Drugs Used For the Management of Diabetes

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References

1) Basic & Clinical Pharmacology, 12e.
Bertram G. **Katzung**, Chapter 41
Publisher: McGraw-Hill, Copyright: 2010

2) Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12e.
Publisher: McGraw-Hill, Chapter 43

Overview

- Diabetes Mellitus & its Major Types
- Drug Treatment of Type I Diabetes
- Drug Treatment of Type II Diabetes

Diabetes Mellitus

	TYPE I	TYPE II
Etiology	Autoimmune destruction of pancreatic β cells	Insulin resistance, with inadequate β cell function to compensate
Insulin levels	Zero	Typically higher than normal
Insulin action	Zero	Decreased
Insulin resistance	Not part of syndrome, but may be present (e.g., in obese patients)	Yes
Age of onset	***(Juvenile onset)*** Typically <30 years	Typically >40 years
Acute complications	Ketoacidosis	Hyperglycemia (can lead to hyperosmotic seizures and coma)
Chronic complications	Neuropathy Retinopathy Nephropathy Peripheral vascular disease Coronary artery disease	Same as Type I
Pharmacologic interventions	Insulin	Oral Hypoglycemic Agents & Insulin

Table 60-1. *Different Forms of Diabetes Mellitus*

- Diabetes secondary to pancreatic disease
- Diabetes secondary to other endocrinopathies
- Diabetes secondary to immune suppression
- Diabetes associated with drug therapy

Drugs with Hyperglycemic Effects

- Epinephrine
- Glucocorticoids
- Diuretics
- Diazoxide
- B_2-Adrenergic receptor agonists*
- Ca^{2+}-channel blockers
- Phenytoin
- Clonidine
- Morphine

Drugs with Hypoglycemic Effects

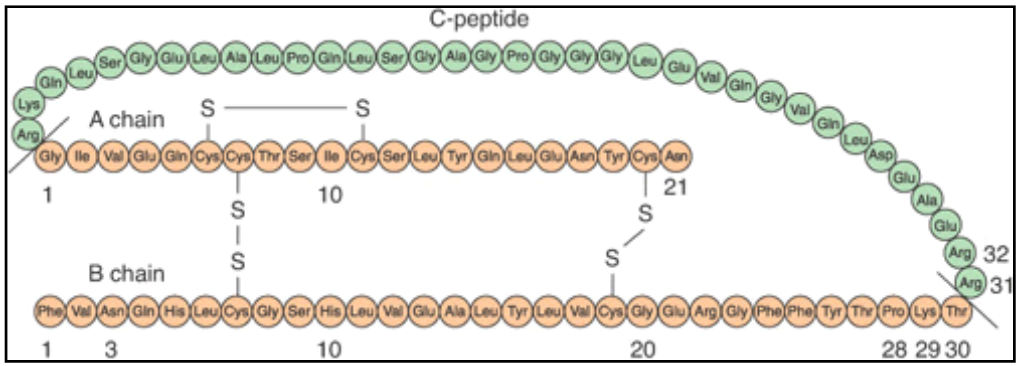
- β -Adrenergic receptor antagonists*
- Salicylates
- Indomethacin
- Ethanol
- Ca^{2+}

- * Beta blockers exert complex actions on regulation of blood glucose.

- √ Diabetes Mellitus and Its Major Types
- ❖ Drug Treatment of Type I Diabetes
  - Insulin
- ❖ Drug treatment of Type II Diabetes
  - Oral Hypoglycemic Agents
  - Insulin

Drug Treatment of Type I Diabetes

- Patient education
- Diet
- Exercise & Physical activity
- Insulin
  - The survival of type I is depend on exogenous insulin (5-10% of diabetic population are type I)



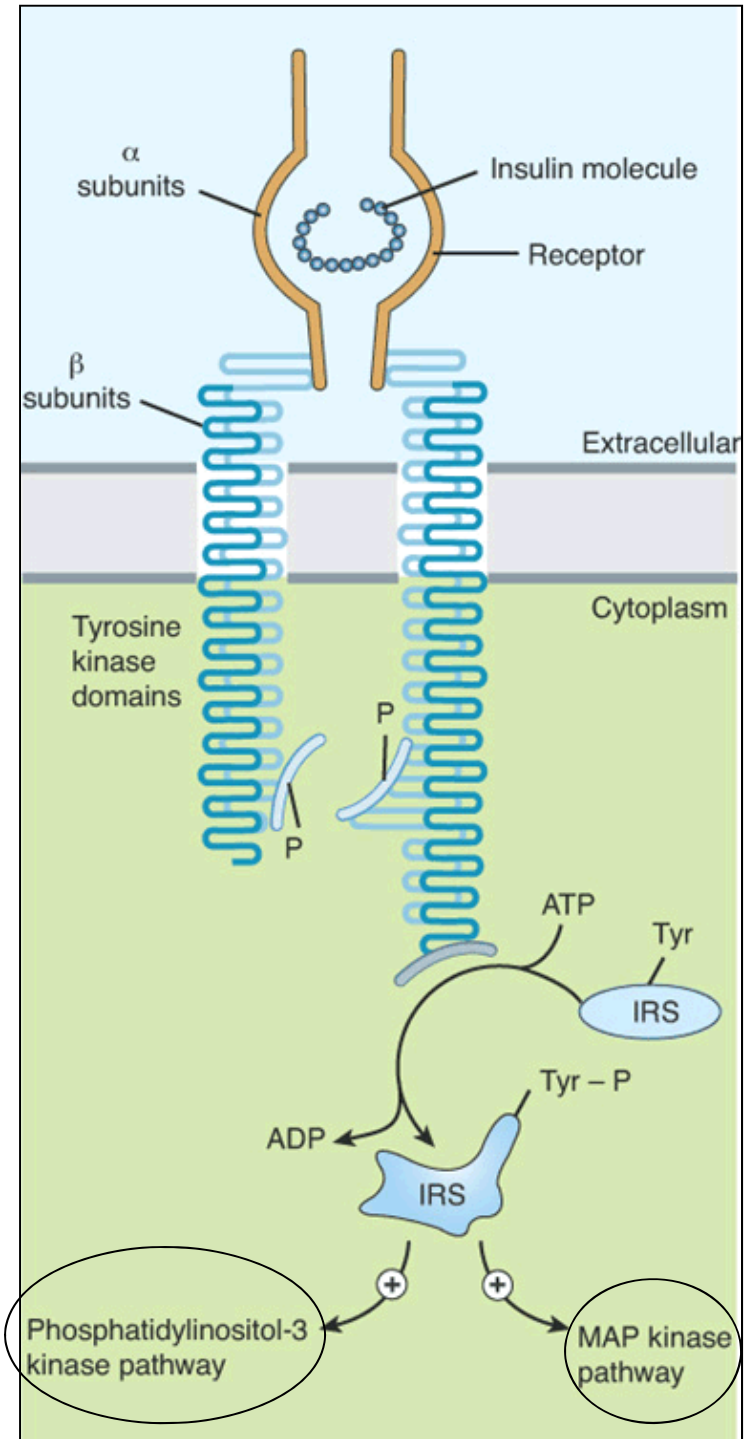


Fig. 41-3. Insulin receptor heterodimer in the activated state.

