- **Diabetes mellitus** (**DM**), is a metabolic disorder of multiple aetiology characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both.
- Diabetes mellitus may present with characteristic symptoms such as thirst, polyuria, blurring of vision, and weight loss. In its most severe forms, ketoacidosis or a non–ketotic hyperosmolar state may develop and lead to stupor, coma and, in absence of effective treatment, death.
- The long–term effects of diabetes mellitus include progressive development of the specific complications of retinopathy with potential blindness, nephropathy that may lead to renal failure, and/or neuropathy with risk of foot ulcers, amputation, Charcot joints, and features of autonomic dysfunction, including sexual dysfunction. People with diabetes are at increased risk of cardiovascular, peripheral vascular and cerebrovascular disease.

Anti-diabetics

Dr. R Padmavathi

Associate Professor
Department of Pharmacology

SIGNS & SYMPTOMS OF DM

- Insulin deficiency causes hyperglycaemia leading to glycosuria, polyuria, polydipsia , polyphagia.
- Increased catabolism:
  - Increased lipolysis (in adipose tissue)
  - Increased fatty acids (in plasma)
  - Oxidation (in liver)
- Decreased anabolism:
  - Osmotic diuresis
  - Dehydration & loss of electrolytes

- KETOACIDOSIS

- DIABETIC COMA

LONG TERM COMPLICATIONS OF DIABETES

Vascular changes

- MICROVASCULAR
- atherosclerosis
- Infaracts
- Gangrene in extremities
- MACROVASCULAR
- Neuropathy
- Nephropathy
- retinopathy

Metabolic changes

- SORBITOL
- Lesions : aorta ,eye lens, kidneys,nerves
- PROTEIN GLYCOSYLATION
- Neuropathy
- Retinopathy
- nephropathy

Immune changes

- INFECTIONS Like TB,UTI,pneumonia
- DEFECTIVE PMN FUNCTION fungal infections,bacterial infections

- Diagnosis of diabetes
- Clinical Symptoms: polyuria, polydipsia, glycosuria, recurrent infections, unexplained weight loss
- Fasting Plasma Glucose concentration ≥ 126 mg / dl
- random blood glucose level of ≥ 200 mg/dl
- Oral glucose tolerance test
  - 2 hr after 75 gm glucose load ≥ 200 mg / dl
- Therapy of DM
- Diet
- Exercise
- Insulin and its enhancers
- Oral hypoglycaemics

