significant renal metabolism

renal excretion

limited clinical usefulness due to short duration of action and multiple effects on many secretory processes

Overview: octreotide:

Somatostatin analog -- longer plasma elimination half-life (80 minutes)

> 40X more potent than somatostatin in inhibiting growth hormone release

only 2X more potent in decreasing insulin secretion

Clinical Use: octreotide

Relatively small effect on insulin secretion (compared to somatostatin) allows clinical use without concern for inducing hyperglycemic states

Octreotide used to manage:

acromegaly, thyrotropin-secreting pituitary adenomas & carcinoid tumors

acute bleeding control: esophageal varices

Following subcutaneous doses every eight hours: reduced symptoms from hormones secreted by hormone-secreting tumors

acromegaly

carcinoid syndrome

gastrinoma

glucagonoma

nesidioblastosis

watery diarrhea

hypokalemia

achlorhydria syndrome

"diabetic diarrhea"

Adverse Effects: octreotide

Gastrointestinal disturbances

Biliary sludge; gallstones (frequency: 20-30% {> 6 months’ treatment}; symptomatic gallstones: yearly frequency -- 1%)

Growth Hormone (Somatotropin, GH)

Overview: GH

Peptide hormone: synthesized in anterior pituitary

Growth promotion:

at open epiphyses: mechanism --

stimulation of insulin-like growth factor I (IGF-I, somatomedins C)

Promotes lipolysis: adipose tissue

Promotes skeletal muscle growth

Growth Hormone: Regulation

Type of Agent

Stimulation (+)

Inhibition (-)

Hypothalamic factors

GHRH

somatotropin

Biogenic amines

alpha-2 adrenergic receptor agonists (clonidine, norepinephrine

beta- adrenergic agonists

beta-adrenergic receptor antagonists (e.g., propranolol)

alpha-2 adrenergic receptor antagonists (e.g., yohimbine)

5-HT (serotonin) stimuli (e.g. L-tryptophan)

5-HT (serotonin) receptor antagonists (e.g., cyproheptadine, methysergide)

Dopaminergic stimuli (e.g., L-DOPA, apomorphine, bromocriptine)

Dopaminergic antagonists (e.g., chlorpromazine)

Hormones

Decreased IGF-I

Increased IGF-I

Estrogen

Progestin

Vasopressin

Glucocorticoids (acutely, glucocorticoids increase growth hormone release)

Glucagon (cholinergic-mediated)

Hypoglycemia (a-adrenergic mediated)

Increased blood sugar

Decreased free fatty acids

Increased free fatty acids

Amino acid (arginine; cholinergic-mediated)

Others

Exercise--a-adrenergic mediated

Antimuscarinic agents (e.g., atropine)

Stress--a-adrenergic mediated

Sleep --cholinergic-mediated

Cholinergic-muscarinic stimulation (e.g., pyridostigmine)

Adapted from Table 328-3 Biller, Beverly, M. K. and Daniels, Gilbert, H. Neuroendocrine Regulation and Diseases of the Anterior Pituitary and Hypothalamus, In Harrison's Principles of Internal Medicine 14th edition, (Isselbacher, K.J., Braunwald, E., Wilson, J.D., Martin, J.B., Fauci, A.S. and Kasper, D.L., eds) McGraw-Hill, Inc (Health Professions Division), 1998, p. 1979.

Chemistry:growth hormone

191-amino acid peptide

structurally similar to prolactin and chorionic somatomammotropin

recombinant DNA growth hormone

somatotropin (191-amino acid form)

somatrem (192 amino acid form (additional methionine)

Pharmacokinetics: growth hormone

Plasma have life: 20-25 minutes

Clearance: hepatic

Administration: intramuscular (peak plasma concentration: 2-4 hours)

Pharmacological Effects: growth hormone

Initial insulin-like effects

increase glucose uptake

increased amino acid uptake

decreased lipolysis

Delayed anti-insulin effect -- impaired glucose uptake; increase lipolysis

Promotes longitudinal growth indirectly through:

Somatomedins, insulin-like growth factors (IGFs)

­ GH stimulates growth plate cartilage & liver synthesis of:

IGF-I I & IGF-I II

Somatomedins: mediator of processes promoting bone growth --e.g., increased of DNA thymidine incorporation & increased RNA uridine incorporation --

­cellular proliferation

­ increased proline to hydroxyproline conversion (cartilage synthesis)

GH deficiency: reduced somatomedin: short stature

Short stature:

IGF-I deficiency (in the presence of high GH): Laron dwarfism

Absence of IGF-I pubertal surge (pygmies)

Criteria for growth hormone deficiency:

growth rate index -- < 4 cm/year

lack of increase serum GH following growth hormone secretagogue challenge

Causes of congenital growth hormone deficiencies:

Most frequent cause: lack of hypothalamic growth hormone-releasing factors, usually due to pit-I gene abnormality

hypophyseal-pituitary disease, e.g. craniopharyngiomas

Growth hormone deficiency manifestation of the newborn:

seizures

hypoglycemia

GH deficiency often associated with multiple pituitary hormonal deficiencies

Growth Hormone-Responsive Clinical Conditions

GH deficiencies

some non-GH deficiencies -- delayed bone age/slow growth rate + GH: increased growth (short-term GH treatment)

Girls with Turner's syndrome: high-dose treatment effective

Adverse Effects: growth hormone

Following rapid growth:

slipped capital femoral epiphyse: limp; lower extremity pain (rare)

leukemia incidence (slight increase -- may not be causal)

Screening suggested for hypothyroidism & diabetes during GH treatment

Impairment of GH response:

untreated hypothyroidism

diabetes mellitus/diabetes insipidus

Thyrotropin-Releasing Hormone (Protirelin, TRH)

Overview: thyrotropin-releasing hormone, TRH

Tripeptide

Location: hypothalamus (and other brain regions)

TRH: portal venous system: pituitary stimulation: thyroid-stimulating hormone (TSH, thyrotrophic) production: thyroid-stimulation and release: thyroxine (T4) & triiodothyronine

TRH stimulation of thyrotropin:

blocked by thyroxine

enhanced by thyroxine deficiency

Chemistry/pharmacokinetics: TRH

Glu-His-Pro-NH2

IV administration

plasma half-life: 4-5 minutes

Pharmacodynamics: TRH

Hyperthyroidism: serum thyrotropin level reduced

Primary hypothyroidism:

thyrotropin levels: high

enhanced thyrotropin response to TRH

Secondary (pituitary) hypothyroidism:

thyrotropin serum levels: low (by sensitive TSH assay) or "inappropriately normal"

TSH often does not increase after TRH

Tertiary (hypothalamic) hypothyroidism:

serum thyrotropin levels: normal or low

thyrotropin response to TRH: normal or attenuated

TRH infusion:

­ increased prolactin released by the pituitary

no effect on growth hormone or ACTH

Pituitary tumors:

some pituitary tumors:

release growth hormone in response to TRH (acromegaly)

release ACTH in response to TRH (Cushing's disease)

failure to release prolactin (prolactinoma).

Thyroid-Stimulating Hormone (Thyrotropin, TSH)

Overview: thyrotropin, TSH

Anterior pituitary hormone

Thyroid function regulation -- stimulation of thyroxine & triiodothyronine production and release

Chemistry: thyrotropin, TSH

consists of two peptides (a and b) with associated carbohydrate side chains

Therapeutic thyrotropin:

source -- bovine anterior pituitaries

homology between bovine & human peptides: 70% (a) & 90% (b).

TSH-b subunit provides thyroid specificity since TSH-a subunit is nearly identical to a subunit of FSH, LH, hCG.

Pharmacokinetics: thyrotropin, TSH

Route of Administration:

intramuscular

subcutaneous

half-life: one-hour

renal degradation

Pharmacodynamics: thyrotropin, TSH

Thyrotropin: thyroid cell adenylyl cyclase activation: increased cyclic AMP production: ­ increased iodine uptake: ­increased thyroid hormone production

Clinical Use: thyrotropin, TSH

Diagnostic/therapeutic:

possible diagnostic use in a metastatic thyroid carcinoma

bovine TSH: top toxic for therapeutic stimulation of radioactive iodine for treatment of metastatic thyroid carcinoma

Corticotropin-Releasing Hormone (CRH)

Overview: corticotrophin-releasing hormone, CRH

hypothalamic hormone;

stimulates ACTH & b-endorphins pituitary release.