IRS, insulin receptor substrate; MAP, mitogen-activated protein; P, phosphate; tyr, tyrosine.0

Katzung

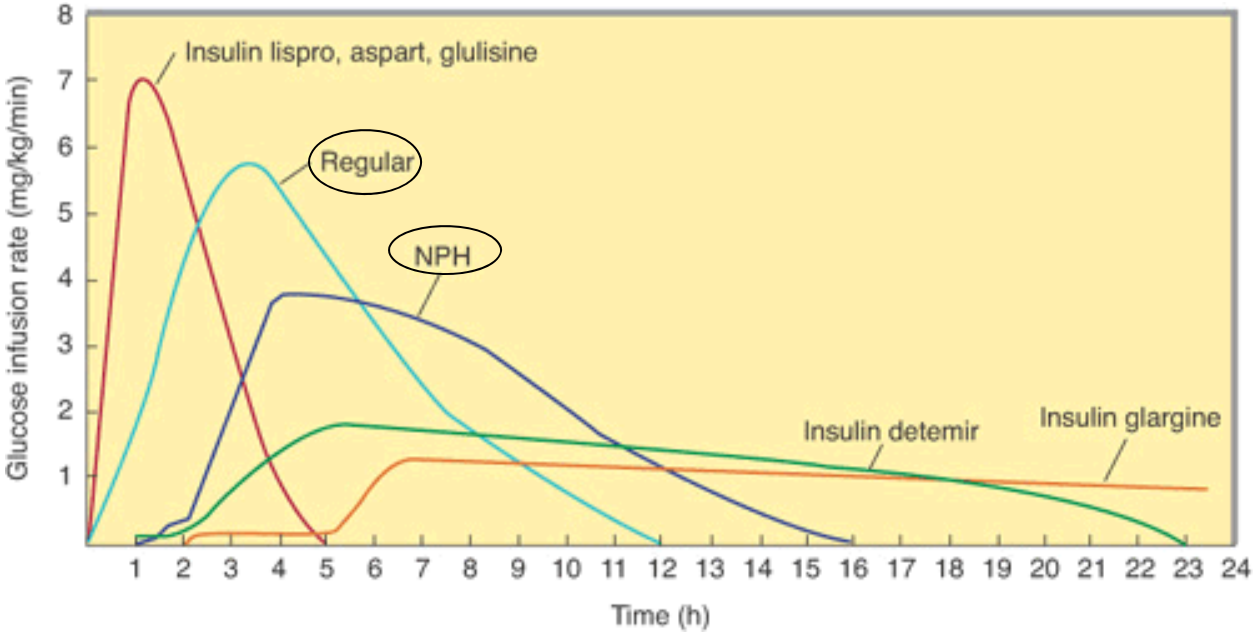
Table 41-4. **Some insulin preparations available in the USA.**[1] * **Top 200: Insulin lispro, regular, NPH, glargine**

Preparation	Species Source	Concentration
Rapid-acting insulins		
*Insulin Lispro, Humalog (Lilly)	Human analog	U100
Insulin Aspart, Novolog (Novo Nordisk)	Human analog	U100
Insulin Glulisine, Apidra (Aventis)	Human analog	U100
Short-acting insulins		
*Regular Novolin R (Novo Nordisk)	Human	U100
Regular Humulin R (Lilly)	Human	U100, U500
Intermediate-acting insulins (Neutral protamine Hagedorn, isophane)		
*Isophane (NPH) Humulin N (Lilly)	Human	U100
NPH Novolin N (Novo Nordisk)	Human	U100
Premixed insulins		
Novolin 70 NPH/30 regular (Novo Nordisk)	Human	U100
Humulin 70 NPH/30 regular and 50/50 (Lilly)	Human	U100
50/50 NPL, Lispro (Lilly) (NPL: insulin lispro protamine)	Human analog	U100
75/25 NPL, Lispro (Lilly) Humalog mix	Human analog	U100
70/30 NPA, Aspart (Novo Nordisk) (NPA: insulin aspart protamine) Novolg mix	Human analog	U100
Long-acting insulins		
Insulin detemir, Levemir (Novo Nordisk)	Human analog	U100
*Insulin glargine, Lantus (Aventis)	Human analog	U100

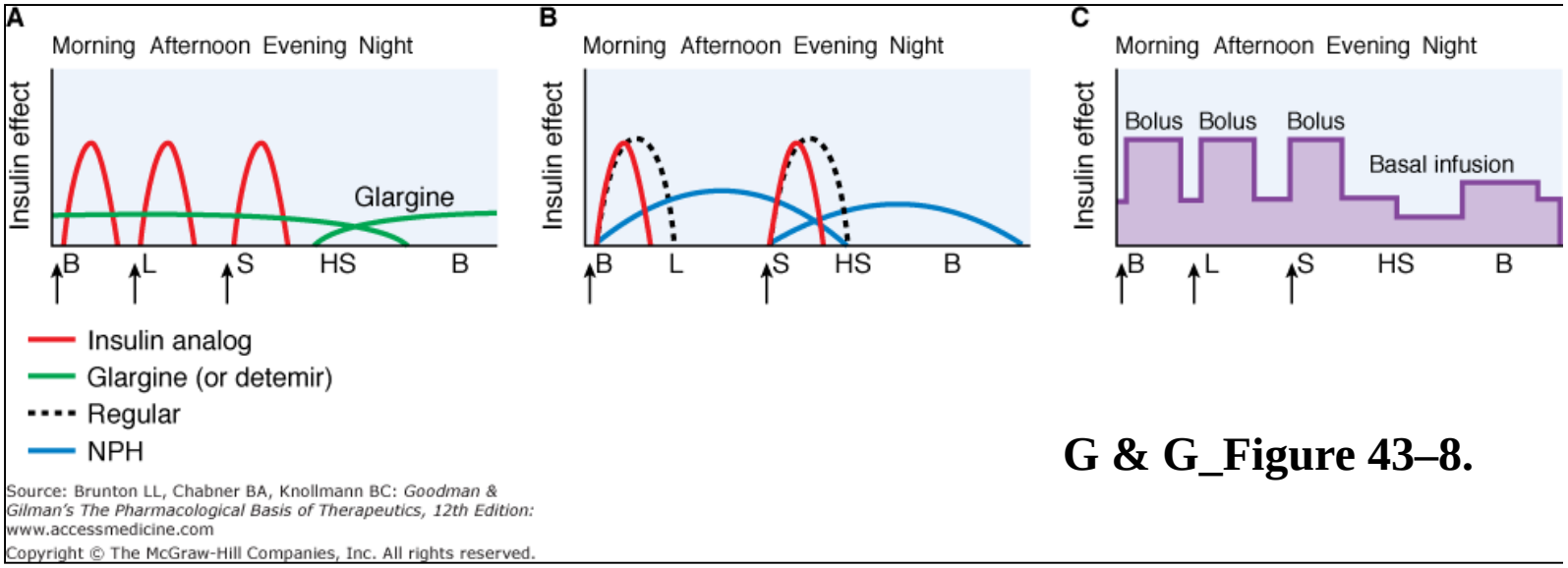
Katzung

[1] These agents (except insulin lispro, insulin aspart, insulin detemir, insulin glulisine, and U500 regular Humulin) are available without a prescription. All insulins should be refrigerated and brought to room temperature just before injection.
NPL, neutral protamine lispro; NPA, neutral protamine aspart. All are available in 100 units/ml (U100) in 10 ml vials for SQ inj.

