

Treatment of Diabetes Mellitus

Classic antidiabetics

- ▶ Sulfonylureas (glimepiride, glipizide, gliclazide)
- ▶ Biguanides (metformin)
- ▶ Alpha-glucosidase inhibitors (acarbose, miglitol)
- ▶ Thiazolidinediones (sensitizers) (pioglitazone, rosiglitazone(withdrawn))
- ▶ Nonsulfonylurea secretagogues (meglitinides): repaglinide, nateglinide

Diabetes Mellitus

- ▶ Heterogeneous disease
- ▶ The Problem:
 - ▶ high blood glucose due relative or absolute deficiency of insulin
- ▶ (Two) types based on insulin requirement:
 - ▶ IDDM (10-20%) (old) Type 1
 - ▶ NIDDM (80-90%) (old) Type 2
- ▶ Diabetics suffer from dysregulated glucose control

Types of DM

- ▶ Type 1 Diabetes Mellitus: The hallmark of type 1 diabetes is selective B-cell destruction and severe or absolute insulin deficiency. Administration of insulin is essential in patients with type 1 diabetes. Type 1 diabetes is further subdivided into immune and idiopathic causes. The immune form is the most common form of type 1 diabetes.
- ▶ Type 2 Diabetes Mellitus: Type 2 diabetes is characterized by tissue resistance to the action of insulin combined with a relative deficiency in insulin secretion. A given individual may have more resistance or more B-cell deficiency, and the abnormalities may be mild or severe. Although insulin is produced by the B cells in these patients, it is inadequate to overcome the resistance, and the blood glucose rises. The impaired insulin action also affects fat metabolism, resulting in increased free fatty acid flux and triglyceride levels and reciprocally low levels of high-density lipoprotein (HDL). Individuals with type 2 diabetes may not require insulin to survive, but 30% or more will benefit from insulin therapy to control the blood glucose.

Types of DM

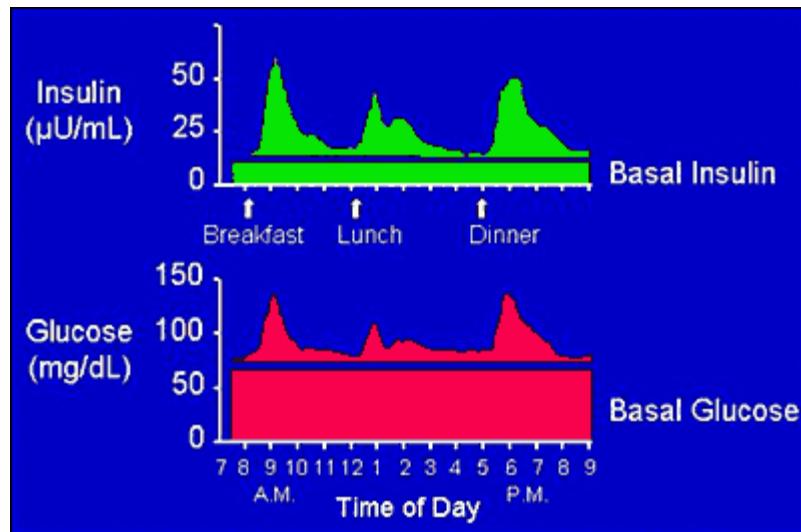
- ▶ Type 3 Diabetes Mellitus: The type 3 designation refers to multiple other specific causes of an elevated blood glucose: pancreatectomy, pancreatitis non-pancreatic diseases, drug therapy, etc.

- ▶ Type 4 Diabetes Mellitus: Gestational diabetes (GDM) is defined as any abnormality in glucose levels noted for the first time during pregnancy. Gestational diabetes is diagnosed in approximately 4% of all pregnancies in the USA. During pregnancy, the placenta and placental hormones create an insulin resistance that is most pronounced in the last trimester. Risk assessment for diabetes is suggested starting at the first prenatal visit. High-risk women should be screened immediately.

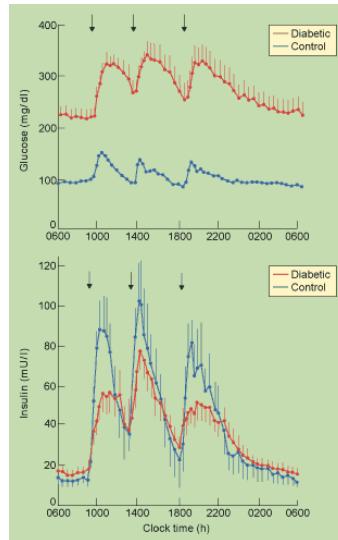
WHO (1998) BMI Classification

	BMI Europeans	Asian	Risk of Co-morbidities
Underweight	<18.5	<18.5	Low but increased risk of other clinical problems
Normal range	18.5-24.9	18.5-22.9	Average
Overweight	≥ 25	≥ 23	
Pre-obese/At risk	25-29.9	23-24.9	Increased
Obese I	30-34.9	25-29.9	Moderate
Obese II	35-39.9	≥ 30	Severe
Obese III	≥ 40		Very severe

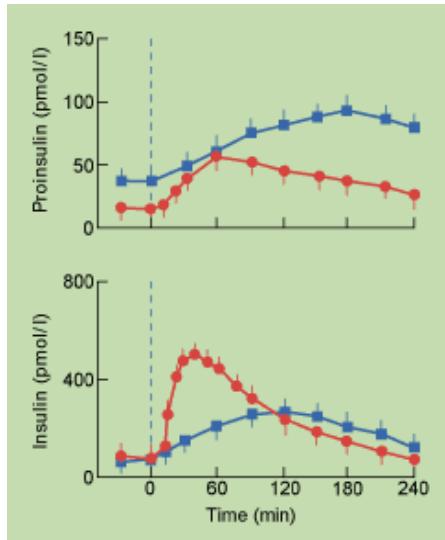
Endogenous Insulin Secretion and Blood Glucose



