Growth Hormone

- is a protein of ~191 AA long
- secreted by somatotropes which constitute the majority of the cells in the APG

It has a dual action

- promotes growth of hard (bone) & soft tissue (cell division and increase in size)
- influences metabolism

Although GH can affect all cells, the major target cells are bones and skeletal muscle. It stimulates the epiphyseal plates of bones. Long term effect is that it prolongs the growth of bones. Its effect on skeletal tissue results in increased muscle mass.

GH works via a direct and indirect effect. The direct action is anti-insulin like and the indirect effect is insulin like.

Direct Effect

- stimulates fat catabolism (lipolysis) from fats deposits for uptake into the cell (results in increased fatty acid levels in blood)
- decreases the rate of glucose uptake and utilization by most tissues (increases blood glucose levels)
- In liver, it stimulates gluconeogenesis and release of glucose into the blood stream

Thus these effects results in higher blood glucose levels, a condition opposite to the effect of insulin which lowers blood glucose levels

Indirect effect

- stimulates the release of small proteins from the liver and other tissues
  - these growth promoting proteins are called Somatomedins or Insulin-like growth factors (IGF’s).
  - They resemble insulin and promote protein synthesis and cell proliferation

Specifically, the actions of the IGF’s include

- stimulates uptake of A.A. from the blood and thus enhances protein synthesis and anabolism in most tissues
- maintains thickness of epiphyseal plates at the end of long bones, thus maintains bone growth
The immediate metabolic effect is thus that blood glucose and fatty acid levels increase. The targeted tissues will use the fatty acids as fuel while the glucose is spared for use by the non-affected tissues e.g the brain which only uses glucose. The overall effect is to promote accumulation of lean body mass

The secretion of GH is controlled by 2 hypothalamic hormones. The secretion of those 2 hypothalamic hormones is stimulated by those conditions indicate regulation of GH is needed.

1. **GH releasing hormone (GHRH) or Somatocrinin.** Secretion of GHRH is stimulated by
   - low blood glucose
   - decreased blood Fatty Acids
   - Increased blood A.A.’s , especially arginine

   Remember that GH presence causes increased blood glucose levels and fatty acid levels. Thus low blood glucose levels and fatty acids indicate a need for GH, and thus GHRG is released.

2. **GH inhibiting hormone (GHIH) or Somatostatin .** Release is stimulated by
   - high blood glucose
   - increased fatty acids
   - decreased A.A.
   - obesity

   In this case, the high levels of glucose and fatty acids indicate that GH has done enough work and its levels need to be controlled.

   In addition, the IGF’s released by GH regulate the release of GH by a typical feedback cycle.
   - Increased levels of GH increases IGF’s which inhibits GH release from APG
   - Increased levels of IGF’s also promotes release of GHIH and inhibit GHRH release
   - GH itself inhibits release of GHRH from the hypothalamus.

See fig 16–7 for a nice diagram

Besides these factors, GH is also influenced by stress, exercise, fasting and sleep.

It turns out for example that there is a daily cycle to GH release. There is a large spike of GH release about an hour after deep sleep sets in. Also, a few hours after eating (when blood sugar levels drop) , smaller spikes in plasma GH are observed.

Net effect of all these combination of factors is that release of GH is highest during adolescence and decreases with age. This may explain the loss of lean body mass with age and the expansion of body fat.
Abnormalities in GH

Disorders of endocrine system usually involve either a hyposecretion or a hypersecretion without feedback regulation

**Hyposecretion of GH** during childhood results in
- slow bone growth, premature closure of the epiphyseal plate
- condition known as **pituitary dwarfism** (small body stature but with normal body proportions)
- can be corrected for by administering growth hormone before puberty
- area of misuse for parents that want their kids to have a height advantage (athletes)

**Hypersecretion of GH**
- If this occurs during childhood, it results in giantism or gigantism (very tall with normal proportions)
- If it occurs during adulthood, it results in **acromegaly**
  - bones in fingers, hand feet face grow (deformation of facial looks)
  - soft tissues thicken
  - usually results from a tumor in pituitary gland

Radical surgery for this is the removal of the pituitary gland (hypophysectomy) with all risks associated with it. Recent advances now rely on using synthetic analogues of somatostatin. Octreotide is a long lasting example (half life is 100 minutes compared to 1-3 minutes for the natural somatostatin).