Extent and duration of action of various types of insulin.



Katzung_Figure 41-5.



G & G_Figure 43–8.

Complication of Insulin Therapy

- ***A. Hypoglycemia:***
  - delay in taking a meal, unusual physical activity, too large dose of insulin or taking longer acting insulin in older patients
  - factors that increase sensitivity to insulin (*e.g.,* exercise, adrenal or pituitary insufficiency)
- First response: a reduction of endogenous insulin secretion (at a plasma G level of ~ 70 mg/dl (3.9 mM); thereafter, a release of the counter-regulatory hormones.
- Symptoms are first detected at a plasma G level of 60-70 mg/dl (3.3 to ~4 mM).

Hypoglycemia, Symptoms

- *Autonomic symptoms*: Includes both *sympathetic* (response to epinephrine: tachycardia, cold sweating, trembling) & *parasympathetic* (nausea, hunger) activation.
- Impaired CNS function [*neuro- symptoms*] difficulty in concentrating, confusion, weakness, dizziness, blurred vision and loss of consciousness or insulin coma (induced by insulin overdose) usually occur at lower plasma G levels than do autonomic symptoms.
- **Treatment:** Glucose administration (orange juice, honey, syrup); 20-50 ml of 50% glucose solution by IV over a period of 2-3 min or 1 mg of glucagon injection (SC or IM)

Diabetic Coma

- Results from an insulin deficit & involves DKA and dehydration.
- Usually develops over hours or days, whereas insulin coma (unconscious hypoglycemic state induced by insulin overdose) develops in a min (rapid onset).

- Even when diabetic coma is suspected, it is good practice to first administer glucose, since giving insulin in insulin coma could easily cause death.

- ***B. Insulin Allergy & Resistance***
  - small amounts of aggregated or denatured insulin in all preparations or minor contaminants
  - sensitivity to a component added to insulin (protamine, phenol, *etc*.).

    heparin
  - *Insulin allergy*, hypersensitivity results from anti-insulin IgE-mediated reactions; antihistamine
  - *Resistance* results from a low titer of circulating IgG anti-insulin antibodies

- ***C. Lipodistrophy at injection site***
  - ***Lipohypertrophy :*** Enlargement of subcutaneous fat depots associated with lipogenic action of insulin; occurs if patients inject themselves repeatedly in the same site.
- ***D. Insulin edema, abdominal bloating and blurred vision***
  - Edema is primarily due to Na^+ retention & increased capillary permeability

'Reverse vaccine' for Type 1 diabetes seems to pass human test!

- In Type 1, the *immune system goes wild* and attacks the pancreatic beta cells.
- Therapy is designed to protect beta cells; it reduces just T cells that attack beta cells.
- Has potential for treating those in early stages of disease (within the last 5 y); as after that many have already lost all of their beta cells.
- It is called *"reverse vaccine"* because it suppresses the immune system instead of stimulating it.
- Designed a molecule that contained the gene for making *proinsulin*. It also included instructions for turning off one specific immune response.

Drug Treatment of Type II Diabetes

- Oral Hypoglycemic Agents
- Insulin

Oral Hypoglycemic Agents

- Insulin secretagogues
  - **Sulfonylurea** & Meglitinides
- **Biguanides**
- a-glucosidase inhibitors
- Thiazolidinediones (TZDs)
- Dipeptidyl-peptidase-IV (DPP-IV) inhibitors (Incretin hormones enhancer)

Sulfonylureas

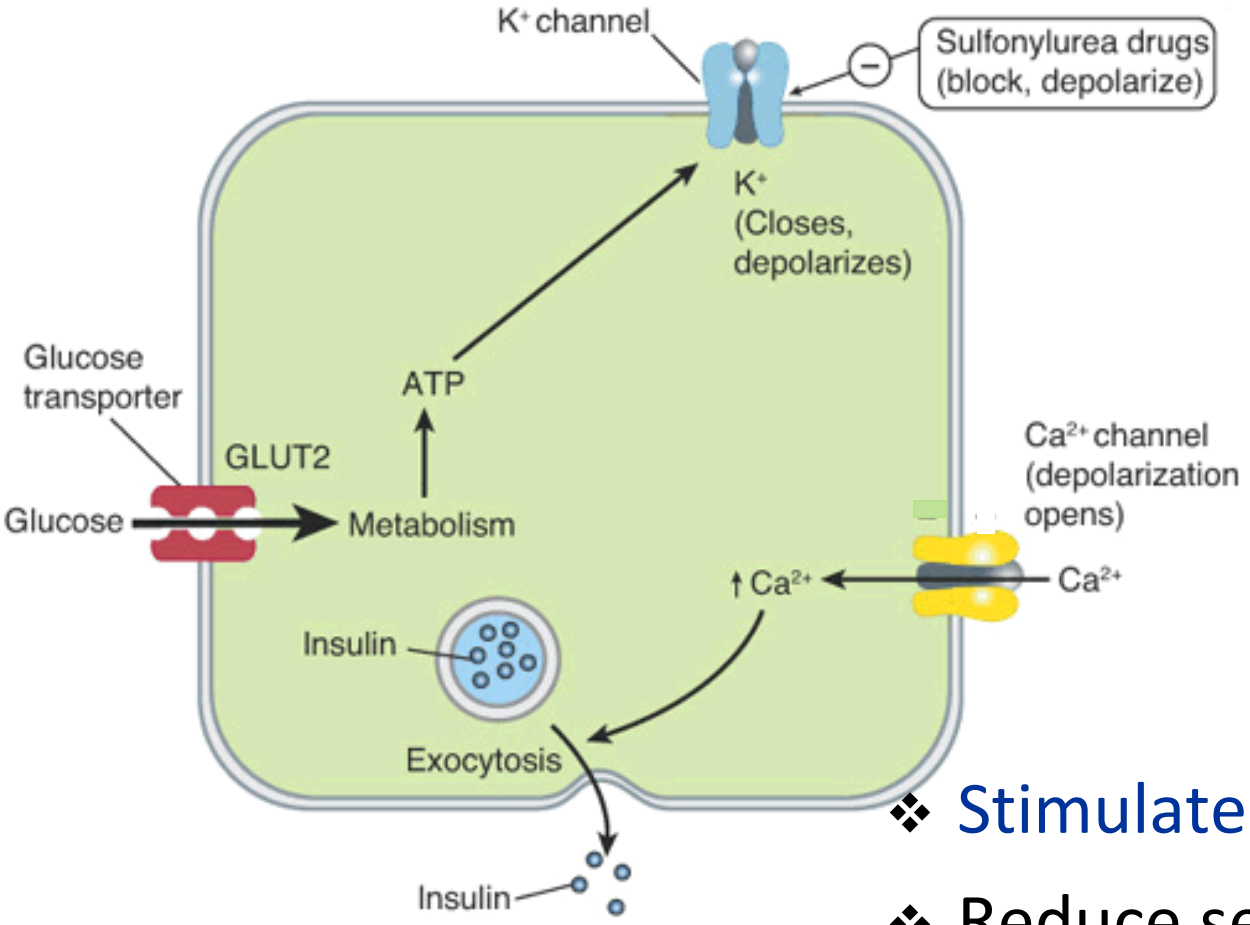
First-Generation Sulfonylureas	Daily Dose	Duration of Action (hours)
Tolbutamide (500 mg tablet)	0.5-2 g in divided doses	6-12
Tolazamide (250 mg & 500 mg tablet)	0.1-1 g as single dose or in divided doses	10-14
Chlorpropamide (100 &250 mg tab)	0.1-0.5 g as single dose	Up to 60
Second-Generation Sulfonylureas		
***Glyburide** (Diabeta, 1.25-2.5-5 mg tablet), (Micronized oral tablet, Glynase 1.5, 3, 6 mg)	0.00125-0.02 g	10-24
Glipizide (glydiazinamide[1]) (5-10 mg) (Glucotrol, Glucotrol XL)	0.005-0.03g (0.02 g in Glucotrol XL)	10-24
Glimepiride (Amaryl) (1-2-4 mg tablet)	0.001-0.004 g	12-24