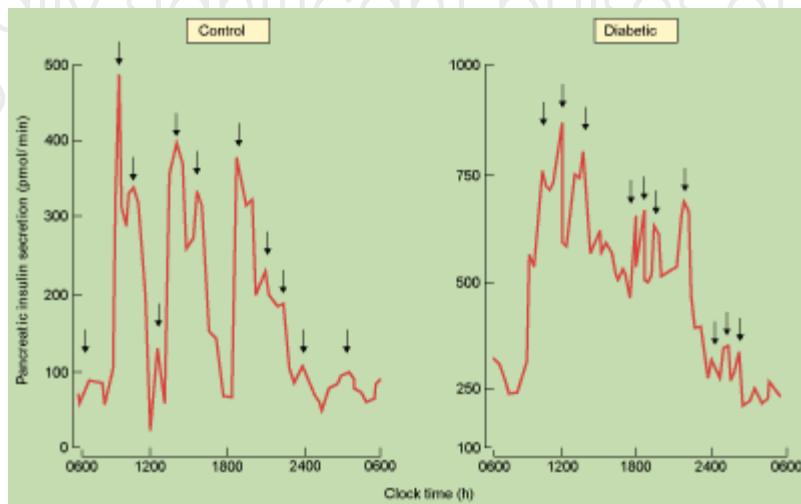
The Difference Between Diabetics and Non-Diabetics



Mean (\pm SEM) insulin and proinsulin responses in normals (Red) and NIDDM (Blue) patients.



24-h insulin-secretion profiles from non-diabetic control and diabetic patients are shown. Meals were eaten at 09:00, 13:00 and 18:00. Arrows indicate statistically significant pulses of secretion



Complications of Diabetes

- ▶ Heart disease
- ▶ Microvascular complications (Type 2)
 - ▶ Retinopathy
 - ▶ 'stocking glove' syndrome
- ▶ Renal Disease
- ▶ Edema

Causes of mortality in T1DM and T2DM

	T1DM	T2DM
▶ Coronary heart diseases	15	58
▶ Cerebro-vascular disease	3	12
▶ Nephropathy	55	3
▶ Diabetic coma	4	1
▶ Malignancy	0	11
▶ Infections	10	4
▶ Others	13	11

Treatment of diabetes mellitus

- ▶ Diet
- ▶ Physical exercise
- ▶ Oral antidiabetic drugs
- ▶ Insulin

Glycaemic Control is ESSENTIAL

- ▶ HbA1c is a measure of glycated hemoglobin
 - ▶ A better measure of longer-term blood glucose levels
- ▶ help clients to reach blood glucose goals
- ▶ Two long-term multicenter studies have shown that tight glycaemic control significantly reduces diabetes complications

What is Glycaemic Index (GI)?

- ▶ Ranking of individual foods according to the effect they have on blood glucose levels (0-100 %)
- ▶ The GI is a measure of how quickly foods that contain carbohydrate raise blood glucose levels.
- ▶ Some carbohydrate foods (with a high GI) cause a rapid rise in blood glucose and others (with a low GI) a gradual rise.
- ▶ It is the combination of foods that matters, e.g.: Cornflakes (high GI) and milk (low GI) = medium GI
- ▶
- ▶ Glycemic index (%) =
$$\frac{\text{Area under the glycemic curve after test food}}{\text{Area under the glycemic curve after glucose}}$$

Average Glycaemic Index of some food groups

Food	Low GI	Medium GI	High GI
Breads	Rye bread Fruit loaf Mixed grain bread chapatti	Wholemeal/white bread Pita bread, croissant *	Baguette
Breakfast cereals	Porridge, All Bran, Special K All varieties of muesli	Sustain, Shredded Wheat Nutrigrain, Vitabrits	Rice Krispies, Rice bubbles Coco Pops, Puffed Wheat Cornflakes
Pasta / Rice /Grains / Potato	Bulgur wheat, buckwheat Pearl barley, noodles All types of pasta	Basmati/brown rice Sweet/boiled potato Couscous	White rice, rice cakes, rice bran Mashed potato Baked potato
Vegetables	Peas carrots	Sweetcorn	Parsnip, pumpkin Instant potato, baked potato

Average Glycaemic Index of some food groups

Food	Low GI	Medium GI	High GI
Fruit	Apricots, orange, grapes Apple, pear, peaches Grapefruit, plums, cherries	Apricots (tinned), pineapple Rockmelon, paw paw Raisins, sultanas Mango, banana, kiwi fruit	Watermelon
Dairy foods	Milk - full cream */skimmed/ semi skimmed/flavoured Yoghurt */Diet yoghurt	Ice cream *	
Snacks & confectionery	Banana/sponge cake * Peanuts * Some chocolates	Sweet muffins *, Mars bars * Muesli bars *, Potato crisps * Some chocolates*	Jelly beans Some biscuits Lucozade
Sugars	Fructose Lactose	Sucrose	Glucose Maltose

Meal Planning

- ▶ Some suggestions for lower GI meals:
- ▶ Breakfast: Porridge, Special K with milk
- ▶ Snack Meal: Lentil soup with bread
 - ▶ Baked beans on toast
 - ▶ Pitta bread with salad or
 - ▶ meat sandwich and fruit yoghurt
- ▶ Main Meal: Chilli beans with baked potato
 - ▶ Basmati rice with vegetable curry
- ▶ Dessert: Slice of fruit loaf
 - ▶ Oatcakes

