Anti Diabetic Drugs

SOURCES:

- BERTRAM G. KATZUNG BASIC & CLINICAL PHARMACOLOGY 15TH EDITION
- GOODMAN AND GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS 13TH EDITION.

Sequence Of Lecture

Core Subject

Spiral Integration

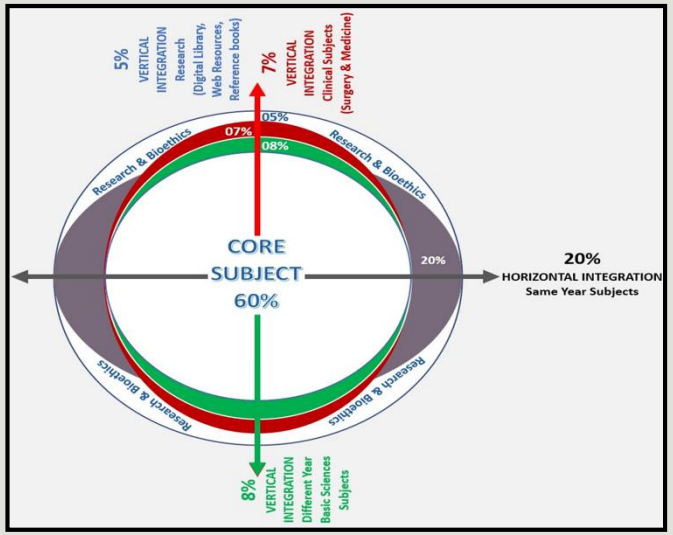
Horizontal Integration

Vertical integration

EOLA(End of lecture assessment)

Digital Library References

(Research, Bioethics, Artificial Intelligence, Family Medicine)



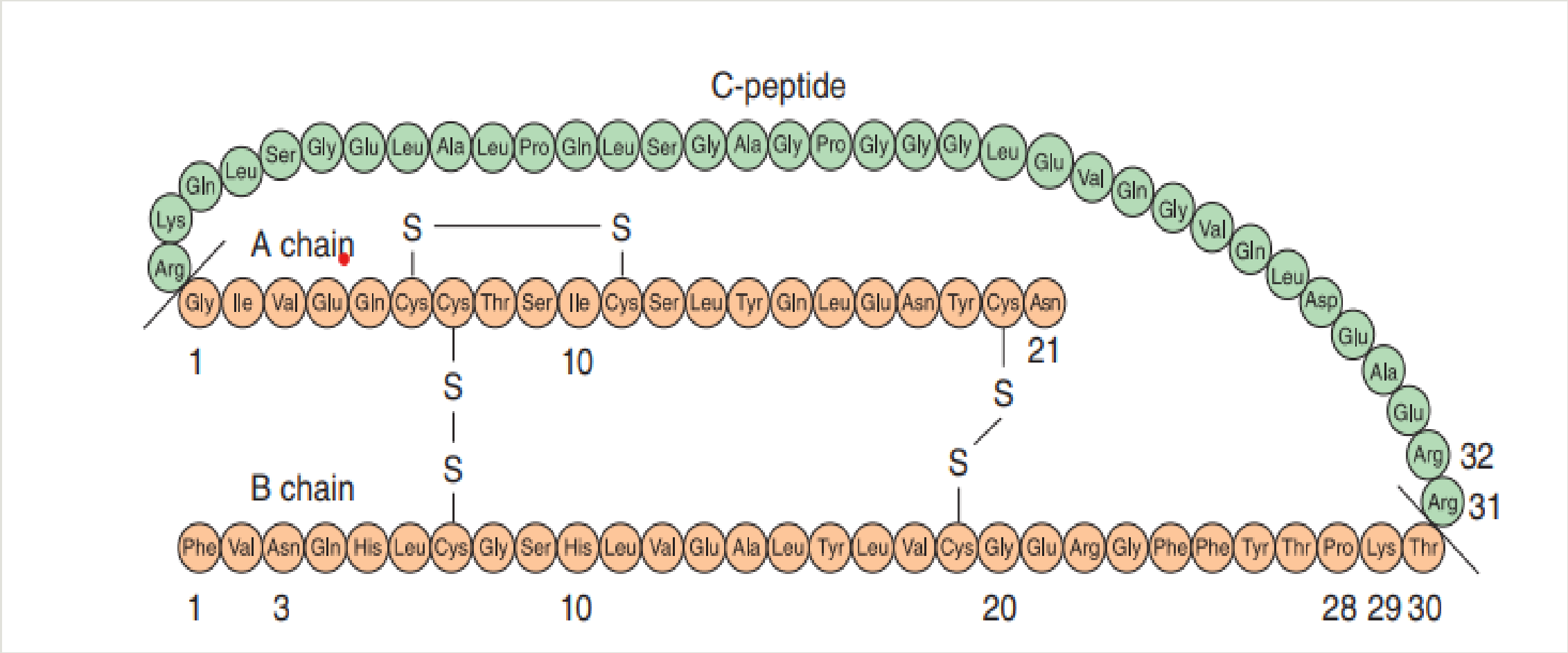
Learning Outcomes

- Brief Pathophysiology of Diabetes mellitus
- Anti Diabetic drugs…Classification
- Insulin:
  - Types
  - Therapeutic uses
  - Regimens
  - Adverse effect

Endocrine Pancreas

- Insulin
- Islet Amyloid Polypeptide
- Glucagon
- Somatostatin
- Pancreatic Peptide
- Ghrelin

Insulin


C-peptide
Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
A chain
1
10
21
S
S
S
S
S
B chain
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr
1
3
10
20
28 29 30
Arg
Arg
Glu
Ala
Glu
Asp
Leu
Gln
Val
Gly
Val
Gln
Gly
Glu
Val
Leu
Gly Gly Gly Pro Gly Ala Gly Ser Gly Leu Gln Leu Pro Leu Ala Leu Glu Gly Ser Leu Gln Lys
Arg
31
32

Insulin Secretion

STIMULATION:

