# Hypoglycemia and insulinoma

Dr. Michael Leonid,MD
Specialist in internal medicine and endocrinology
11/2017

# Glucose metabolism

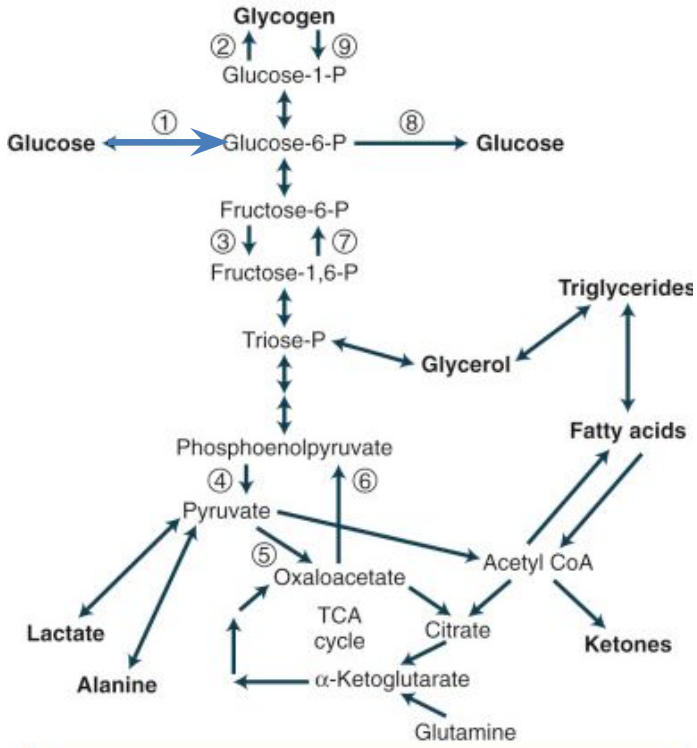



Figure 34-1

# Plasma glucose concentration in the fasting state(insulin low glucagon high)

- Dependent on net glucose influx – net glucose consumption.
- **Liver** is **major source** of endogenous glucose production(through glycogenolysis and glyconeogenesis by influence of countrregulatory hormones), + kidneys (minimal role).
- **Liver amount** of glycogen is an average **70 gram.**
- **Brain is the major glucose consumer- 50%,**erythrocytes-20%
- Muscle and fat -**up to 20 %.**
- **Free glucose pool in liver and extracellular fluid** is **10-20g.**

  **Fasting glucose consumption :2.2 mg/kg/min.**

  **Preformed glucose** can provide less than 8 hours supply

# Gluconeogenetic substrates and metabolism in prolonged fasting

- **Lactate** synthesized in muscle released into plasma and converted to pyruvate in liver .
- **Alanine and glutamine** released into plasma as a result of protein breakdown and converted to pyruvate in liver.
- **Glycerol** released from breakdown of triglycerides in fat tissue and converted to glycose in liver. Free fatty acid converted to keto bodies

**24-48 fasting and more**

- Gluconeogenesis depleted oxaloacetate and activity of Krebs cycle decreased.
- Accumulation of Acetyl-CoA and channeling it to ketogenesis.
- Almost total dependence on fat as energy source!
- **Ketone bodies** can be used as **energy substrates** in the **heart** and skeletal muscle, and also the **brain**.