Diet and Insulin

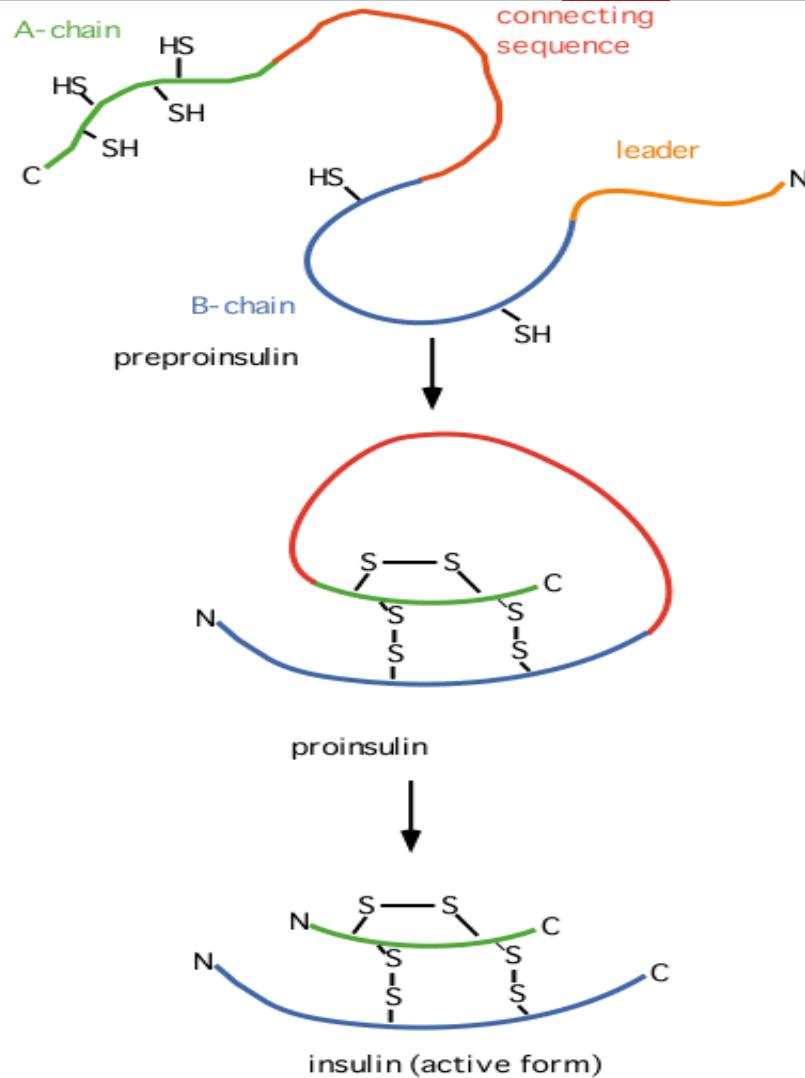
- ▶ Considerations
- ▶ Timing of meals/insulin
- ▶ Snacks?
- ▶ Treatment of Hypoglycaemia
- ▶ Effects of alcohol
- ▶ Activity
- ▶ Illness

Pharmacologic Solutions

- ▶ Insulin (for Type 1 diabetes)
 - ▶ Many different forms (differ in solubility, speed and duration of action)
- ▶ GLP-1 analogue
- ▶ Oral Antidiabetic drugs (for Type 2 diabetes)
 - ▶ Sulfonylureas
 - ▶ Biguanides
 - ▶ Alpha-Glucosidase Inhibitors
 - ▶ Thiazolidinedions
 - ▶ DPP-4 inhibitors
 - ▶ SGLT-2 (Sodium glucose co-transporter 2) inhibitors

Processing of pre-pro-insulin to active insulin

- * Pre-pro-insulin is synthesized as a random coil on membrane-associated ribosomes
- * After membrane-transport the leader sequence (yellow) is cleaved off by a protease and the resulting pro-insulin folds into a stable conformation.
- * Disulfide bonds form between cysteine side chains.
- * The connecting sequence (red) is cleaved off to form the mature and active insulin molecule.