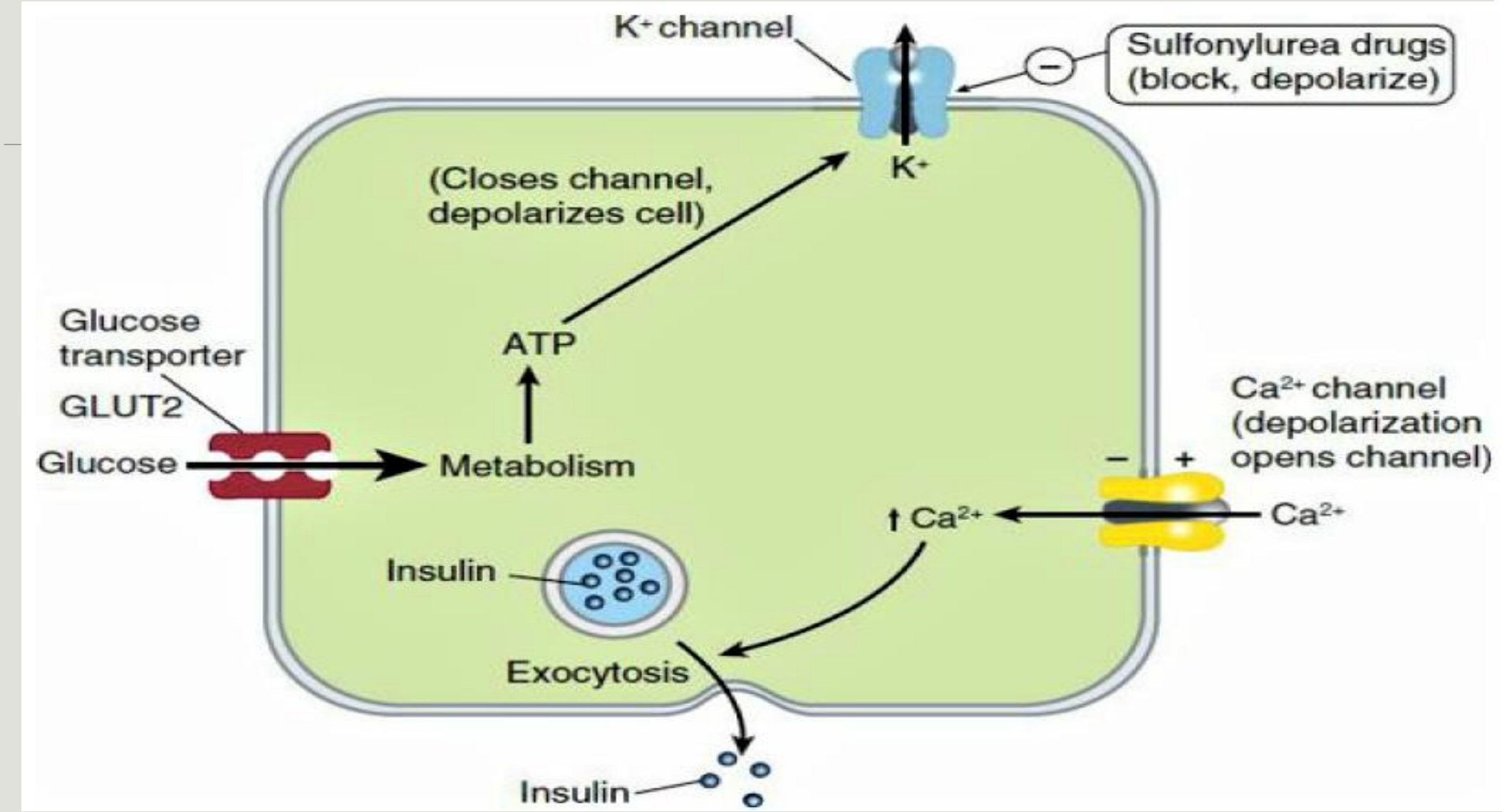
- Glucose, mannose
- Amino acids (especially gluconeogenic amino Acids, leucine, arginine)
- Hormones
  - Glucagon-like Polypeptide 1 (GLP-1)
  - Glucose-dependent insulinotropic polypeptide (GIP)
  - Glucagon
  - Cholecystokinin
- High concentrations of fatty acids
- β-adrenergic sympathetic activity

Insulin Secretion

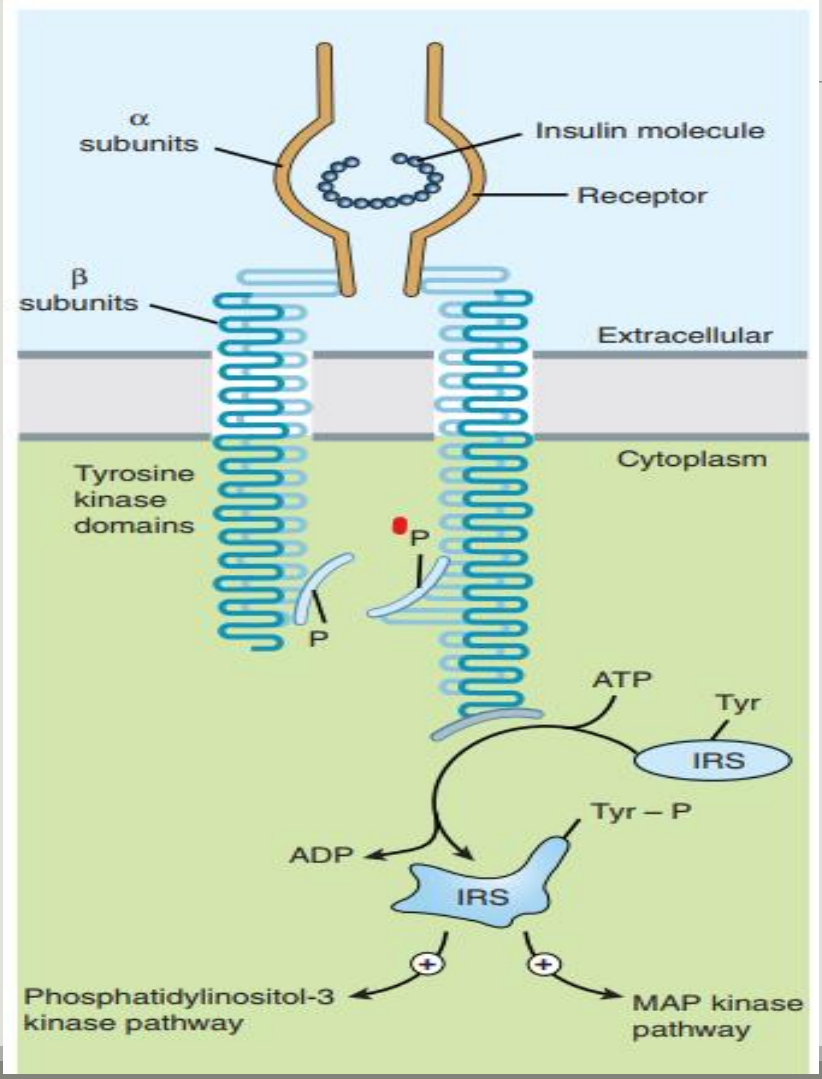
INHIBITION:

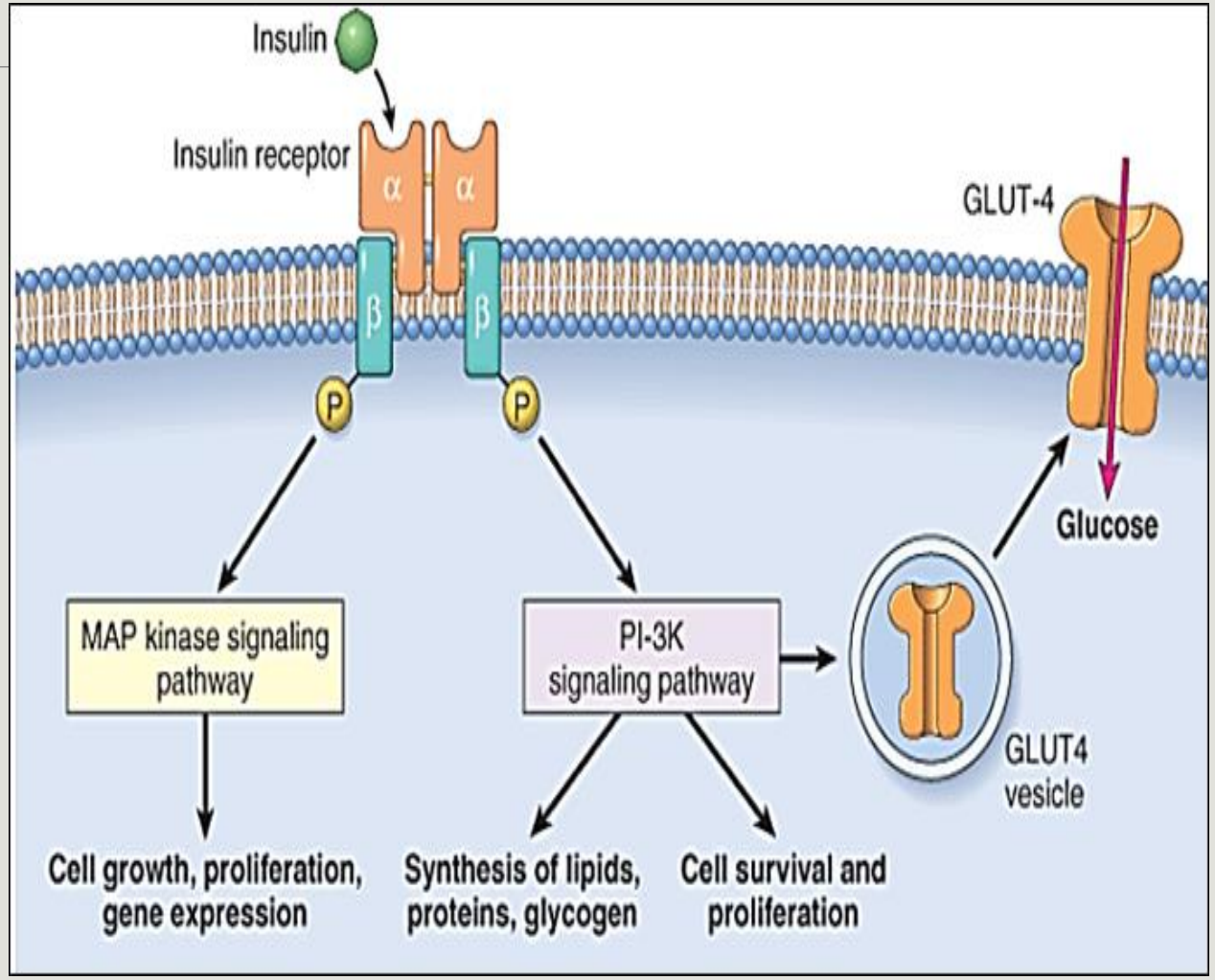
- **Insulin,Islet amyloid polypeptide**
- **Somatostatin**
- **Leptin**
- **Alpha adrenergic sympathetic activity**
- **Chronically elevated glucose**
- **Low concentrations of fatty Acids**

