Blood Glucose Regulation

By Dr Jemil Makadia

Importance

- Blood concentration of glucose is regulated within narrow limits as hypoglycemia and hyperglycemia are associated with significant morbidity and mortality.
- Nervous system and RBC exclusively depend on glucose as a source of energy
- It reflects the net balance of availability and utilization of glucose by the cell and tissues of the body
- Renal threshold for glucose is 180 mg/dl
- Sudden decrease in blood glucose level leads to convulsion
- Much lower conc can be tolerated if hypoglycemia develops slowly enough for adaptation to occur

Normal Blood glucose level

mg/dl	Normal	IGT	DM
Fasting	70-110	110-126	>126
PP2BS	<140	140-200	>200
Random	<200	-	-

Role of Liver

- It plays central role
- Blood from adipose tissue, intestine, spleen, pancreas are going directly to the liver via portal circulation
- Various metabolic pathways occurs in liver like gluconeogenesis, glycogen synthesis and glycogenolysis

Mechanisms

- Several mechanisms operate to regulate the blood glucose level
  - Metabolic
    - Liver
    - Extrahepatic tissue
  - Hormonal
    - Insulin
    - Glucagon
    - Epinephrine and NA
    - Growth hormone
    - Glucocorticoids

- **Metabolic regulation**
  - Liver and Extrahepatic tissue
    - GLUT-2
      - Present in liver
      - Insulin independent
    - GLUT-4
      - Present in extrahepatic tissue
      - Insulin dependent

- Hexokinase/Glucokinase
  - Hexokinase
    - Low Km
    - All extrahepatic tissue
    - Active all the time
  - Glucokinase
    - High Km
    - Liver
    - Active after meal
- Liver has net uptake of glucose in high blood glucose level but it is net producer of glucose in low and normal glucose level

- **Hormonal regulation**
  - Hormones decrease blood glucose level
    - Insulin
  - Hormones increase blood glucose level
    - Glucagon
    - Adrenaline
    - NA
    - Growth hormone
    - Glucocorticoids

- **Insulin**
  - From β-cell of pancreas
  - Increase in glucose level will stimulate insulin
  - GLUT-2
  - Increases- Glycolysis, TCA
  - Liver
    - Increases
      - FA synthesis
      - Glycogen synthesis
      - Protein synthesis
    - Decreases
      - Ketogenesis
      - Gluconeogenesis

- Adipose tissue
  - Increases
    - Glucose uptake
    - FA synthesis
  - Decreases
    - Lipolysis
- Muscles
  - Increases
    - Glucose uptake
    - Glycogen synthesis
    - Protein synthesis

- **Mechanism of insulin secretion**

β-cell of pancreas freely permeable to glucose via GLUT-2

↓

Glucose is phosphorylated by glucokinase to Glu-6-P

↓

Increase glycolysis, TCA

↓

Increase ATP

↓

Inhibit ATP-sensitive K+ channel

↓

Depolarization of cell membrane

↓

Increase Ca++ influx

↓

Exocytosis of Insulin

- Concentration of insulin in blood parallels that of blood glucose
- Release of inulin also increase by
  - Amino acids
  - Free FA
  - Ketone bodies
  - Glucagon
  - Secretin
  - Sulfonylurea drugs

- Insulin does not affect glucose uptake in the liver but enhance long term uptake by actions on enzymes required for glycolysis, glycogen synthesis and gluconeogenesis
- Cytokines secreted by macrophages infiltrating adipose tissue along with glucocorticoids secreted by adipose tissue have insulin antagonistic effect which explain insulin resistance in obese people.
-

- **Glucagon**
  - Opposes the actions of insulin
  - Secreted by α-cell of pancreas, act via cAMP
  - Effect on liver phosphorylase but not on muscle
  - Increases
    - Glycogenolysis
    - Gluconeogenesis
    - Ketogenesis
    - Lipolysis
  - Decreases
    - Glycolysis
    - TCA cycle
    - Glycogen synthesis

- **Epinephrine and norepinephrine**
  - Secreted by adrenal medulla
  - Result of stressful stimuli (fear, excitement, hemorrhage, hypoxia, hypoglycemia)
  - Inhibit insulin release
  - Promote hyperglycemia by glycogenolysis in liver and muscle

- **Growth hormone**
  - Stimulated by hypoglycemia
  - Promotes FA mobilization from adipose tissue

- **Glucocorticoids**
  - Increases gluconeogenesis from amino acids
  - Decrease glucose utilization by extrahepatic tissue

Muscle glycogen in fasting condition

- **Lactic acid (cori's cycle) and Glucose-Alanine cycle**
  - In fasting condition alanine output from muscle will increases
  - Muscle glycogen maintain blood glucose level in fasting condition

Stages of maintenance of blood glucose

- **Absorptive stages**
  - Start from feeding and last for 3-4 hrs after meal
  - Dietary glucose goes to liver and then to most tissue
  - Excess of glucose is stored as glycogen in liver and muscle
- **Post absorptive phase**
  - Will last for 16-18 hrs after absorption
  - Liver glycogenolysis becomes the main source of glucose
  - Muscle uses its glycogen for energy
  - Gluconeogenesis will start after 24 hrs of fasting

- **Starvation**
  - After 24 hrs, gluconeogenesis is the main source of glucose
  - FA from adipose tissue becomes fuel for most tissue
  - Lactate and glycerol ae reutilized for gluconeogenesis
  - High rate of hepatic gluconeogenesis will last for few days in early starvation

- **Prolonged starvation**
  - After 2-3 days to 3 weeks (intermediate starvation)
    - Hepatic gluconeogenesis decreases
    - Gluconeogenesis in kidney will start increasing
    - Fat as a source of energy for most of the tissues
    - Proteins in muscle produce glucogenic amino acids to produce glucose
  - If starvation more than 3weeks known as prolonged starvation
    - Lipid store depleted
    - Complications and death may occurs

Thank You