Chemistry: corticotropin-releasing hormone, CRH

Human CRH: 41-amino acid peptide

Pharmacokinetics: corticotropin-releasing hormone, CRH

Route of Administration: IV

serum half-life (first phase): approximately nine minutes

widely metabolized; < 1% excreted unchanged in the urine

Pharmacodynamics: corticotropin-releasing hormone, CRH

Diagnostic use only:

Cushing's syndrome -- distinguishing between Cushing's disease and ectopic ACTH secretion-- limited usefulness;

Adrenocorticotropin (corticotropin, ACTH, ACTH1-24 )

Overview: ACTH

peptide hormone;

synthesis site: anterior pituitary

Major endocrine function: stimulation of cortisol synthesis & release from adrenal cortices

Synthetic corticotropin-derivative use clinically to assess adrenocortical status

reduced adrenocortical response to corticotropin administration: adrenocortical insufficiency

Chemistry: ACTH

single 39-amino acid peptide

amino acids 1-24: required for full biological activity

amino acids 25-39: species specificity

Synthetic, human ACTH1-24: cosyntropin

Amino terminal sequence (1-13): identical to melanocyte-stimulating hormone (a-MSH)

with excess ACTH pituitary secretion hyperpigmentation due to a-MSH activity due to ACTH

Pharmacokinetics: ACTH

Porcine & synthetic corticotropin: well absorbed following intramuscular administration

Corticotropin: no oral administration due to GI proteolysis

half-life: < 20 minutes

Tissue concentration: in liver & kidney

Pharmacodynamics: ACTH

ACTH stimulates adrenal cortex to produce glucocorticoid, mineralocorticoid, & androgen.

ACTH increases cholesteryl esters activity ( cholesterol: pregnenolone step: rate-limiting in steroid hormone production)

ACTH promotes adrenal hypertrophy & hyperplasia

corticotropin may cause increased in skin pigmentation

Clinical Use:ACTH

ACTH adrenal stimulation: inadequate response in adrenal-insufficiency

Cosyntropin may be used rule out adrenal-insufficiency

following cosyntropin, plasma cortisol should exceed 18 ug/dL

subnormal response: primary or secondary adrenocortical insufficiency

Primary adrenocortical insufficiency: increased endogenous plasma ACTH levels

Secondary adrenocortical insufficiency: decreased endogenous plasma ACTH levels

Differentiation of "late-onset" (non-classic) congenital adrenal hyperplasia from states of ovarian hyperandrogenism

21-hydroxylase deficiency: ACTH stimulation: incremental increase in plasma 17-hydroxyprogesterone (substrate for the deficient enzyme)

11-hydroxylase deficiency: ACTH stimulation: increase 11-deoxycortisol

3-b-hydroxy-D 5 steroid dehydrogenase deficiency: ACTH stimulation: increase in 17-hydroxypregnenolone

Therapeutics: corticotropin -- no advantage over direct glucocorticoid administration

Gonadotropin-Releasing Hormone (GnRH., luteinizing hormone-releasing hormone {LHRH};Gonadorelin)

Overview: Gonadotropin-releasing hormone (GnRH)

Synthesis site: arcuate nucleus of the hypothalamus

Controls gonadotropins FSH & LH release

Chemistry:GnRH

decapeptide

For pharmacological use -- synthetic forms (analogs)

Leuprolide, nafarelin, buserelin, goserelin, histrelin

Synthetic forms -- more potent & longer lasting then GnRH

Pharmacokinetics:GnRH

GnRH Route of Administration: IV or subcutaneous

GnRH analogues Route of Administration: subcutaneous, nasal spray, intramuscular

GnRH half-life: 4 minutes

GnRH analog half-life: three hours

Sites of degradation: hypothalamus & pituitary

Pharmacodynamics:GnRH

Binding site: receptors on pituitary gonadotropes

pulsatile IV administration (frequency every 1-4 hours): FSH & LH secretion stimulation

continuous GnRH administration (or GnRH analog depot formulation): inhibition of gonadotropin release

Clinical Uses:GnRH

Diagnostic Applications:GnRH

Assessment of delayed puberty-- (a) constitutional delay or (b) hypogonadotropic hypogonadism

LH response to GnRH distinguishes between causes.