Insulin…MOA

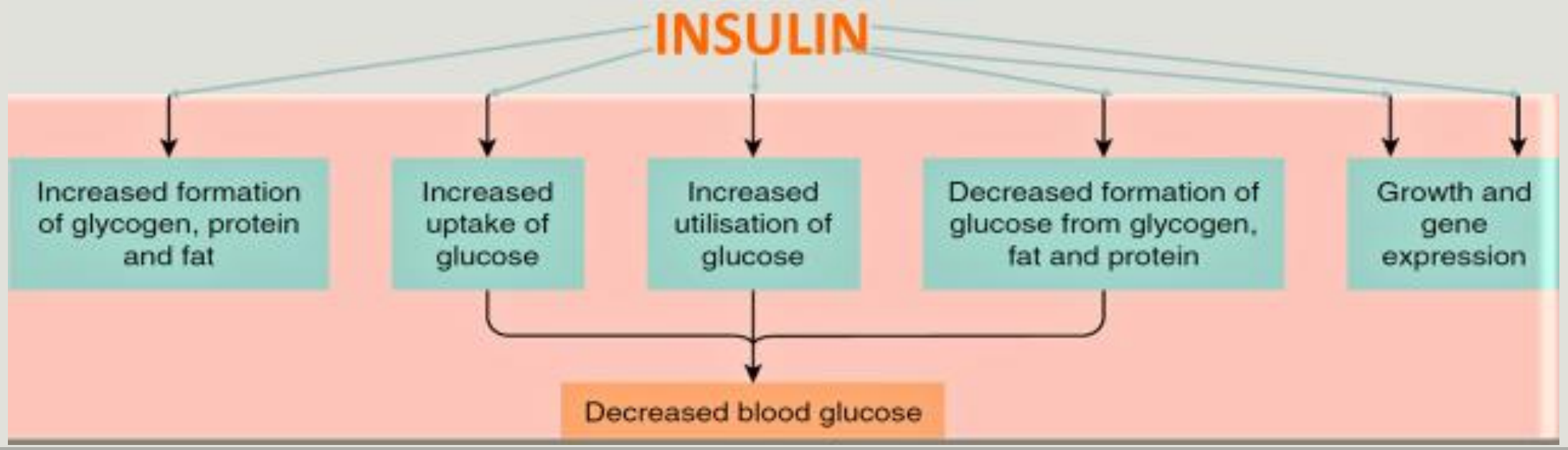

K+ channel
Sulfonylurea drugs
(block, depolarize)
K+
(Closes channel,
depolarizes cell)
ATP
Glucose
transporter
GLUT2
Glucose
Metabolism
Ca2+ channel
(depolarization
opens channel)
Ca2+
↑ Ca2+
Ca2+
Insulin
Exocytosis
Insulin

Insulin..MOA


α subunits
Insulin molecule
Receptor
β subunits
Extracellular
Cytoplasm
Tyrosine kinase domains
P
P
ATP
Tyr
IRS
Tyr – P
ADP
IRS
Phosphatidylinositol-3 kinase pathway
MAP kinase pathway


Insulin
Insulin receptor
α
α
β
β
P
P
GLUT-4
Glucose
MAP kinase signaling pathway
PI-3K signaling pathway
GLUT4 vesicle
Cell growth, proliferation, gene expression
Synthesis of lipids, proteins, glycogen
Cell survival and proliferation

Type of metabolism	Liver cells	Fat cells	Muscle
Carbohydrate metabolism	↓ Gluconeogenesis ↓ Glycogenolysis ↑ Glycolysis ↑ Glycogenesis	↑ Glucose uptake ↑ Glycerol synthesis	↑ Glucose uptake ↑ Glycolysis ↑ Glycogenesis
Fat metabolism	↑ Lipogenesis ↓ Lipolysis	↑ Synthesis of triglycerides ↑ Fatty acid synthesis ↓ Lipolysis	
Protein metabolism	↓ Protein breakdown	–	↑ Amino acid uptake ↑ Protein synthesis



Diabetes Mellitus (DM)

"Elevated blood glucose associated with absent or inadequate pancreatic insulin secretion, with or without concurrent impairment of insulin action"

Types & Pathophysiology of DM

- Deficiency or Impairment of action of insulin……Hyperglycemia
- Type 1 DM
  - Severe or absolute insulin deficiency…….Replacement therapy
  - Immune-mediated (1a) & Idiopathic (1b)
  - Age / genetic
- Type 2 DM
  - Tissue resistance to insulin & relative insulin deficiency
- Gestational DM

Potential Drug Targets

- Drugs That lower Glucose
- Force it into the cells
- Increase Insulin Content
- Increase Insulin Sensitivity
- Decrease Glucose Absorption

Anti-diabetic Agents

PARENTERAL ANTI-DIABETIC DRUGS

- Insulin
- Incretin Mimetics / Glucagon-like Peptide-1 (GLP-1) Receptor Agonists
- Amylin Analog

Anti-diabetic Agents

ORAL ANTI-DIABETIC DRUGS

- Drugs that stimulate insulin release – Insulin Secretagogues
  - Sulfonylureas
  - Meglitinide Analogs
  - D-Phenylalanine Derivative

Anti-diabetic Agents

ORAL ANTI-DIABETIC DRUGS

- Drugs that lower glucose level by action on liver, muscle & adipose tissue
  - Biguanides
  - Thiazolidinediones – Insulin Sensitizers

Anti-diabetic Agents

- **Drugs that affect absorption of glucose**
  - **α– glucosidase Inhibitors**
- **Drugs that prolong incretin action**
  - **Dipeptidyl Peptidase-4 (DPP-4) Inhibitors**

Anti-diabetic Agents

- **Drugs inhibiting the reabsorption of glucose**
  - **Sodium–glucose co-transporter 2 (SGLT-2) Inhibitors**
    - **Canagliflozin**
    - **Dapagliflozin**
    - **Empagliflozin**
- **Miscellaneous**
  - **Colesevelam hydrochloride**
  - **Bromocriptine**

Anti-diabetic Agents

- **Parenteral**
  - **Insulin**
  - **Incretin Mimetics / Glucagon-like Peptide-1 (GLP-1) Receptor Agonists**
  - **Amylin Analog**
- **Oral**

Anti-diabetic Agents

- **Parenteral**
  - **INCRETIN MIMETICS**

    GLP-1
  - **GIP**

  Glucagon-like Peptide-1 (GLP-1) Receptor Agonists
  - **Exanitide…Exanitide LAR**
  - **Liraglutide**
  - **Albiglutide**
  - **Dulaglutide**

Pancreatitis
Thyroid C cells

Anti-diabetic Agents

- **Parenteral**
- **AMYLIN ANALOG**
  - **Pramlinitide(IAPP)**
  - **IAPP analog with substitutions of proline at positions 25, 28, & 29**

Anti-diabetic Agents

- **PARENTERAL**
  - **INSULIN**

  - **Short Acting**
    - **Regular Insulin**
    - **Rapidy Acting**
      - **Lispro, Aspart, Glulisine**
  - **Long Acting**
    - **NPH(Neutral Protamine Hegadron)**
    - **Insulin Glargine**
    - **Insulin Detemir**
    - **Insulin Degludec….Zinc & phenol**
    - **Mixtures of Insulin**

TABLE 41–5 Summary of bioavailability characteristics of the insulins.