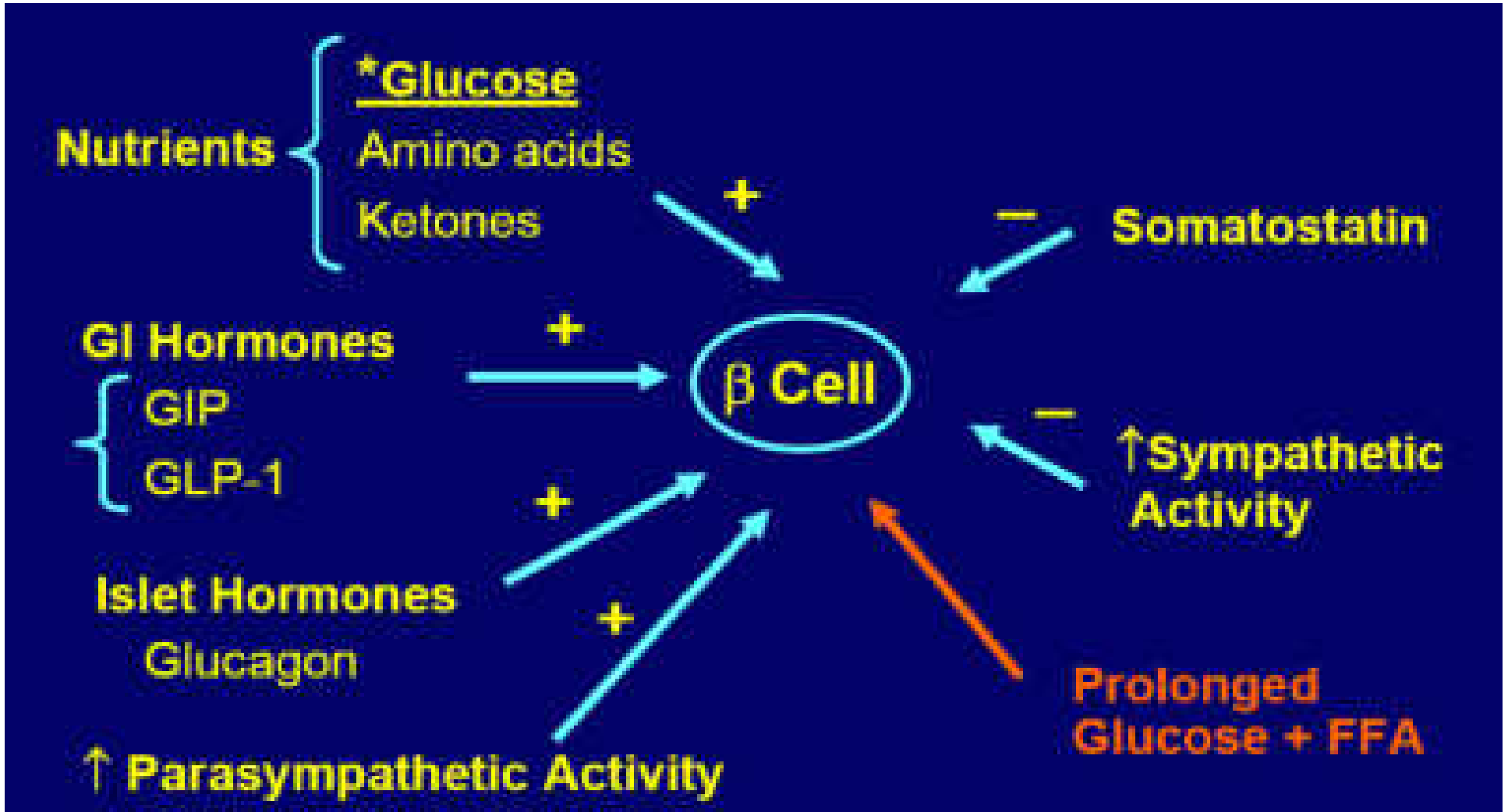
HISTORY

- Canadian scientist (1921)
  - Fredrick G. Banting
  - Charles H. Best

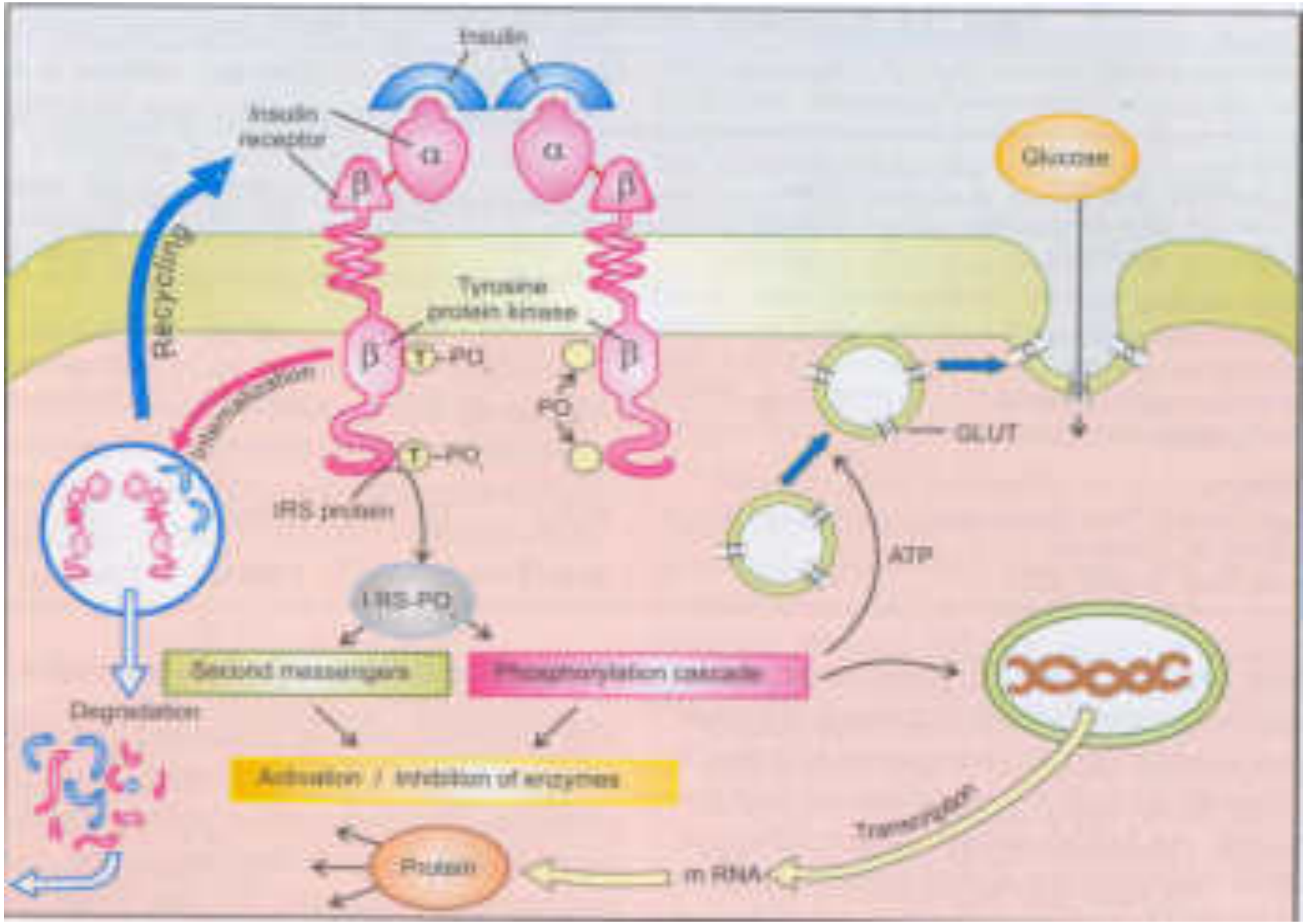
- extracted insulin
  - from dog's pancreas

- INSULIN
- A polypeptide hormone with two peptide chains that are connected by disulfide bonds.
- Synthesized as a precursor (pro-insulin) that undergoes proteolytic cleavage to form insulin and C peptide, both of which are secreted by the ß cells of the pancreas triggered by high blood glucose.
- Insulin and glucagon regulate blood glucose levels.
- ACTIONS :
- Controls intermediary metabolism, having actions on liver, muscle and fat.
- Conserves fuel by facilitating the uptake and storage of glucose, amino acids and fats after meal.

Regulation of Insulin Secretion



Mechanism of action of insulin



Sources of insulin :

- Human insulin is produced by recombinant DNA technology using special strains of Escherichia coli or yeast that have been genetically altered to contain the gene for human insulin.

Insulin administration :

- Because insulin is a polypeptide, it is degraded in the gastrointestinal tract if taken orally. It therefore is generally administered by subcutaneous injection

- Different types of insulin preparations
- Conventional preparations of insulin
  - Produced from beef or pork pancreas
  - 1 % of other proteins
  - Potentially antigenic
- Highly purified insulin preparations
- Human insulins
- Newer insulin analogs

ANALOGUES.....