Diagnosing of DM

FPG

≥ 7.0 mmol/l
≥ 126 mg/dl
5.6–6.9 mmol/l
100–125 mg/dl
5.5 mmol/l
<100 mg/dl

Diabetes

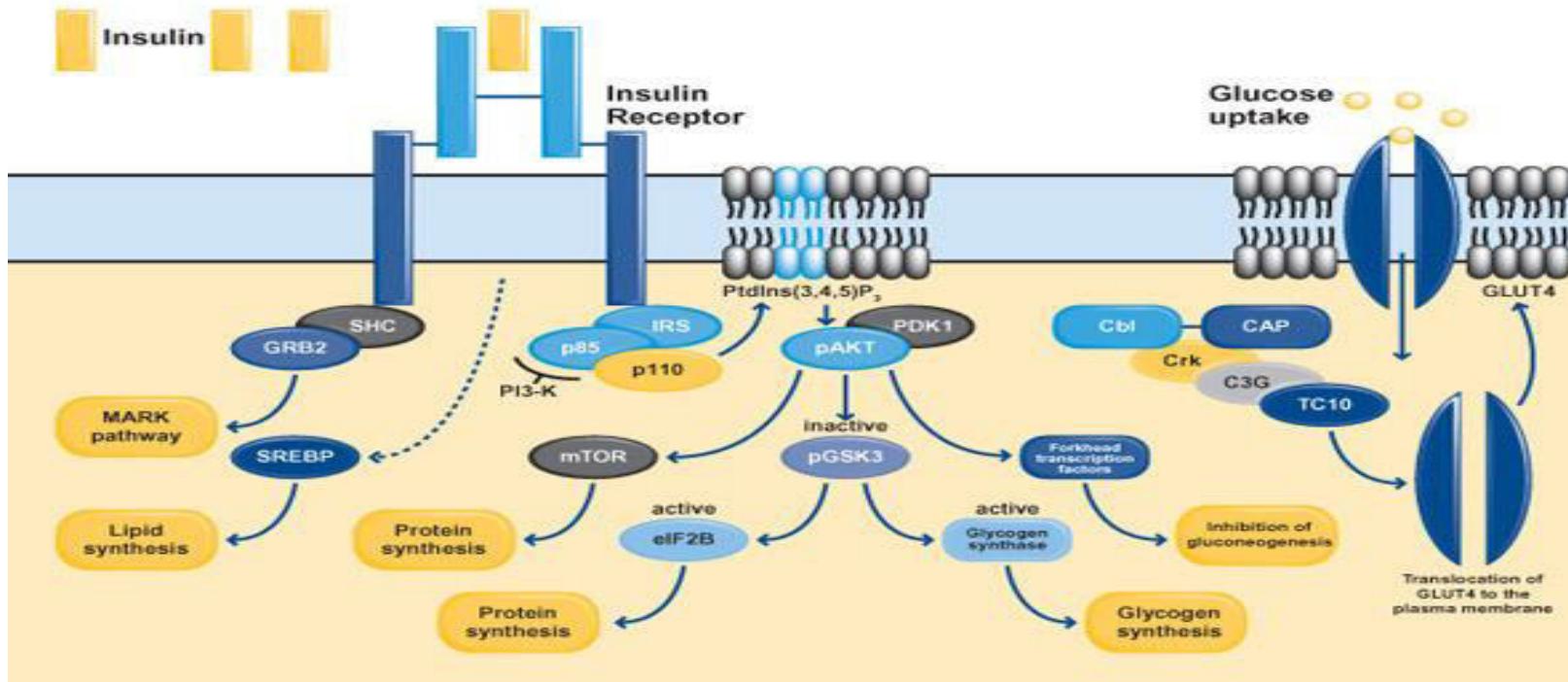
Prediabetes

Normal

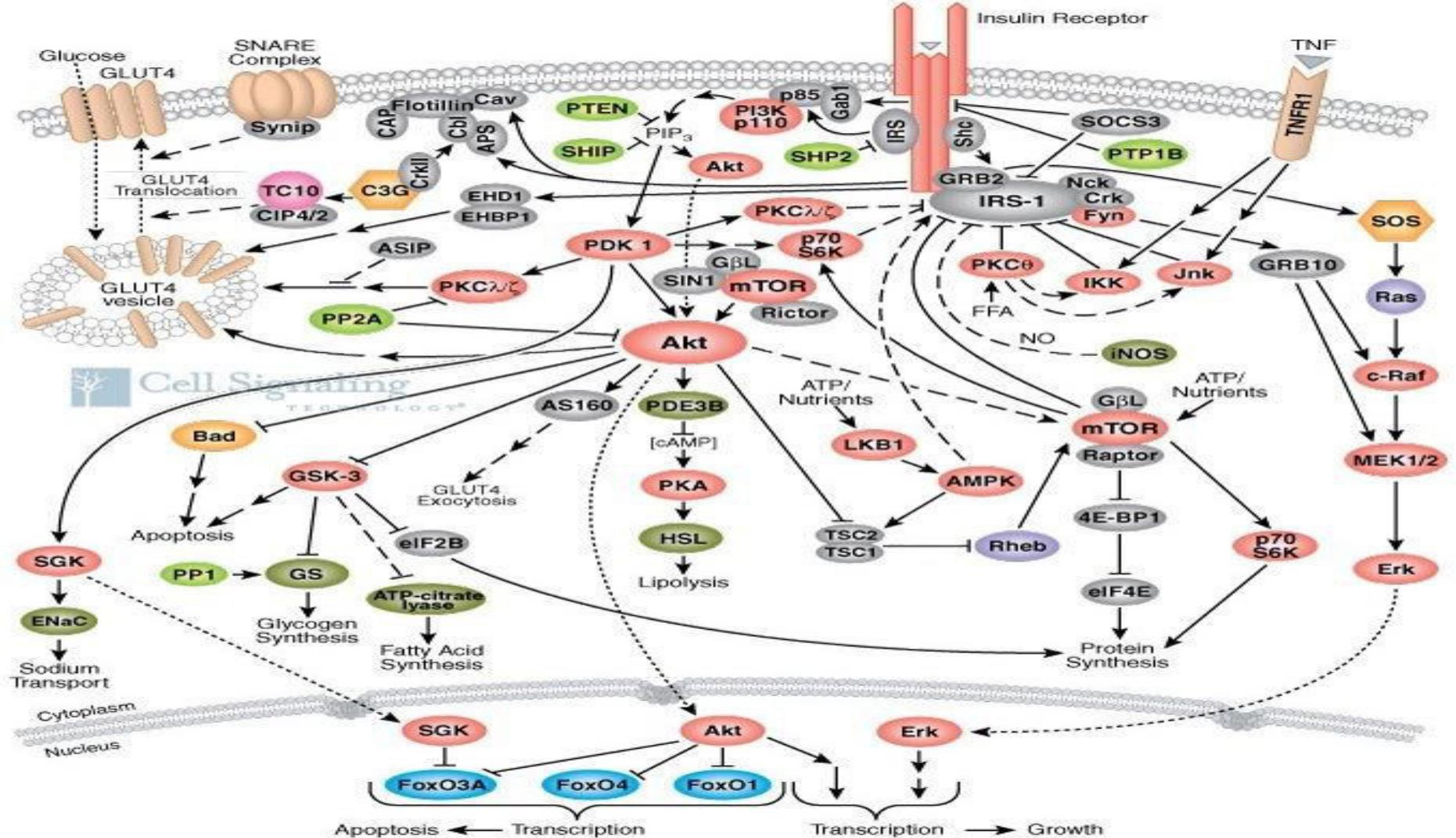
OGTT

11.1 mmol/l
200 mg/dl
7.8–11.0 mmol/l
≥ 140 –199 mg/dl
7.8 mmol/l
<140 mg/dl

Insulin signalling pathway



Activation of the insulin receptor evokes increased transcription of SREBP and the phosphorylation of members of the IRS family, SHC and Cbl. Upon tyrosine phosphorylation, these proteins interact with signaling molecules through their SH2 domains, which results in the activation of a variety of signaling pathways, including PI 3-kinase signaling, MAPK activation and the activation of the Cbl/CAP complex. These pathways act in a coordinated manner to regulate glucose, lipid and protein metabolism.