Insulin Preparations	Onset of Action	Peak Action	Effective Duration
Insulins lispro, aspart, glulisine	5–15 min	1–1.5 h	3–4 h
Human regular	30–60 min	2 h	6–8 h
Technosphere inhaled insulin	5–15 min	1 h	3 h
Human NPH	2–4 h	6–7 h	10–20 h
Insulin glargine	0.5–1 h	Flat	~24 h
Insulin detemir	0.5–1 h	Flat	17 h
Insulin degludec	0.5–1.5 h	Flat	>42 h

Mixtures Of Insulin

Premixed insulins

70 NPH/30 regular (Novolin, Novo Nordisk; Humulin, Lilly)

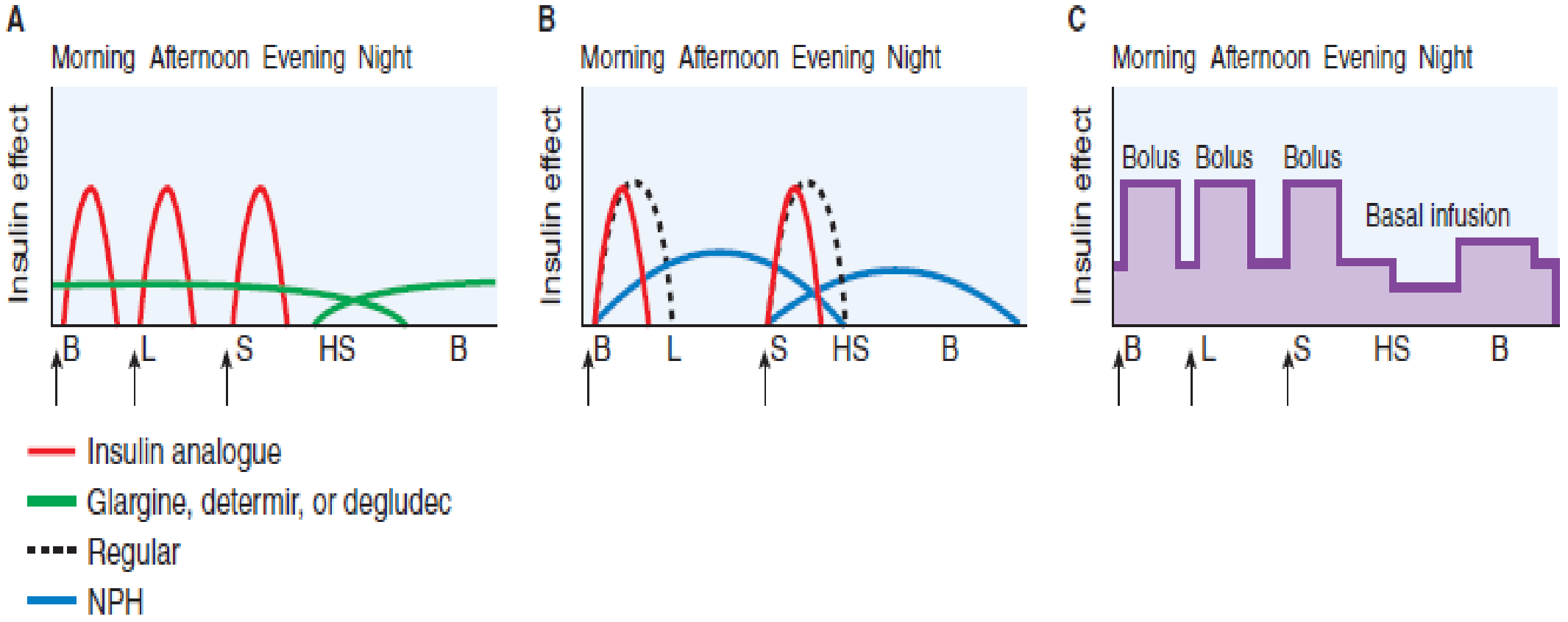
75/25 NPL, Lispro (Humalog mix 75/25, Lilly)

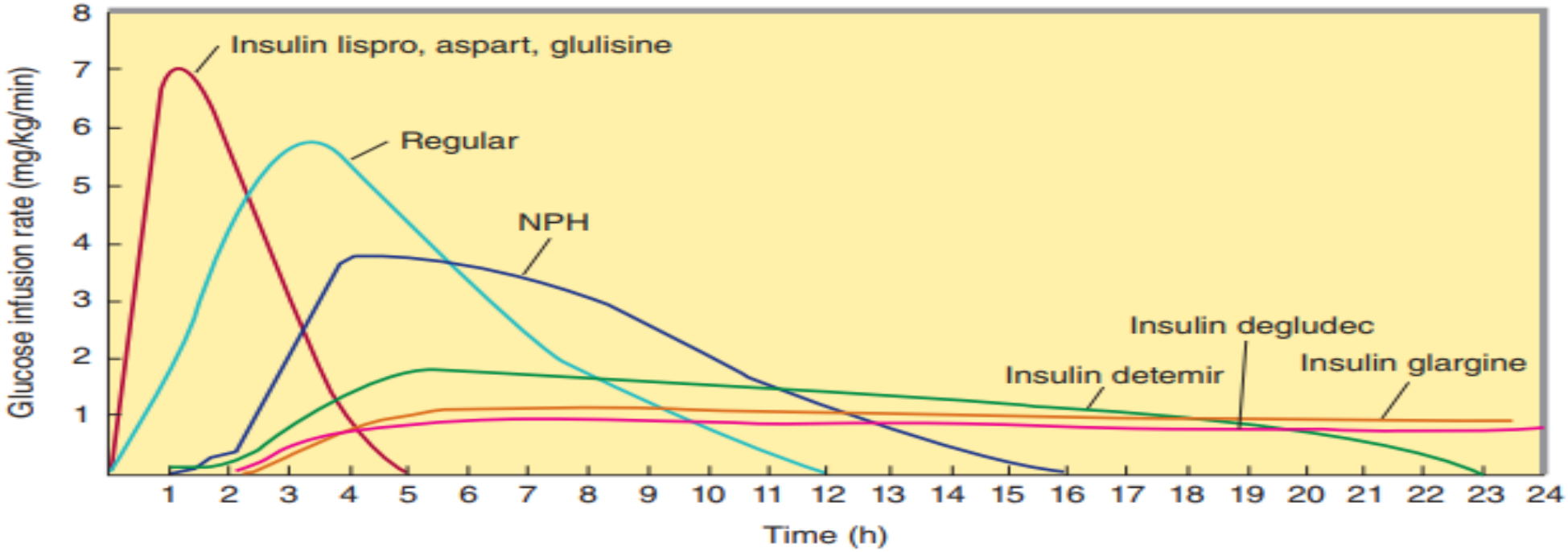
50/50 NPL, Lispro (Humalog mix 50/50, Lilly)

70/30 NPA, Aspart (Novolog mix 70/30, Novo Nordisk)

70/30 Degludec/Aspart (Ryzodeg, Novo Nordisk)

Different types of Insulin





a) **Enumerate different types of Insulin with one example of each type. Draw graphs to show the extent and duration of action of different types. (03)**

b) **Write down the complications of Insulin Therapy with pharmacological management. (02)**

Insulin

Uses of Insulin Therapy

- **Type 1 DM**
- **Type 2 DM……routine / emergency**
- **Gestational DM**
- **Diabetic ketoacidosis**
- **Hyperosmolar Hyperglycemic Syndrome**

