Hypothalamic &Anterior pituitary hormones

GROWTH HORMONE (SOMATOTROPIN)

Pharmacodynamics

- Mediates its effects via cell surface receptors of the JAK/STAT cytokine receptor superfamily
- Has complex effects on
  - growth, body composition
  - carbohydrate, protein, and lipid metabolism
- The growth-promoting effects are mediated through IGF-1
- GH has anabolic effects in muscle and catabolic effects in lipid cells

Clinical Pharmacology

- GROWTH HORMONE DEFICIENCY
- PEDIATRIC PATIENTS WITH SHORT STATURE
- Other Uses of Growth Hormone

Clinical uses of recombinant human growth hormone

Primary Therapeutic Objective	Clinical Condition
Growth	Growth failure in pediatric patients associated with: Growth hormone deficiency Chronic renal failure Prader-Willi syndrome Turner syndrome
	Small for gestational age with failure to catch up by age 2
	Idiopathic short stature in pediatric patients
Improved metabolic state, increased lean body mass, sense of well-being	Growth hormone deficiency in adults
Increased lean body mass, weight, and physical endurance	Wasting in patients with AIDS
Improved gastrointestinal function	Short bowel syndrome in patients who are also receiving specialized nutritional support

Parder-Willi Syndrome: occurs during pregnancy associated with hormone deficiency, hypotonia and poor weight gain.

Turner Syndrome: missing one X of the chromosomes. asssociated with short stature and failure of ovaries.

Toxicity & Contraindications

- A rarely reported side effect is intracranial hypertension, which may manifest as vision changes, headache, nausea, or vomiting

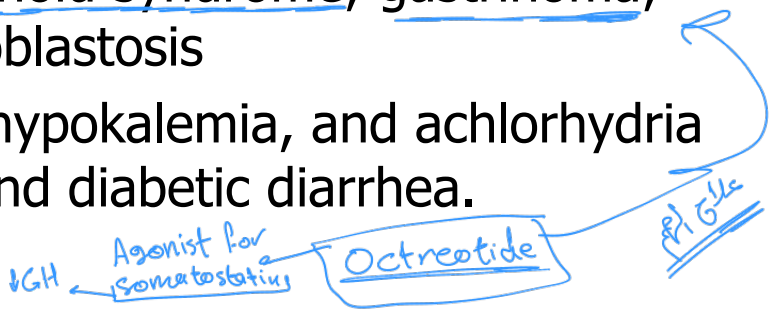
MECASERMIN DRUG

- Is a complex of
  - recombinant human IGF-1 (rhIGF-1)
  - recombinant human insulin-like growth factor-binding protein-3 (rhIGFBP-3)
- For treatment of severe IGF-1 deficiency
- The most important adverse effect is hypoglycemia

GROWTH HORMONE ANTAGONISTS

- **Somatostatin**
  - **It inhibits the release of GH, glucagon, insulin, and gastrin**
  - **has limited therapeutic usefulness**
- **Octreotide**
  - reduces symptoms caused by a variety of hormone-secreting tumors
    - acromegaly; the carcinoid syndrome; gastrinoma; glucagonoma; nesidioblastosis
    - the watery diarrhea, hypokalemia, and achlorhydria (WDHA) syndrome; and diabetic diarrhea.

Nesidioblastosis: Proliferation of Beta cells of islets of langerhans along side with hypertrophy (Dysfunction).



Pegvisomant

Q/All the Following except ---

- Is a GH receptor antagonist
- Useful for the treatment of acromegaly
- The polyethylene glycol (PEG) derivative of a mutant GH, B2036,

THE GONADOTROPINS

Hypothalamus → Gonadotropine releasing Hormone
↓
Anterior pituitary
↓
LH, FSH

- FSH
- LH
- human Chorionic Gonadotropin (hCG)
- Are dimers that share
  - an identical α chain
  - in addition to a distinct β chain