1921 : Insulin extracted by Banting & Best.

Conventional insulin preparations from beef/pork pancreas (antigenic)

1970s : Highly purified porcine insulins : Single peak insulins & Monocompetent insulins (greater efficacy & lesser side effects)

1980s : Human insulins by recombinant DNA technology (still better)

1990 : Insulin analogues with novel pharmacokinetics (*Eli Lilly& Co.)*

Conventional insulin preparations

	Type	Onset (Hr)	Peak (Hr)	DOA (Hr)
Short acting	Regular insulin Semilente	0.5 -1 1	2-4 3-6	6-8 12-16
Intermediate acting	Lente Isophane(NPH)	1-2	8-10	20-24
Long acting	Ultra lente Protamine Zinc Insulin (PZI)	4-6	14-18	24-36

- Regular insulin, a short-acting preparation used to treat type 1 and type 2 diabetes and for hyperglycemia (abnormally high blood sugar) experienced during pregnancy.
- Administered subcutaneously as with other insulins (the only preparation that also may be administered intramuscularly and intravenously)
- Neutral protamine Hagedron (NPH) or isophane insulin is a suspension of crystalline zinc insulin combined at neutral pH with a positively charged polypeptide, protamine
- Delayed absorption of the insulin because of its conjugation with protamine, forming a less-soluble complex
- Highly purified insulin preparations

-Single peak insulins :Purified by gel filtration method

-Mono competent insulins: After gel filtration purified by ion exchange chromatography

- Human insulins :Human (Actrapid, monotard, insulatard, mixtard)
- Obtained by recombinant DNA technology

- Insulin analogues (designer insulins)
- Molecules produced by genetic engineering wherein the amino acid sequence in human insulin is changed to alter its pharmacokinetic properties, without affecting its affinity and efficacy.

Types of insulin analogues :

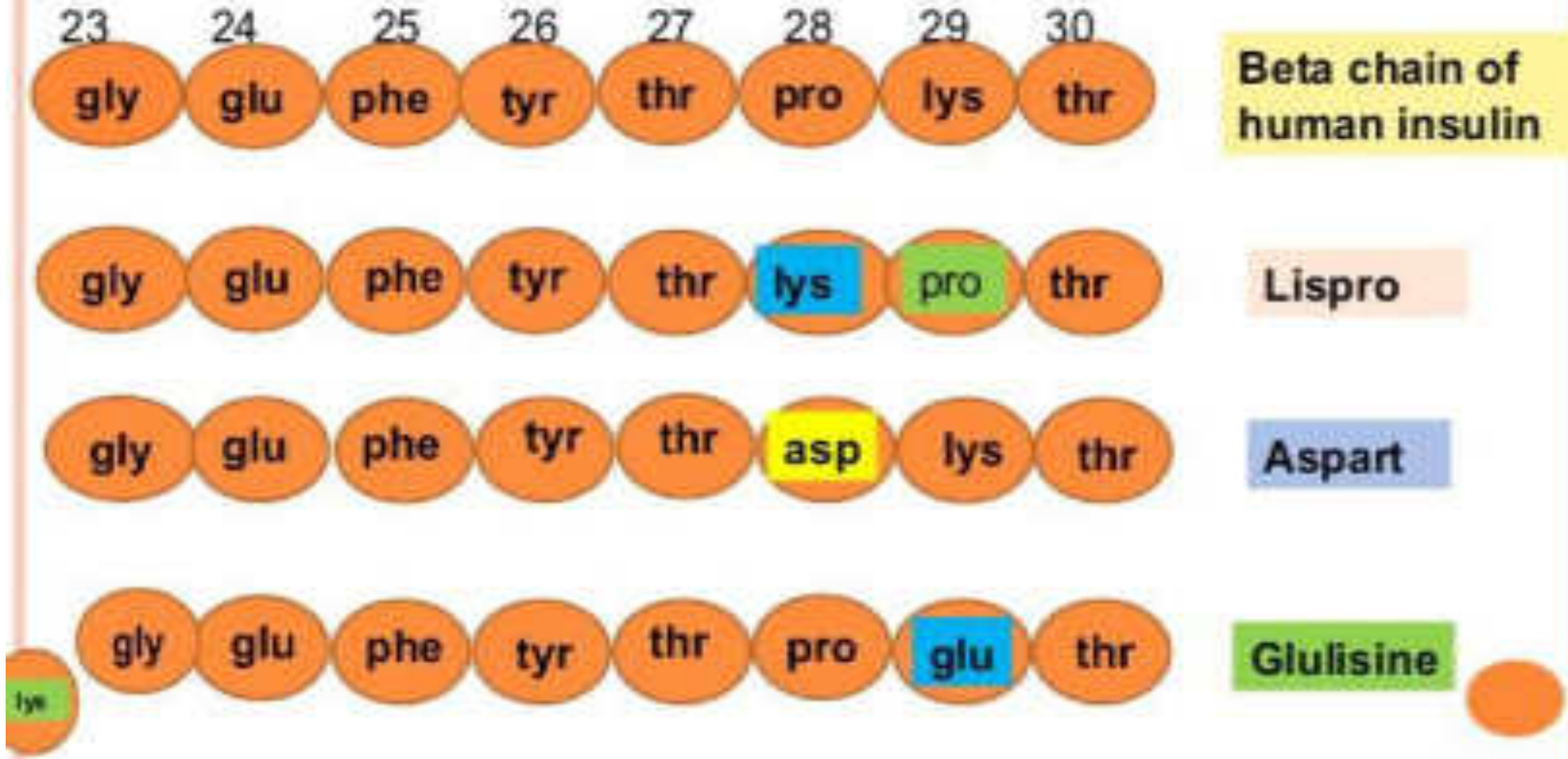
1. Rapid-acting :