Insulin

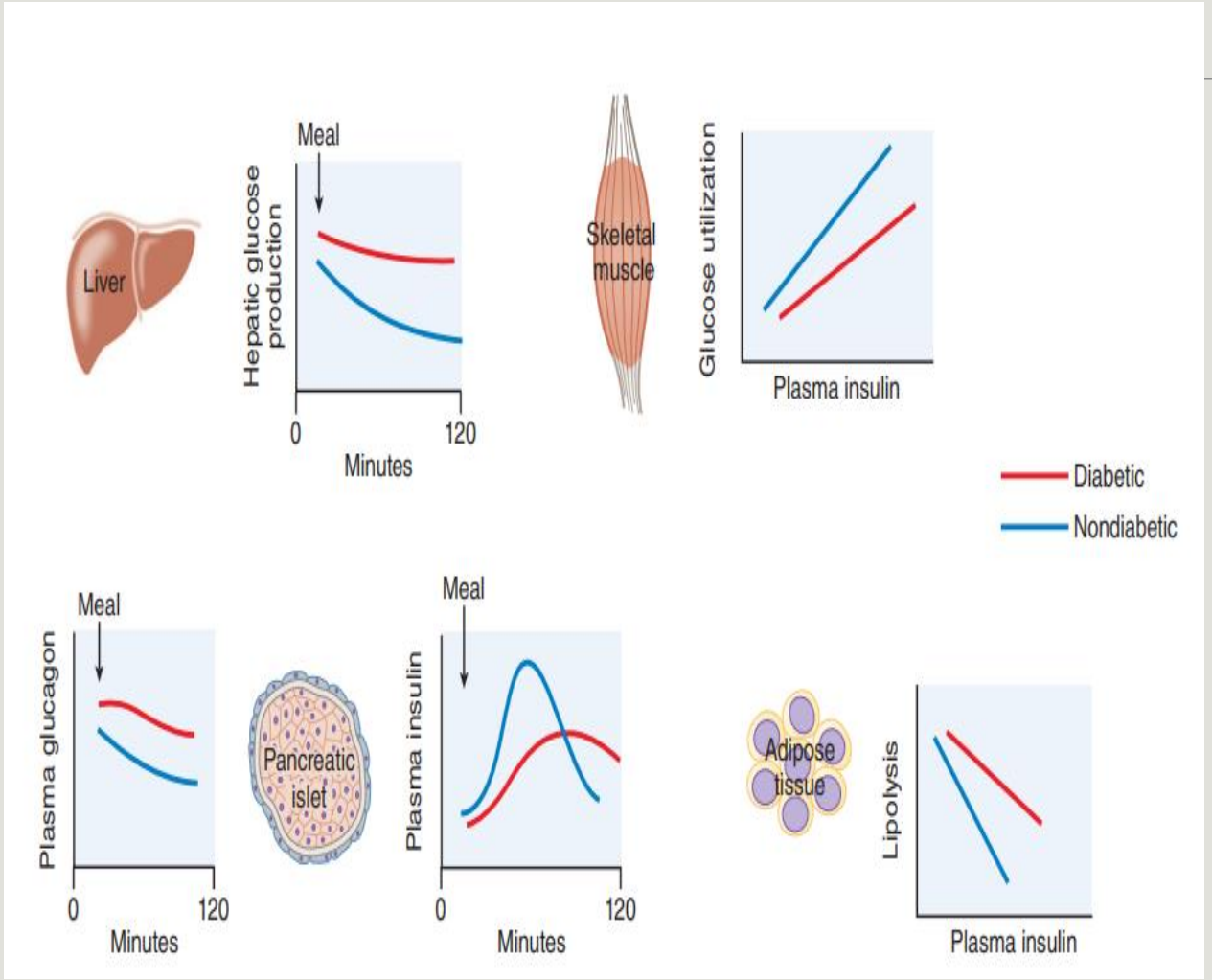
Methods of Delivery System Of Insulin

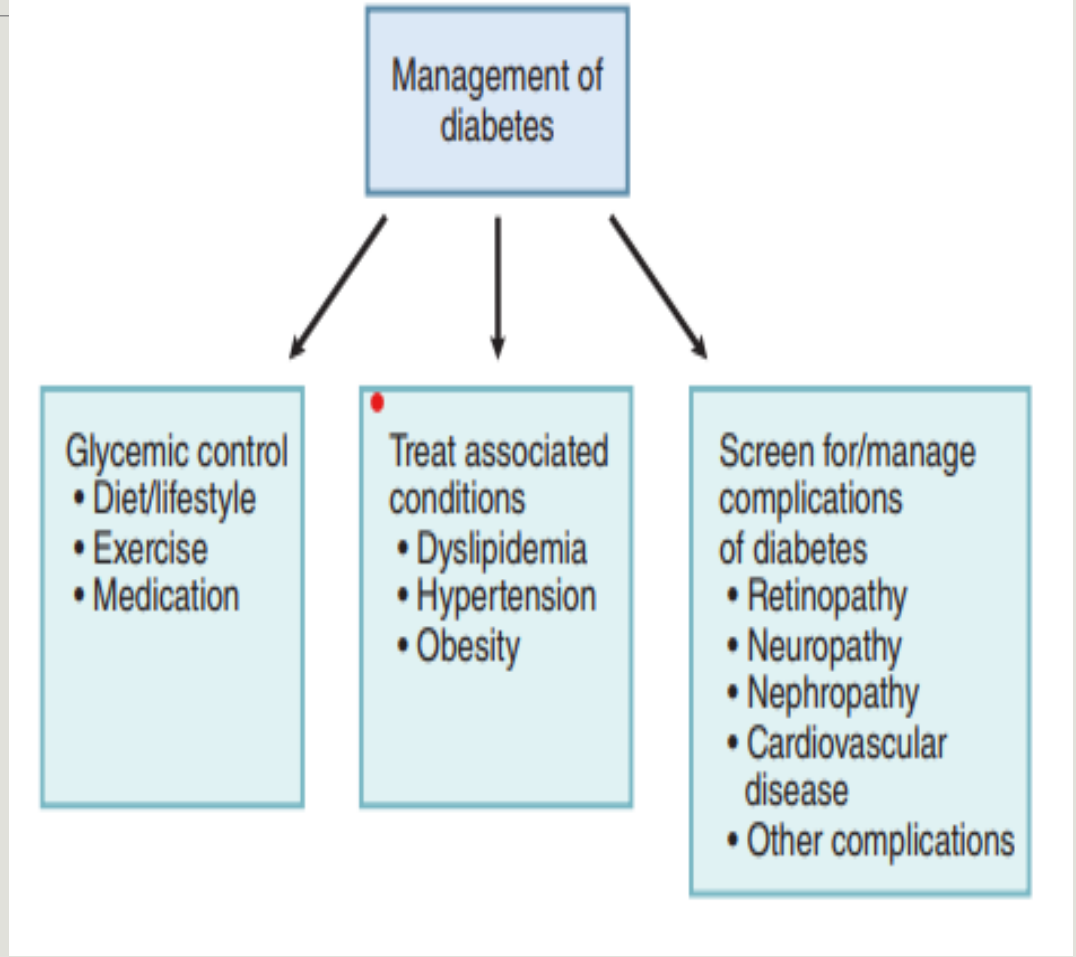
- Insulin Syringes & needles
- Insulin Pens
- Continuos Subcutaneous Insulin Infusion Devices (CSII, Insulin Pumps)
- Inhaled Insulin

Complications or Adverse Effects of Insulin Therapy

- Hypoglycemia
- Immunogenicity
- Lipodystrophy at Injection Sites

Diabetes Mallitus





Anti Diabetic Agents

Drugs that stimulate insulin release – Insulin Secretagogues

Sulfonylureas

- First Generation
  - Tolbutamide, Chlorpropamide, Tolazamide, Acetohexamide
- Second Generation
  - Glyburide(Glibenclaimide), Glipizide, Glimepiride, Gliclazide