Chemistry & Pharmacokinetics

- MENOTROPINS: is a Drug causes stimulation of ovaries.
- FOLLICLE-STIMULATING HORMONE
  - **Urofollitropin**,
  - **follitropin alfa** and **follitropin beta**
- LUTEINIZING HORMONE
  - **Lutropin**,
- HUMAN CHORIONIC GONADOTROPIN

Goal of Drugs? to treat INFERTILITY

Pharmacodynamics

- Effects through G protein-coupled receptors

Clinical Pharmacology

- OVULATION INDUCTION
  - to induce ovulation in women with anovulation due to:
    - hypogonadotropic hypogonadism
    - polycystic ovary syndrome
    - obesity
- MALE INFERTILITY ⇒ The man can't impregnate the woman after 1 year of regular sexual intercourse.

POS: a condition in which the ovaries produce an abnormal amount of androgens, male sex hormones that are usually present in women in small amounts. ✗

Toxicity & Contraindications

- **ovarian hyperstimulation syndrome**
- **multiple pregnancies**
- Headache, depression, edema, precocious puberty

contra

toxicity

GONADOTROPIN-RELEASING HORMONE & ITS ANALOGS

- *Pulsatile* GnRH secretion is required to stimulate the gonadotroph cell to produce and release LH and FSH
- Sustained, *nonpulsatile* administration of GnRH or GnRH analogs *inhibits* the release of FSH and LH by the pituitary

Chemistry & Pharmacokinetics

- **STRUCTURE**
  - GnRH is a decapeptide (10) found in all mammals
  - **Gonadorelin** is an acetate salt of synthetic human GnRH
  - Synthetic analogs include **goserelin, histrelin, leuprolide, nafarelin**, and **triptorelin**.
- **PHARMACOKINETICS**
  - GnRH analogs can be administered subcutaneously, intramuscularly, via nasal spray or as a subcutaneous implant

Nafa siad: lets go to his trip

Q) All, except!

Pharmacodynamics

- GnRH exhibit complex dose-response relationships that change dramatically from the fetal period through the end of puberty.

Clinical Pharmacology

- STIMULATION
  - Female infertility
  - Male infertility
  - Diagnosis of LH responsiveness
- SUPPRESSION
  - Controlled ovarian hyperstimulation
  - Endometriosis
  - Uterine leiomyomata (uterine fibroids)
  - Prostate cancer
  - Central precocious puberty → Before the age of 12 or 13
  - Other
    - advanced breast and ovarian cancer

Toxicity

about to faint

- Headache, light-headedness, nausea, and flushing
- Contraindications to the use of GnRH agonists in women include
  - pregnancy and breast-feeding

GNRH RECEPTOR ANTAGONISTS

- **Ganirelix** and **cetrorelix**
  - Pharmacokinetics
    - absorbed rapidly after subcutaneous injection
  - Clinical Pharmacology
    - preventing the LH surge during controlled ovarian hyperstimulation
  - Toxicity
    - nausea and headache

PROLACTIN

- Is a 198-amino-acid peptide hormone
- Its structure resembles that of GH

- Prolactin ⇒ synthesis of the milk from the mammalian glands in the breasts

- Oxytocin ⇒ ejection of the milk from the breast.

DOPAMINE AGONISTS

- **Bromocriptine , cabergoline, pergolid and Quinagolide**
- **Pharmacokinetics**
  - All available dopamine agonists are active as oral preparations
- **Clinical Pharmacology**
  - HYPERPROLACTINEMIA
  - PHYSIOLOGIC LACTATION => Doesn't want to lactate.
  - ACROMEGALY
- **Toxicity & Contraindications**
  - **nausea, headache, light-headedness, orthostatic hypotension, and fatigue**

DRUGS USED IN DIABETES MELLITUS

Oral antidiabetes drugs

- Main drug classes can classified according to,
- (How drugs have been developed)
- Efficacy الفاعلية
- Safety
- Suitability
- Availability
- Cost
- Drug interactions
- New drug classes & their place in therapy

