ANTIDIABETIC DRUGS

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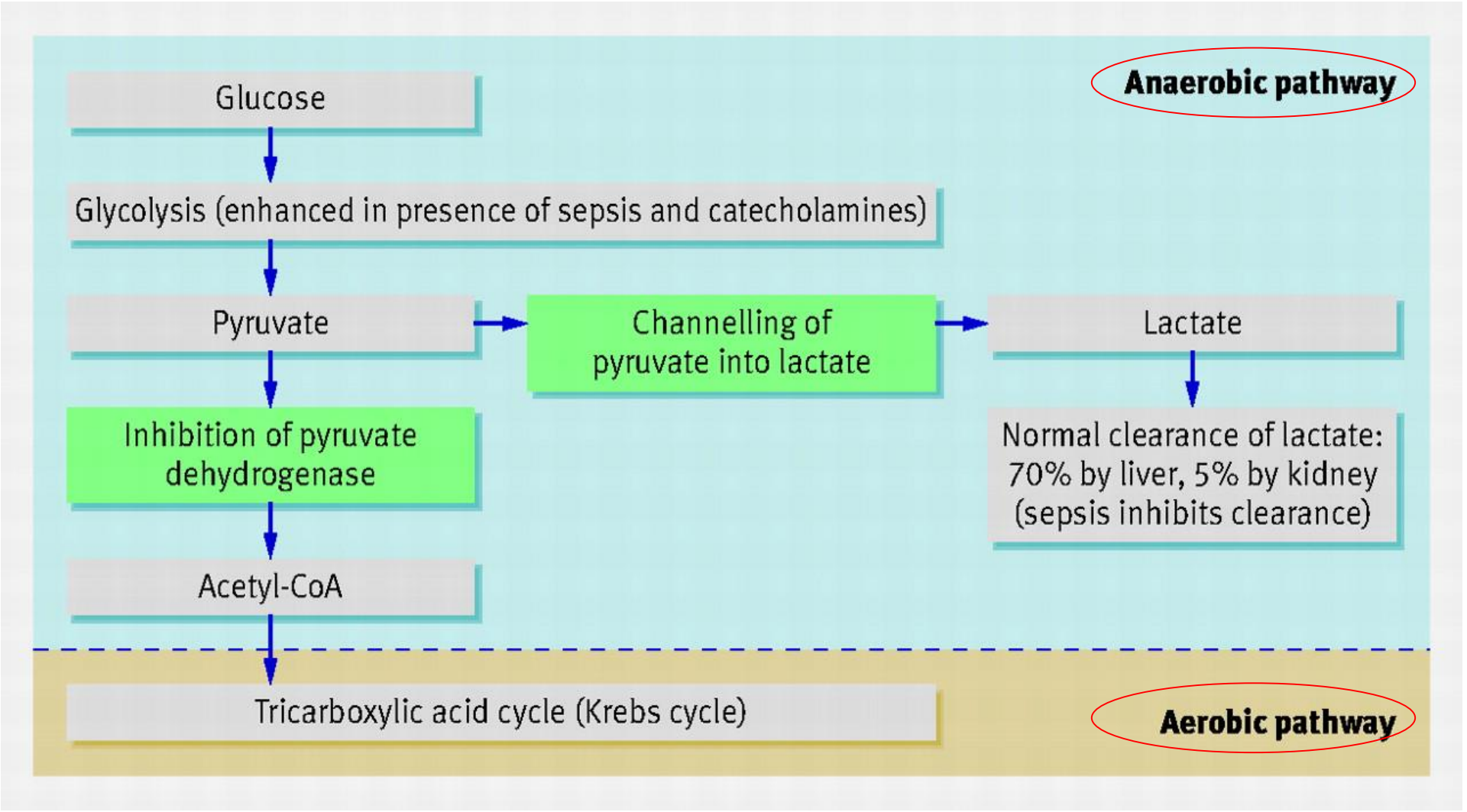
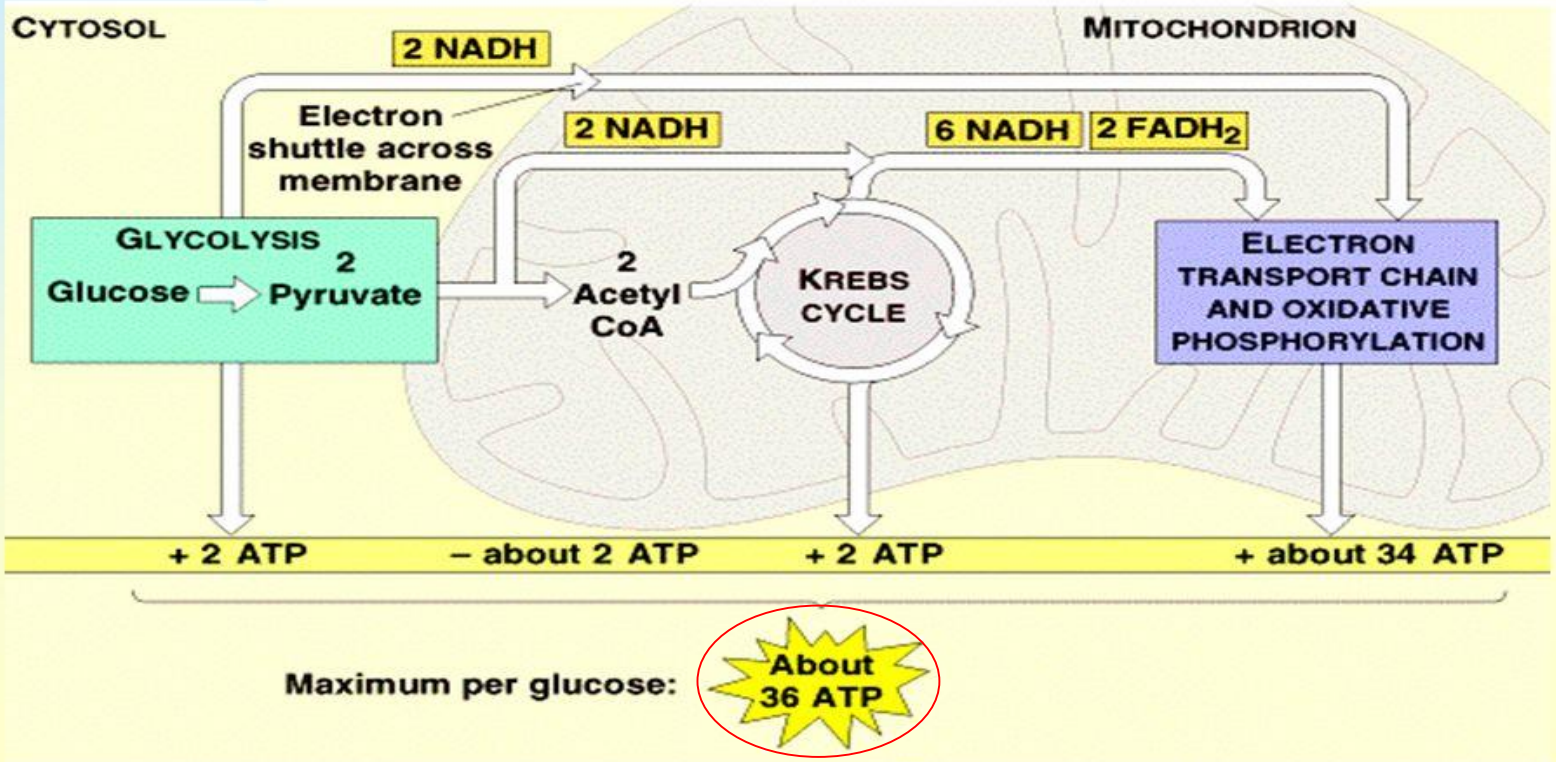
Glucose metabolism

Cell energy supply



ATP Yield during Cellular Respiration



• Aerobic respiration is **far more energy-efficient** than anaerobic respiration:

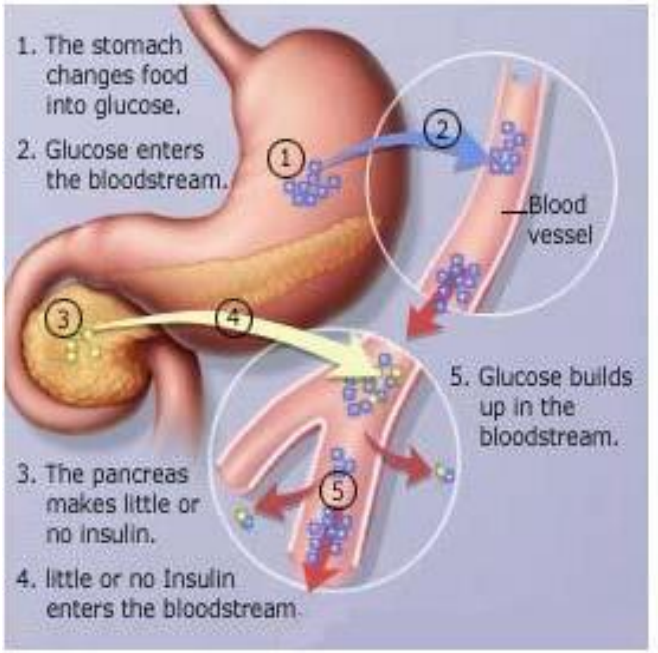
- aerobic processes produce up to 38 ATP per glucose
- anaerobic processes yield only 2 ATP per glucose

Types of diabetes

- **Type 1 diabetes**
- **insulin dependent**
- also known as juvenile diabetes
- autoimmune disorder

- **Type 2 diabetes**
- also known as adult onset diabetes
- occurs in later life
- caused by insulin resistance
- body needs more insulin than secreted or the insulin is less effective