Following subcutaneous GnRH bolus:

peak LH response > 15.6 mIU/mL: normal {indicating puberty will occur soon}

peak LH response impaired suggests hypogonadotropic hypogonadism (probably indicative of pituitary/hypothalamic dysfunction {could be still seen in constitutional adolescence delay})

Therapeutic Applications: GnRH

Stimulation: Infertility due to hypothalamic hypogonadotropic hypogonadism (both sexes)

GnRH: stimulation of pituitary function

programmable pump technology allows pulsatile GnRH treatment (frequency: every 90 minutes)

Inhibition: management of prostate cancer, uterine fibroids, endometriosis, polycystic ovary syndrome, precocious puberty

by continuous administration of GnRH analog agonists {leuprolide, nafarelin, goserelin and, histrelin}

Other uses:

in vitro fertilization approaches: GnRH analog

suppression of endogenous gonadotropin release

then exogenous gonadotropins added to promote synchronous follicular development.

Toxicity: GnRH

For diagnosis, occasional headache, abdominal discomfort, flushing

GnRH analogs: initial bone pain exacerbation in prostate cancer & hot flushes {both sexes}

Increased risk of osteoporosis in women if treatment > 6 months duration

Follicle-Stimulating Hormone (FSH)

Overview:FSH

Glycoprotein hormone

Synthesis site: anterior pituitary

Function:FSH

FSH + LH (luteinizing hormone): gonadal function regulation-- mediated by increasing cAMP levels in gonadal tissue

FSH -- principal function:

gametogenesis and follicular development stimulation in women

spermatogenesis in men

FSH site of action: immature ovarian follicular cells: promoting development of the mature follicle and oocyte

FSH + LH required for correct ovarian steroidogenesis

{LH stimulates and production; FSH stimulates androgen conversion into estrogens (granulosa cells)}

Testes-- Site of action for FSH: Sertoli cells, enhance androgen-binding protein production

Modified FSH molecules

Obtained from postmenopausal women's urine

one agent --FSH-like characteristics; 4% potency

another agent --LH-like characteristics

FSH-LH combination: menotropins

Another preparation: also from postmenopausal women's urine but with no LH is urofollitropin

Leutinizing Hormone (LH)

Glycoprotein hormone (two chains)

Site of synthesis: anterior pituitary

Major physiological role:

regulation of gonadal steroid hormone production

Site of action-- male:

testicular Leydig cells: stimulation of testosterone production

Site of action -- female:

mature follicle: induce ovulation;

stimulation of corpus luteum (in menstrual cycle luteal phase): to produce progesterone & androgens

Note: no LH preparation available for clinical use. Human chorionic gonadotropin (very similar structure) may be used as a leutinizing hormone substitute

Gonadotropins (hMG, Menotropins & FSH, Urofollitropin)

Overview:gonadotropins

Human menopausal gonadotropins (hMG): Composition

mixture, partially catabolized human FSH & LH {extraction -- postmenopausal women's urine}

standardized for FSH & LH content

used for treating infertility --

in women: stimulation of ovarian follicle development

in man: spermatogenesis

both sexes: hMG must be used with luteinizing hormone (human chorionic gonadotropin, hCG) to ensure:

ovulation implantation women

testosterone production & full masculinization in men

Pharmacokinetics:gonadotropins

7-12 day course daily hMG or urofollitropin (simulating ovarian cycle follicular phase in women with hypothalamic amenorrhea):

FSH levels increase to 2X baseline;

LH levels increase to 1.5X baseline (hMG only; not with urofollitropin)

Pharmacodynamics:gonadotropins

Women: hMG or FSH treatment of gonadotropin-deficient women: ovarian follicular growth/maturation

Ovulation: chorionic gonadotropin requirement following follicular maturation

Men with gonadotropin deficiency: chorionic gonadotropin pre-treatment: external sexual maturation

Subsequent hMG treatment: permatogenesis, fertility

Clinical Use:gonadotropins

Indication: pituitary or hypothalamic hypergonadism with infertility

Population of anovulatory women would these conditions may benefit from human menopausal gonadotropin:

primary amenorrhea

secondary amenorrhea

polycystic ovary syndrome

anovulatory cycle

hMG & FSH: used in in vitro fertilization programs for ovarian hyperstimulation

Men with hypogonadotropic hypogonadism become fertile following hMG administration: success frequency = 50%.