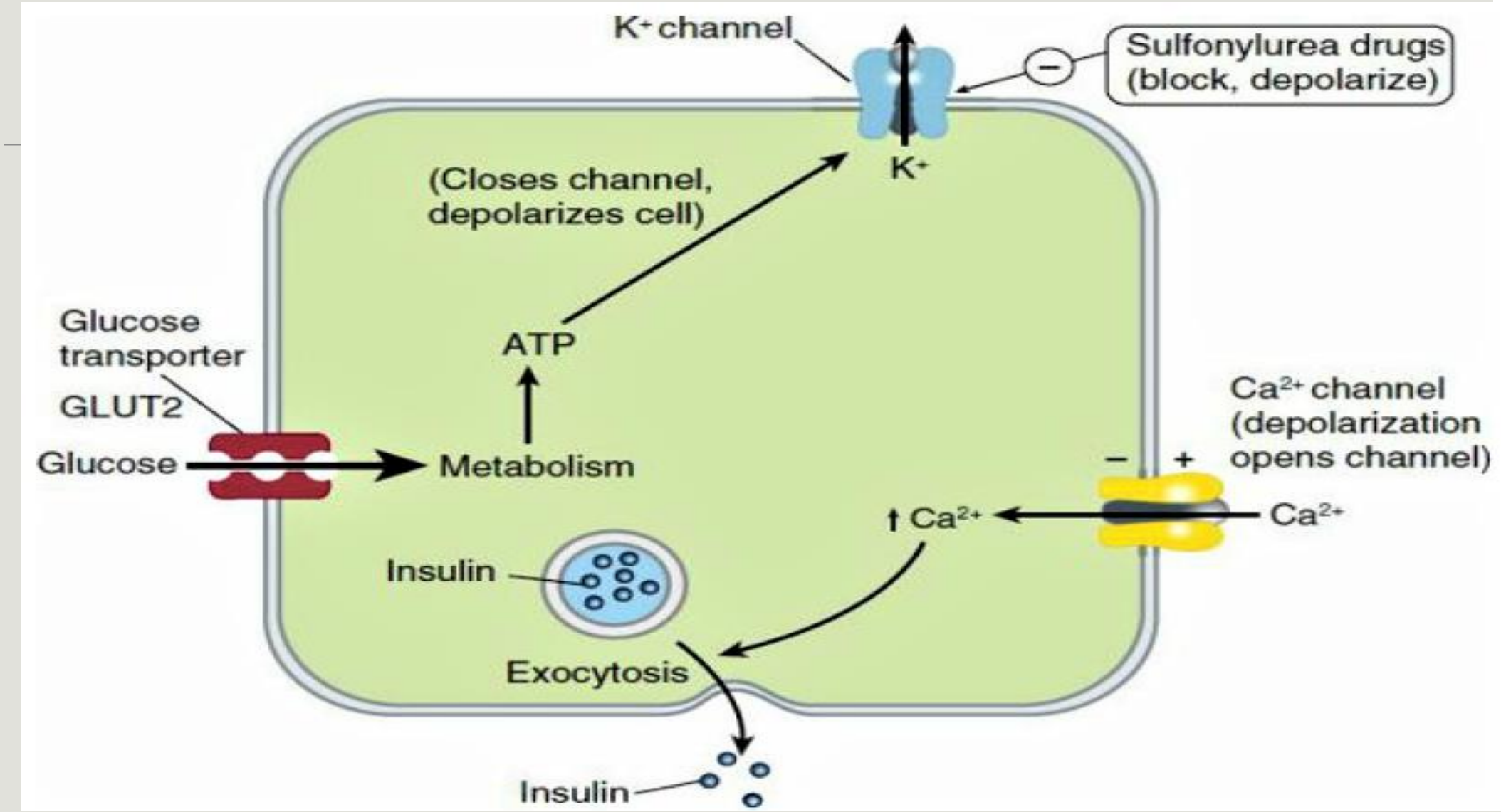
Meglitinide analogs

- Repaglinide
- Mitiglinide

D-phenylalanine derivative

- Nateglinide

MOA


K+ channel
Sulfonylurea drugs
(block, depolarize)
K+
(Closes channel,
depolarizes cell)
ATP
Glucose
transporter
GLUT2
Glucose
Metabolism
Ca2+ channel
(depolarization
opens channel)
Ca2+
↑ Ca2+
Ca2+
Insulin
Exocytosis
Insulin

EOLA

- Ideal time to give Sulfonylureas to a Diabetic Patient
- Possible adverse effects with Sulfonylureas
- Contraindications To the use of Sulfonylureas
- Drug Interactions of Sulfonylureas

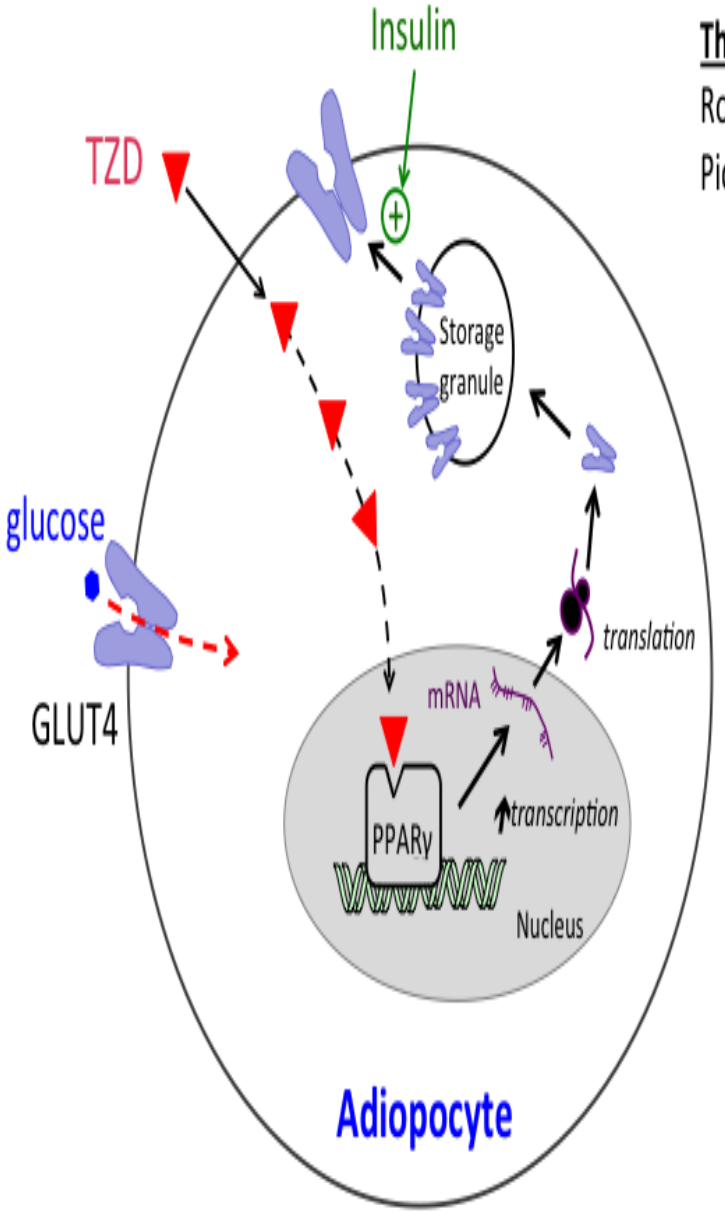
Anti diabetic agents

- Drugs that lower glucose level by action on liver, muscle & adipose tissue
  - Biguanides
    - **Metformin……Glucophage**
  - Thiazolidinediones – Insulin Sensitizers
    - Pioglitazone
    - Rosiglitazone

Production of Lactic Acid with Metformin

Pathophysiology of lactic acidosis from metformin……due to inhibition of gluconeogenesis….. by blocking pyruvate carboxylase…….the first step of gluconeogenesis(which converts pyruvate to oxaloacetate)

Blocking this enzyme leads to accumulation of lactic acid



Thiazolidinediones (TZDs):

Rosiglitazone - PPARγ

Pioglitazone - PPARγ > PPARα

PPARγ expression:

Adipose tissue

Skeletal muscle (↑in obesity)