- **Gestational diabetes**
- acquired during pregnancy
- product of hormonal changes & also hereditary genes
- usually stops after childbirth



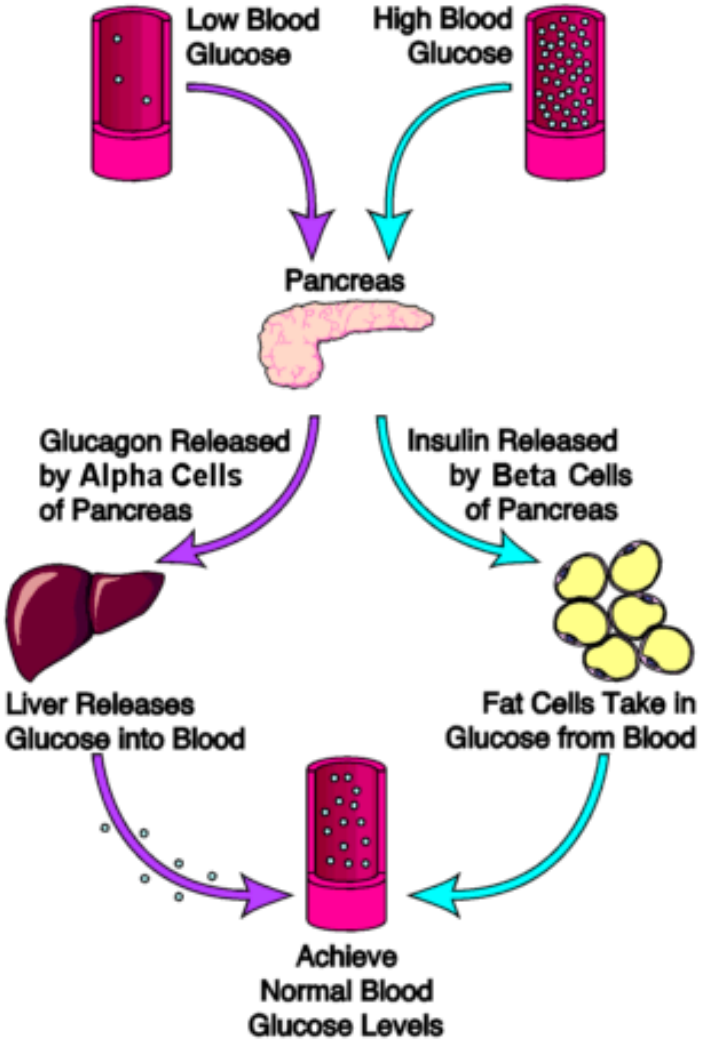
DIABETES

KNOW THE SYMPTOMS

Normal regulation of blood glucose

- ***Insulin & glucagon*** are the hormones which maintain blood glucose in a very narrow range

- It is the production of *insulin & glucagon* by the pancreas which determines if a patient has:
  - **diabetes**
  - **hypoglycemia**
  - **some other glucose problem**



www.endocrineweb.com/insulin.html

Co-discovery of insulin

F. G. Banting

(1891–1941)

J. J. R. Macleod

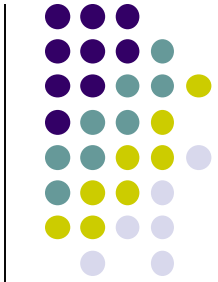
(1876–1935)

C. H. Best

(1899–1978)

Nobel Prize in Medicine for 1923 for the discovery of insulin, ignoring Charles Best. This incensed Banting who then chose to share half of the prize money with Best.

Glucose transporters

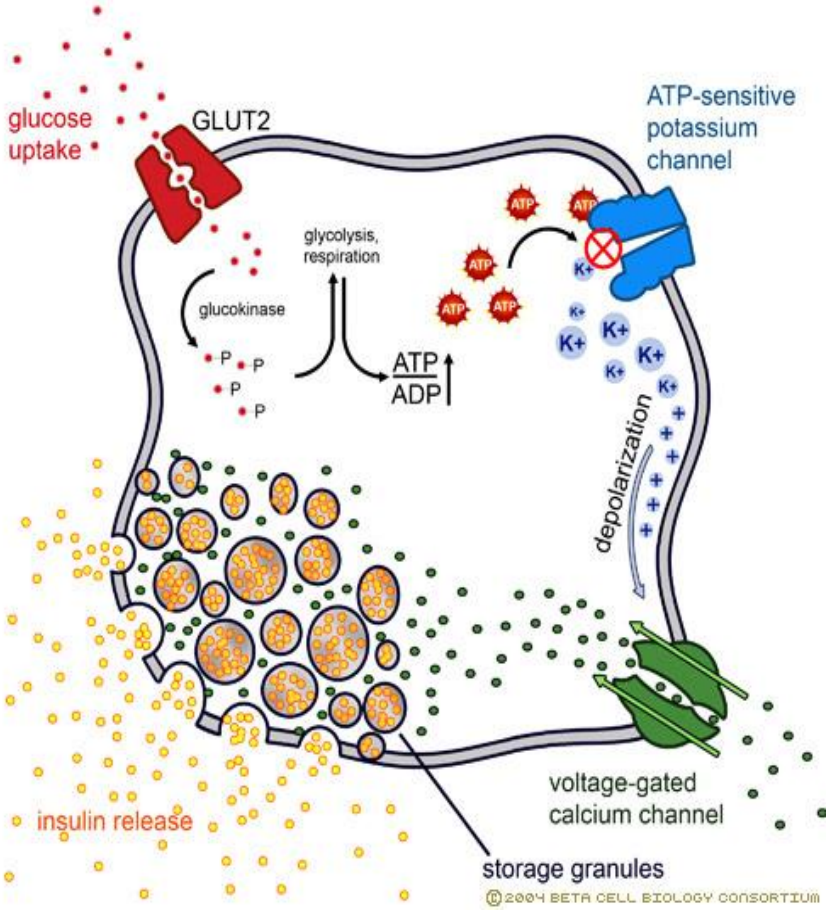


- There are 3 classes & 14 types of GLUT proteins
  - GLUT1 - erythrocytes & endothelial cells of barrier tissues (such as the BBB; responsible for the low level of basal glucose uptake required to sustain respiration in all cells)
  - **GLUT2** - renal tubular cells, liver cells, pancreatic β-cells, small intestine epithelium
    - bidirectional transporter (bidirectionality is required in liver cells to uptake glucose (glycolysis) & release of glucose (gluconeogenesis); in pancreatic β-cells free flowing glucose is required so that the intracellular environment of these cells can accurately gauge the serum glucose levels)
  - GLUT3 - neurons
  - **GLUT4** - adipose tissues & striated muscle (skeletal muscle & cardiac muscle) – *insulin*-regulated glucose transporter

Insulin secretion

- Rise of blood glucose levels
- The uptake of glucose

  (GLUT2 transporter)
- Glycolytic phosphorylation ⇒ rise in the ATP:ADP ratio
- Inactivation of the K^+ channel (ATP-dependent)
- Depolarization of the membrane
- Ca^{2+} channel opening
- Exocytotic release of insulin



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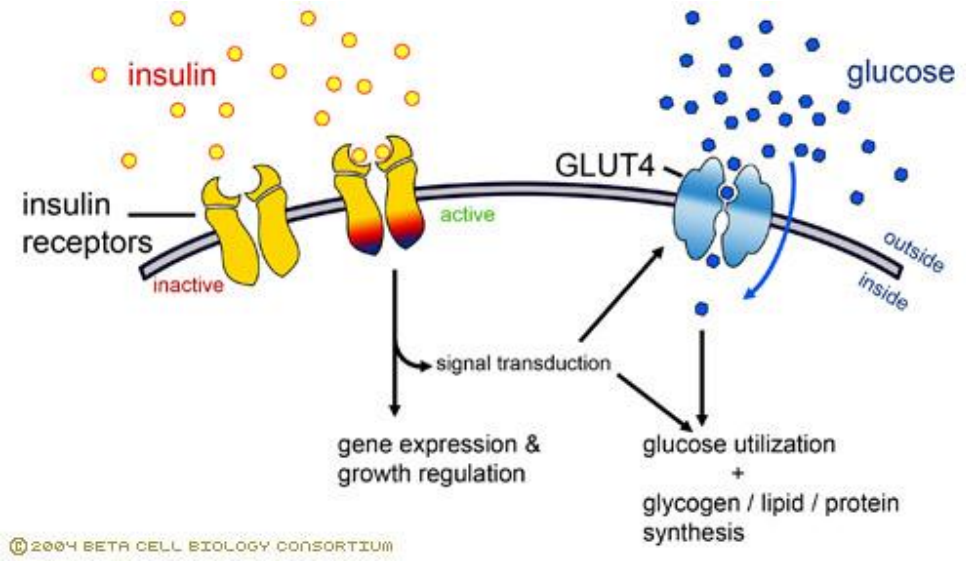
Insulin-mediated glucose uptake