[1]Outside USA.

Table 41-6.

*Top 200: Glyburide

Mechanisms of Action of Sulfonylurea*



Interaction:
Ca^{2+} blockers (high conc.)
Thiazides & Diazoxide
(K^+ channel opener)

- Stimulate insulin secretion*
- Reduce serum glucagon

Figure 41-2. Katzung

* Secondary failure

Meglitindes: Repaglinide (Prandin)® (0.5, 1 & 2 mg tablet) Nateglinide (Starlix) ® (60, 120 mg tablet)

- Insulin secretagogues, same MOA as sulfonylureas.
- **Repaglinide:** No sulfur in structure ⟶ it is used in type 2 diabetic patients with sulfur or sulfonylurea allergy.
- Activity complicated by drugs that induce or inhibit CYP450.
  - Barbiturate & carbamazepine decrease repaglinide conc, however erythromycin, ketoconazole & miconazole which inhibit CYP3A4 accumulate repaglinide.
- should be used cautiously in patients with hepatic insufficiency.

Table 38-2 Pharmacokinetic properties of oral hypoglycemic agents

Drug	Administration	T ½ (hrs)	Plasma Protein Binding	Duration (hrs)	Metabolite Activity	Elimination
FIRST-GENERATION SULFONYLUREA						
Tolbutamide	Oral	3-5	>90%	6-12	None	95% M, R
Tolazamide	Oral	7	>90	12-14	Weak	90% M, R
Chlorpropamide	Oral	24-48	>90%	Up to 60	Moderate	90% M, R
SECOND-GENERATION SULFONYLUREA						
Glipizide	Oral	3-7	>90%	24	None	90% M, R
Glyburide[1]	Oral	10-16	>90%	24	None	50% M, R
Glimepiride	Oral	5-9	>99%	24	Weak	99% M, R
MEGLITINIDE						
Repaglinide	Oral	1-2	>98%	2-3	None	99% M, F
Nateglinide	Oral	1.5-2	>98%	2-3	Weak	85% M, R

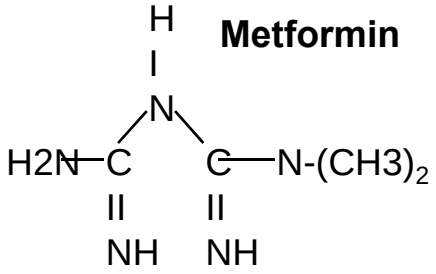
M, Metabolized; *R*, renal excretion; *F*, feces.

Adopted from Brody's Human Pharmacology

- Completely absorbed from GI.
- High plasma pr binding (interaction with sulfonamide & salicylates).
- Extensively metabolized by liver & most excreted by kidney.
  - If creatinnin clearance CrCl < 50 ml/min, avoid use of glyburide.
- Side effects: Hypoglycemic reactions/GI disturbances (nausea & vomiting), anemia, hypersensitivity & dermatological reactions (sensitive to sunlight). Problem in elderly patients with impaired hepatic or renal function who are taking longer-acting agents.

Biguanides

- ***Metformin hydrochloride oral tablet** (Glucophage)® 500, 850 & 1000 mg oral tablet
  - extended release: 500, 750 & 1000 mg *top 200
- **Metformin Hydrochloride oral solution**, (Riomet 500mg/5ml Solution)
- **Combinations:**
  - **Glipizide; Metformin hydrochloride**
  - (2.5;250 mg, 2.5;500 mg, 5;500mg)
  - **Glyburide; Metformin hydrochloride**
  - (1.25;500 mg, 2.5;500 mg, 5;500mg)
  - **Repaglinide; Metformin hydrochloride**
    - (Prandimet: 1,500 mg; 2,500 mg)



Metformin Hydrochloride "Euglycemic agent"

- decreases fasting & postprandial hyperglycemia, but doesn't cause hypoglycemia.
- Mechanism of Action:
- 1)decreases hepatic gluconeogenesis
- 2)decreases intestinal absorption of glucose
- 3) improves insulin sensitivity by improving glucose uptake and glucose utilization in SKM.
- Clinical use: In combination with Sulfonylurea or TZD in type II diabetes with insulin resistance.
- Toxicity:
  - **GIT**; anorexia, nausea, vomiting, abdominal discomfort, diarrhea (20%)
  - **Lactic acidosis** most likely in patients with renal failure.
  - Precautious in hepatic insufficiency.

Metformin, Contraindication

- Contraindicated for use in patients with *renal failure* or *renal impairment* (defined as serum creatinine >= 1.4-1.5 mg/dl or CrCl < 60 ml/min). Regular monitoring of renal function is necessary.

- Certain medications with metformin may also increase *lactic acidosis; cationic drugs (eg., triamterene).*

- Contraindicated with excessive ethanol (ethanol potentiates metformin effect on lactate metabolism).