Another example of GH abnormalities is Laron Dwarfism. In this case, the GH receptor is unoperational, resulting in failure of tissues to produce IGF’s.

**Insulin and Glucagon**

- Pancreas is a mixed gland containing endocrine as well as exocrine cells
- Acinar cells are the exocrine cells which produce digestive enzymes

Other cells are organized in **Islets of Langerhans**; they contain two types of cells
- alpha cells: produce the hormone **glucagon**
- beta cells: produce the hormone **insulin**

Both hormones are important in the overall blood glucose balance during meals and in-between meals or fasting

1. **Glucagon (Fig. 16-18)**
   - 29 Amino Acid long peptide and a hyper glycemic hormone
     - promotes breakdown of glucogen into glucose units (glycogenolysis)
     - promotes the release of glucose into the blood stream from the liver
     - promotes synthesis of glucose from lactic acid, proteins and fatty acids (gluconeogenesis)
     - Secretion is prompted by low blood sugar levels and inhibited by high sugar levels
2. Insulin (Fig. 16-18)

- 51 Amino Acid peptide consisting out of two chains linked together by disulfide bonds
- Main effect is to lower blood glucose levels
- Does so by
  - enhancing membrane transport of glucose into the muscle cells, adipocytes and liver;
  - Insulin triggers
    - Net glycogen synthesis
    - Amino acid uptake and protein in muscle
    - Converts glucose into fats in adipose tissues and liver
- secretion of insulin is triggered by
  - high blood glucose, high A. A. levels, high fatty acid levels
  - also released due to actions of glucagon, thyroxin, GH

Clinical Aspect

Diabetes Mellitus

- Results from hyposecretion or hypoactivity of insulin
- Overall result is that
  - blood glucose is not absorbed into the cells and blood glucose levels rise
  - Fats are used for energy source but breakdown results in excess Acetyl CoA which is converted into ketone bodies
  - Ketone bodies are acidic and results in ketoacidosis; blood pH drops
  - Results in increase in breathing to blow off CO2 but if persists acidosis may inhibit many physiological processes
- Three cardinal signs of diabetes are :
  - Polyuria :
    - excess urine formation sue to glucose spills over in urine and drags water with it
    - ketones spill over as well and since they are negatively charged, they drag electrolytes with them
  - Polydipsia : person feels extremely thirsty and drinks a lot because of the dehydration
  - Polyphagia : person tends to eat a lot

There are Two types of Diabetes:

A. Type I or Insulin-dependent diabetes mellitus (IDDM or TIDM)
- due to an autoimmune disease that destroys the beta cells
- occurs usually before age 15 ( juvenile onset diabetes)
- at early age person makes no insulin anymore and cells thus start using fats from fat breakdown
- results in high blood cholesterol and effects of fat diets on vascular system
- symptoms in long run are arteriosclerosis, strokes, heart attacks, renal shut down, gangrene, blindness
- also effects nervous system and can result in loss of sensation, impotence, bladder problems
- Although insulin injections overcome the immediate metabolic problems like acidosis, the long term problems are only delayed
B. Type II or NON-insulin dependent diabetes mellitus (NIDDM or T2DM)

- occurs usually after age 40 (mature onset diabetes)
- hereditary predisposition is striking, indicating a genetic link
- Type II patients produce insulin but don't have enough insulin receptors
- 90% of cases are overweight patients indicating a link between obesity and NIDDM as well
- Ketosis is not a major problem in this group and symptoms can be managed by weight loss and diet

See Figure 16-19 and Read pages 635-638 as well.