

Endocrine Pharmacology

Growth Hormone (GH) – Molecular & Cellular Mechanism

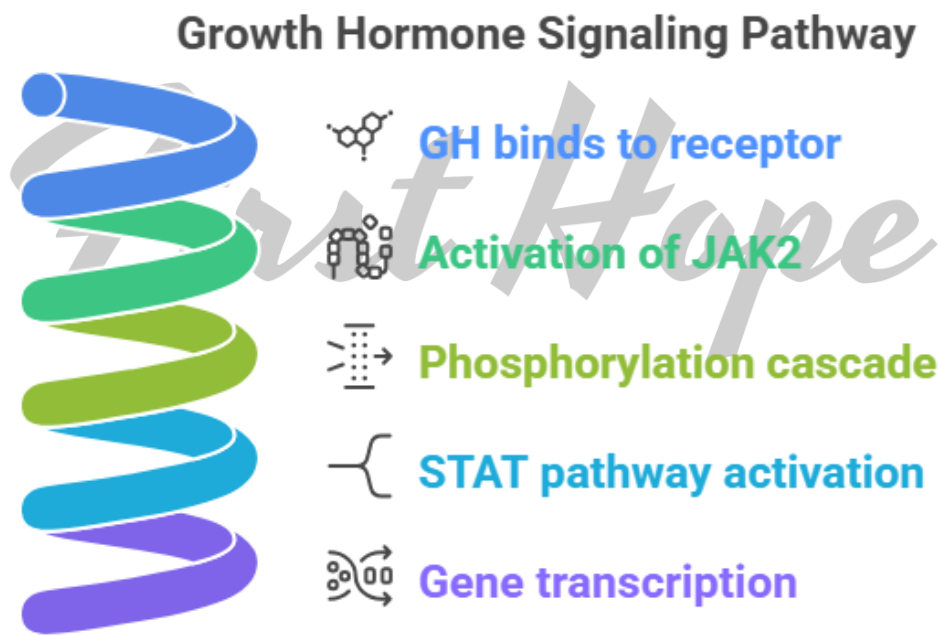
Basic Nature

- GH is a peptide hormone
- Synthesized and secreted by somatotroph cells of anterior pituitary
- Water-soluble → cannot enter cell, acts via cell surface receptors

Receptor Type

- GH receptor belongs to cytokine receptor superfamily
- It is intrinsic enzyme-linked receptor (no intrinsic kinase activity)
- Requires JAK (Janus kinase) for signaling

Step-by-step mechanism



1. GH binds to receptor

- One GH molecule binds to two receptor molecules → causes dimerization.

2. Activation of JAK2 (Janus Kinase 2)

- Receptor has no intrinsic enzyme activity.
- It is associated with JAK2 (tyrosine kinase).
- Binding → activates JAK2.

3. Phosphorylation cascade

- JAK2 phosphorylates:
 - The receptor itself

- Intracellular proteins (STAT proteins)

4. STAT pathway activation

- **STAT (Signal Transducers and Activators of Transcription) proteins:**
 - Get phosphorylated
 - Form dimers
 - Move into nucleus

5. Gene transcription

- **STAT dimers activate genes → synthesis of:**
 - IGF-1
 - Proteins for growth and metabolism

IGF-1 Mediated Effects

- GH acts indirectly via IGF-1
- **IGF-1:**
 - Promotes bone growth (epiphyseal plate)
 - Increases cell division
 - Enhances protein synthesis

Metabolic Effects

- **Protein metabolism:** ↑ protein synthesis
- **Fat metabolism:** ↑ lipolysis
- **Carbohydrate metabolism:**
 - Anti-insulin effect
 - ↑ blood glucose

Prolactin – Molecular & Cellular Mechanism

Basic Nature

- Peptide hormone secreted by lactotroph cells
- Main role: milk production (lactation)

Receptor Type

- Prolactin receptor is also a cytokine receptor
- Uses JAK-STAT pathway (similar to GH)

Mechanism

1. Prolactin binds receptor

- Causes receptor dimerization

2. JAK2 Activation

- Activates intracellular tyrosine kinase (JAK2)

3. STAT activation

- STAT proteins are phosphorylated
- Move into nucleus

4. Gene transcription

- **Activates genes for:**
 - Milk protein synthesis (casein, lactalbumin)
 - Enzymes for lactose synthesis

Physiological Effects

- Development of mammary glands
- Initiation and maintenance of lactation

Regulation (Important for Pharmacology)

- **Dopamine inhibits prolactin**
 - Via D2 receptors
- **Drugs:**
 - Dopamine agonists (bromocriptine) → ↓ prolactin
 - Dopamine antagonists (antipsychotics) → ↑ prolactin

Thyroid Hormones (T3, T4) – Molecular & Cellular Mechanism

Basic Nature

- Derived from tyrosine + iodine
- Lipid-soluble → act like steroid hormones

Transport in Blood

- **Bound to proteins:**
 - Thyroxine-binding globulin (TBG)
- Only free hormone is active

Cell Entry

- T3/T4 enter cell via transporters
- T4 converted to T3 (active form) inside cell

Receptor Type

- Nuclear receptor (intracellular receptor)
- Located in Nucleus

Mechanism

1. Conversion of T4 to T3

- Occurs inside cells by deiodinase enzymes

2. T3 binds nuclear receptor

- TR is already bound to DNA at thyroid response elements (TRE)

3. Receptor activation

- Without T3 → receptor suppresses gene expression
- With T3 → receptor activates gene transcription

4. Gene transcription changes

- **Increased synthesis of:**
 - Metabolic enzymes
 - Na^+/K^+ -ATPase
 - β -adrenergic receptors

Cellular effects

- ↑ Basal metabolic rate (BMR)
- ↑ Oxygen consumption
- ↑ Heat production
- ↑ Sensitivity to catecholamines (via β -receptors)
- Essential for brain development and growth

Physiological Effects

- ↑ Basal metabolic rate (BMR)
- ↑ Oxygen consumption
- ↑ Heat production
- **Essential for:**
 - Brain development

- Growth

Pharmacological Note

- Slow onset due to gene transcription mechanism
- Long duration due to protein binding

Insulin – Molecular & Cellular Mechanism

Basic Nature

- Peptide hormone from β -cells of pancreas
- **Main role:** decrease blood glucose

Receptor Type

- Tyrosine kinase receptor
- **Has:**
 - 2 α -subunits (outside)
 - 2 β -subunits (inside)

Mechanism

1. Insulin binds receptor

- Binds to α -subunit

2. Autophosphorylation

- β -subunits phosphorylate themselves (tyrosine residues)

3. Activation of IRS (Insulin Receptor Substrates)

- IRS proteins get phosphorylated

4. Two major pathways

a) PI3K-AKT Pathway (Metabolic effects)

- IRS $\rightarrow$ activates PI3K
- PI3K $\rightarrow$ activates AKT (Protein Kinase B)
- **Effects:**
 - Translocation of **GLUT-4 to membrane** $\rightarrow$ $\uparrow$ glucose uptake (muscle, fat)
 - $\uparrow$ Glycogen synthesis
 - $\uparrow$ Lipid synthesis
 - $\downarrow$ Gluconeogenesis



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