- *Insulin* binding to the *insulin* receptor allows the glucose transporter (GLUT4) to **transport glucose into the cell**

with

- a concomitant ⇓ **in hepatic glucose release**



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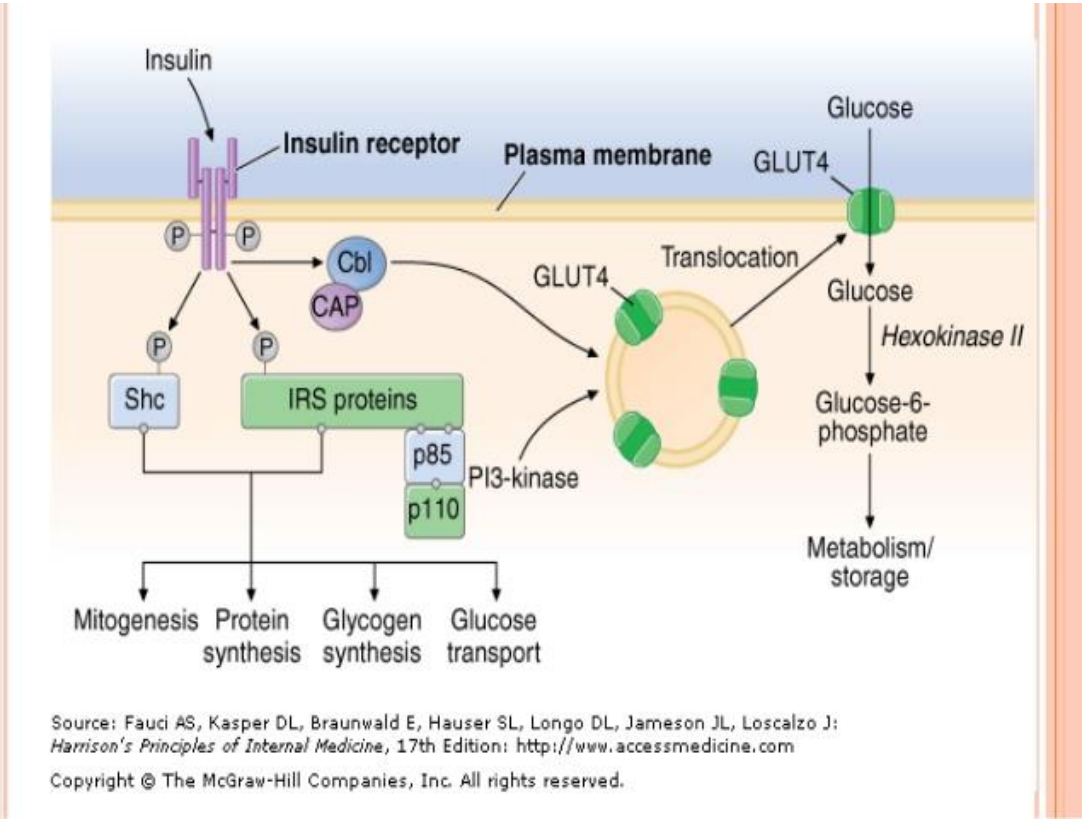
Actions of *insulin*

- Regulates glucose metabolism
- Stimulates lipogenesis
- Diminishes lipolysis
- ⇑ amino acid transport into cells
- Modulates transcription (altering the cell content of numerous mRNAs)
- Stimulates growth, DNA synthesis & cell replication

(the last are the effects that it holds in common with the *insulin*-like growth factors – *IGFs & relaxin*)

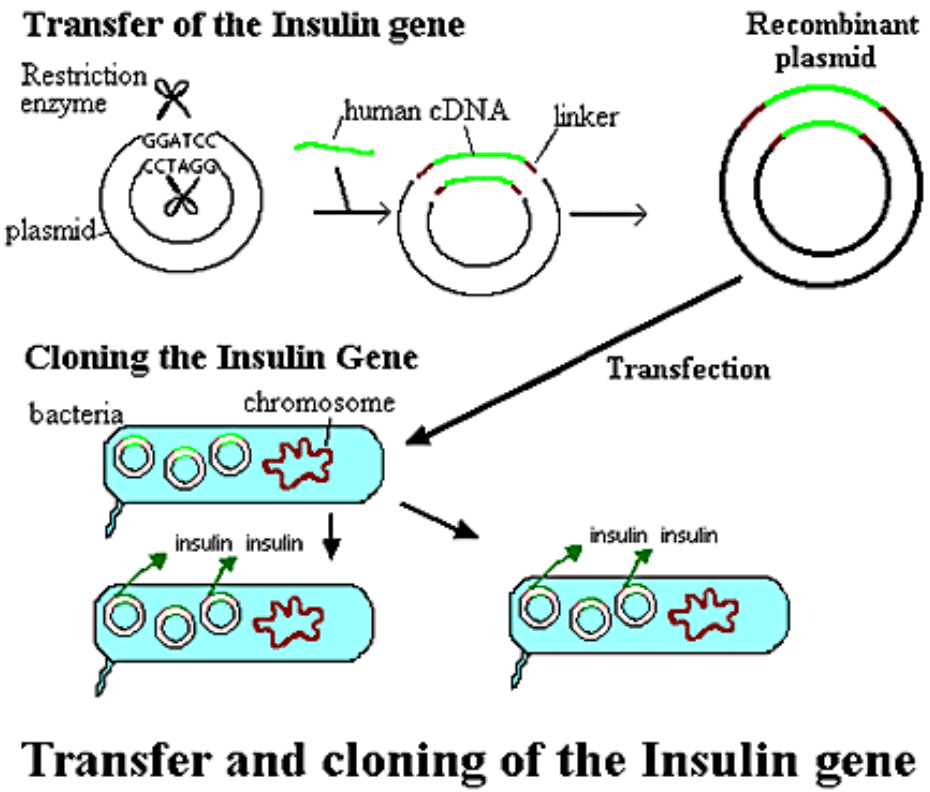


Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Human *insulins*

- ***Human recombinant insulin***
  - ***insulin lispro***
  - ***insulin aspart***
  - ***insulin glargine***

are the commonly-used insulins



Transfer and cloning of the Insulin gene

Zinc as a component of *insulin*

_Zn_ functions in _insulin_ production in B-cells & duration of action:

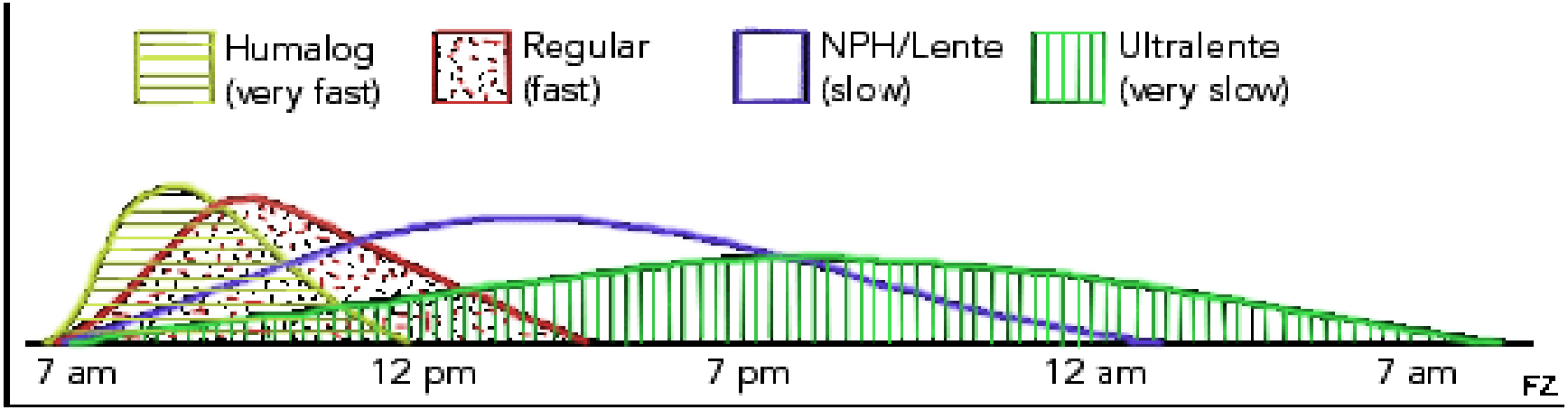
- Completing proinsulin & formation of *insulin* hexamers (small amounts of *Zn*)
- This ⇑ proinsulin solubility & better *insulin* storage
- Addition of higher amounts of *Zn* → crystallisation of *insulin* & formation of insoluble *zinc* salts (microcrystal character of precipitated granule of insulin ⇓ proteolysis):

➢ after s.c. inj. act as depot forms with slow release of *insulin* (⇑ duration of action)

Insulin types

Insulin type	Action begins	Peak	Duration
Insulin Lispro (Humalog®)	**5 min**	**1 h**	**2 - 4 h**
Regular Insulin (Humulin R®)	**15 - 30 min**	**2 - 4 h**	**4 - 6 h**
Isophane Insulin (*HumuLIN N*®)	**30 - 60 min**	**4 - 8 h**	**20 - 22 h**
Insulin Zinc (Lente®)	**60 min**	**9 - 12 h**	**22 - 24 h**
Insulin Detemir (Levemir®)	**3 - 4 h**	**3 - 9 h** (up to approximately 14 h)	**up to 24 h**
Insulin Glargine (Lantus®)	**1.1 h**	**No pronounced peak**	**24 + h**
Insulin Degludec (Tresiba®)	**30 - 90 min**	**No peak in activity**	**24 + h** (up to 42 h)