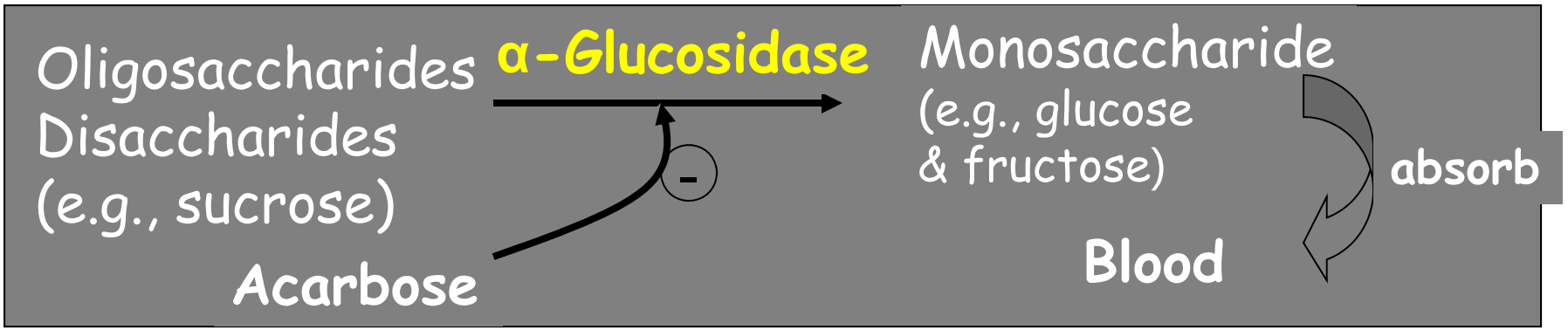
Metformin

- Used in polycystic ovarian syndrome (PCOS)*:
  - reduces insulin resistance
  - significantly increases FSH, SHBG and lowers serum androgen, restores normal menstrual cycles & ovulation & may help to resolve PCOS-associated infertility.

*Non FDA approved indication

α-Glucosidase Inhibitors

- Acarbose (Precose)® & Miglitol (Glyset) ® 25, 50 & 100 mg
- Target α-glucosidase
- Decrease intestinal digestion and absorption of ingested starch
- Good in control of postprandial hyperglycemia
- Infrequently prescribed in US
  - GI side effects/ relatively minor glucose-lowering benefit



Problems With Currently Available Oral Hypoglycemic Agents (e.g., sulfonylureas/meglitinide/biguanides) and Insulin?

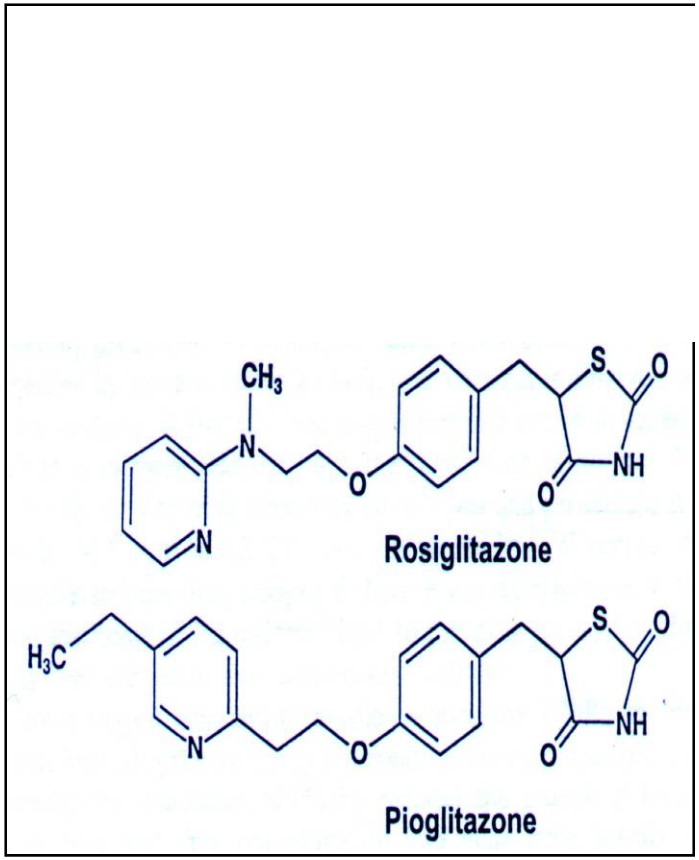
Insulin Sensitizing Agents: Thiazolidinediones

