Insulin & Oral Antidiabetic Drugs

Diabetes mellitus

Definition: a syndrome of disordered metabolism due to a combination of hereditary and environmental causes.

Classification:

Type 1: Lack of insulin.

Type 2: Cells resistance to insulin

Signs & symptoms:

- **Very thirsty**
- **Feeling tired**
- **Using the toilet often to urinate**
- **Constant hunger**
- **High level of glucose in urine & in fasting blood**

TABLE 67.1 Features of Type I and Type II Diabetes Mellitus

Characteristic	Type I	Type II
Onset (age)	Usually <30	Usually >40
Type of onset	Abrupt	Gradual
Nutritional status	Often thin	Often obese
Clinical symptoms	Polydipsia, polyuria, polyphagia	Often asymptomatic
Ketosis	Present	Usually absent
Endogenous insulin	Absent	Variable
Insulin therapy	Required	Sometimes
Oral hypoglycemics	Usually not effective	Often effective
Diet	Mandatory with insulin	Mandatory with or without drugs

Harms (complications)

▲ Acute

Diabetic ketoacidosis (DKA)

Nonketotic hyperosmolar coma

▲Chronic

Microvascular disease: impotence & poor wound healing

Atherosclerosis : Strokes, coronary heart disease

Renal failure, retinal damage, nerve damage

Infective disease: Tuberculosis

Diabetic ketoacidosis (DKA) is a potentially life-threatening complication in people with diabetes mellitus. It happens predominantly in those with type 1 diabetes, but it can occur in those with type 2 diabetes under certain circumstances. DKA results from a shortage of insulin; in response the body switches to burning fatty acids and producing acidic ketone bodies that cause most of the symptoms and complications

Hyperosmolar hyperglycemic state (HHS) is a complication of diabetes mellitus (predominantly type 2) in which high blood sugars cause severe dehydration, increases in osmolarity (relative concentration of solute) and a high risk of complications, coma and death

Treatment

Type 1: Insulin must be injected or inhaled

Type 2: Food control, exercise, medicines

(1) agents which increase insulin secretion;

(2) agents which increase the sensitivity of target organs to insulin;

(3) agents which decrease glucose absorption

(4) Insulin needed for patients with serious complications or an emergency.

TABLE 67.2 Antidiabetic Drugs

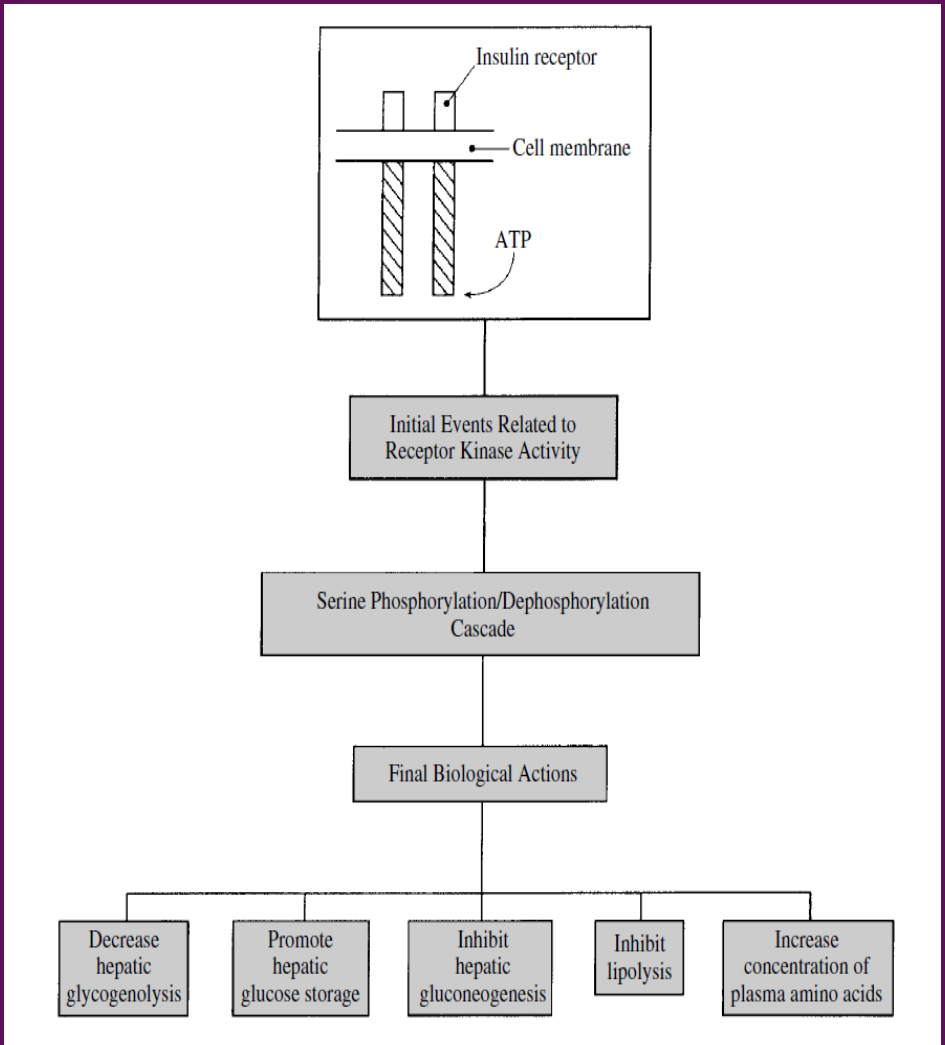
Augment Insulin Supply	Enhance Insulin Action	Delay Carbohydrate Absorption
Sulfonylureas Meglitinides Insulins	Biguanides Thiazolidine-diones	α-Glucosidase inhibitors