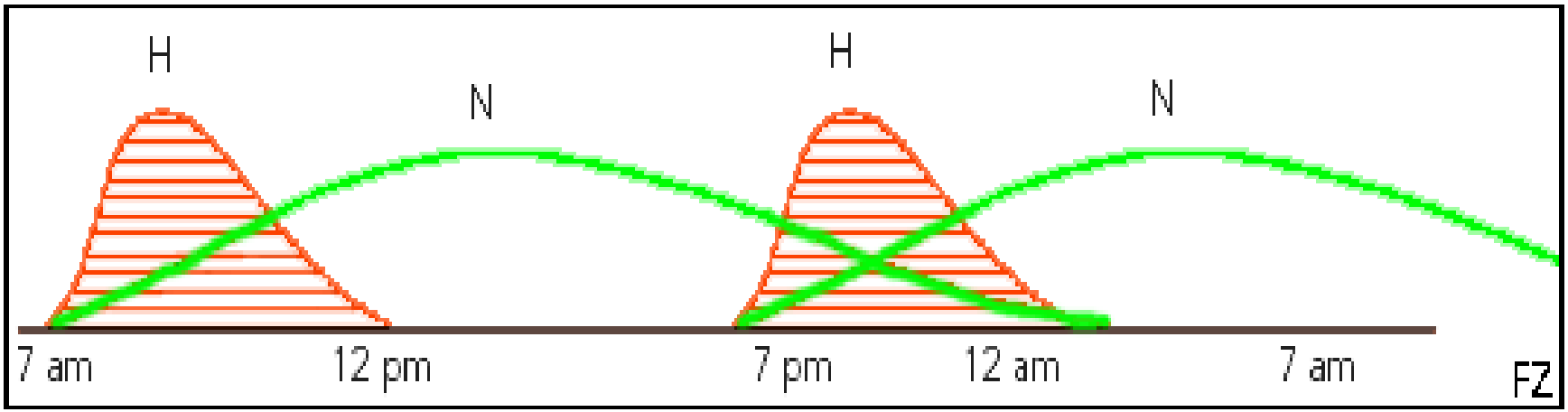
Example of insulin types



- Pre-Mixed Insulins: 50/50 or 70/30 Combined Regular & NPH or Lente insulins
  - 50/50 is 50% NPH & 50% Regular
  - 70/30 is 70% NPH & 30% Regular

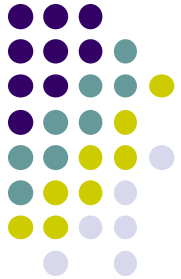
www.sokkari.com/insulin/insulin.htm

Example of *insulin* treatment programs



- **Split** Mix Dose of 2 injections of **rapid** & **intermediate *insulin***

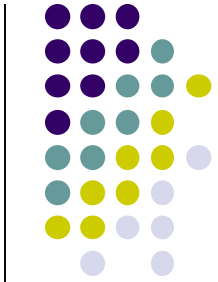
Side effects of *insulin*



- **Hypoglycemia** - can be brought about by:
  - taking too much insulin
  - missing or delaying meals
  - exercising or working more than usual
  - an infection or illness (especially with diarrhea or vomiting)
  - a change in the body's need for insulin
  - diseases of the adrenal, pituitary, or thyroid gland, or progression of kidney or liver disease
  - interactions with other drugs *(oral hypoglycemics, salicylates, sulfonamides & certain antidepressants)*
  - consumption of alcoholic beverages
- **Lipodystrophy**
- **Allergy to *insulin***

ORAL HYPOGLYCEMIC AGENTS

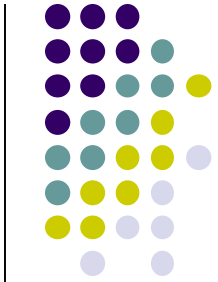
Type 2 diabetes



Current pharmacologic treatments for type 2 diabetes:

- ⇑ ***insulin*** **availability** (either through direct insulin administration or through agents that promote insulin secretion)
- **Improving sensitivity to *insulin*** (in the periphery)
- ⇑ **urinary glucose excretion**
- **Delaying the delivery** & **absorption of carbohydrate from the GIT**

Principles of the treatment

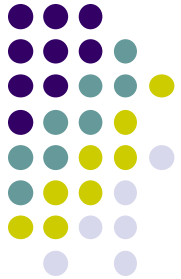


- Initial therapy in type 2 diabetes patients should begin with diet, weight reduction, exercise
- Oral medication is initiated when 2 - 3 months of diet & exercise alone are unable to achieve or maintain their optimal plasma glucose levels:
  - however, a trial of diet & exercise alone should be reserved for patients with **asymptomatic hyperglycemia**
  - if patients are **symptomatic**, **oral antidiabetic agents** or ***insulin*** should be initiated (in concert with diet & exercise)
  - ***metformin*** (in the absence of contraindications)

Classification of oral hypoglycemic drugs

- **SULFONYLUREAS**
- **MEGLITINIDES**
- **GLP-1 based therapies:**
  - **DDP-4 inhibitors**
  - **GLP-1 agonists – inj.**
- **BIGUANIDES**
- **GLITAZONES (THIAZOLIDINEDIONES)**
- **GLIFLOZINES**
- **ALPHA-GLUCOSIDASE INHIBITORS**

SULFONYLUREAS
SU



I. generation:

- ***acetohexamide***
- ***chlorpropamide***
- ***tolazamide***
- ***tolbutamide***

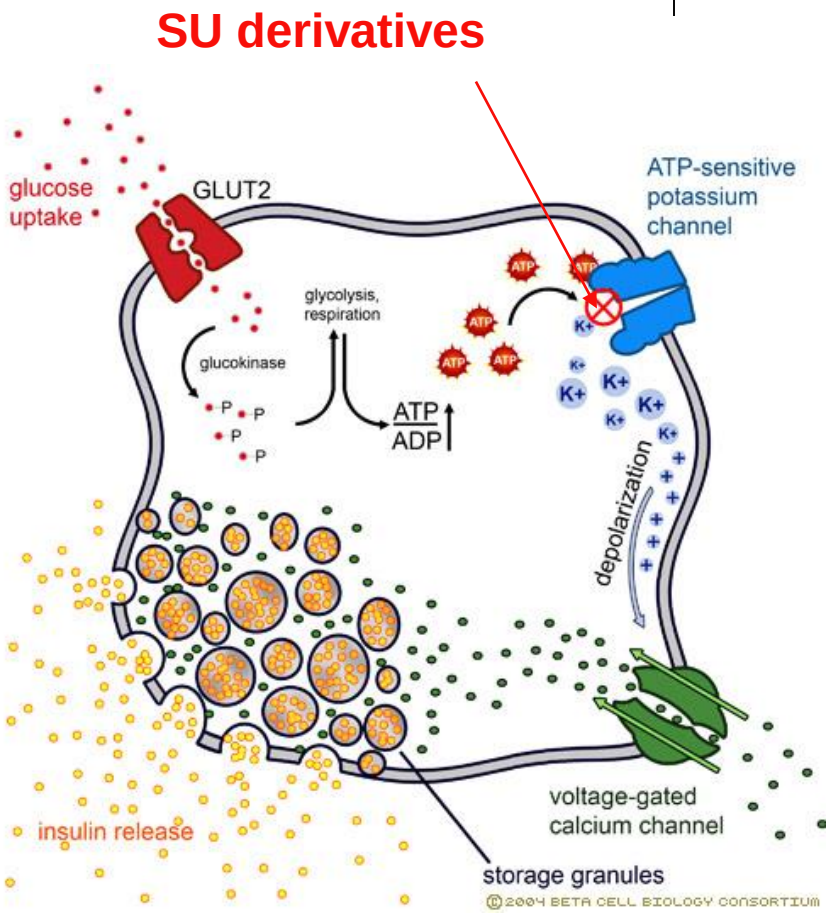
II. generation:

- ***glibenclamide***
- ***glyburide***
- ***glipizide***
- ***glicazide***
- ***glimepiride***

The second generation *SU* are primarily used now.

The mechanism of action of *SU*

- K^+ channel blockers
- The effect on the pancreatic B-islet cells is to allow an influx of Ca^{2+} into the cell
- This causes an ⇑ in the release of *insulin*



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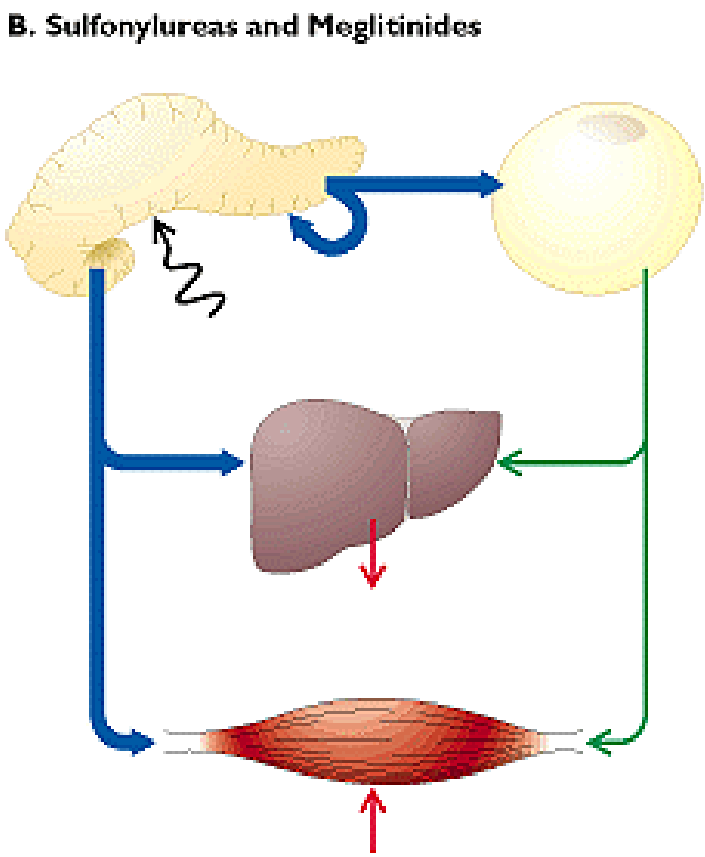
Tissue effects of *SU*

***SU* work:**

- **Primarily by stimulating pancreatic *insulin* secretion**
- This in turn:
  - ↓ hepatic glucose output
  - ↑ peripheral glucose disposal



diabetesindia.com/diabetes/oral_hypoglycemic_...