- Rosiglitazone (Avandia)®

2, 4 & 8 mg

- *Pioglitazone (Actos)®

15, 30 & 45 mg

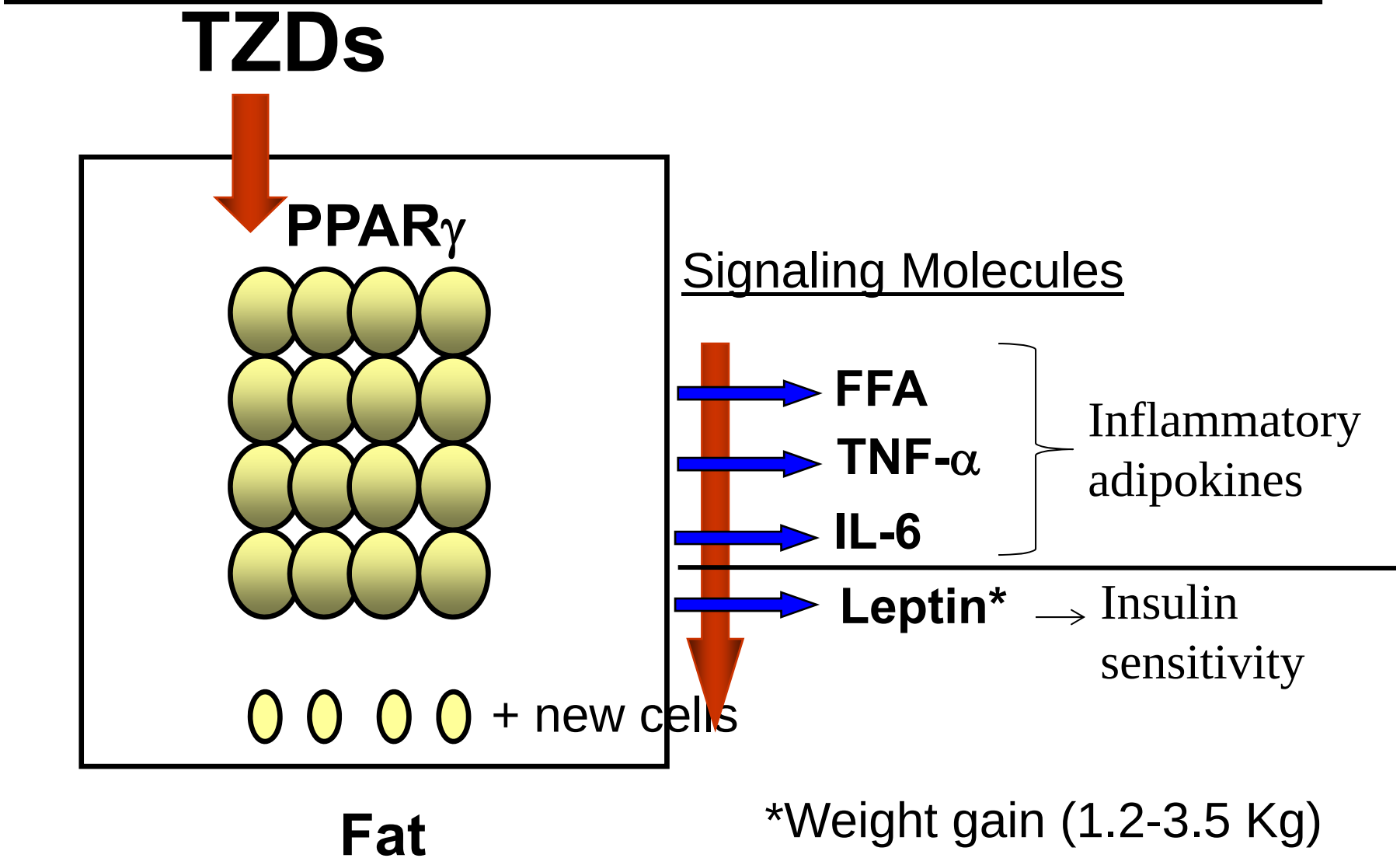


* Top 200

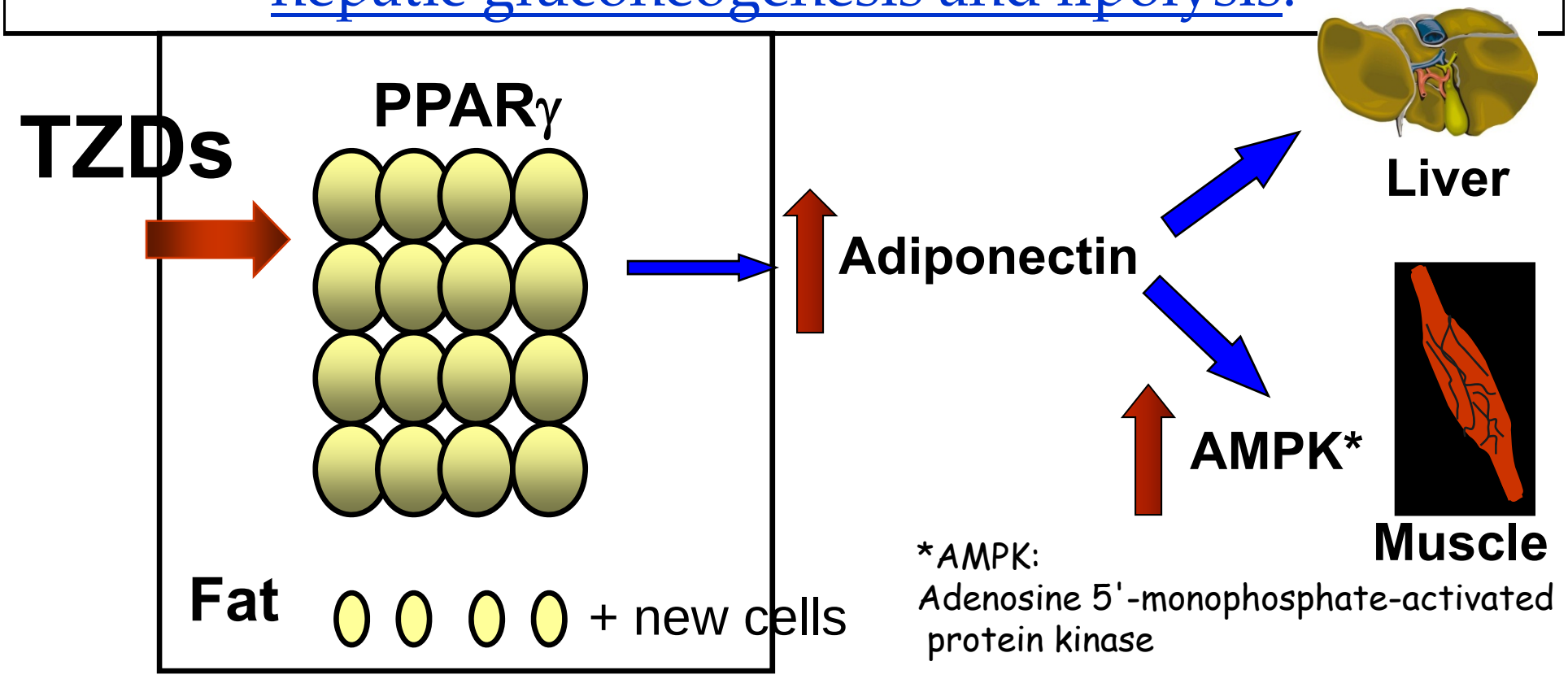
Peroxisome Proliferator-Activated Receptors (PPARs)

- Members of superfamily of nuclear receptors
- Three main members of PPAR: α, γ, and δ
- PPARα
  - receptor for fibrates [fenofibrate (micronized)™, lipid lowering drugs]
  - stimulates β oxidation of fatty acids
- PPARγ
  - receptor for TZDs
  - highly expressed in fat & promotes adipogenesis & insulin-mediated glucose uptake in peripheral tissues

TZDs decrease the release of adipose-derived inflammatory adipokines (signaling mediators)



TZDs increase the release of adiponectin and cause insulin sensitivity by elevating AMPK. AMPK increases SKM & hepatic fatty acid oxidation, stimulates G transport into SKM (by enhancing Glut-4) & also inhibits hepatic gluconeogenesis and lipolysis.



TZDs also cause redistribution of fat from visceral to subcutaneous stores.

Molecular and Cellular Biochemistry **224:** 29–37, 2001.

Hepatic over-expression of peroxisome proliferator activated receptor γ2 in the ob/ob mouse model of non-insulin dependent diabetes mellitus

Roshanak Rahimian, Esther Masih-Khan, Maggie Lo, Cornelis van Breemen, Bruce M. McManus and Gregory P. Dubé

The Vancouver Vascular Biology Research Center and the Department of Pathology and Laboratory Medicine, St. Paul's Hospital, University of British Columbia, Vancouver, Canada

Received 16 January 2001; accepted 9 April 2001

Abstract

Studies of the molecular basis of insulin resistance have focused on the peroxisome proliferator activated receptor gamma (PPARγ, γ1 and γ2). The aim of this study was to determine whether the insulin resistance in liver of diabetic animals is associated with abnormal expression of these receptors. PPARγ mRNA and protein expression levels were quantified in liver of 9-week-old male ob/ob mice as a model of diabetes and compared to age- and gender-matched wild type control animals of the same genetic background. Semi-quantitative reverse transcription-polymerase chain reaction, using 18S rRNA as an internal standard, indicated that PPARγ2 mRNA was significantly upregulated in ob/ob liver vs. that in wild type mice. Western blotting revealed greater immunoreactivity of PPARγ2 in liver from ob/ob mice relative to that in wild type mice. An index of insulin resistance (product of serum glucose and insulin concentration) was correlated with liver PPARγ2 mRNA expression ($r = 0.776$; $p < 0.001$). The findings that liver PPARγ2 expression is (1) significantly elevated in the ob/ob model of diabetes and (2) positively associated with an index of insulin resistance, suggests a possible compensatory response through which type II diabetic and obese organisms strive to maintain insulin sensitivity of the liver. (Mol Cell Biochem **224**: 29–37, 2001)

Key words: adipose, insulin resistance, liver, PCR, PPARγ, ob/ob mouse

Abbreviations: PPAR – peroxisome proliferator activated receptor; RT-PCR – reverse transcription-polymerase chain reaction; cDNA – complementary DNA; NIDDM – non-insulin dependent diabetes mellitus; aP2 – adipose lipid binding protein; SDS-PAGE – SDS-polyacrylamide gel electrophoresis; TBS-T – Tris-buffered saline containing 0.25% Tween-20