Toxicity: gonadotropins

Ovarian overstimulation with hMG: ovarian enlargement (uncomplicated) -- frequency 20% of patients

"Hyperstimulation syndrome": more serious: frequency = 0.5-4%

hMG-induced ovarian enlargement

ascites

hydrothorax

hypovolemia (shock may occur)

hemoperitoneum (secondary to ruptured ovarian cyst)

fever

arterial thromboembolism

Possible abnormal development/premature corpus luteum degeneration in some patients

in men: gynecomastia -- occasionally

Other Effects:gonadotropins

frequency multiple births following hMG treatment: 25%

Contraindications:gonadotropins

Human menopausal gonadotropin and urofollitropin should not be used in the presence of uterine, tubal, or ovarian diseases or pregnancy

Hypothalamic/ Pituitary Agents

Generic

Trade name

bromocriptine

Parlodel

chorionic gonadotropin (hCG)

generic, Profasi

corticotropin

generic, ACTH

cosyntropin

Cortrosyn

desmopressin

DDAVP, Stimate

gonadorelin acetate (GnRH)

Lutrepulse

gonadorelin hydrochloride (GnRH)

Factrel

goserelin acetate

Zoladex

histrelin

Supprelin

leuprolide

Lupron

menotropins (hMG)

Pergonal, Humegon

nafarelin

Synarel

octreotide

Sandostatin

oxytocin

generic, Pitocinit, Syntocinon

pergolide

Permax

protirelin

Thypinone, Relefact TRH

sermorelin (GHRH)

Geref

somatrem

Protropin

somatropin

Humatrope, Nutropin

thyrotropin (TSH)

Thytropar

Human Chorionic Gonadotropin (hCG)

Overview:hCG

hCG -- produced by the placenta; excreted into the urine

glycoprotein; 92-amino acid a-chain + 145-amino acid b-chain.

a-chain-- closely resembles FSH, LH, TSH a-chain

b-chain-- closely resembles LH b-chain

Similar to LH structurally;

Used to treat women & men with LH deficiency

Function:hcG

Ovarian corpus luteum stimulation to produce progesterone

placental maintenance

Pharmacokinetics:hCG

intramuscular administration; well-absorbed

half-life: 8 hours (compared to LH half-life -- 30 minutes)

Pharmacodynamics:hCG

human chorionic gonadotropin (hCG) stimulates gonadal steroid hormone production

Cells affected:

female: interstitial & corpus luteum cells produce progesterone

male: Leydig cells produce testosterone

hCG administration: simulates midcycle LH surge: promote ovulation in hypogonadotropic states

Clinical Uses:hCG

Diagnostic:hCG

pre-pubertal boys with undescended gonads: hCG can distinguish between retained testes (cryptorchid) and retracted testes (pseudocryptorchid)

if transient testicular descent occurs with hCG administration: permanent pubertal descent

if transient testicular descent does not occur with hCG administration, orchiopexy will be required to insurer spermatogenesis

Constitutional puberty delay vs. hypogonadotropic hypogonadism: distinguished using repetitive hCG administration

with hCG administration: serum testosterone & estradiol levels increase in constitutional puberty delay -- not in hypogonadotropic hypogonadism states

Therapeutic:hCG

hCG + human menotropin: ovulation in women with hypogonadotropic hypogonadism or as part of in vitro fertilization approach

hCG: testicular testosterone stimulation in men with hypogonadotropic hypogonadism (increased intratesticular testosterone: promotes spermatogenesis; menotropins often also required for fertility)

Toxicity:hCG

headache, edema, gynecomastia, pretentious puberty, depression, hCG antibody production (rare)

Contraindications:hCG

presence of androgen-dependent neoplasia

presence of precocious puberty

Prolactin

Structure:prolactin

198-amino acid peptide

Site of production: anterior pituitary

resembles growth hormone

Function:prolactin-- hormone primarily responsible for lactation

lactation requires appropriate circulating concentrations of progestins, estrogen, corticosteroids & insulin.