# Cori and alanine –pyruvate cycle

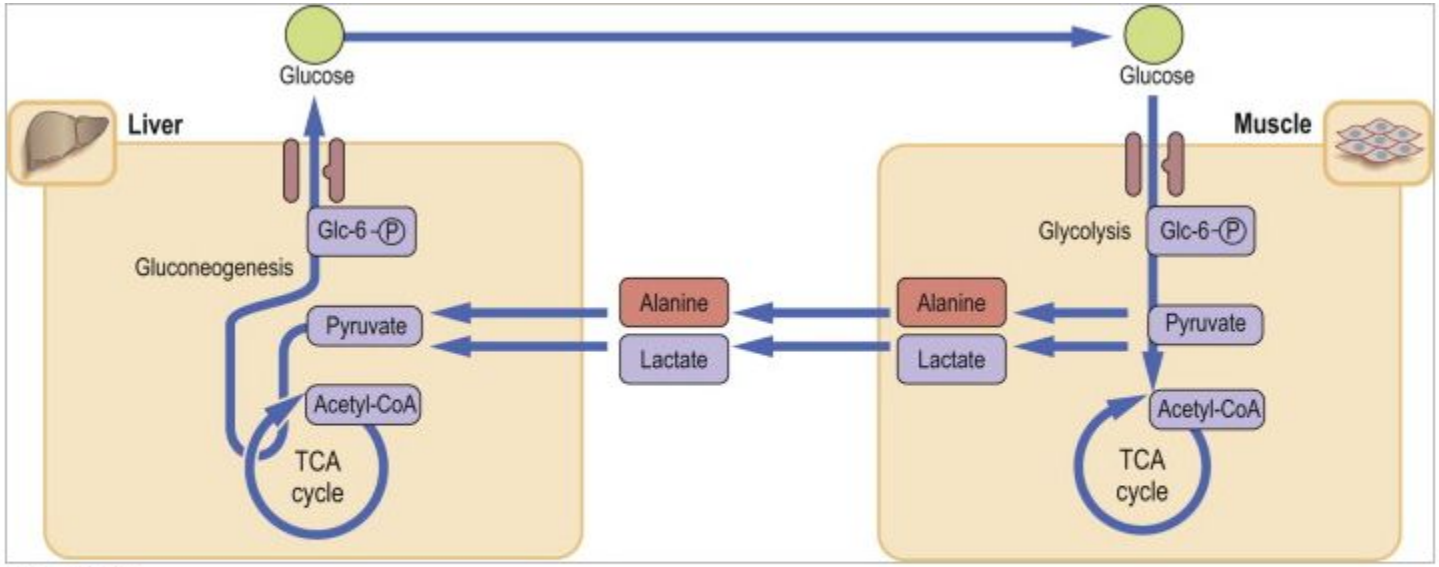



Fig. 21.12

Cori cycle and glucose–alanine cycle.

The Cori (glucose–lactate) cycle allows recycling of lactate back to glucose. Alanine is derived mostly from muscle proteolysis.

# Plasma glucose in fed state(insuin high glucagon low) and exercise

**Fed state**

- Dependent on net glucose influx – net glucose consumption
- Absorption of glucose into the circulation increases to more than twice of net glucose production in the fasting state depending on carb content of the meal, gastric transit, digestion and absorbtion.
- Endogenous production of glucose is suppressed.
- **Fat ,muscle, liver** glucose utilization accelerates.
- Exercise **increases muscle glucose utilization several times greater than those in fasting state** .To keep euglycemia glucose production must be increased!

# Hypoglycemia

- Imbalance between glucose production and utilization.
- Clinical hypoglycemia is a plasma glucose concentration low enough to cause symptoms or signs, including impairment of brain function..
- **Whipple triad:**

  1)symptoms and signs or both consistent with hypoglycemia.

  2)Low reliable measured plasma glucose concentration.

  3)Resolution of those symptoms and signs after the plasma glucose concentration is raised(**no matter how**)