Table 38-3 Pharmacokinetic properties of antihyperglycemic agents

Drug	Administration	T ½ (hrs)	Plasma Protein Binding	Metabolite Activity	Elimination
BIGUANIDE					
Metformin	Oral	2-4	Negligible	None	R
THIAZOLIDINEDIONE					
Rosiglitazone	Oral	3-4	>99%	Weak	99% M, R
Pioglitazone	Oral	3-7 16-24	>99%	Moderate	M, F, R
α-GLUCOSIDASE INHIBITOR					
Acarbose	Oral	NA	None	None	F
Miglitol	Oral	2	None	None	R

NA, Not absorbed; *R*, renal excretion; *M*, metabolized; *F*, feces

Adopted from Brody's Human Pharmacology

- ✓ Patients with impaired renal function are at risk with Metformin (used only in patients with normal renal function).
- ✓ TZD: Cautious in heart and liver disease; regular monitoring of liver function is necessary; with high plasma protein binding such as verapamil and diazepam.
- ✓ Combination of rosiglitazone with insulin increases the risk of heart failure & edema (it is not approved).

- ✓ Glimepiride; Rosiglitazone(Avandaryl™)/ Metformin; Rosiglitazone (Avandamet™)/ Glimepiride; Pioglitazone (Duetact™)/Metformin;Pioglitazone (Actoplus Met™)

Drug Interaction of TZDs

Rosiglitazone

- metabolized by hepatic cyp2C8, but doesn't induce or inhibit any cyp isoforms.
- Accumulation of rosiglitazone may occur when co-administered with drugs that inhibit CYP2C8 such as trimethoprim.
- With insulin, increase the risk of heart failure & edema.

Pioglitazone

- metabolized by hepatic cyp3A4 & cyp2C8 & induces cyp3A4.
  - e.g., Diazepam, Cyclosporine, Ethinyl estradiol & Norethindrone

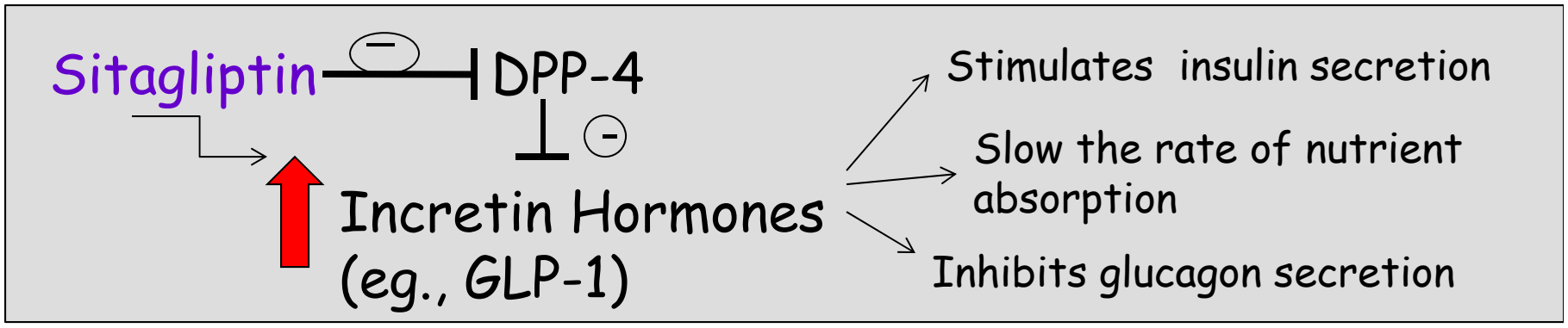
Dipeptidyl-peptidase-IV (DPP-4) inhibitors

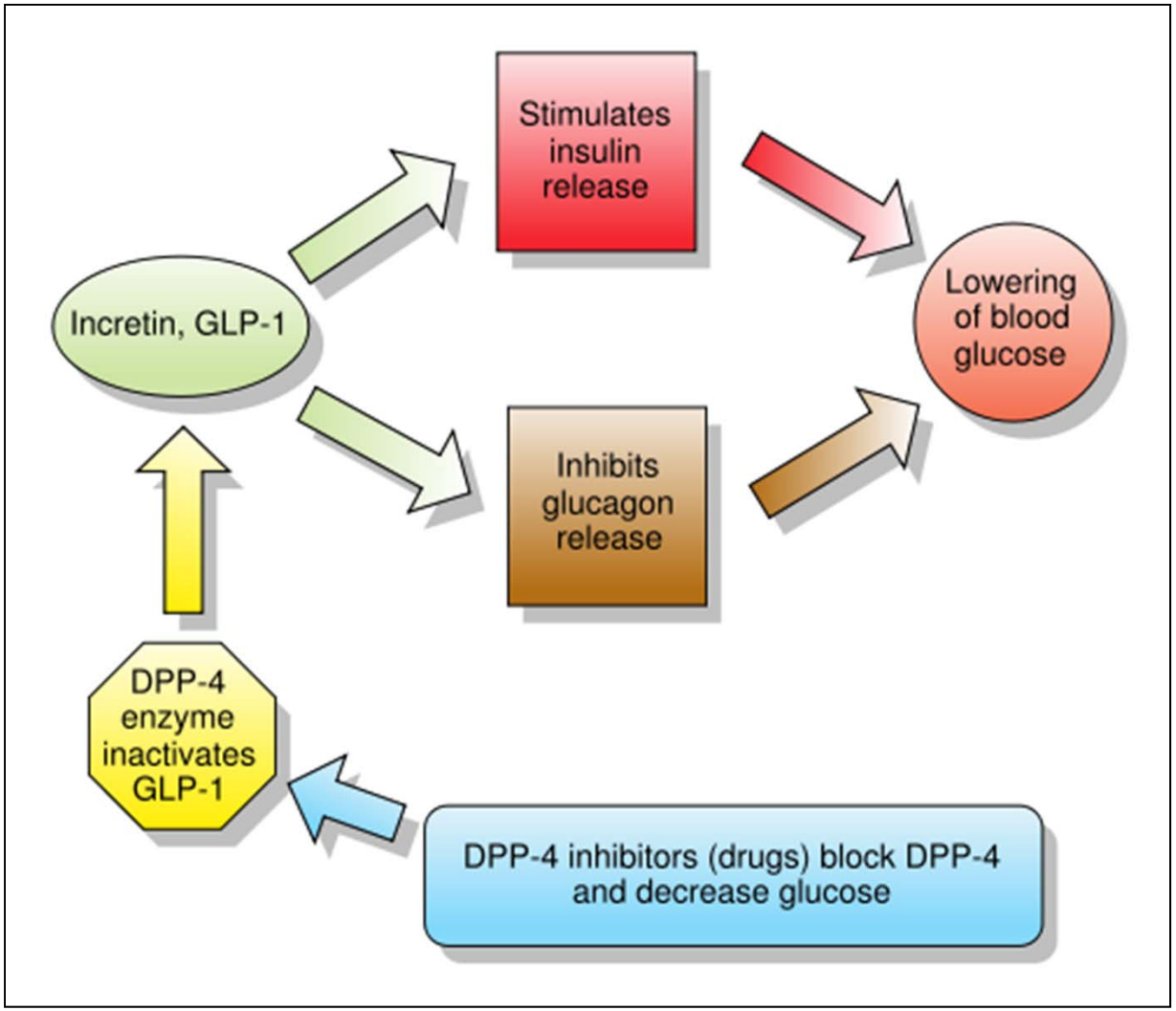
- *Sitagliptin (Januvia™) 25, 50 & 100 mg
  - Sitagliptin; Metformin
  - *Sitagliptin; Simvastatin
- Saxagliptin (Onglyza™) 2.5, 5 mg
  - Saxagliptin; Metformin
- Linagliptin (Tradejenta™) 5 mg
  - Linagliptin; Metformin
- Alogliptin (Nesina™): was approved by the FDA in Jan 2013. 6.25, 12.5 & 25 mg
  - Alogliptin; Metformin
  - Alogliptin; Pioglitazone