Abnormal prolactin levels:

Deficiency:prolactin-- may be associated with pituitary deficiency states

Manifestations:

lactation failure

luteal phase defect

Excess:prolactin --may be associated with hypothalamic destruction due to reduced dopamine delivery to the pituitary {dopamine = prolactin-inhibiting hormone}

Hyperprolactinemia may cause:

galactorrhea

hypogonadism

Hyperprolactinemia symptomatic management:

administration of bromocriptine & other dopamine agonists inhibit prolactin secretion

Bromocriptine and Other Dopamine Agonists

Overview:bromocriptine & other dopamine agonists

Bromocriptine:

Background:bromocriptine

most widely used drug for treating hyperprolactinemia

ergot derivatives: dopamine agonist properties

decreases serum prolactin

shrinks pituitary (prolactin-secreting) tumors

Mechanism of Action:bromocriptine

dopamine-like action

Site of action:

reduces dopamine turnover in the tuberoinfundibular neurons of the arcuate nucleus (increasing hypothalamic dopamine)

pituitary: activates dopamine receptors causing prolactin release inhibition

Effects on other hormones:

normal subjects: increases pituitary growth hormone release

patients with acromegaly: suppresses growth hormone release (paradoxical response)

Pergolide -- also used for hyperprolactinemia management

Clinical Uses:bromocriptine

Prolactin-secreting adenomas

bromocriptine-- initial treatment

85% response rate at six months-- judged by tumor size reduction and decreasing serum prolactin levels

Amenorrhea-Galactorrhea:

bromocriptine -- management of clinical sequelae of hyperprolactinemia, including:

amenorrhea, galactorrhea, infertility, hypogonadism

amenorrhea/galactorrhea recurrence if treatment is discontinued

Physiologic lactation:

bromocri

ptine-prolactin secretion suppression following parturition/abortion ® prevents breast engorgement when breastfeeding not desired/required

possible increase in stroke risk in women receiving bromocriptine postpartum

Acromegaly:

bromocriptine +/- pituitary surgery, radiation therapy, octreotide: treatment of acromegaly

bromocriptine responsiveness in these patients depends on prolactin as well as growth hormone secretion by pituitary tumor

Parkinson's Disease:

Bromocriptine:

Overview:bromocriptine

ergot alkaloid--partial agonist at presynaptic dopamine D2 receptors

Used to treat hyperprolactinemia (at lower doses)

Oral administration; variably absorbed from the GI tract; the plasma levels -- 1-2 hours

Excreted in bile & feces

Clinical Use:bromocriptine

first-line drug in Parkinsonism

compared with levodopa: less likelihood of response fluctuation and dyskinesias

Variable clinical use of bromocriptine (sometimes early in treatment; sometimes prescribed to patients becoming refractory to levodopa)

customization of levodopa and bromocriptine required on a patient to patient basis to achieve optimal clinical response

Hypotensive reaction to bromocriptine: care required during initial dosing

Stop Treatments If: psychiatric disturbance, ergotism, cardiac arrhythmia, erythromelalgia (painful, swollen feet)

Adverse Effects: bromocriptine:

In patients with small pituitary adenomas:

discontinue following conception since adenoma growth does not occur during pregnancy

Patients with large pituitary adenomas:

discontinue but monitor for tumor progression: if tumor growth persists during pregnancy, bromocriptine will be required

Gastrointestinal:bromocriptine

Common initial side effect: anorexia, nausea, vomiting {reduced when medication is taken with food)