- Plasma glucose threshold is dynamic but accepted threshold **is 70 mg/dl**

# Normal response to hypoglycemia

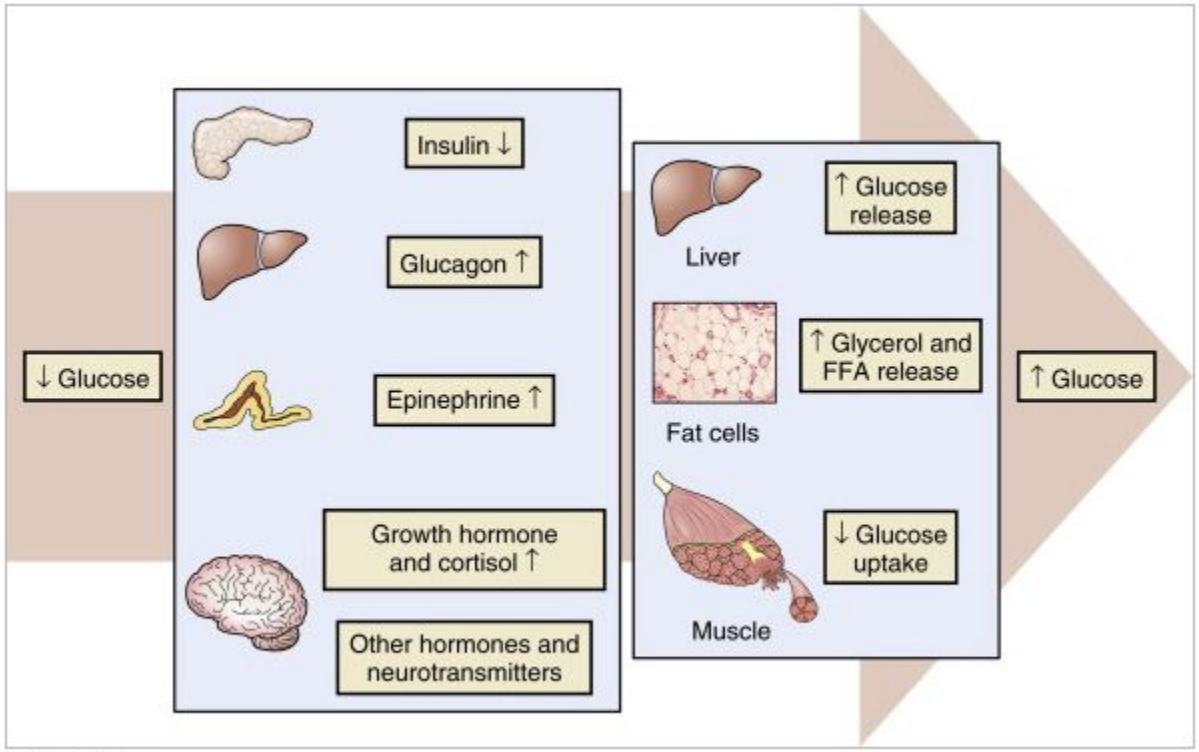



Figure 47-2

# Symptoms of hypoglycemia

- Autonomic:

1. Palpitation ,tremor, anxiety- adrenergic.
2. Sweating , hunger and paresthesias-cholinergic.

- Neuroglycopenic:

1. Cognitive, behavioral changes,
2. Coma ,seizures.

# Acute treatment

- PO 15 g carbohydrates with re-evalution after 15 minutes.
- Severe hypoglycemia (**event requiring assistance of another person to actively administrated every kinds of treatment**)especially with impaired conscience best treated by IV glucose **(preferably by 5-10% glucose ).**
- **Be careful** about IM and SC 1mg Glucagon :**may induce insulin secretion** in advanced Type2 diabetes and may **cause nausea and vomiting .**

# Evaluation(1)

- Reliable glucose test in plasma(not only by glucometer!)
- Whipple triade
- Fasting or reactive : postprandial ?
- **Seek insulin and secretagogues:** most common cause of hypoglycemia.
- Other causes :

Medications and substances:

1. Alcohol(inhibits gluconeogenesis by increase NADH/NAD ratio).
2. Rare: quinine and pentamidine(beta-cell toxicity / insulin release?), salicylates(inhibition of hepatic glucose output).
1. Severe illness : sepsis, CHF, hepatic and renal disease.

# Evaluation(2)

- Cortisol and growth hormone deficiency.
- Autonomic failure.
- Autoimmune hypoglycemia.
- Reactive hypoglycemia :

  1)In patients with altered gastric motility ,after gastectomy and pyloroplasty may be part of “late dumping syndrome”.