Main oral antidiabetes drug classes for type 2 diabetes

Considering the defects in type 2 diabetes

- Drugs to increase ***insulin secretion***

  1. **Sulphonylureas**

- Drugs to improve ***insulin action*** (Insulin sensitivity)

  2. **Biguanides**

Sulphonylureas: classification

1st generation

- **Tolbutamide**
- Tablet strength 500mg
- T ½ 8 hours
- 1-3 times/day
- Max. daily dose 2g
- With meals

- Chlorpropamide

2nd generation

- **Glibenclamide**
- Tablet strength 5mg
- T ½ 10 hours
- 1-2 times /day
- Max. daily dose 15mg
- With meals
- (up to10mg before breakfast >10mg add before dinner)

- *Glipizide**
- *Gliclazide**

Sulphonylureas

- Chance of hypoglycaemia with sulphonamides
- First used for diabetes in 1954
- Efficacy: very effective (good blood glucose lowering capacity)
- Potency: glibenclamide>tolbutamide
- Hypoglycaemia: glibenclamide> tolbutamide

2nd generation

1st generation

SU: mechanism of action

Main action

- Promote insulin secretion ("secretogauge") by degranulation of beta cells of the pancreas (release of stored insulin)

- Action by closure of K channels on the beta cell membrane and facilitate Ca^{++} entry to beta cells

Other possible actions (long term effects)

- Increase insulin receptor number at target tissue
- Increase glucose uptake by muscle
- Reduced glycogenolysis

Pharmacokinetics

- Well absorbed from GIT ⇒because it's oral
- Highly protein bound
- Metabolized in the liver
- Excreted by the kidneys
- Some drugs have active metabolites

Sulphonylureas: indications

- Non obese type 2 diabetes: not responding to dietary therapy

- Non obese Type 2 diabetes: presenting with a complication

  eg. a foot ulcer, UTI (together with dietary therapy)

Adverse effects

common

- ***Hypoglycaemia***

More with long t ½ drugs

Tolbutamide causes

Prolonged hypoglycaeamia

t ½ 36 hours

Weight gain

very rare

- Nausea.vomiting,diarrhoea
- Neutropenia, low platelets
- Skin rashes: ***erythema multiforme, Steven Johnson syndrome***
- Jaundice with chlorpropamide ⇒ because of the active metabolite.
- Disulfiram like reaction with chlorpropamide (N+V)
- Liver impairment

Contraindications / cautions

- Type 1 diabetes
- Pregnancy
- Breast feeding
- Liver disease
- stressful states eg, severe infections, MI, surgery
- Hyperglycaemic emergencies (DKA & HONK)

Caution

- Renal impairment
- Elderly
  (tolbutamide has a short half life and is not excreted by the kidneys, hence is preferred to glibenclamide)

Sulphonylurea(SU) failure

- Failure to lower blood glucose with SU

  Primary failure

- If it occurs with in 1 month of starting therapy

  Secondary failure

- due to beta cell exhaustion and failure to produce insulin and insulin resistance

  Insulin therapy is recommended for both types

Tolbutamide

- Short acting
- Metabolized in the liver
- Safer in patients with renal impairment
- Safer in elderly

Chlorpropamide.

- Longer duration of action
- Risk of prolonged hypoglycaemia
- Should not be used in elderly

Glibenclamide

- Widely used
- Can be given as a single daily dose
- Started with a daily dose of 5mg in the morning before breakfast
- Max dose is 15 mg/day

Biguanides

metformin 500mg

Mechanism of action

- *Increase glucose uptake by muscle in the presence of insulin*
- *Increase* **insulin receptor number and affinity** *of target tissue*
- *Inhibition of hepatic* ***gluconeogenesis***
- *Reduced intestinal glucose absorption*
- *Reduced appetite and weight loss*

Metformin: Pharmacokinetics and indications

- Well absorbed
- Renal excretion (unchanged)

Indications

- Obese type 2 diabetes not responding to diet alone
- Obese type 2 diabetes presenting with a complication such as UTI or a foot ulcer
- Type 2 diabetes: when hypoglycaemia is a risk to life