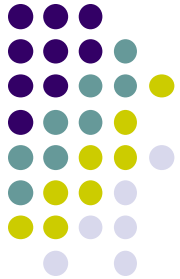
MEGLITINIDES

MEG

- ***Repaglinide*** (*meglitinide* drug class) **acts like an extremely short-acting *SU*** (an insulin secretagogue)
- The effect of ***repaglinide*** on the pancreas is very **similar to that of the *SU***

- It is potentially useful as a ***SU*** **replacement**

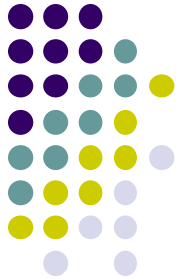
Advantages of *MEG*



- Because of the **short duration,** the patient **does not have continuous high levels of insulin** & the resulting adverse effects
- **Its biggest advantage** over the other oral hypoglycemic medications ⇒ **it allows for flexible timing & missed meals**
- ***Repaglinide*** **has been approved for use with** ***metformin*** & the combination appears to be a very effective

INCRETINS

Glucagon-like peptide-1-based therapies



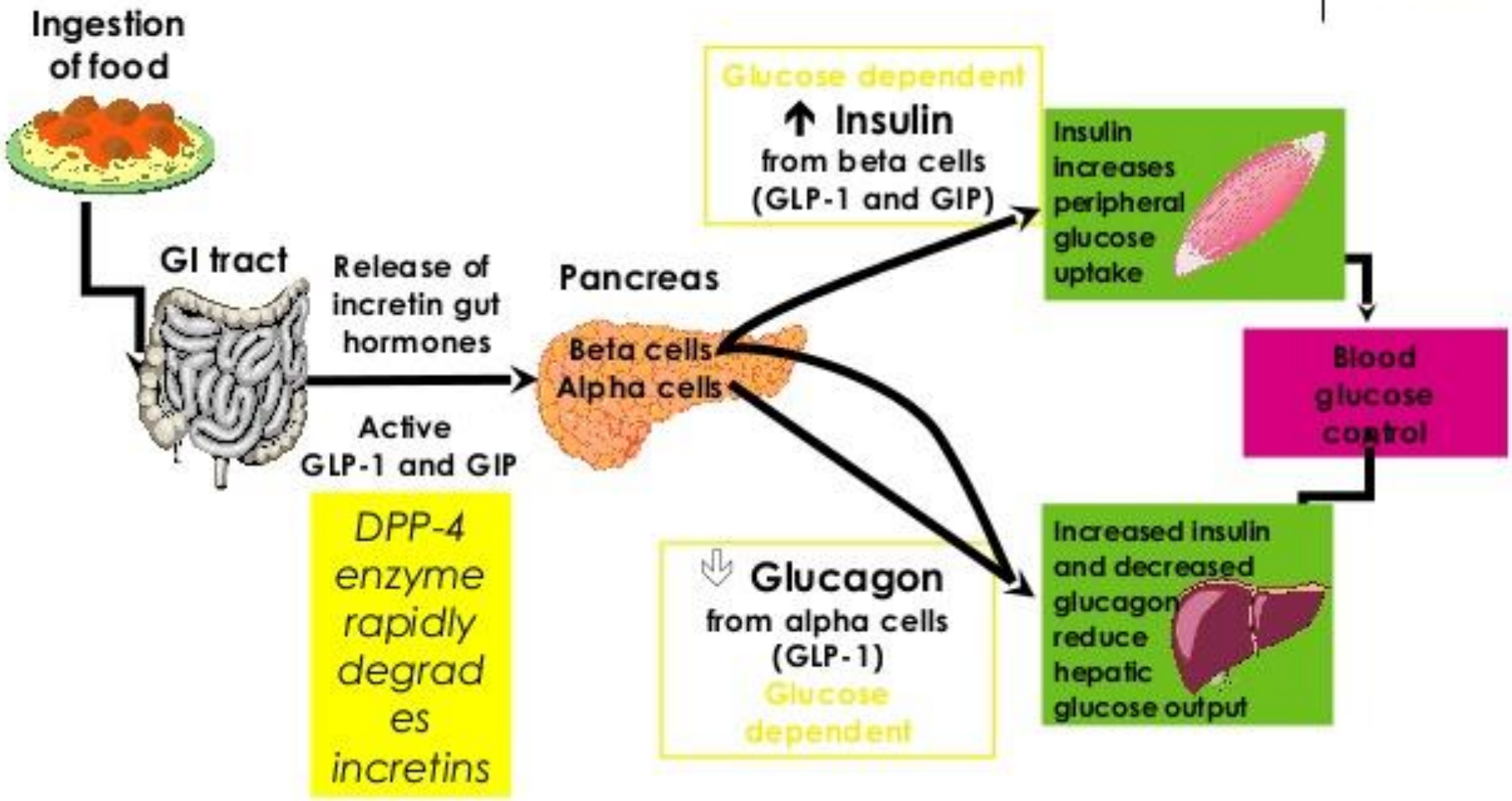
There are two **incretins**, known as gut hormones:

- GIP (glucose-dependent insulinotropic peptide) &
- GLP-1 (glucagon-like peptide-1)
  - they share many common actions in the pancreas but have distinct actions outside of the pancreas
  - they are released in the setting of a meal but not with *i.v.* carbohydrate &
  - stimulate *insulin* synthesis & secretion

They exert their main effect by:

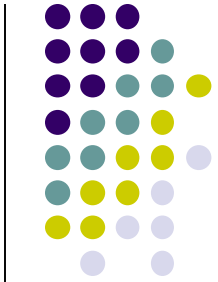
- stimulating glucose-dependent *insulin* release
- slowing gastric emptying
- inhibiting inappropriate post-meal *glucagon* release

Incretins and glycemic control



Adapted from 7. Drucker DJ. *Cell Metab.* 2006;3:153–165. 8. Miller S, St Onge EL. *Ann Pharmacother* 2006;40:1336-1343.

GLP-1-based therapies



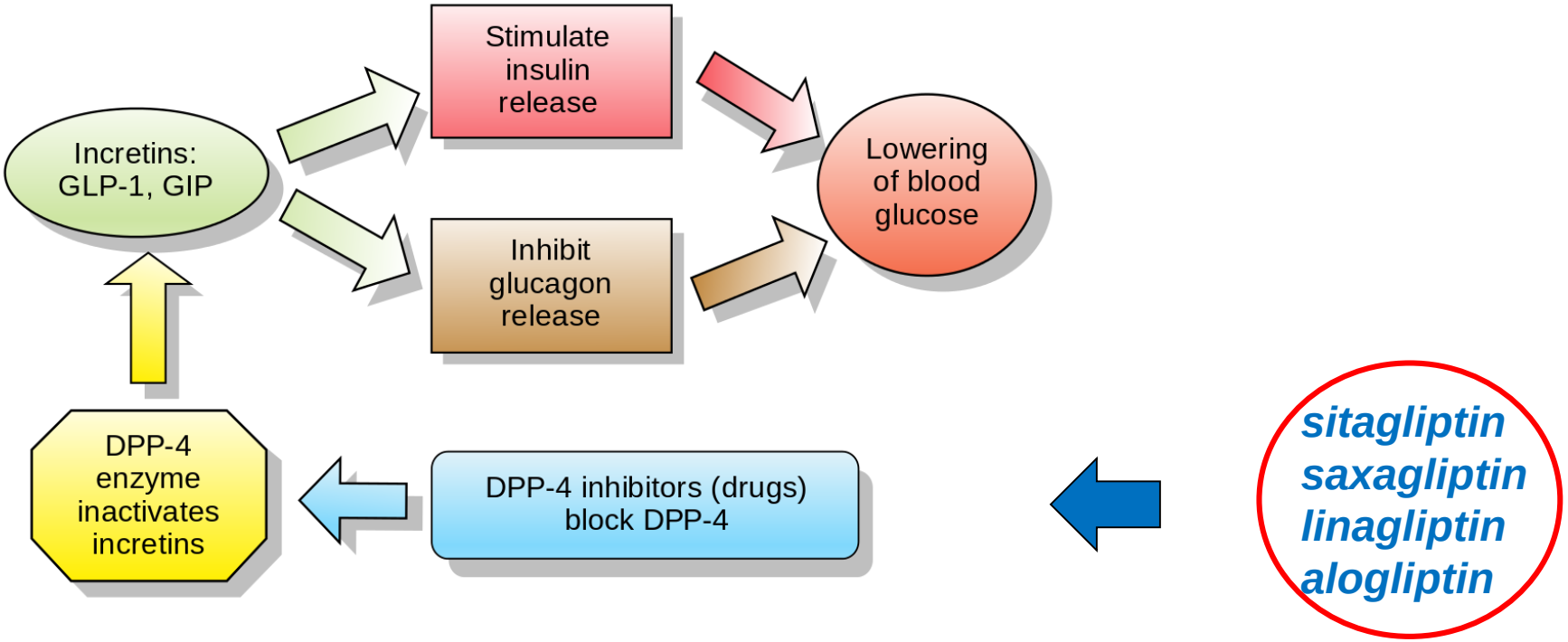
GLP-1-based therapies:

- DPP-4 inhibitors (dipeptidyl peptidase-4)
- GLP-1 receptor agonists

- Affect glucose control through several mechanisms, including:
  - enhancement of glucose-dependent *insulin* secretion
  - slowed gastric emptying
  - reduction of postprandial glucagon & of food intake

DPP-4 inhibitors
MOA

- ⇓ the degradation of the incretins (GLP-1 & GIP) resulting in:
- ⇑ *insulin* production in the pancreas β-cells
- ⇓ of *glucagon* production from pancreatic α- cells
- reduced production of glucose by the liver



GLP-1 RECEPTOR AGONISTS

Incretin mimetics

- ***Exenatide*** (Byetta)
- ***Lixisenatide*** (Lyxumia)
- ***Albiglutide*** (Tanzeum)
- ***Dulaglutide*** (Trulicity)