Pancreatic β cells

Vascular endothelium

Macrophages

CNS

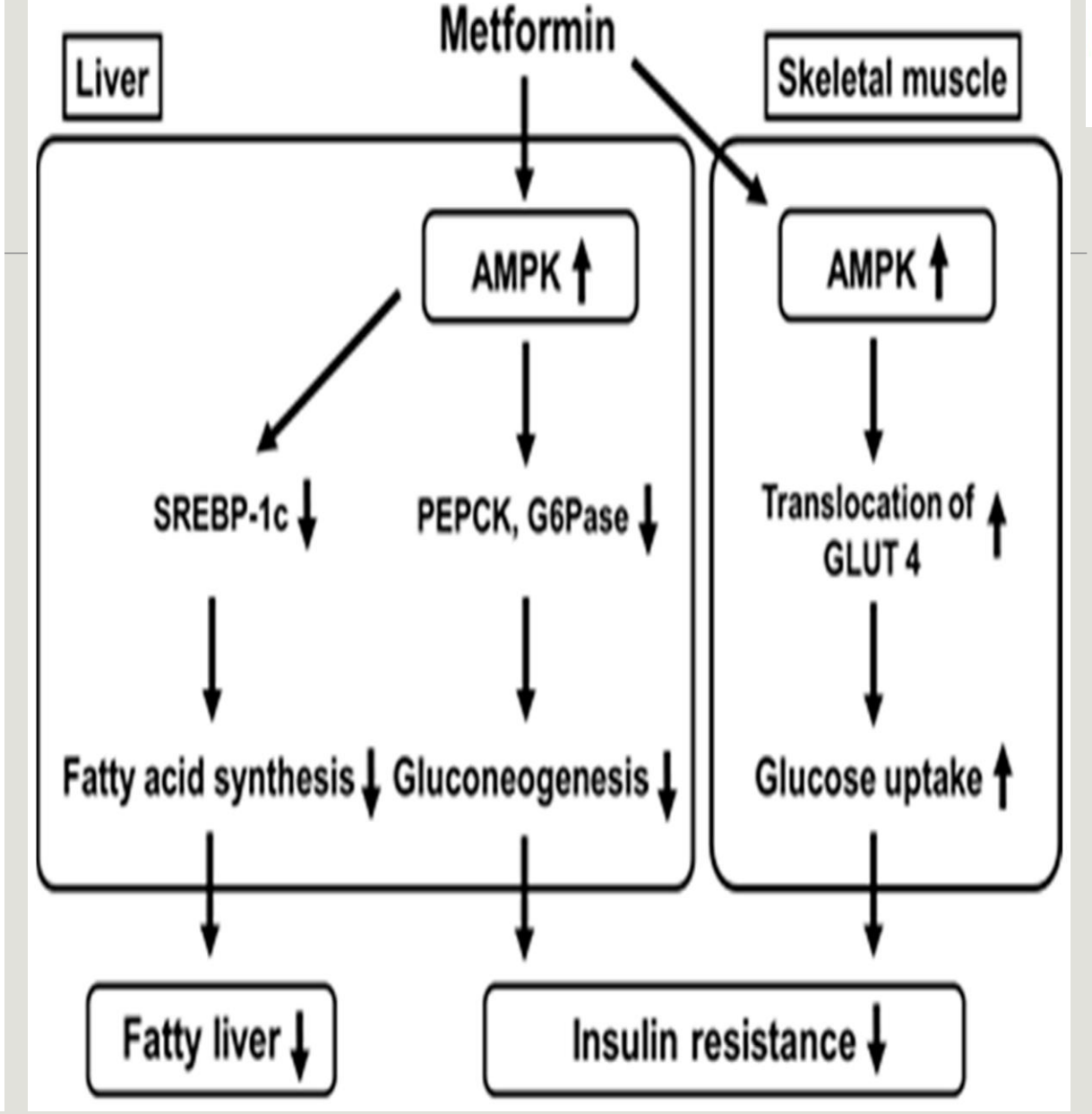
PPARα expression:

Liver

Heart

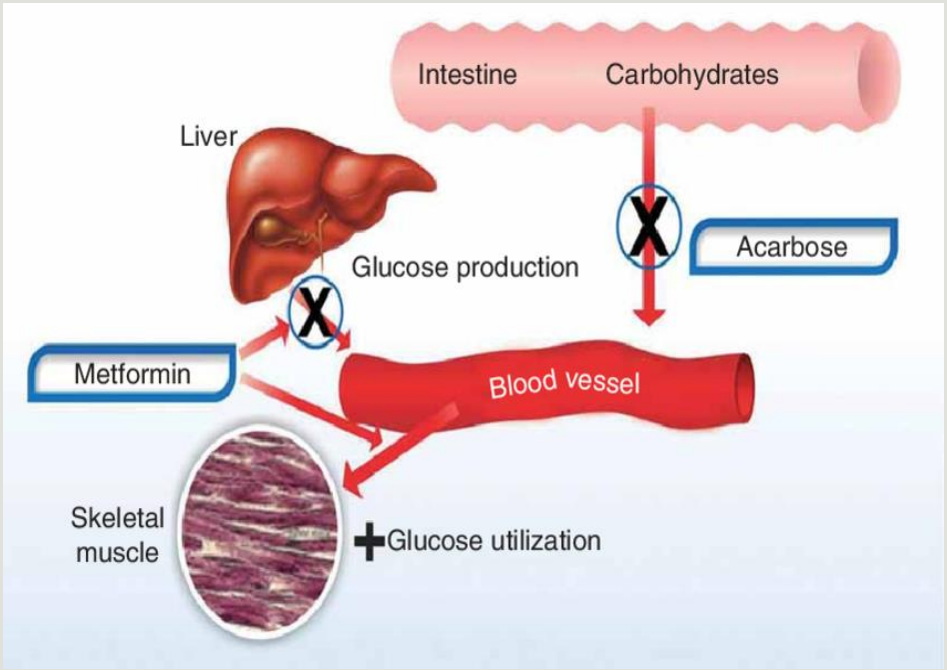
Skeletal muscle

Vascular wall



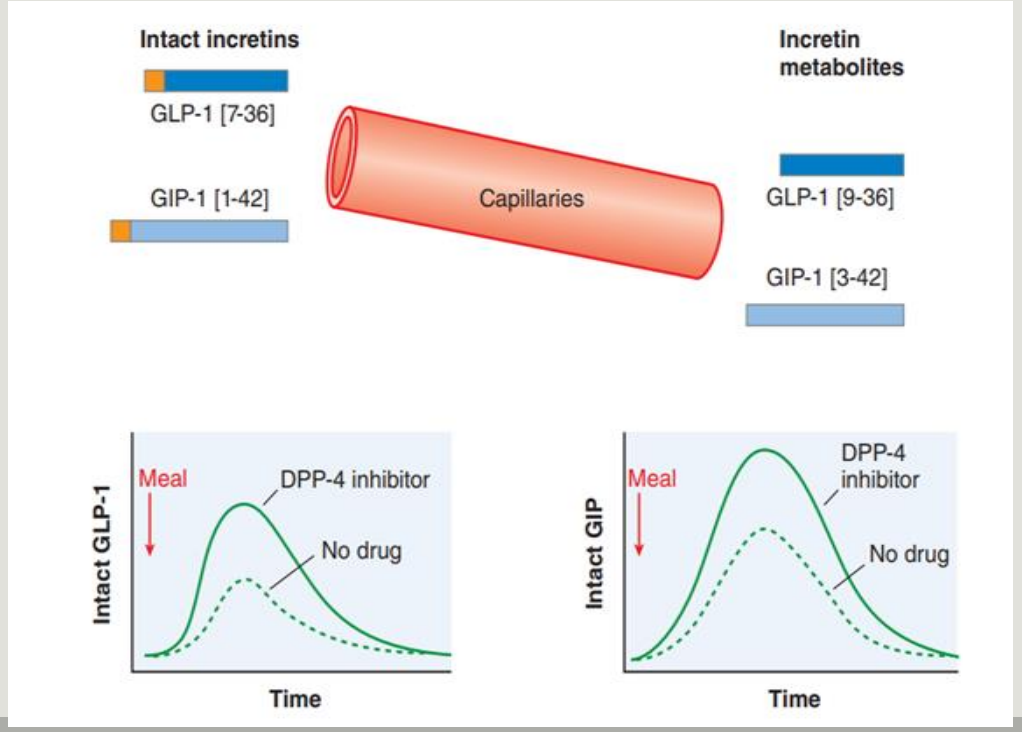
Anti diabetic agents

- **<u>Drugs that affect absorption of glucose</u>**
  - **α– glucosidase Inhibitors**
    - **Acarbose**
    - **Miglitol**
    - **Voglibose**