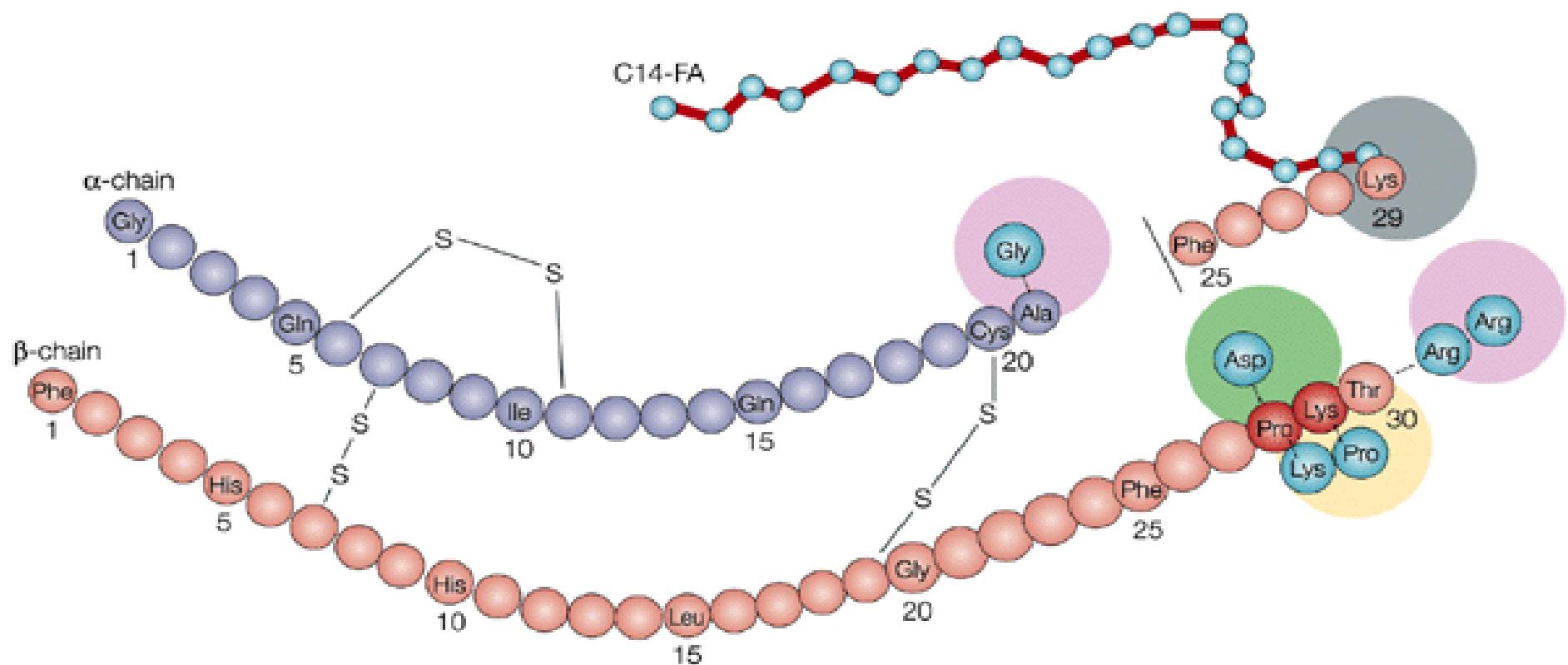
- ▶ Insulin LisPro (HUMALOG):
 - ▶ B28-B29 Pro-Lis conversion
- ▶ Insulin aspart (NOVOLOG):
 - ▶ B28 Asp
- ▶ Insulin glulisin (APIDRA):
 - ▶ B3 Asp and B29 Glu
- ▶ Regular insulin
- ▶ NPH Insulin (HUMULIN-N)
- ▶ Insulin detemir (LEVEMIR):
 - ▶ Fatty acid side chain (to the end of B chain)
- ▶ Insulin glargine (LANTUS) (HOE901):
 - ▶ A21 Asn→Gly
 - ▶ B chain C-term +2xArg
 - ▶ Acidic IEP
 - ▶ Soluble, peakless, ultra-long acting
- ▶ Insulin degludec (TRESIBA)
 - ▶ Multihexamerisation (hexadecanedioic acid to lysine at the B29 position)
 - ▶ Onset of action of 30-90 minutes (lasts more than 24 h)
 - ▶ S.c. 3 times/week

