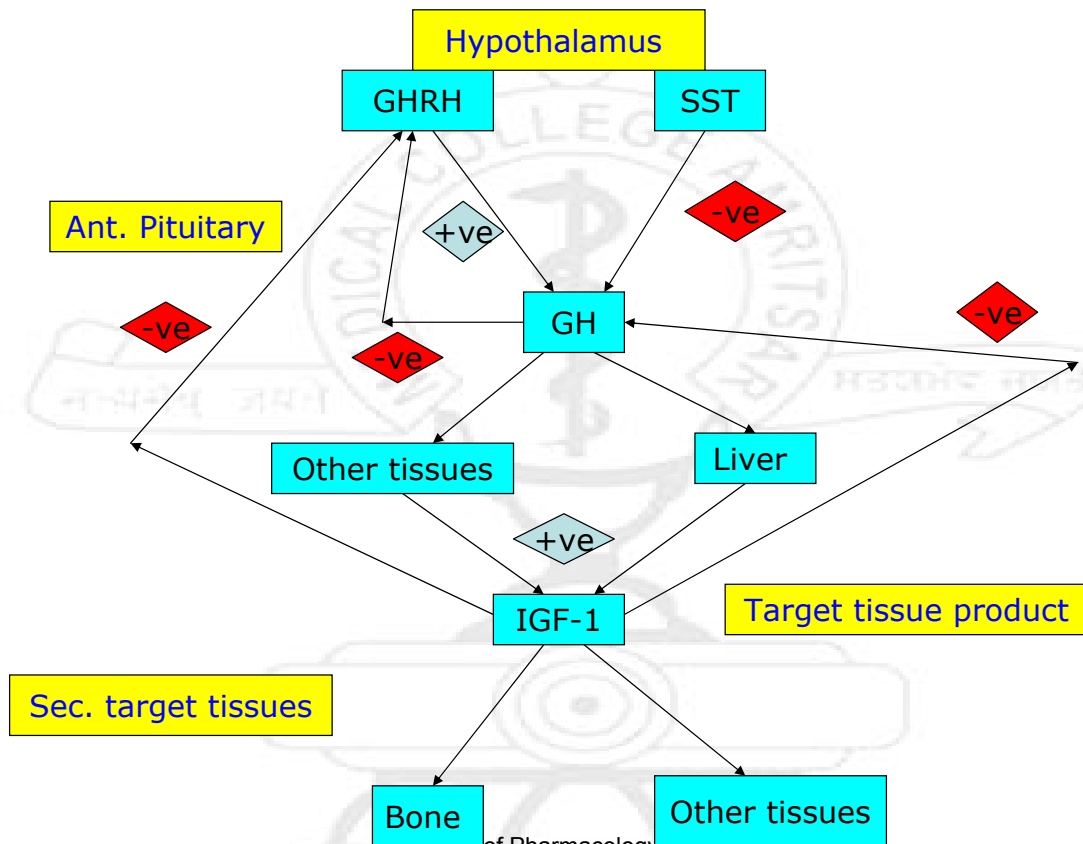


Growth Hormone



Growth Hormone

- Gene encoding on chromosome 17
- Somatotropin is biosynthesis form made by recombinant DNA technology
- Somatrem is similar
- Natural GH not used due to rise of transmission of Creutzfeldt Jacob disease –lethal infection
- Acts on many organs to produce somatomedin which causes muscle, bone and tissue to increase growth i.e. protein synthesis, and size and number of cells

GH- Regulation of secretion

- Synthesized and secreted by somatotropes of anterior pituitary
- GH secretion –high in children, reaches maximum level in adolescent and decreases in age related manner
- Occurs in irregular pulse, falls between these pulses
- Amplitude of secretory pulses is maximum at night, shortly after onset of deep sleep

GH –regulation of secretion

- GHRH-hypothalamic neurons in arcuate nucleus increase GH secretion by binding to GPCRs on somatotropes increase intracellular cAMP & Ca⁺⁺
- Somatostatin(SST) synthesized by neurons, neuroendocrine cells of GIT, pancreas. decrease GH secretion by family of GPCRs, ↓ cAMP accumulation, activation of K⁺ channels, activation of tyrosine phosphatase
- Two SST-14 & SST-18

SST-Somatostatin

- Five receptors subtypes
- SSTR 1-4 bind with SST with equal affinity
- Type 5 SSTR has 10 to 15 times more selectivity for Somatostatin –28
- SSTR 2 & SSTR 5- imp. for regulation of GH

Somatostatin Analogues

- Somatostatin-28
- Somatostatin-14
- Octreotide
- Lanreotide
- Vapreotide
- Used in syndrome of GH excess-acromegaly

GH-Modulators of secretion

- Dopamine, 5-HT, α_2 -receptor agonists increase GH secretion
- β -receptor antagonists, FFA, IGF-1 and GH inhibit release
- Hypoglycemia, exercise, stress, emotional excitement, ingestion of protein rich meals increase GH

Mechanism of action-GH

- Acts on GH receptor - a widely distributed cell surface receptor, belongs to cytokine receptor superfamily
- Similar to prolactin receptor, interleukin and erythropoietin receptors
- Extracellular domain binds to GH
- Intracellular domain mediates signal transduction
- Single GH molecule bind to two identical receptor molecule

MOA

- GH- GHR-ligand occupied receptor dimer lacks inherent tyrosine kinase activity, provides docking site for two molecules of Janus Kinase 2(JAK-2) a cytoplasmic tyrosine of Janus Kinase family
- Juxtaposition of two JAK-2 molecules leads to trans-phosphorylation and autoactivation of JAK-2 with phosphorylation of cytoplasmic proteins that mediate downstream signaling events