  2)Prediabetes - characteristically have a delay in early insulin release that impairs suppression of endogenous glucose production and reduces the early efficiency of glucose uptake, which leads to **hyperglycemia and late hyperinsulinemia with hypoglycemia .Usually very mild .**

  **3) Roux –en-Y gastric bypass –postprandial endogenous hyperinsulinemic hypoglycemia.**
- Factitious

# Gold standard:72 hours fast protocol

- Recommended to admit to the hospital and supervise.
- Stop all medications that might interfere with test.
- Admission is preferred before a standard evening meal so that the response to a meal can be assessed, as well as the response to a fast.
- Measure plasma glucose, insulin, C-peptide, and β-hydroxybutyrate (on the same venipuncture specimen) every 6 hours until plasma glucose reaches 60 mg/dL (3.3 mM). Then measure every 1 to 2 hours.
- Patient must be active during the test, may drink water.
- End after 72 hour or if plasma glucose concentration fall below 55 mg/dl with/without symptoms .
- Draw blood for plasma glucose, insulin, C-peptide, β-hydroxybutyrate, and sulfonylurea at the end of the test.
- Give 1mg glucagon IM /IV at the end of the test and measure plasma glucose 30 min afterward.

# Interpretation

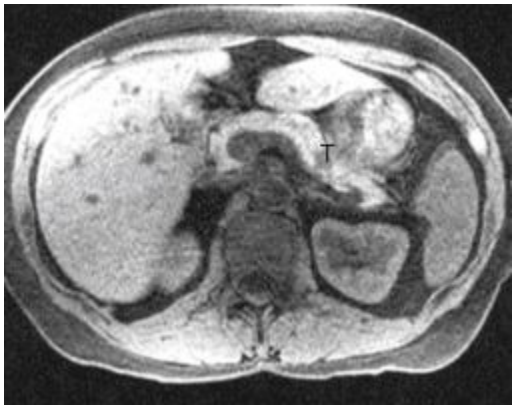
| Symptoms, Signs, or Both | Glucose (mg/dL) | Insulin (μU/mL) | C-Peptide (nmol/L) | Proinsulin (pmol/L) | β-Hydroxybutyrate (mmol/L) | Glucose Increase After Glucagon (mg/dL) | Circulating Oral Hypoglycemic Agent | Antibody to Insulin | Diagnostic Interpretation |
|---|---|---|---|---|---|---|---|---|---|
| No | <55 | <3 | <0.2 | <5 | <2.7 | <25 | No | No | Normal |
| Yes | <55 | ≫3 | <0.2 | <5 | ≤2.7 | >25 | No | Neg (Pos) | Exogenous insulin |
| Yes | <55 | ≥3 | ≥0.2 | ≥5 | ≤2.7 | >25 | No | Neg | Insulinoma, NIPHS, PGBH |
| Yes | <55 | ≥3 | ≥0.2 | ≥5 | ≤2.7 | >25 | Yes | Neg | Oral hypoglycemic agent |
| Yes | <55 | ≫3 | ≫0.2 † | ≫5 † | ≤2.7 | >25 | No | Pos | Insulin autoimmune |
| Yes | <55 | <3 | <0.2 | <5 | ≤2.7 | >25 | No | Neg | IGF ‡ |
| Yes | <55 | <3 | <0.2 | <5 | >2.7 | <25 | No | Neg | Not insulin- or IGF-mediated |

# Insulinoma

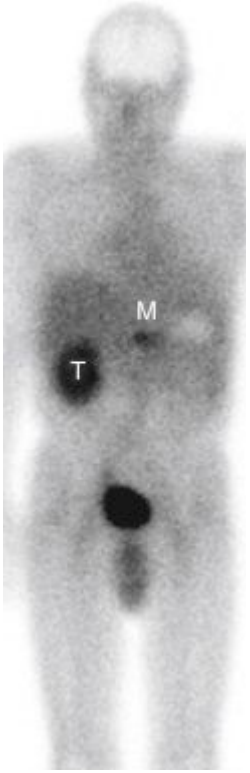
- 1:250.000 individuals.
- 90% benign.
- Usually sporadic and solitary ,may be part of MEN1.
- Evenly distributed in in the head, body, and tail of the pancreas.
- Localization : CT, MRI-75%.

1. IUS, somatostatin scan- improves diagnostic accuracy.
2. Selective arterial catheterization with calcium infusion(seldom needed).
3. Intraoperative US-”unlocalized cases”.

# Insulinoma in the tail of pancreas on MRI



# Malignant insulinoma with metastasis to liver on somatostatin scan



# Treatment

- Surgery.
- Malignant cases :diazoxide,streptozocin, somatostatin analogues.
- Multiple carbohydrate administration.