Section 1 Insulin

- **Chemistry: 51 aa arranged in two chains (A & B) linked by disulfide bridges.**
- **Secretion: By βcells in pancreatic islet.**
- **Degradation: Liver & kidney**

  Endogenous: Liver (60 %) & kidney (35 %-40 %)

  Exogenous: Liver (35 %-40 %) & kidney (60 %)
- **T1/2 in plasma: 3-5 min**



Biochemical and Pharmacological Actions of Insulin

In addition to its effects on stimulating glucose uptake by tissues, insulin has five major physiological effects on fuel homeostasis. It can

(1) diminish hepatic glycogenolysis by inhibiting glycogen phosphorylase;

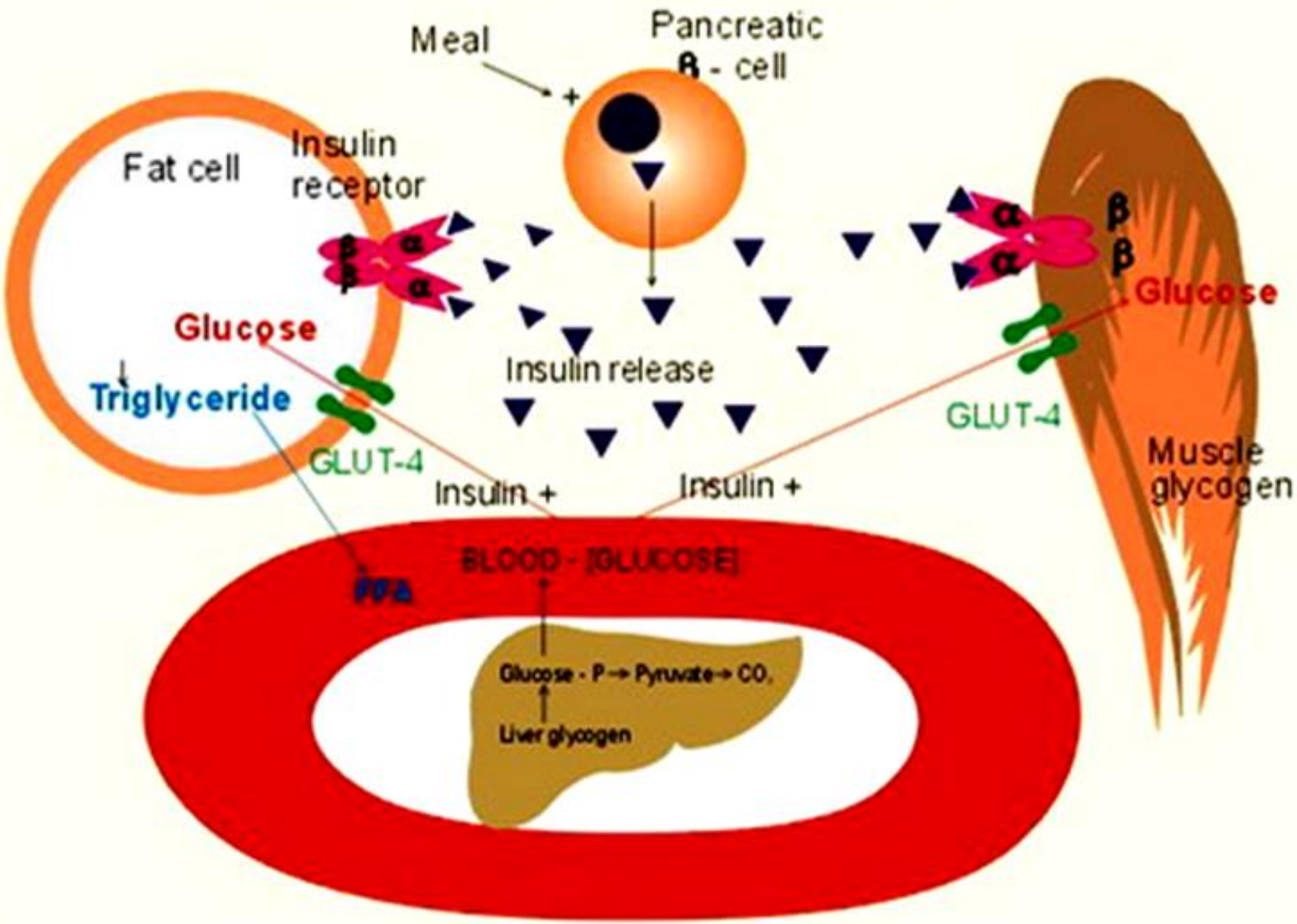
(2) promote hepatic glucose storage into glycogen by stimulating glycogen synthetase;

(3) inhibit hepatic gluconeogenesis (i.e., convert noncarbohydrate substrates like amino acids into glucose);

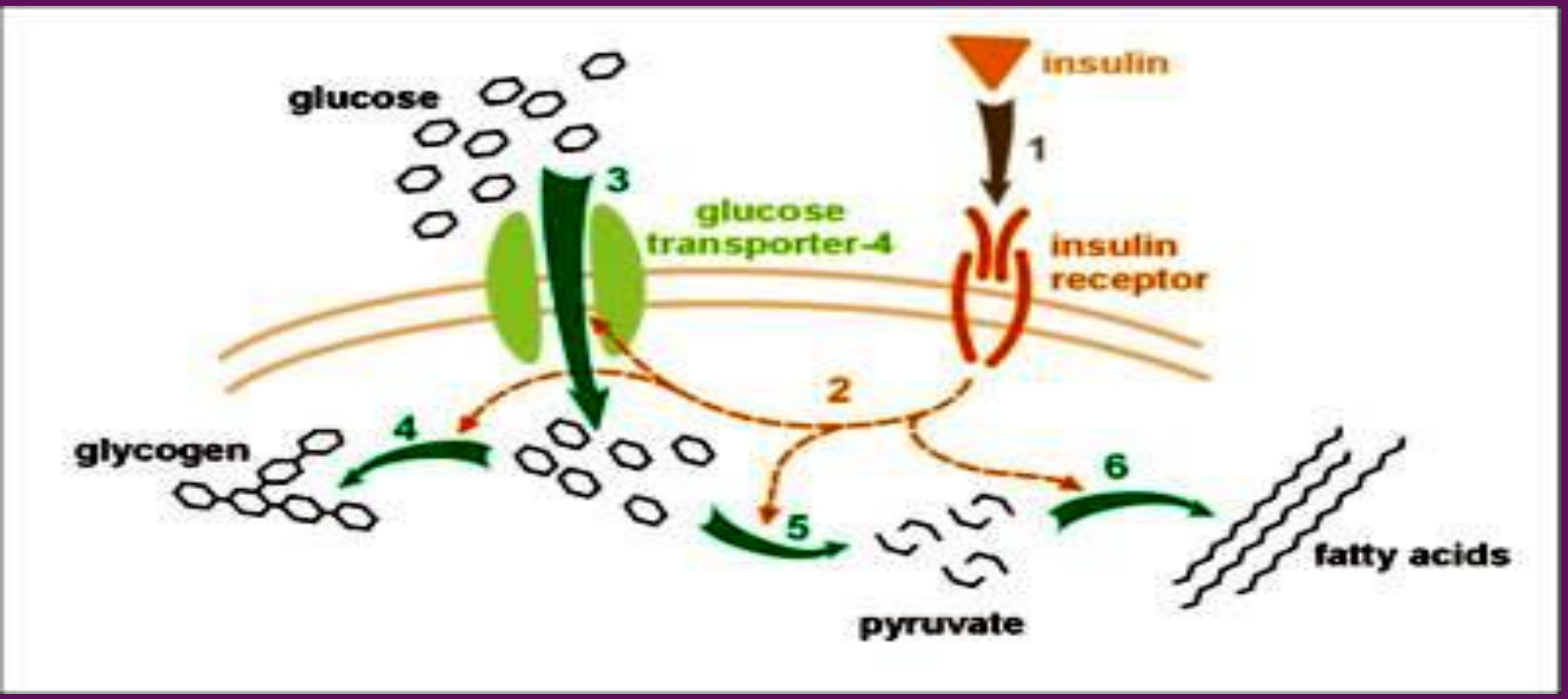
(4) Inhibit lipolysis by inhibiting hormone-sensitive lipase activity, thereby decreasing plasma free fatty acid and glycerol levels;