FAST-ACTING

SHORT-ACTING

LONG-ACTING

ULTRA-LONG-ACTING



Fast-acting analogues



Insulin lispro



Insulin aspart

Long-acting analogues



Insulin glargine



Detemir insulin

RELATIVE EFFECTS OF INSULIN ANALOGS

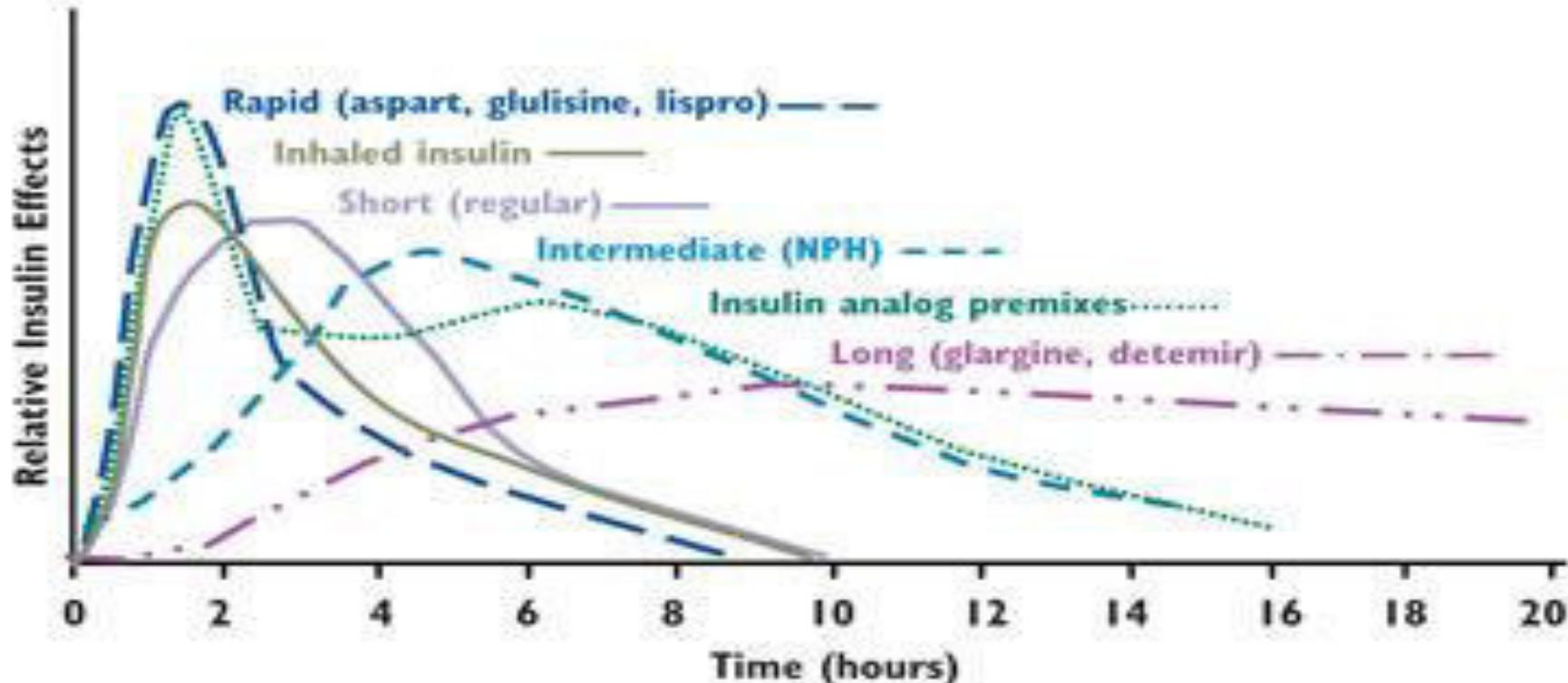


Figure 1. Representative time action profiles of selected exogenous insulins.
Source: References 25, 26.

Basics of insulin therapy 1.

- ▶ Estimation of insulin dose:
- ▶ Basal insulin requirement 40%
- ▶ Prandial insulin requirement 60%
- ▶ Prandial insulin dose must be the highest in the morning (because of the relative insulin résistance)
- ▶ Endogeneous insulin secretion in a nondiabetic adult is about 30 U/day
- ▶ The daily insulin requirement in diabetes mellitus is higher, than the endogeneous insulin secretion in a healthy human being, becuse in the former cases the insulin is not administered intraportally.

Basics of insulin therapy 2.

The insulins available are divided into:

Insulin	starts working after (minutes)	time of strongest action (h)	length of action (h)
Ultrashort	10-20	1-2	4
Short acting	30	1-4	<8
Intermediate acting	30 - 120	4 - 12	<24
Long acting	240	10 - 12	<36

Basics of insulin therapy 4.

The name of insulins available in Hungary

- ▶ Ultra short acting (analogue): Humalog and Novorapid
- ▶ Short acting (human insulin): Humulin R and Actrapid
- ▶ Intermediate acting (human insulin): Humulin N and Insulatard
- ▶ Long acting (human insulin): Humulin L and Ultratard
- ▶ Long acting (analogue): Lantus

Insulin Preparations

- ▶ NPH insulin - Neutral Protamine Hagedorn / Isophane
 - ▶ insulin treated with protamine and zinc @ neutral pH (7.2)
 - ▶ protamine is a basic protein that readily complexes with insulin and zinc to yield particles that slowly dissolve in body fluids
 - ▶ forms a fine precipitate of protamine zinc insulin
 - ▶ onset of 1-2 hrs, peak of 6-12 hrs, duration of 18-24 hrs
- ▶ Glargin Insulin (Lantus®)
 - ▶ pH 4 solution
 - ▶ A substituted form of insulin in which Asp at position 21 is replaced by Gly
 - ▶ and two Arg residues are added to the C-terminus of the B-chain
 - ▶ this insulin analog has low solubility at neutral pH
 - ▶ upon sc injection the solution is neutralized, leading to microprecipitate formation
 - ▶ results in slow release over 24 h with no pronounced peak
 - ▶ can be used as basal insulin injection on a once daily injection basis

Insulin Preparations

- ▶ Regular insulin
 - ▶ crystalline zinc insulin; 1 mg = 27.5 units
 - ▶ Crystalline (uncomplexed) insulin may be given intravenously
- ▶ Lispro insulin (Humalog®)
 - ▶ structurally modified human recombinant insulin
 - ▶ change eliminates the ability to dimerize
 - ▶ results in faster absorption rates
 - ▶ administer 0 - 15 min pre-meal vs. 30 - 45 min
 - ▶ peak action in 0.5 - 1 h vs. 1.5 - 2 h
- ▶ Insulin Aspart (Novolog®)
 - ▶ structurally modified human recombinant insulin
 - ▶ change eliminates the ability to dimerize/hexamelize
 - ▶ results in faster absorption rates - similar to Lispro
- ▶ Glulisine Insulin (Apidra®)
 - ▶ structurally modified recombinant human insulin
 - ▶ change eliminates the ability of Glulisine insulin
 - ▶ to dimerize or form zinc hexamers
 - ▶ results in faster absorption rates - similar to modified insulins

Insulin Preparations

- ▶ Detemir Insulin (Levimir®) fatty acid derived, long-acting
 - ▶ fatty-acid moiety is attached to Lys-29, that is now the last amino acid of the B chain
 - ▶ lipid moiety responsible for slow absorption in subcutaneous space
 - ▶ Once in the circulation, detemir is bound to albumin, slowing its transport across the endothelium
 - ▶ Less weight gain in type 2 diabetics than seen with NPH-insulin
 - ▶ Not a 24 hr. formulation; requires 2 injections in type 1 diabetics may serve as a basal insulin for type 2 diabetics with once daily injection
 - ▶ No weight gain compared to NPH treatment - early data suggest the “weight neutrality effect” may be due to FA, enabling more efficient crossing of BBB, enhancing insulin's appetite regulatory effect

Basics of insulin therapy 5.