- They have blood-sugar lowering actions alone
- Can also be combined with other medications such as *pioglitazone, metformin, SU* &/or *insulin* to improve glucose control

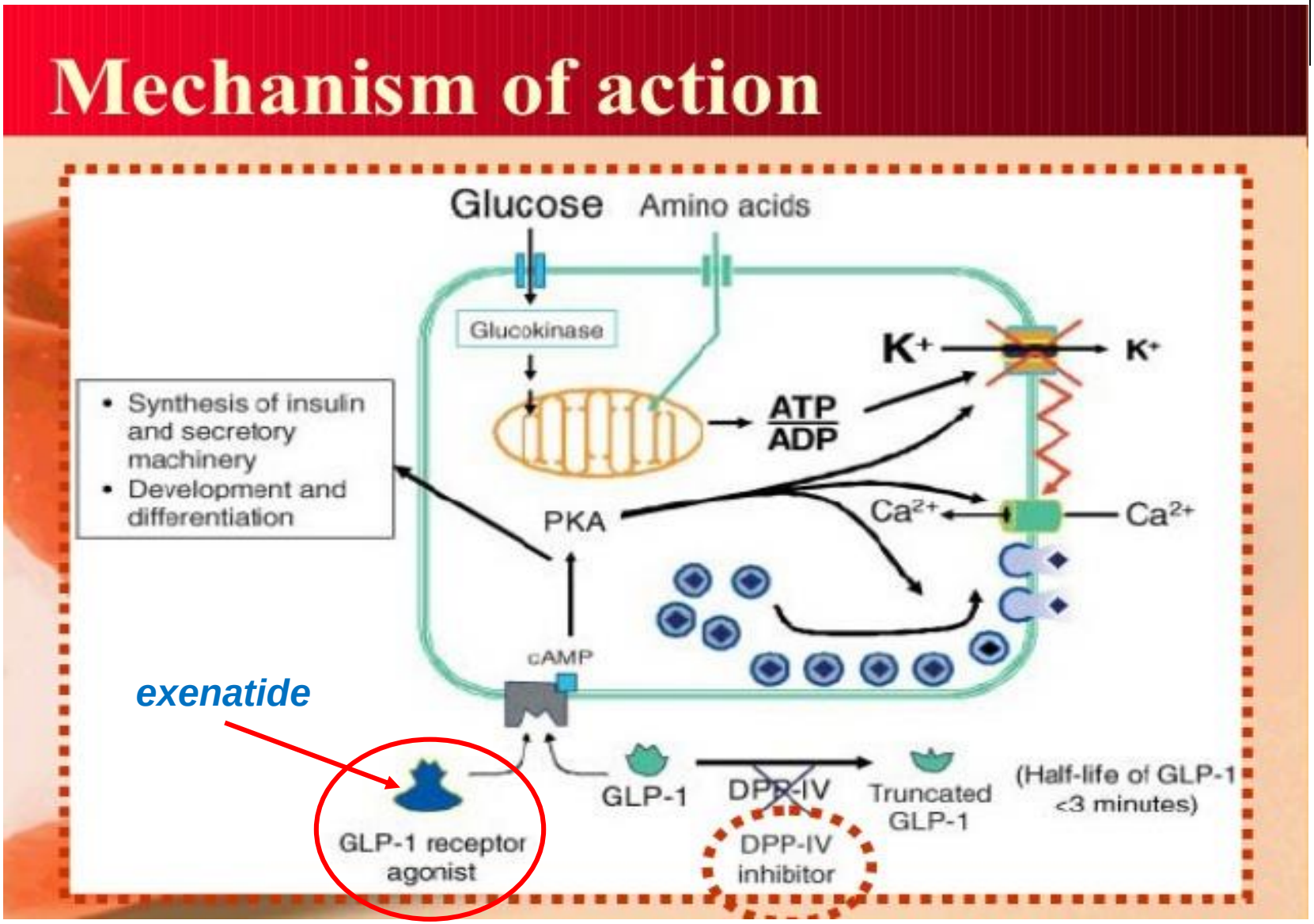
- Secondary effects of drug administration reduce:
  - ❖ the rate of gastric emptying &
  - ❖ ⇓ food intake

  (mitigating the potential severity of hyperglycaemic events after meals)

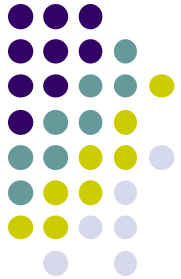
- **Injected**

(twice per day)

Exenatide


Mechanism of action
Glucose
Amino acids
Glucokinase
K+
K+
ATP
ADP
• Synthesis of insulin and secretory machinery
• Development and differentiation
PKA
Ca2+
Ca2+
cAMP
exenatide
GLP-1 receptor agonist
GLP-1
DPP-IV
Truncated GLP-1
(Half-life of GLP-1 <3 minutes)
DPP-IV inhibitor

BIGUANIDES
BG

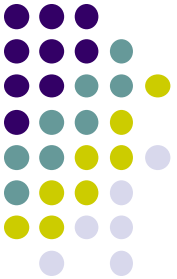


- Two drugs in this category are:

- *phenformin*
- ***metformin***

- The use of *phenformin* has ⇓ considerably
- It is usually ***metformin*** **that is now used when a biguanide is prescribed**

The MOA of *BG*

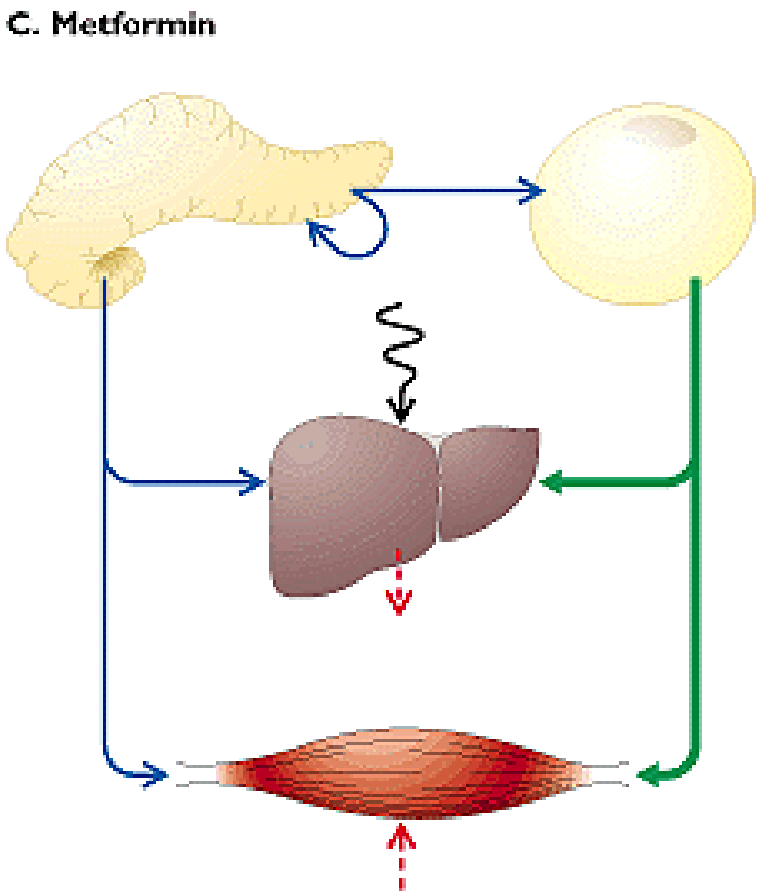


- Has been well studied in liver, adipose tissue, skeletal & heart muscles
- *BG* **do not stimulate** endogenous ***insulin*** **secretion**
- Therefore they are sometimes called **anti-hyperglycemic** agents rather than **hypoglycemic agents**
- Their tissue effects result rather in ⇓ **insulinemia**
- Most of tissue effects are the result of the activation of AMPK (AMP-activated protein kinase) by *metformin*

Tissue effects of *BG*

***BG* work mainly by:**

- ⇓ excessive hepatic glucose production
- ⇑ insulin sensitivity
- ⇑ glucose utilization in peripheral tissues (by muscles & adipocytes)
- possibly ⇓ food intake & thus ⇓ intestinal glucose absorption



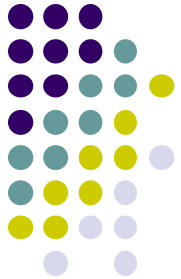
diabetesindia.com/diabetes/oral_hypoglycemic_...