(5) promote the active transport of amino acids into cells for incorporation into protein, thereby producing a net positive nitrogen balance.

Effects Of Insulin On Target Cells



The insulin receptor is a heterotetrameric tyrosine kinase receptor composed of two α and two β subunits. Insulin binds to the α subunit on the extracellular surface of the cell and activates tyrosine kinase activity in the intracellular portion of the β subunit



Effect of insulin on glucose uptake and metabolism. Insulin binds to its receptor (1) which in turn starts many protein activation cascades (2). These include: translocation of Glut-4 transporter to the plasma membrane and influx of glucose (3), glycogen synthesis (4), glycolysis (5) and fatty acid synthesis (6).

- Sources of exogenous insulin

  * **Bovine & porcine insulin**

  * **Human insulin by replacement of porcine insulin 30-alanine in B chain by threonine**

  * **Recombinant human insulin by Escherichia coli**

Clinical use

1. Diabetes mellitus

* **The only effective drug for type 1 diabetes**
* **The following situations of type 2 diabetes**

  (1) Not effectively controlled by food limitation & oral antidiabetic drugs;

(2) **nonketotic hyperosmolar hyperglycemia coma;**

(3) **Accompanies serious infection**

2. Others

* **Hyperkalemia**
* **A component of GIK solution which is for limiting myocardial infarction & arrhythmias**

Context Glucose-insulin-potassium (GIK) infusion is a widely applicable, low-cost therapy that has been postulated to improve mortality in patients with acute myocardial infarction

Distribution of potassium between the intracellular and the extracellular fluid compartments is regulated by physiologic factors such as insulin and catecholamines which stimulate the activity of the Na+-K+ ATPase.

- **Adverse reactions**

1. **Insulin allergy: itching, redness, swelling, anaphylaxis shock**
2. **Insulin resistance**
3. **Hypoglycemia: nausea, hungry, tachycardia, sweating, and tremulousness.**

   * **First aids needed while convulsions & coma happens**

4. **Lipodystrophy at injection sites: atrophy**

Insulin Preparations

Commercially available insulins differ in their onset of

action, maximal activity, and duration of action.They can be classified as

- *rapid acting* (0–5 hours),
- *short acting* (0–8 hours),
- *Intermediate acting* (2 to 16 hours),
- *long acting* (4 to 36 hours

Oral Antidiabetic Drug **Classification**

Sulfonylureas

Thiazolidinediones

Biguanides

α-glucosidase inhibitors

Meglitinides

Ⅰ. Sulfonylureas

- Representative Drugs

1st generation:

tolbutamide chlorpropamide tolazamide

2nd generation:

glybenclamide glyburide

glipizide glymepride

3rd generation:

glyclazide

- Pharmacological effects

1. **Hypoglycemic effect**
2. **Antidiuretic effect**

   chlorpropamide & glybenclamide

3. **Antiplatelete-aggregation effect**

   glyclazide

- Hypoglycemic mechanism

1. **Rapid mechanism**: stimulation of insulin secretion

The primary mechanism of action of the sulfonylureas is direct stimulation of insulin release from the pancreatic B-cells.