- Rapid acting analogues: insulin lispro, insulin aspart, and insulin glulisine
- These insulin preparations reach peak plasma concentration in 30-60 mins.
- Insulin lispro is an insulin analogue in which a lysine and a proline residue are switched

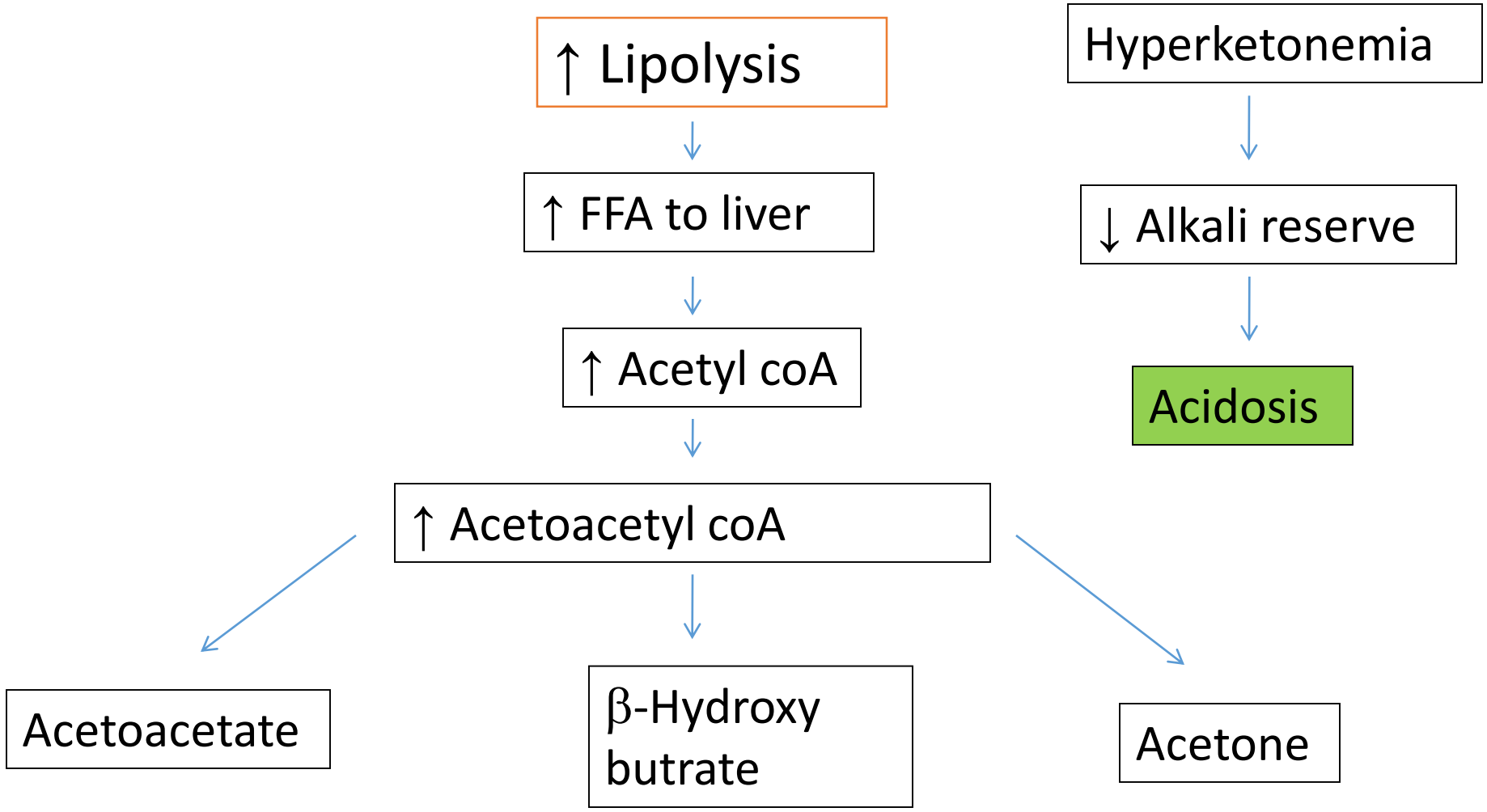
2. Long-acting analogues : Insulin glargine, Insulin detemir

- The length of time to reach peak plasma concentration 3 to 4 hours and the maximum duration is 20 to 24 hours.

LISPRO , ASPART & GLULISINE



Pathogenesis of DKA
(How ketoacidosis occurs)



- Uses of insulin
- Diabetes mellitus
    - Must for type I diabetics
    - Can be used in type II diabetes

-Patients with diabetes require long term insulin

- An intermediate acting insulin(eg: isophane insulin) or a long acting analogue (eg: glargine) is often combined with soluble insulin or short acting analogue (eg: lispro) taken before meals.