Metformin
SE

- Commonly reported side effects of ***metformin*** include:
  - nausea, vomiting, diarrhea, flatulence...
- **Hypoglycemia** does not occur when ***metformin*** is used alone
- **Lactic acidosis** reported (< 1/10 000) have occurred predominantly in patients with **poor renal function**

GLITAZONES

TZD or thiazolidinediones

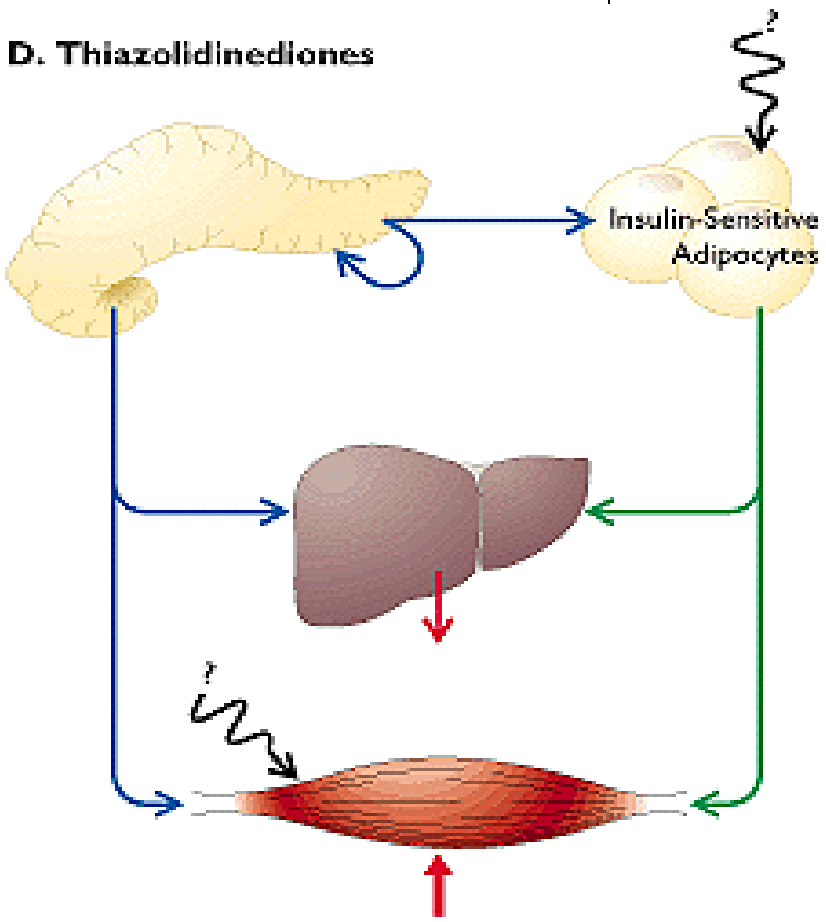


- ***TZD*** *(glitazones)* ⇒ developed in 1997
- Offer ***metformin*-like mechanism** for treatment of type 2 diabetes
- The first, ***troglitazone*** was taken off the market in 1999 (hepatic toxicity)
- ***Rosiglitazone*** **&** ***pioglitazone*** have been available since 1999

The MOA of *TZD*

- The **primary effect of *TZD* is peripheral,** with
  ⇑ *insulin* **sensitivity &**
  ⇑ **glucose uptake**
- The *TZD* have some effect on hepatic glucose uptake & sensitivity

  (to a lesser degree)
- **They do not stimulate the pancreas to produce more *insulin***



diabetesindia.com/diabetes/oral_hypoglycemic_...

Advantages of *TZD*

- ***TZD* are hepatically metabolized & thus can be used safely in patients with renal dysfunction**
- **They can be dosed once daily,** although ***rosiglitazone*** works better with twice-daily dosing
- Reports have suggested that *rosiglitazone* works better in women (the reason ⇒ not known)

GLIFLOZINS

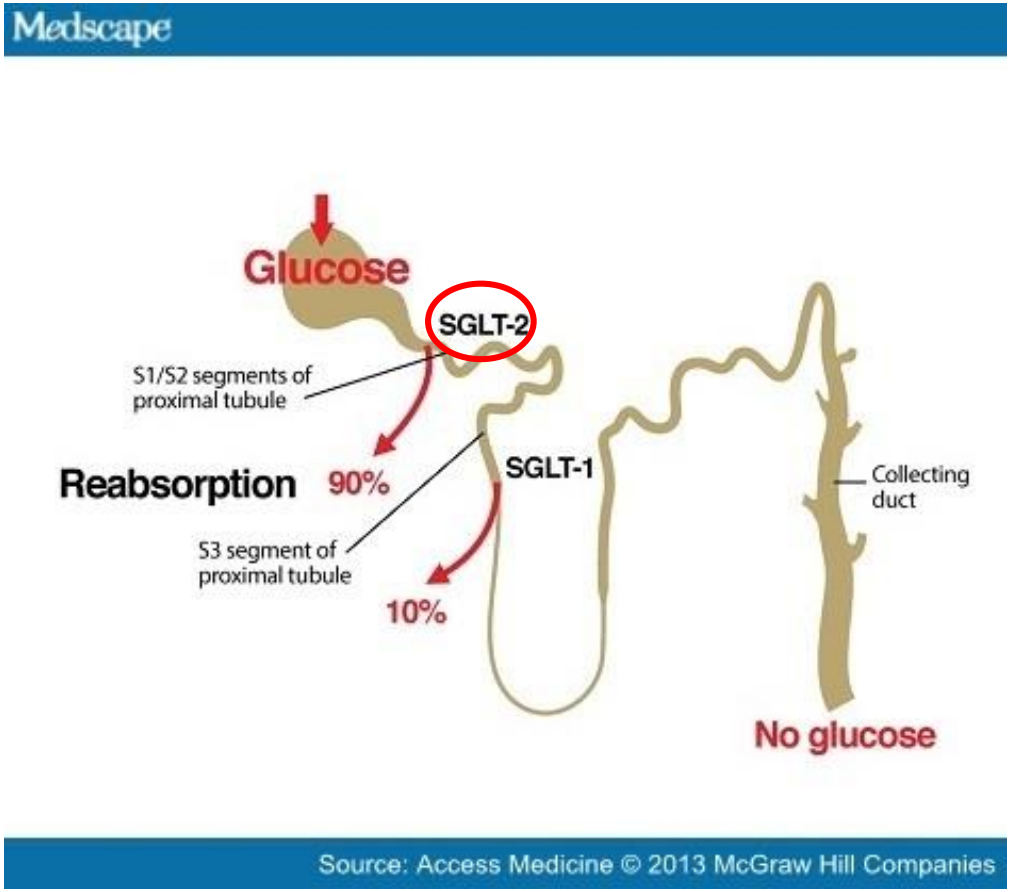
SGLT2 inhibitors

Normal renal glucose handling:

- 100% reabsorption of glucose in proximal tubules by sodium-glucose transport protein 2:
  - SGLT-2 = 90%
  - SGLT-1 = 10%

In DM:

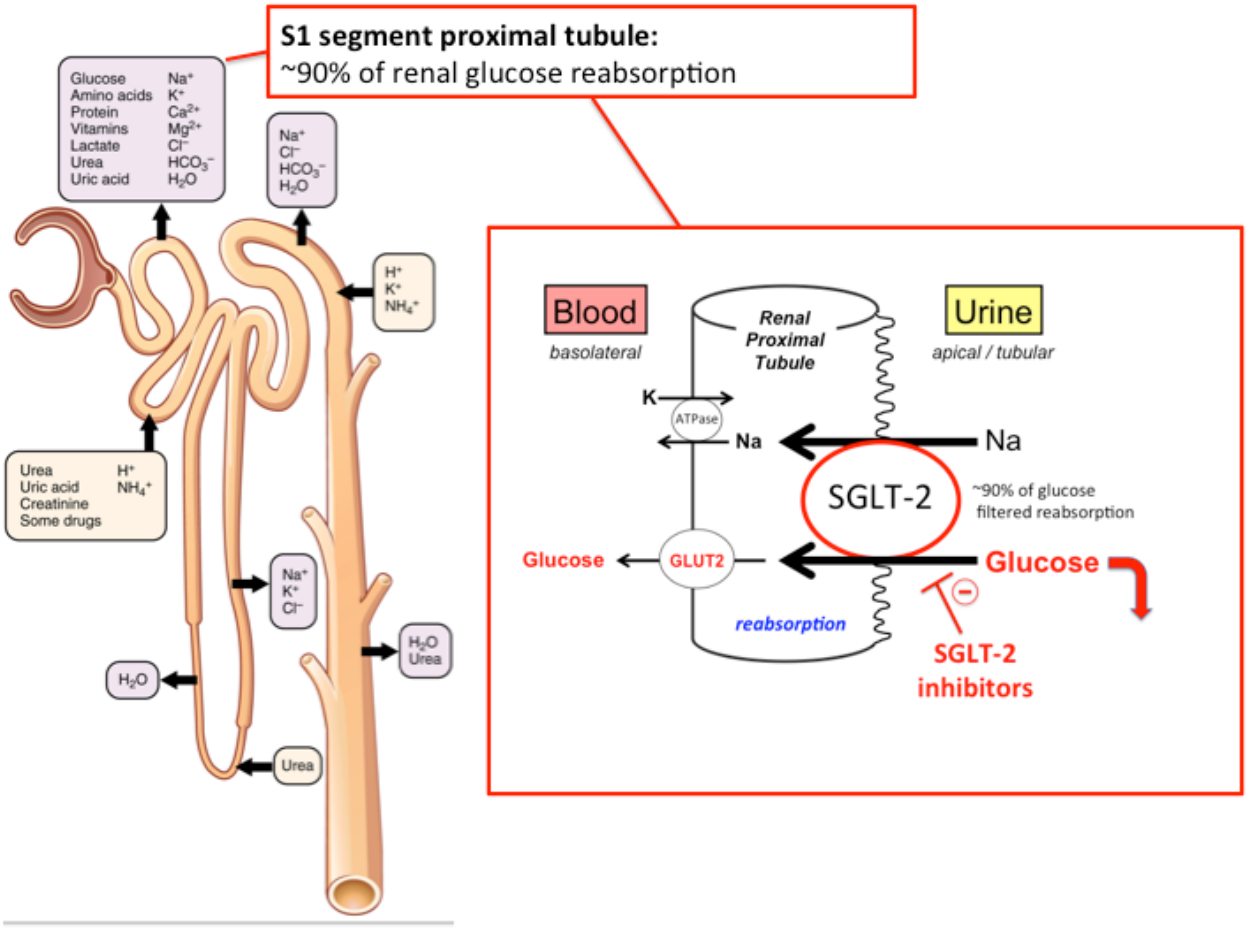
- filtered load exceeds reabsorption capacity