Sulfonylurea receptor in β-cell membrane activated

↓

ATP-sensitive K^+-channel inhibited

↓

Cellular membrane depolarized

↓

Ca^{2+} entry via voltage-dependent Ca^{2+} channel

↓

Insulin release

2. **Long term profit involved mechanism**

①Inhibition of glucagon secretion by pancreas α cells;

②Ameliorating insulin resistance

③ Increase insulin receptor number & the affinity to insulin

- Clinical use

1. **Type 2 diabetes mellitus**
2. **Diabetes insipidus: chlorpropamide**

- Adverse reactions

1. **Gastrointestinal disorders**
2. **Allergy**
3. **Hypoglycemia**

   Chlorpropamide forbidden for ageds & patients with functional disorder in liver or kidney.

4. **hepatic injury**

Diabetes insipidus (DI) is a condition characterized by excessive thirst and excretion of large amounts of severely dilute urine, with reduction of fluid intake having no effect on the concentration of the urine.

Ⅱ. Thiazolidinediones (Tzds)

Thiazolidinediones (sometimes termed glitazones) are a novel class of drugs that were initially identified for their insulin-sensitizing properties.

They all act to decrease insulin resistance and enhance insulin action in target tissues.

- Representative Drugs

  rosiglitazone　　troglitazone

  pioglitazone　　ciglitazone

- Pharmacological effects

  - Improving function of pancreas β cells
  - Ameliorating insulin resistance
  - Ameliorating fat metabolic disorder
  - Preventing and treating type 2 diabetes mellitus and their cardiovascular complications

- Mechanism (possible)

Peroxisome proliferator-activated receptor-γ(PPAR-γ) activated

Nuclear genes involved in glucose & lipid metabolism and adipocyte differentiation activated