- Soluble insulin is used (intravenously) in emergency treatment of *hyperglycemic emergencies*

- diabetes ketoacidosis

- Hyperosmolar nonketotic hyperglycemic coma

- Short term treatment of patients with type 2 diabetes or impaired glucose tolerance during inter-current events (eg: operations, infections, myocardial infarction)

- During pregnancy, for *gestational diabetes* not controlled by diet alone.
- Emergency treatment of *hyperkalemia*: insulin is given along with glucose to lower extracellular potassium via redistribution into cells.
- Unwanted effects:
- Hypoglycemia (if severe, can cause hypoglycaemic coma)

-Can be controlled by giving a snack or sweet drink; if the patient is unconscious: iv glucose or im glucagon

- Rebound hyperglycemia (Somogyi effect)- can follow insulin induced hypoglycaemia
- Allergic reactions- urticaria, angioedema and rarely anaphylaxis

-more common with insulin from animal sources

- Lipodystrophy

-atrophy of subcutaneous fat at the site of injection may be due to immune response to contaminating proteins

-lipohypertrophy: enlargement of subcutaneous tissue can also occur due to the local action of insulin

- Insulin induced edema

- Oral hypoglycemics

- Agents that are given orally to reduce the blood glucose levels in diabetic patients

- Five types of oral antidiabetic drugs are currently in use:

- Biguanides :metformin

- Sulfonylureas: glimepiride, glyburide,

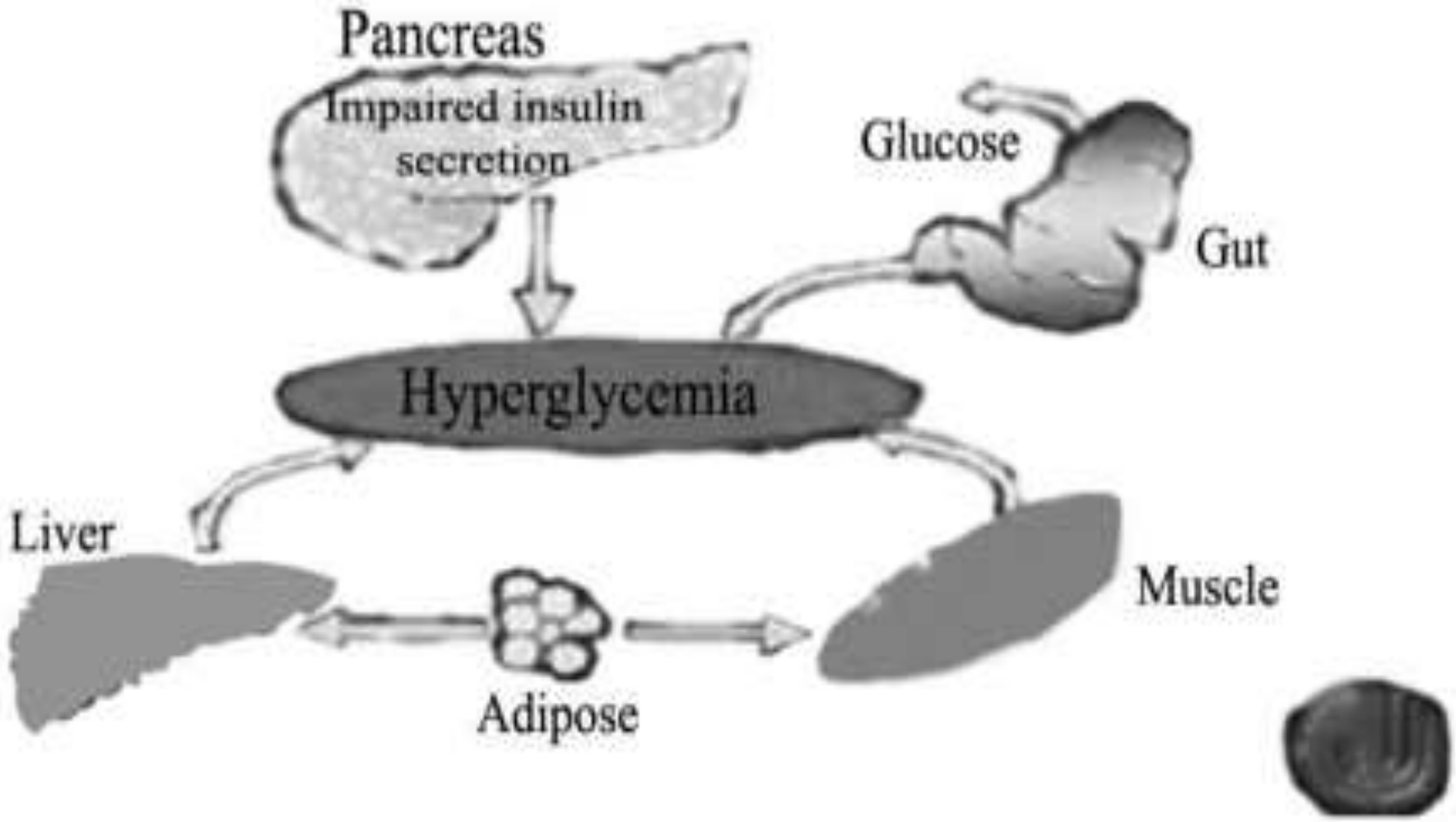
  tolbutamide, glibenclamide, glipizide

- Meglitinides : nateglinide, repaglinide

- Thiazolidinediones : pioglitazone, rosiglitazone

- Alpha -glucosidase inhibitors: acarbose, viglibose, miglitol

Sites of Action for Oral Therapies for Type 2 Diabetes



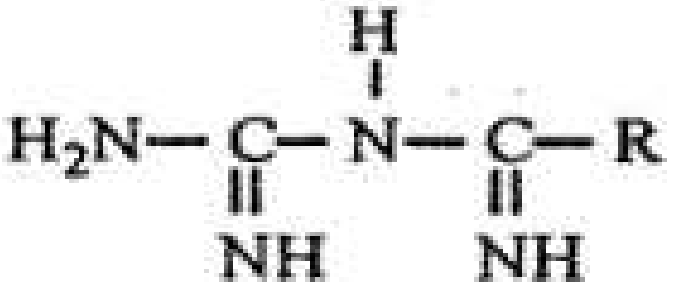
- Biguanides

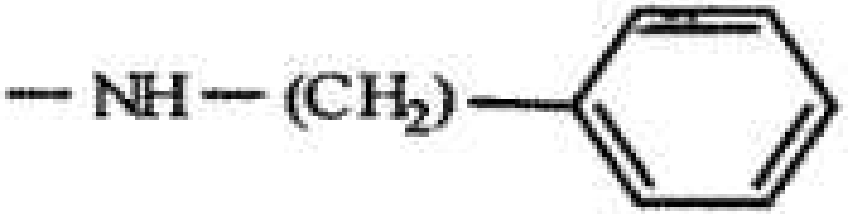
➢ Metformin : is the only drug of this class presently available in market