Metformin: Adverse effects

Common

- ***Gastrointestinal disturbances***
- Anorexia , nausea, vomiting, diarrhoea
- Malabsorption
  (B12 absorption)

Start with a low dose
Immediately after meals
1-3 times /day
Max daily dose 3g (1gx3)

Rare

- ***Lactic acidosis***
  (A serious condition)
- ***Hypoglycaemia***
  (Very rare)

Metformin:

contraindications and caution

- Major organ failure (liver, heart, respiratory, renal)
- Radiological investigations with contrast (dye)
- Pregnancy & breast feeding
- Surgery (perioperative)
- Type 1 diabetes
- Hyperglycaemic emergencies

Caution

- Elderly and people with renal impairment
  Use a lower daily dose (<2g)

Comparison of

Sulphonylureas	Metformin
Weight gain	No weight gain (weight loss)
Hypo: common	Hypo: rare
GIT side effects rare	GIT side effects common
Metabolised in liver	Not metabolized
Excretion liver/renal	Renal excretion

- ***A sulphonylurea drug may be combined with metformin***
- ***Two sulphonylurea drugs should not be combined***

New oral antidiabetes drugs

- **Alpha glucosidase inhibitors** eg. acarbose

Delayed conversion of disaccharides to monosaccharides

Problems: intolerable GIT side effects

Liver toxicity (hepatitis),monitor liver function

Meglitinides: insulin secretogauges (non SU)

eg repaglinide, nateglinide

Thiozolidinediones: Improves insulin sensitivity

eg pioglitazone, rosiglitazone

Problems: Heart failure and liver failure

Insulin

- Polypeptide with 2 peptide chains
- Linked by 2 disulphide Bonds
- Metabolic activity is common to all mammalian species
- Daily secretion 30-40 units

Pharmacokinetics

- Injected because digested if swallowed
- Absorbed in to the blood inactivated in the liver & kidney.
- 10% appear in urine.
- T 1/2 is 5 min
- Peak plasma concentration is in 30-90 min

Insulin Receptors

- Bound to a receptor Tyrosine kinase on the surface of target cell.
- Insulin receptor complex enters the cell

Preparations of Insulins.

- Source of Insulin(Human,Bovine,Porcine)
- Formulation
  - Short acting
  - Intermediate acting
  - Long acting
  - Bi phasic

Short Duration Of action Insulins

- Rapid onset of action
  - Soluble Insulin
  - Insulin Lispro ⇒ Faster Asorption

Intemediate duration of action

- Isophane Insulin - A suspension with protamine

- Amorphous - Insulin zinc suspension

Longer duration of action Insulin

- Insulin Zinc suspension -Crystalline

Biphasic Insulins

- Mixture of soluble insulin & Isophane insulin
- Most commonly used ones are human Insulins
- Soluble Insulin at 10-50% of total Insulin concentration
- Remove the need for patients to mix Insulin

Indications for use of Insulin.

- Type 1 Diabetes mellitus in children.
- Type 11 Diabetes
  - Diabetic ketoacidosis خطيرة!
  - Non ketotic hyper osmolar coma
  - Surgery
  - Infections
  - Pregnancy

Side effects of Insulin

- Hypoglycaemia
  - Warning signs due to Neuroglycopenia (refers to a shortage of glucose (glycopenia) in the brain, usually due to hypoglycemia.)
  - Coma ,Convulsions & Death, ↓↓ concentration, no coordinated movement.
- Allergic reactions
- Lipoatrophy (adverse immunologic response)
- Lipohypertrophy (lipogenic properties of insulin)

All the following, except.

Q) # Soluble Insulin

- Short duration of action
- Used 30m before meals
- 3 times a day
- Colourless.
- Is given I.V in diabetic ketoacidosis.

Q →

Insulin zinc suspensions

- Amorphous
- Crystalline

Dose of Insulins

- 100u/ml
- Total daily output is 30-40 units a day
- A dose of over 100u/day is due to noncompliance.