Anti diabetic agents

- **Drugs that prolong incretin action**
  - **Dipeptidyl Peptidase-4 (DPP-4) Inhibitors**
    - **Sitagliptin**
    - **Saxagliptin**
    - **Linagliptin**
    - **Vildagliptin**
    - **Alogliptin**



Anti diabetic agents

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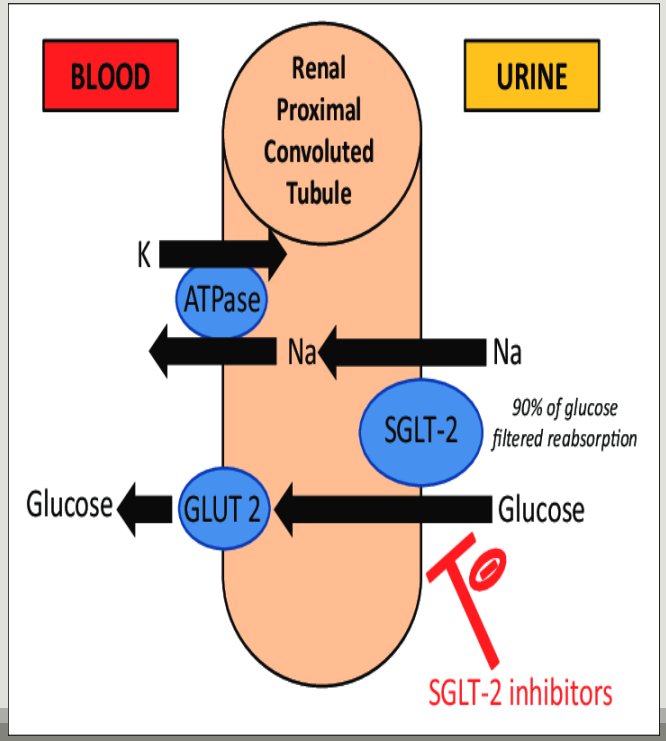
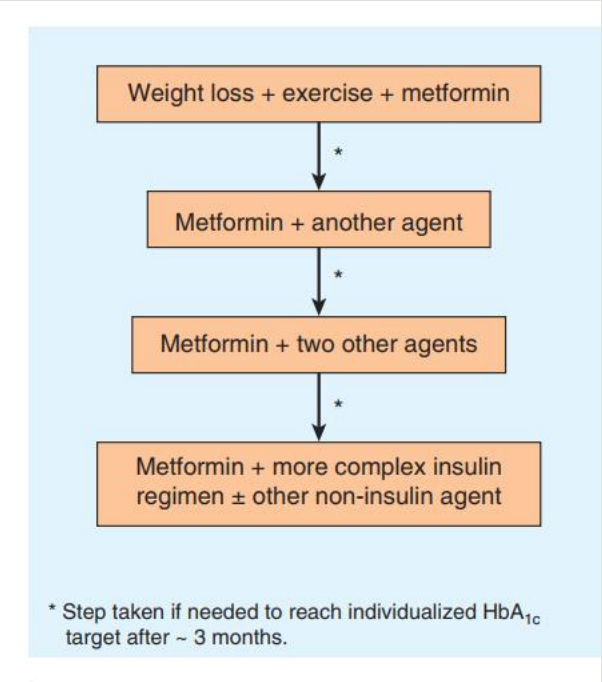
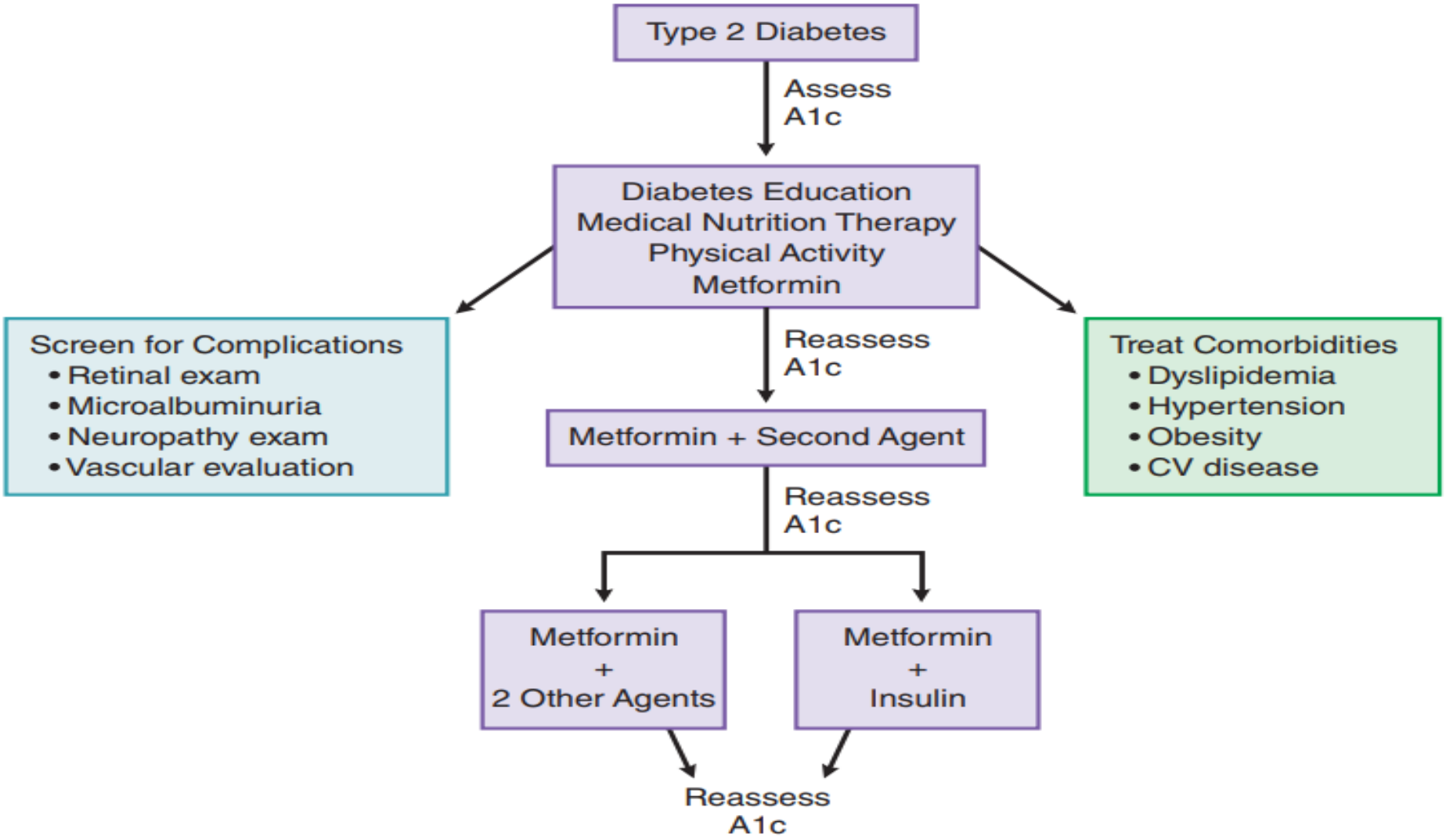


Clinical Pharmacology

- Type 1 DM
- Type 2 DM
- Hypoglycaemia
- Diabetic Ketoacidosis
- Hyperosmolar hyperglycaemic syndrome



Algorithm for Type 2 DM



Digital Library References
Research, Bioethics, Family Medicine, Artificial Intelligence

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