➢ It does not cause hypoglycaemia

- MOA : Suppress hepatic gluconeogenesis
- ↑ uptake & utilization of glucose by skeletal muscles which reduces insulin resistance
- Inhibit alimentary absorption of glucose
- Interfere with mitochondrial respiratory chain & promote peripheral glucose utilization by enhancing anaerobic glycolysis

General formula



R	
Phenformin	
Buformin	$-NH-(CH_2)_3-CH_3$
Metformin	$-NH-(CH_3)_2$

- Unwanted effects :

- Anorexia, nausea, vomiting, diarrhoea
- Metallic taste, Loss of weight , Skin rashes
- Lactic acidosis: rare
- Vitamin B12 deficiency: due to malabsorption

Usually does not cause hypoglycemia even in large doses

- Contra indications

metformin should not be given to patients with

- Renal failure
- Hepatic disease
- Hypoxic pulmonary disease, Heart failure or shock

- Sulfonylureas

- 1st gen : Tolbutamide and Chlorpropamide

- 2nd gen : glibenclamide, glipizide, glimperide

- ADR :

- Weight gain, Hypoglycaemia

- May decrease iodide uptake by thyroid

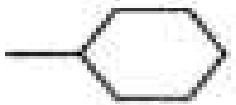
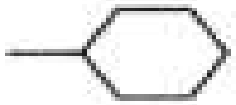
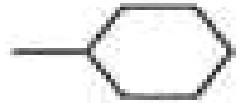
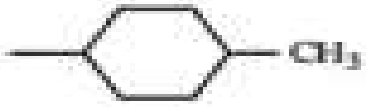
- oedema , worsens osteoporosis, LDL elevation.

- Contraindicated in liver failure, renal failure patients

Mechanism of action

- Primarily augment phase 2 of insulin secretion
- Presence of at least 30% functional β-cells essential for their action.
- Minor action: ↓ glucagon secretion
- Extra pancreatic action: ↑sensitivity of peripheral tissue to insulin by ↑insulin receptors

General Formula:

First Generation Analogs	R_1	R_2
Tolbutamide	H_3C-	-C_4H_9
Chlorpropamide	Cl-	-C_3H_7
Tolazamide	H_3C-	
Acetohexamide	H_3CCO-	
Second Generation Analogs		
Glyburide (Glibenclamide)		
Glipizide		
Gliclazide	H_3C—	
Glimepiride		

- Meglitinides

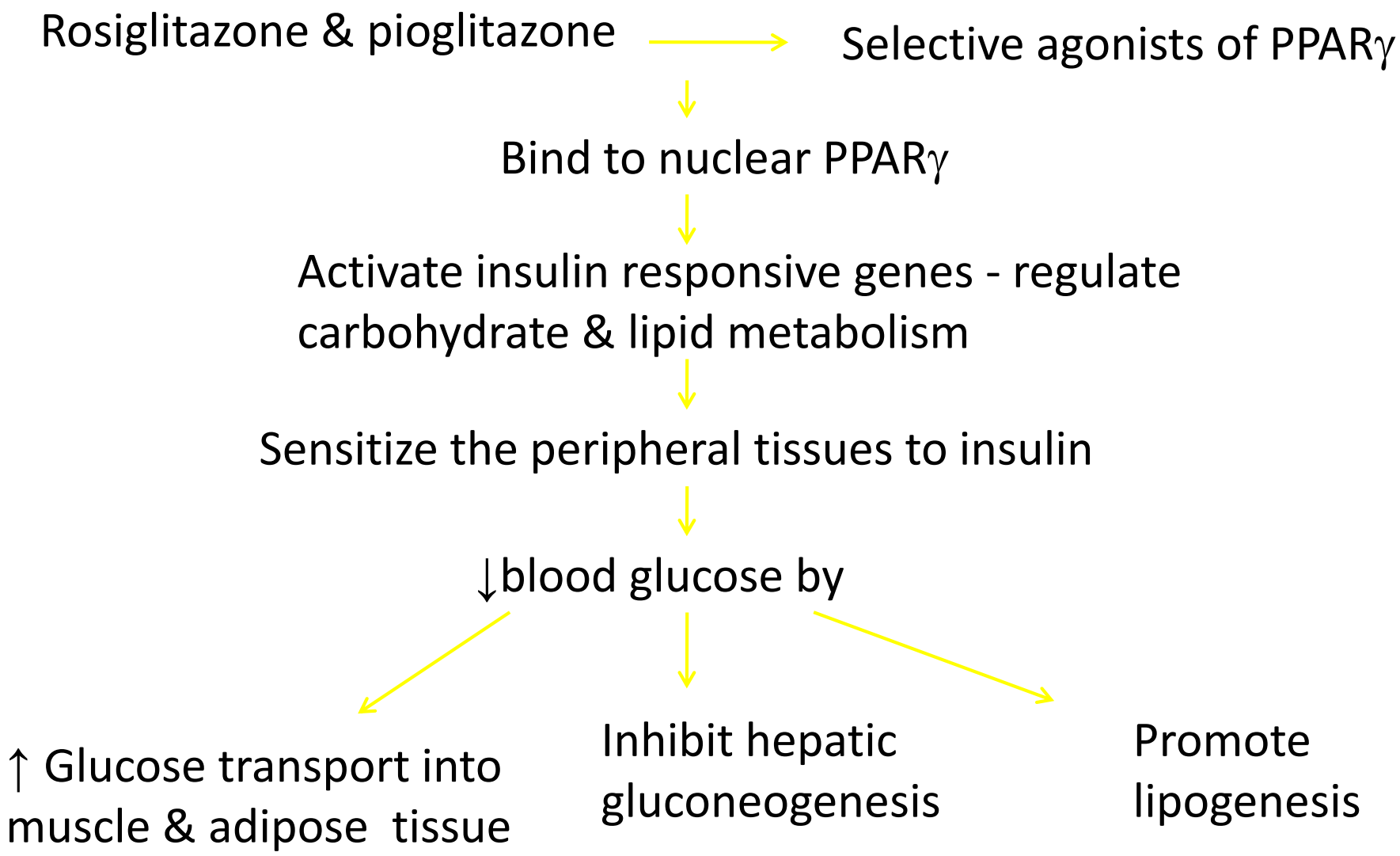
- These act, like the sulfonylureas, but they don’t have sulfonylurea moiety.
- These include repaglinide and nateglinide
- MOA : Same as sulfonylureas .
- Short duration of action and a low risk of hypoglycaemia.
- Given orally, rapidly metabolized by liver enzymes