Others GI side effects:

constipation, dyspepsia, symptoms of reflux esophagitis

peptic ulceration with bleeding

Cardiovascular:bromocriptine

Common: postural/orthostatic hypotension (early in therapy)

digital vasospasm -- occurs with long-term treatment {reversible by decreasing dosage}

cardiac arrhythmias: indication for drug discontinuation

Dyskinesias:bromocriptine

similar to levodopa dyskinesias; reduction in total dopaminergic agents indicated

Mental Disturbances:bromocriptine

More common/severe with bromocriptine than with levodopa. Symptoms include:

confusion, hallucinations, delusions, etc.

psychiatric effects dissipate with drug discontinuation

Miscellaneous Adverse Effect:bromocriptine

headache, nasal congestion, pulmonary infiltrates, erythromelalgia (may be associated with arthralgia), increased arousal

Posterior Pituitary Hormones

Overview:posterior pituitary hormones

Oxytocin

Vasopressin

Synthesis Site:

hypothalamus: posterior pituitary: stored : released

Oxytocin:Overview

Levels:

physiologic levels:cause milk ejection in lactating women

pharmacological doses:

induce uterine contraction/maintain labor

Chemistry:oxytocin

9-amino acid peptide

Pharmacokinetics: oxytocin

IV administration for labor stimulation

nasal spray: postpartum lactation induction

catabolism: renal & hepatic

half-life: (circulating) 5 min.

Pharmacodynamics: oxytocin

influences ionic currents in myometrial smooth muscle : uterine contraction

uterine sensitivity to oxytocin: ­ increases in pregnancy

inhibition of oxytocin-induced myometrial uterine contraction:

magnesium sulfate

b-adrenergic receptor agonists

inhalation anesthetics

promotes myoepithelial cell contraction (surrounding mammary alveolar) : milk ejection

normal lactation requires oxytocin

Clinical Uses:oxytocin

Diagnostic Applications:oxytocin

Checking placental circulatory reserve:

IV oxytocin near-term: uterine contractions: decrease fetal blood supply: fetal heart rate response monitored (abnormal response may suggest intrauterine growth retardation; may suggest advisability of cesarean section

Therapeutic Uses:oxytocin

labor induction

promoting dysfunctional labor

when early vaginal delivery is required

Rh factor concerns, maternal diabetes, preeclampsia

uterine inertia

incomplete abortion

control of postpartum uterine bleeding

enhance impaired milk ejection (nasal Route of Administration)

Toxicity:oxytocin

serious toxicity: rare

reported adverse reactions include: hypertensive reactions, uterine rupture, water intoxication, fetal death, afibrinogenemia

Contraindications:oxytocin

fetal distress, abnormal fetal presentations, factors predisposing to uterine rupture

Vasopressin:Overview:

peptide hormone

released by posterior pituitary in reaction to:

rising plasma tonicity

decreasing blood pressure

antidiuretic properties

vasopressor properties

vasopressin deficiency: : diabetes insipidus

Structure:vasopressin

nonapeptide

Pharmacokinetics:vasopressin

Routes of administration:

IV, intramuscular, intranasal

half-life: 20 minutes

Renal & hepatic catabolism

minimal vasopressin excreted unchanged in the urine

Pharmacodynamics:vasopressin

Receptor types:

V1-- vascular smooth muscle (vasoconstriction)

V2 -- renal tubule cells: antidiuresis

Mechanism: (1) increased water permeability and (2) increased collecting tubule water resorption

extrarenal V2 receptors--promote coagulation factor VIIIc and von Willebrand factor release.

Desmopressin acetate (DDAVP, 1-desamino-8-D-arginine vasopressin)

synthetic vasopressin derivative

long-acting

limited V1 receptor activity

significant antidiuretic/vasopressor ratio compared to vasopressin (4000: 1)

Clinical Use:vasopressin

Vasopressin & desmopressin: alternative treatment for pituitary diabetes insipidus

Nocturnal enuresis (desmopressin at bedtime) -- mechanism: reduced night urine production

IV vasopressin: may be effective in managing esophageal variceal bleeding and colonic diverticular leading

Toxicity:

Vasopressin (not desmopressin): vasoconstriction -- cause issues in patients with coronary vascular disease

Unusual side effects include: agitation, allergic reactions, abdominal cramping, headache, nausea.