- Clinical use

Insulin resistance & type 2 diabetes mellitus

- Adverse reactions

Troglitazone occasionally induces hepatic injury

Ⅲ. Biguanides

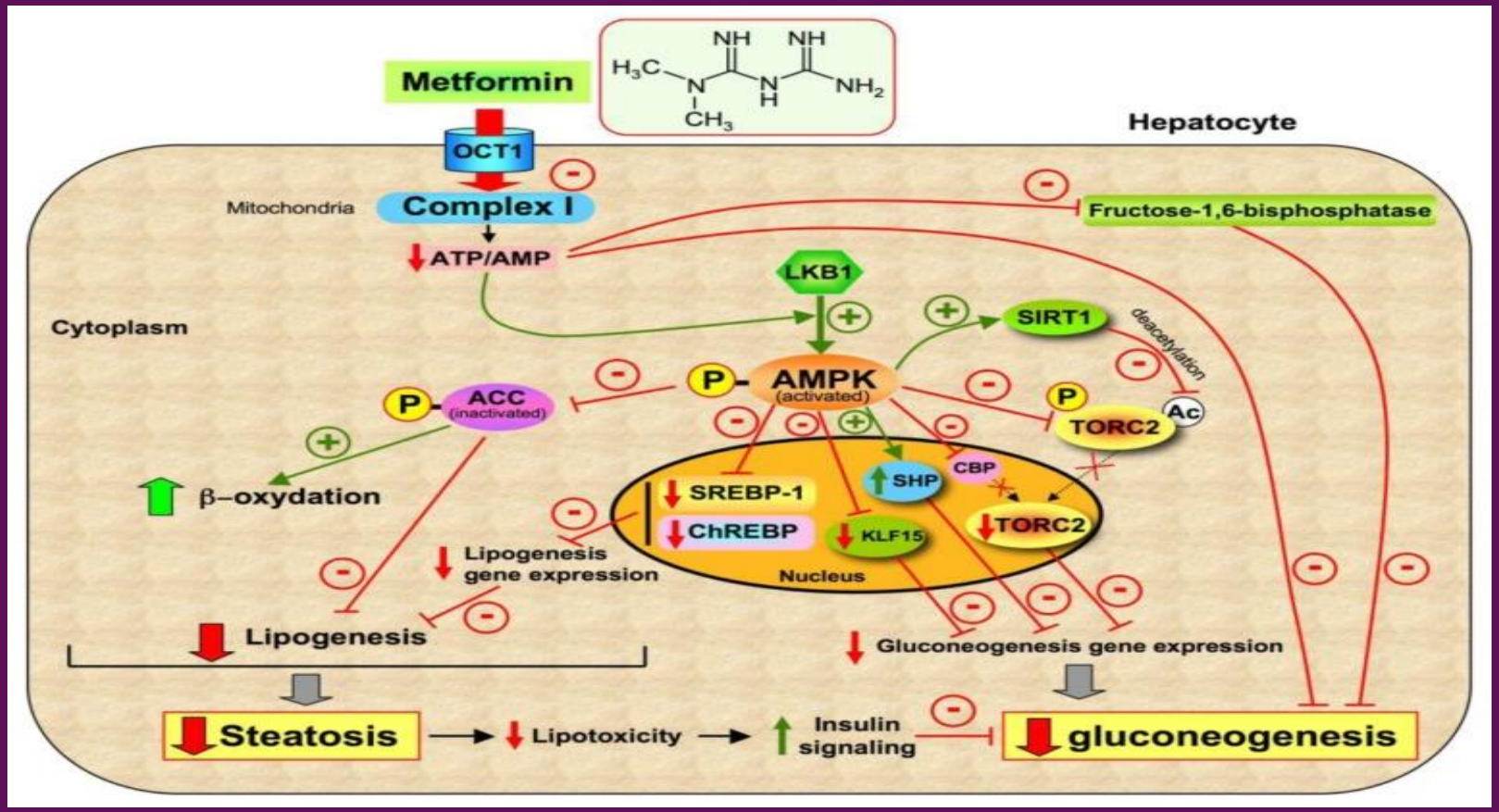
- Representative Drugs

  phenformin metformin

- Key points

  - insulin secretion unchanged, and appetite unchanged
  - Hypoglycemic mechanism remains unclear
  - Use for obese diabetes and type 2 diabetes
  - Alone or co-administered with insulin or **Sulfonylureas**
  - Metformin also used to treat atherosclerosis for down-regulation of LDL& VLDL
  - lactic acidosis are major adverse reactions

Arteriosclerosis occurs when the blood vessels that carry oxygen and nutrients from your heart to the rest of body (arteries) become thick and stiff



After hepatic uptake through OCT1, the mitochondria is the primary target of metformin which exerts specific and AMPK-independent inhibition of respiratory-chain complex 1. The resultant mild decrease in energy status leads to acute and transient inhibition of energy-consuming gluconeogenic pathway. In addition, through AMPK-dependent and -independent regulatory points, metformin can lead to the inhibition of glucose production by disrupting gluconeogenesis gene expression. In parallel, the LKB1-dependent activation of AMPK triggered by ATP depletion could reduce hepatic lipogenesis and exert an indirect effect on hepatic insulin sensitivity to control hepatic glucose output. organic cation transporters (OCT)

Ⅳ. α-glucosidase inhibitors

- **Representative Drugs**

  acarbose voglibose miglitol

- **Key points**

- **To inhibit digestion of starch & disaccharides via competitively inhibiting intestinal α-glucosidase (sucrase, maltase, glycoamylase, dextranase)**
- **Used alone or together with sulfonylureas to treat type 2 diabetes**
- **Main adverse reaction: flatulence, diarrhea, bellyache.**
- **Patients with inflammatory bowel disease & kidney impaired forbidden.**

V. Meglitinides

- Representative Drugs

  Repaglinide

- Key point

  - To increase insulin release by inhibiting ATP-sensitive K^+-channel
  - Unlike sulfonylureas, they have no direct effect on insulin release
  - Used alone or together with biguanides to treat type 2 diabetes
  - Carefully used for patients with kidney or liver impaired.