- Glitazones

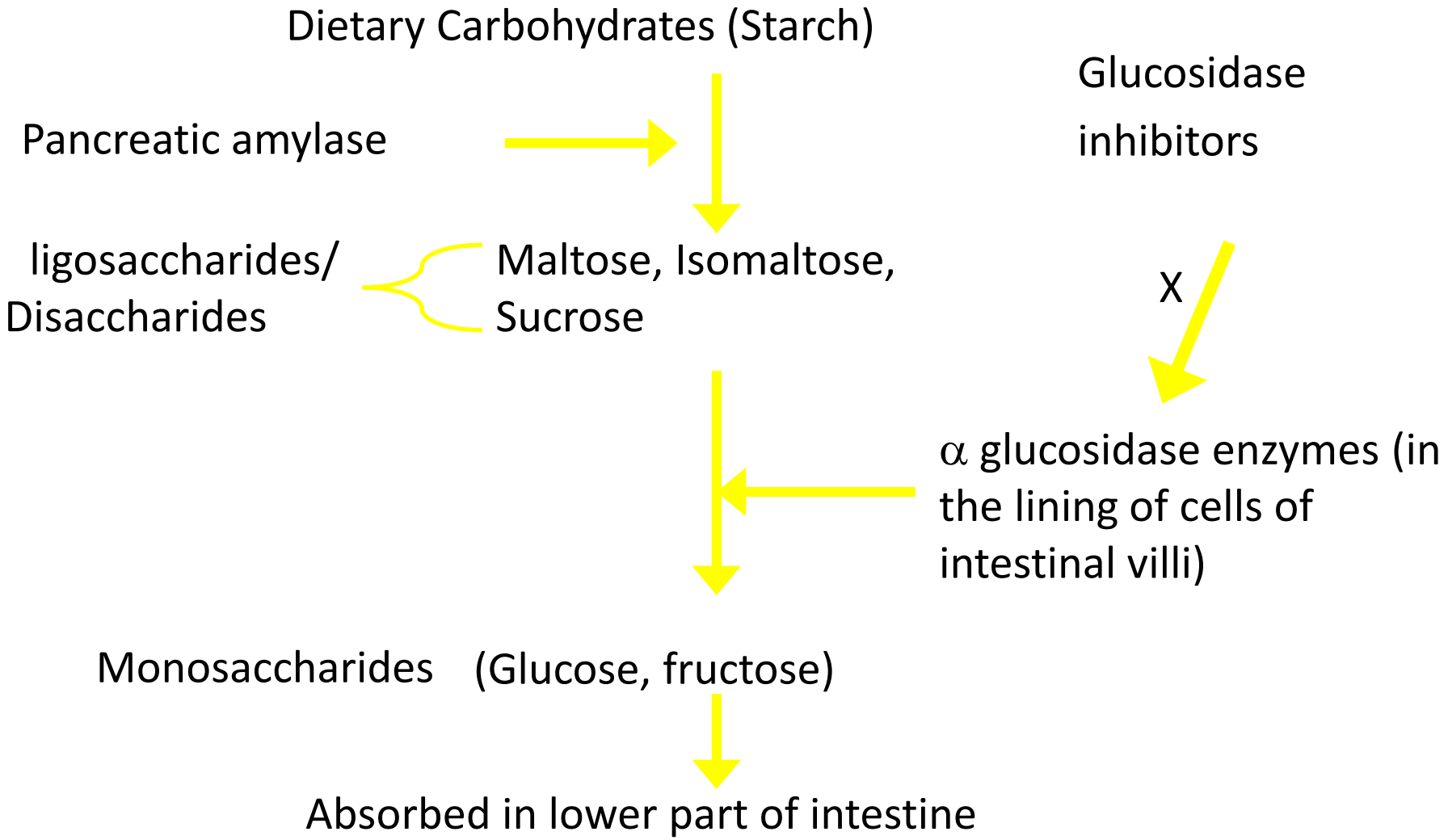
- Currently marketed thiazolidinediones: Rosiglitazone and Pioglitazone

ADRS: Weight gain: due to fluid retention & edema

- ↑ Extracellular fluid volume
- Worsening of CHF
- ↑ Deposition of subcutaneous fat
- Mild anemia: due to hemodilution
- Hepatotoxicity : rare
- Rosiglitazone: ↑risk of fractures especially in elderly women
- MOA:


Rosiglitazone & pioglitazone
Selective agonists of PPARγ
Bind to nuclear PPARγ
Activate insulin responsive genes - regulate carbohydrate & lipid metabolism
Sensitize the peripheral tissues to insulin
↓blood glucose by
↑ Glucose transport into muscle & adipose tissue
Inhibit hepatic gluconeogenesis
Promote lipogenesis

- α-Glucosidase inhibitors
- Acarbose, voglibose
- Unwanted effects : flatulence, loose stools or diarrhoea, and abdominal pain and bloating.
- Like metformin, it may be particularly helpful in obese type 2 patients, and it can be co-administered with metformin.
- Contraindicated in inflammatory bowel disease & intestinal obstruction


Dietary Carbohydrates (Starch)
Pancreatic amylase
ligosaccharides/
Disaccharides
Maltose, Isomaltose,
Sucrose
Glucosidase
inhibitors
X
α glucosidase enzymes (in
the lining of cells of
intestinal villi)
Monosaccharides (Glucose, fructose)
Absorbed in lower part of intestine

- RECENT DRUGS: PEPTIDE ANALOGS

- Injectable Incretin mimetics (insulin secretagogues)

- Glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (glucose-dependent insulinotropic peptide, GIP)

- Both GLP-1 and GIP are rapidly inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4).

- Exenatide (first GLP-1 agonist)

- Liraglutide (a once-daily human analogue 97% homology

Side-effects: -decreased gastric motility, nausea, weight loss

- DIPEPTIDYL PEPTIDASE-4 INHIBITORS

- Increase blood concentration of the incretin GLP-1 by inhibiting its degradation

  by dipeptidyl peptidase-4.

- Examples: vildagliptin, sitagliptin, saxagliptin, Linagliptin

INJECTABLE AMYLIN ANALOGUES

- Actions:

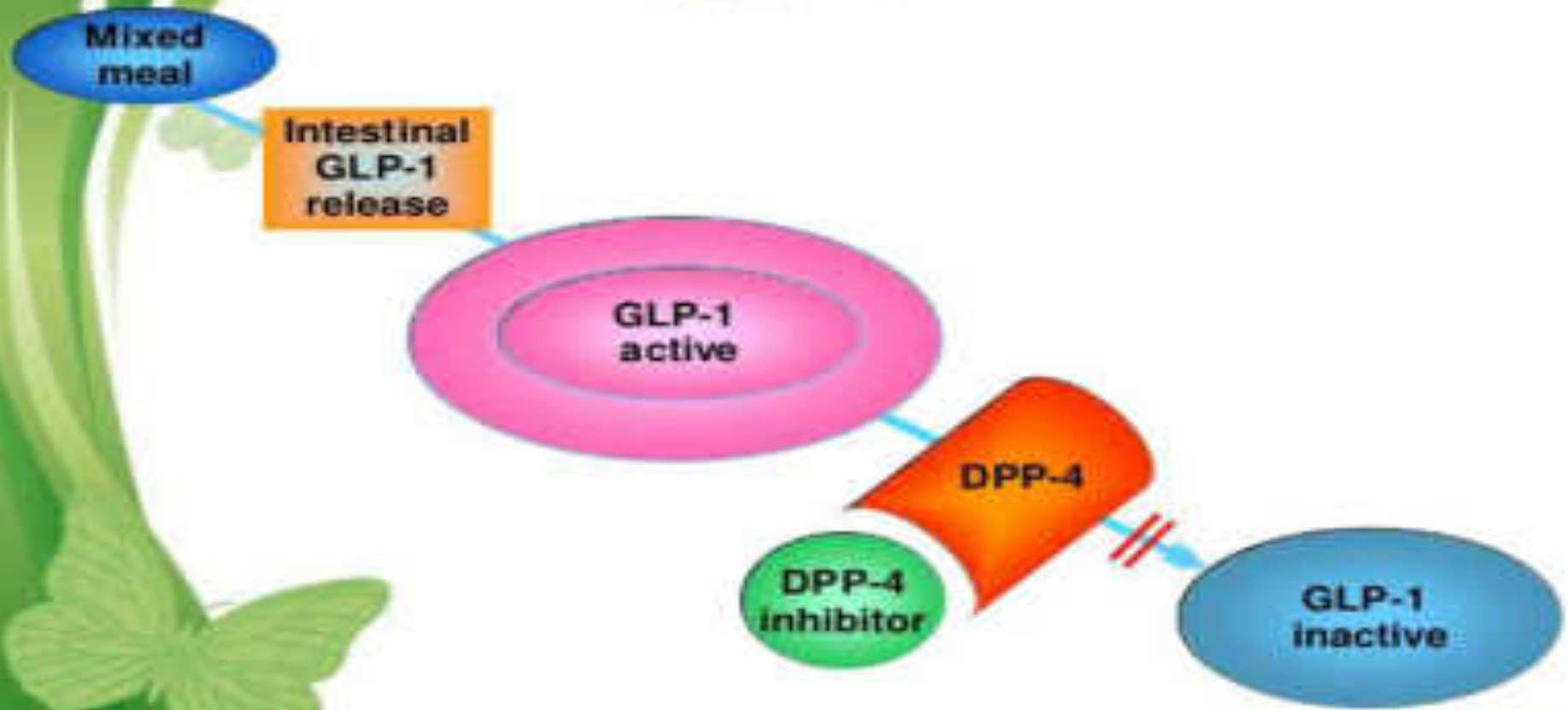
– Slow gastric emptying

– Suppress glucagon.

- Pramlintide (the only clinically available amylin analogue: administered by subcutaneous injection)

- Adverse effect :nausea

Inhibition of DPP-4 Increases Active GLP-1



Adapted from Rothenberg P, et al. Diabetes. 2000;49(suppl 1):A33.