Gliflozins
MOA

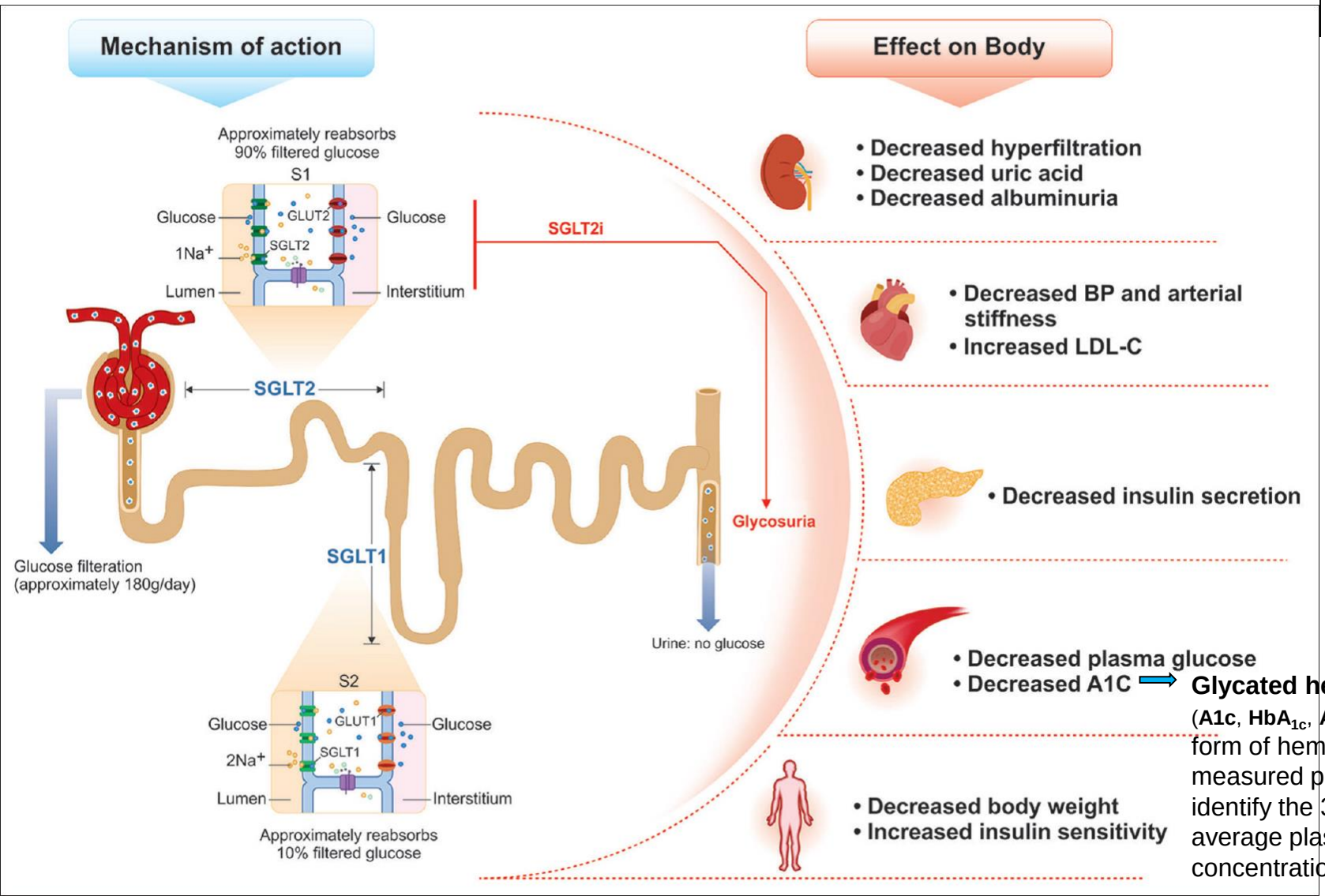
- ⇓ reabsorption of glucose in the kidney & therefore **lower blood sugar**

- Act by ⇓ **SGLT2** (also called **SGLT2 inhibitor)**



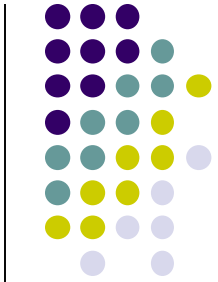
Gliflozins

Tissue effects



Glycated hemoglobin (**A1c**, **HbA_{1c}**, **A1C**, or **Hb_{1c}**) is a form of hemoglobin that is measured primarily to identify the 3-month average plasma glucose concentration

Gliflozins
Clinical use & SE



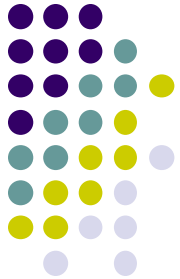
Uses:

- Treatment of type 2 DM:
  - can improve glycemic control in conjunction with excercise & diet
  - reduce body weight
  - reduce systolic & diastolic BP
  - can be combined with *metformin, sulfonylureas, pioglitazone & insulin*

SE:

- *Gliflozins (canagliflozin, dapagliflozin, empagliflozin)* may lead to **ketoacidosis**
- Other side effects include:
  - ⇑ risk of urinary tract infections
  - candidal vulvovaginitis
  - hypoglycemia

ALPHA-GLUCOSIDASE INHIBITORS - AGI



- ***Acarbose* is an *AGI* that slows down the breakdown of:**
  - disaccharides
  - polysaccharides
  - other complex carbohydrates

into monosaccharides:

  - the enzymatic generation & subsequent absorption of glucose is delayed & the postprandial blood glucose values are ⇓

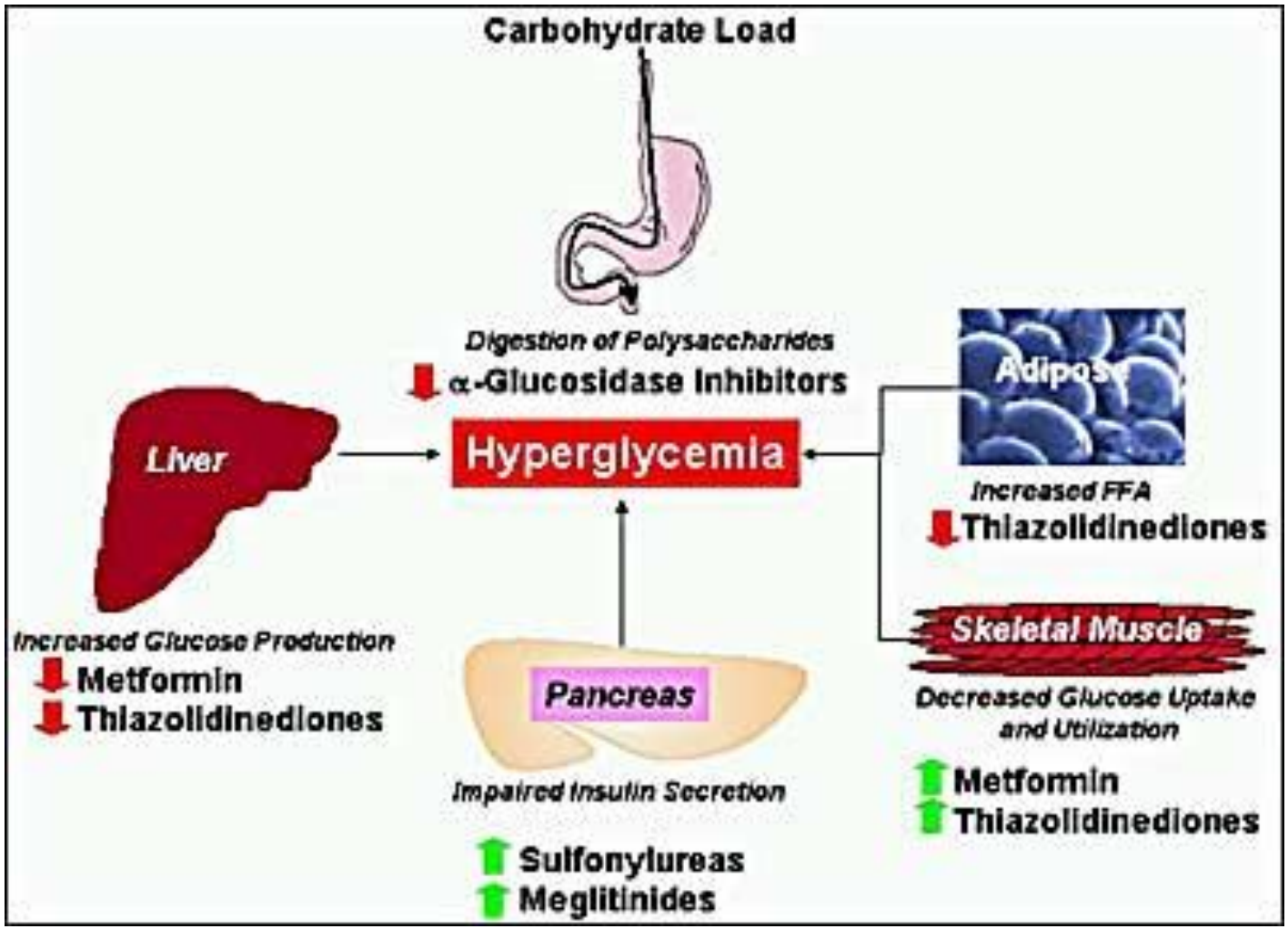
- *AGIs* **do not prevent** the **absorption of carbohydrates** & complex sugars, but they do delay their absorption

Disadvantages of *AGI*

- One **disadvantage** with the use of *acarbose* is that it is to be taken along with the **first bite of a meal**
- Moreover, it has to be taken 3x daily with meals
- These factors often lead to **non compliance** & a ⇓ in the efficacy of the drug

In generic products image may vary on the product received.

Summary of some oral hypoglycemics - sites of action



www.endotext.org/.../diabetes16/diabetes16.htm

Drawing by Alexandra Sternin