Treatment schemes with insulin.

- ▶ Intensive conservative regimens
- ▶ 3x short actin insulin (before the main meals) +1x intermediate acting insulin (at bedtime)
- ▶ 3x ultrashort acting insulin (before the main meals) + 2x intermediate acting insulin (in the morning and at bedtime)
- ▶ Conservative regimens
- ▶ 2x premixed insulin (before breakfast and dinner)
- ▶ Insulin pump therapy
- ▶ With ultra short acting insulin
- ▶ Continuously pumped low dose of the ultrashort acting insulin subcutaneously (for replacement of basic insulin secretion) with increased velocity of infusion before meals (for replacement of prandial insulin secretion)

Insulin pump



How does the insulin get into your body?

► Insulin in the blood

Flexible tubing delivers insulin from the pump reservoir to the infusion set

Insulin pump

A tiny tube called a cannula is inserted under your skin to deliver insulin



Insulin premixes

- ▶ a. Mixtures of Lente insulins provide an insulin with peak and duration which is the average of insulins mixed together
- ▶
- ▶ b. Mixtures of regular and intermediate or long-acting insulins may result in complexing of regular insulin by excess protamine in NPH.

Humalog®

Insulin lispro injection
(rDNA origin)

Humulin® R

REGULAR
insulin human injection, USP
(rDNA origin)

Humulin® N

NPH
human insulin
(rDNA origin)
isophane suspension

Humulin® L

LENTEN[®]
human insulin
(rDNA origin)
zinc suspension

Humulin® U

ULTRALENTE[®]
human insulin
(rDNA origin)
extended zinc suspension

Humulin® 70/30

70% human insulin
isophane suspension
30% human insulin injection
(rDNA origin)

Humulin® 50/50

50% human insulin
isophane suspension
50% human insulin injection
(rDNA origin)

Now available in
the Pen delivery system

Now available in
the Pen delivery system

Now available in
the Pen delivery system

Insulin Delivery Systems

- ▶ Insulin Syringes and Needles
 - ▶ Disposable plastic syringes with needles attached are available in 1-mL (100 units), 0.5-mL (50 units), and 0.3-mL (30 units) sizes.
- ▶ Insulin Pens
 - ▶ Cartridges of insulin lispro, insulin aspart, and insulin glargine
 - ▶ prefilled pens
 - ▶ for regular insulin (U100, U500), insulin lispro, insulin aspart, insulin glulisine, insulin detemir, insulin glargine, insulin degludec, NPH, 70%,
 - ▶ NPH/30% regular, 75% NPL/25% insulin lispro,
 - ▶ 50% NPL/50%, insulin lispro,
 - ▶ 70% insulin aspart protamine/30% insulin aspart, and
 - ▶ 70% insulin degludec/30% insulin aspart

Insulin Delivery Systems

- ▶ Continuous Subcutaneous Insulin Infusion Devices (CSII, Insulin Pumps)
 - ▶ External open-loop pumps for insulin delivery.
- ▶ Inhaled Insulin
 - ▶ dry powder formulation of recombinant regular insulin
 - ▶ small, single-use device, color coded cartridge
 - ▶ delivering 4, 8 or 12 units immediately before the meal.
 - ▶ pharmacokinetic studies: peak levels are reached in 12–15 minutes and decline to baseline in 3 hours
 - ▶ Pharmacodynamic studies: median time to maximum effect with inhaled insulin is approximately 1 hour

Adverse effects of insulin

- ▶ lipodystrophy
- ▶ insulin allergy
- ▶ antibody-related insulin resistance
- ▶ prolonged circulation of injected insulin may contribute to hypoglycemia
- ▶ immune complex deposition

The clinical picture of type 1 diabetes mellitus

- ▶ The patient cannot survive without insulin replacement (insulin dependent diabetes)
- ▶ At diagnosis the patients are mostly young, with a major peak between 12 and 15 years of age. But over 10% of diabetic subjects over 65 years require insulin. T1DM can be manifested at any age.
- ▶ T1DM usually presents acutely with hyperglycaemic symptoms (polyuria, polydipsia, weight loss) and tiredness.
- ▶ Nausea, vomiting and drowsiness usually denote impending ketoacidosis.
- ▶ Minor symptoms include cramps, blurred vision and superficial infections.
- ▶ Subtle abnormalities of insulin secretion and glucose tolerance can be detected during the prediabetic phase. In this phase antibodies against beta cell antigens are found (ICA, GADA, anti-IA2).
- ▶ Some T1DM patients experience a temporary remission after starting the insulin treatment: „honeymoon period”. Good glycaemic control with low insulin doses are characteristic for this period. This is due to the correction of hyperglycaemia, as hyperglycaemia itself directly damages the beta-cells („glucotoxicity”). Remission ends when continuing autoimmune damage has destroyed a critical mass of beta-cells.
- ▶ Long standing T1DM patients are susceptible to microvascular complications specific to diabetes, and to nospecific macrovascular disease.
- ▶ Mortality in T1DM is increased 4- to 7-fold over the matched nondiabetic population. The main causes of death are the nephropathy and coronary heart disease.
- ▶ A proportion of T1DM patients survive without significant complications for many years.