*top 200, Sitagliptin, Simvastatin

Sitagliptin (Januvia™) 25-50-100 mg Tablet

- An inhibitor of dipeptidyl peptidase-4 (DPP-4) enzyme
- DPP-4 enzyme inactivates incretin hormones.
- Incretin hormones, including glucagon-like peptide-1 (*GLP-1),* are released by the intestine, and levels are increased in response to a meal.
- Incretin hormones are extremely potent stimulators of pancreatic B cells. They slow the rate of nutrient absorption by reducing gastric emptying and also inhibit glucagon release.
- GLP-1 (7-37) is not very useful for treatment since it must be administered by continuous subcutaneous infusion.




Stimulates insulin release
Incretin, GLP-1
Lowering of blood glucose
Inhibits glucagon release
DPP-4 enzyme inactivates GLP-1
DPP-4 inhibitors (drugs) block DPP-4 and decrease glucose

Exenatide (Byetta ™) 5-10 mcg solution pen injection

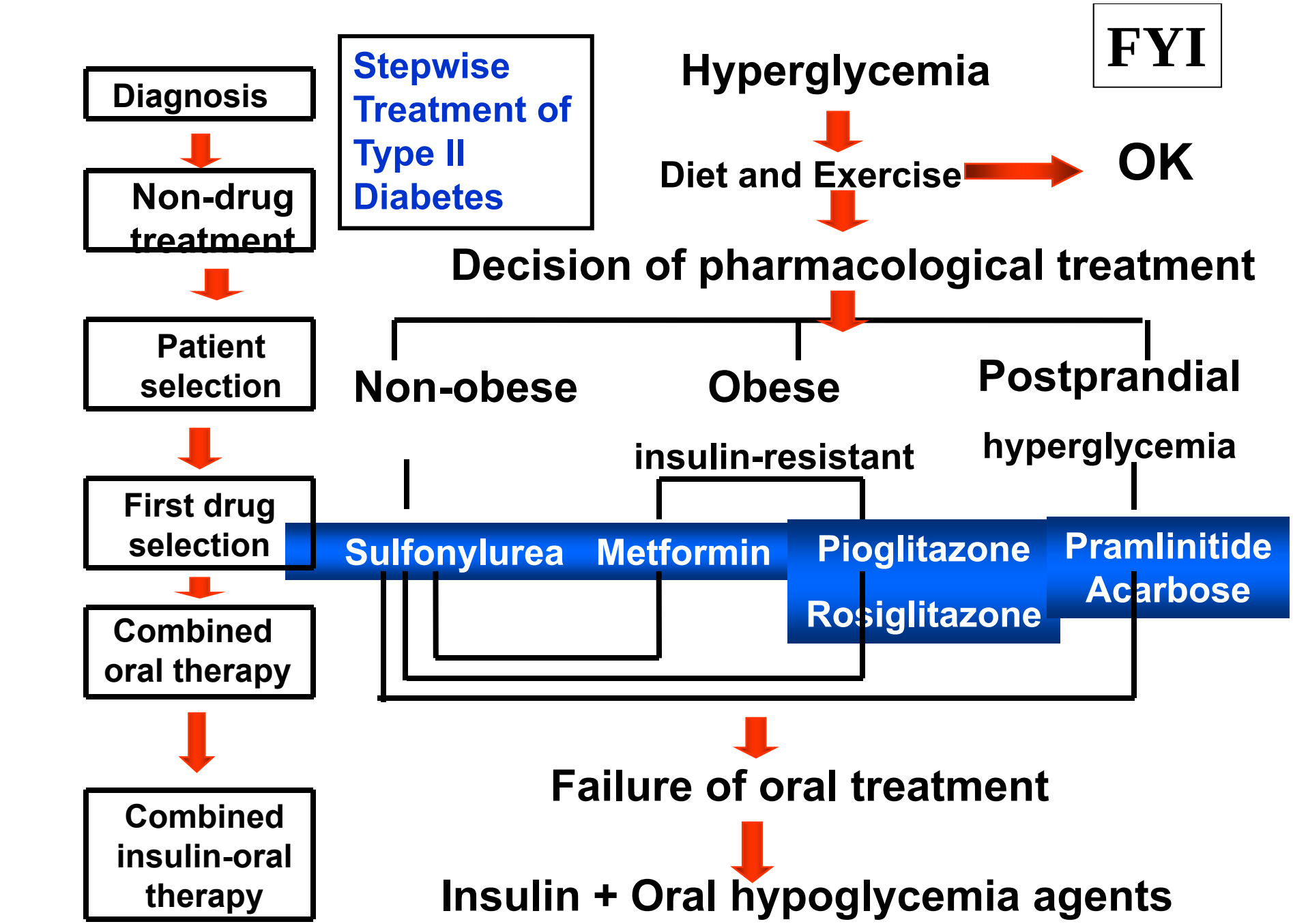
- A functional analog of the human incretin GLP-1 .
- GLP-1 increases insulin secretion only in presence of elevated plasma glucose levels.
- Secondary effects of drug: reduces gastric emptying and decreases food intake.

Liraglutide (Victoza ™) box, 2 pens, 3 ml Liraglutide 6mg/1mL, Solution for injection

- GLP-1 receptor agonist and belongs to a class of incretin mimetics with 97% aa sequence homology to endogenous GLP-1 (7—37) (approved by FDA in 2010)
- contraindicated in patients with history of certain types of thyroid cancer.

Pramlintide Acetate (SymlinPen™) 0.6mg/1mL (SQ)

- A synthetic analog of amylin, modulates postprandial hyperglycemia.
- It is administered in addition to insulin in those who are unable to achieve their target postprandial serum glucose.
- 1) Suppresses glucagon release, 2) delays gastric emptying, and 3) has CNS-mediated anorectic effects.
- Side effects: Hypoglycemia, GI symptoms (nausea, vomiting, and anorexia).



Diabetes Care 22: 1568, 1999

(Except for rosiglitazone)