MOA

- Signaling events:
- Signal transducers and activators of transcription (STATs)
- Shc (an adaptor protein that regulates Ras/MAPK signaling pathway)

GH- MOA

- Acts directly on adipocytes to increase lipolysis.
- Hepatocytes to stimulate gluconeogenesis
- Anabolic and growth promoting effects mediated via induction of IGFs (IGF-1 & IGF-2)
- IGF-1 more potent growth promoting mediator
- IGF-1 interacts with cell surface receptors present in all tissues
- Receptors bind IGF-1 & IGF-2 with high affinity

Growth Hormone deficiency syndromes

- Growth Hormone deficiency is short stature in children
- Replacement therapy used for > 30 yrs
- Recombinant human growth hormone in GH deficient adults
- AIDS - associated wasting

Contraindications

- Open heart surgery or abdominal surgery
- Multiple accidental traumas
- Acute respiratory failure
- Neoplasia
- During antitumour therapy

Diagnosis of GH deficiency

- Children with short stature and low age adjusted growth velocity- Idiopathic or isolated GH deficiency (hypothalamic defect)
- Height \leq 2 to 2.5 SD below normal
- Delayed bone age
- Growth velocity below 25th percentile
- GH $<$ 10 μ g/ litre following provocative test (insulin induced hypoglycemia) – GH deficiency stimulated
- GH deficient adults – pituitary adenoma / surgery/ radiotherapy

Treatment of GH deficiency

- Action of GH is species specific
- GH from human cadaveric pituitary
- Recombinant GH
- Somatropin – native resemblance
- Somatrem
- Evening s/c OD administration
- Circulating half life 20 mins
- Biological half life 9 to 17 hrs
- Prefilled syringes available
- Encapsulated somatotropin (NUTROPIN DEPOT) injected i/m once or twice monthly

.....Treatment of GH deficiency

- Sermorelin acetate- synthetic human GHRH used for treatment of idiopathic GH deficiency
- Less efficacious than GH but well tolerated and less expensive
- GH response ($> 2\mu\text{gm/l}$) to test dose of sermorelin prior to initiating therapy
- Sermorelin used to distinguish between pituitary and hypothalamic disease
- GH used in congenital or acquired GH deficiency in children
- To increase height in Turner's Syndrome

.....Treatment of GH deficiency

- Initial response and compliance monitored with serum IGF-1 levels
- Long term response by close evaluation of height
- Pronounced increase in growth velocity in first 2 yrs of therapy. Continue till growth ceases or till adulthood
- Starting dose 3-4 $\mu\text{gm/kg}$ once daily by s.c. inj.
- 12.5 $\mu\text{gm/kg}$ in older patients
- Increase levels of IGF-1
- 100 $\mu\text{gm/kg}$ in AIDS - associated wasting

Side effects of GH therapy

- In first 8 weeks – intracranial hypertension, papilledema, visual changes, headache, nausea and/or vomiting
- Fundoscopic examination at initiation of therapy and at periodic intervals
- Leukemia
- Increase type 2 diabetes mellitus

.....Side effects of GH therapy

- In adults side effects on therapy initiation
 1. Peripheral edema
 2. Carpal tunnel syndrome
 3. Arthralgia
 4. Myalgia
- Symptoms decrease with decrease in dose

Acromegaly and Gigantism

Agents used in GH excess

- Somatostatin Analogues

1. Somatostatin – 28
(prosomatostatin)
2. Somatostatin – 14
3. Octreotide
4. Lanreotide
5. Vapreotide

Somatostatin Analogues

- Octreotide binds preferentially to SSTR-2 and SSTR-5 receptors on GH secreting tumors
- Injection octreotide (100µg) s.c thrice daily
- Monitor serum GH and IGF-1 levels to assess effectiveness
- Goal – decrease GH levels < 2µg/lit & IGF-1 levels within normal range for age and sex
- Octreotide decreases tumor size
- Octreotide inhibits TSH secretion and is treatment of choice in thyrotrope adenoma that over secrete TSH and not good candidate for surgery

Side effects of Octreotide

- Diarrhea , Nausea, Abdominal Pain – 50% of patients
- Gall stones
- Long acting slow release prep once every 4 weeks- 20 -30 mg is given who respond to short acting octreotide
- Side effects do not require cessation of therapy

LANREOTIDE

- Long acting analogue of Somatostatin causes prolonged suppression of GH – inj 30 mg im
- Similar efficacy to long acting octreotide but shorter duration of action 10 to 14 day interval

OCTREOTIDE

- Metastatic carcinoid tumors (flushing and diarrhoea)
- Adenomas secreting VIP (watery diarrhoea)
- Octreotide labeled with indium or technetium used for diagnostic imaging of neuroendocrine tumors such as pituitary adenoma and carcinoids

Acromegaly

- Arthropathy
- Carpal tunnel syndrome
- Generalised visceromegaly
- Hypertension
- Glucose intolerance
- Headache, lethargy, excess perspiration, sleep apnoea

.....Acromegaly

- Progresses slowly, delayed diagnosis
- Decrease life expectancy
- Increase death rate due to CVS disorders, upper airway obstruction, gastrointestinal malignancies
- Increased circulating GH or IGF-1
- Trans sphenoidal surgery, radiation or drugs

GH-Preparations & Dosage

- Somatostatin (Methionyl HGH)
 - Protropin (5mg = 13 IU/vial)
 - Somatonorm (2mg = 5.2 IU/vial)
- Somatotropin (Non- Methionyl HGH)
 - Genotropin (12 and 16 IU/vial)
 - Humatrope (4 and 16 IU/vial)

Dose 0.4-0.7 IU/Kg/week
1/7th of calculated dose injected I/M
daily