Clinical forms of diabetes mellitus

- ▶ Primary diabetes mellitus manifested in adulthood
- ▶ Polygenic type 2 diabetes mellitus
- ▶ MODY (maturity onset diabetes in the young) - mutation of the genes of glucokinase and hepatic nuclear factor alpha 1-4
- ▶ MIDD (maternally inherited diabetes and deafness) - mitochondrial gene mutation
- ▶ Mixed type 1 and type 2 diabetes mellitus
- ▶ LADA (Latent Auto-Immune Diabetes of the Adult)
- ▶ Type 1 diabetes mellitus
- ▶ Gestational diabetes mellitus (GDM)
- ▶ Classification based on the clinical picture is not always possible.

The clinical picture of type 2 diabetes mellitus

- ▶ T2DM denotes diabetic patients who can survive long term without insulin replacement, although many receive insulin to improve their glycaemic control.
- ▶ Prevalence if T2DM is about 2-3%, but is extremely common in certain communities (50% of pima indians in the USA).
- ▶ Patients are mostly older and obese and present with insidious hyperglycaemic symptoms. Many cases are diagnosed incidentally or because of the presence of diabetic complications.
- ▶ Specific microvascular complications are less common in T2DM compared to T1DM. However retinopathy (especially with maculopathy rather than proliferative changes), nephropathy and neuropathy all occur.
- ▶ T2DM carries a high risk of large vessel atherosclerosis, commonly associated with hypertension, hyperlipidaemia (especially hypertriglyceridaemia) and obesity. Myocardial infarction is also common and accounts for 60% of deaths.
- ▶ T2DM is not „mild diabetes”: overall mortality is increased 2-3 fold and life expectancy reduced by 5-10 years compared to the nondiabetic population.

Some important statistics concerning T2DM

- ▶ Very common - 75% of all diabetic patients
- ▶ Disease of ageing - most patients are over 60 years of age
- ▶ Obesity common - two thirds are overweight
- ▶ Genetic factors - 40% of the patients have family history of T2DM
- ▶ Male predominance - 3:2 male excess

Characteristics of the metabolic syndrome

- ▶ Insulin resistance
- ▶ Hyperinsulinaemia
- ▶ Central obesity
- ▶ Glucose intolerance and T2DM
- ▶ Hypertension
- ▶ Dyslipidaemia (elevated triglyceride and decreased HDL cholesterol)
- ▶ Abnormal endothelial functions
- ▶ Procoagulant state
- ▶ Accelerated arteriosclerosis
- ▶ Hyperuricaemia

Aims of physical exercise

- ▶ In T1DM:
 - ▶ maintenance of the patient's fitness.
 - ▶ Elimination of the „down phenomenon” in the morning and in the afternoon.
- ▶ In T2DM:
 - ▶ regain of ideal body weight.
 - ▶ Decrease of insulin resistance.
 - ▶ Transformation of T2DM to IGT/IFG,
 - ▶ transformation of IGT/IFG to normal glucose tolerance.

Causes of insulin resistance

- ▶ Abnormal β-cell secretory product
- ▶ Abnormal insulin molecule
- ▶ Incomplete conversion of proinsulin to insulin
- ▶
- ▶ Circulating insulin antagonists:
 - ▶ Elevated levels of counter regulatory hormones, e.g.,
 - ▶ growth hormone, cortisol, glucagon, or catecholamines
 - ▶ Anti-insulin antibodies
 - ▶ Anti-insulin receptor antibodies
- ▶
- ▶ Target tissue defects
- ▶
- ▶ Insulin receptor defects
- ▶
- ▶ Post receptor defects*

Causes of insulin resistance

- ▶ Other categories of abnormal glucose metabolism:
- ▶ Impaired glucose tolerance (IGT)
- ▶ Gestational diabetes mellitus (GDM)
- ▶ Previous abnormality of glucose tolerance (Prev AGT)
- ▶ Potential abnormality of glucose tolerance (Pot AGT)
- ▶ (latent diabetes)
- ▶ Steroid diabetes

- ▶ Nonketotic Hyperosmolar Coma (Type 2 = iatrogenic)
- ▶ glucocorticoids most common cause
- ▶ also induced by drugs that inhibit insulin secretion e.g., b-blockers, diazoxide

Drugs Which May Affect Glycaemic Control

- ▶ ACE Inhibitors
 - ▶ ↓ glucose by improving insulin sensitivity
- ▶ Alcohol
 - ▶ ↓ glucose by reducing hepatic glucose production
- ▶ Diuretics
 - ▶ ↑ glucose by ↑ insulin resistance
- ▶ Glucocorticoids
 - ▶ ↑ glucose by impairing insulin action
- ▶ Phenytoin
 - ▶ ↑ glucose by ↓ insulin secretion
- ▶ Beta blockers
 - ▶ May ↓ by ↓ insulin secretion
- ▶ Nitrates
 - ▶ Insulin sensitization

Basics of treatment of diabetic ketoacidosis and nonketotic hyperosmolar coma

- ▶ Absolute deficiency of the body for water and electrolytes (NaCl and K)
- ▶ Absolute deficiency of insulin
- ▶ Absolute deficiency of glucose
- ▶ Absolute deficiency of glycogen stores

- ▶ 1000 ml of physiologic saline hourly
- ▶ 4-8 U short acting insulin /hour iv (with a pump)
- ▶ 10 ml of 10% KCl in intravenous infusion /hour
- ▶ 5% glucose infusion if blood sugar level decreases to 10 mmol/l

SOM

► **Mechanism of Action:**

- In the pancreatic b cell, somatostatin receptors are coupled to voltage-gated calcium channels;
- Somatostatin blocks the channel - reducing Ca^{2+} influx & inhibiting insulin secretion

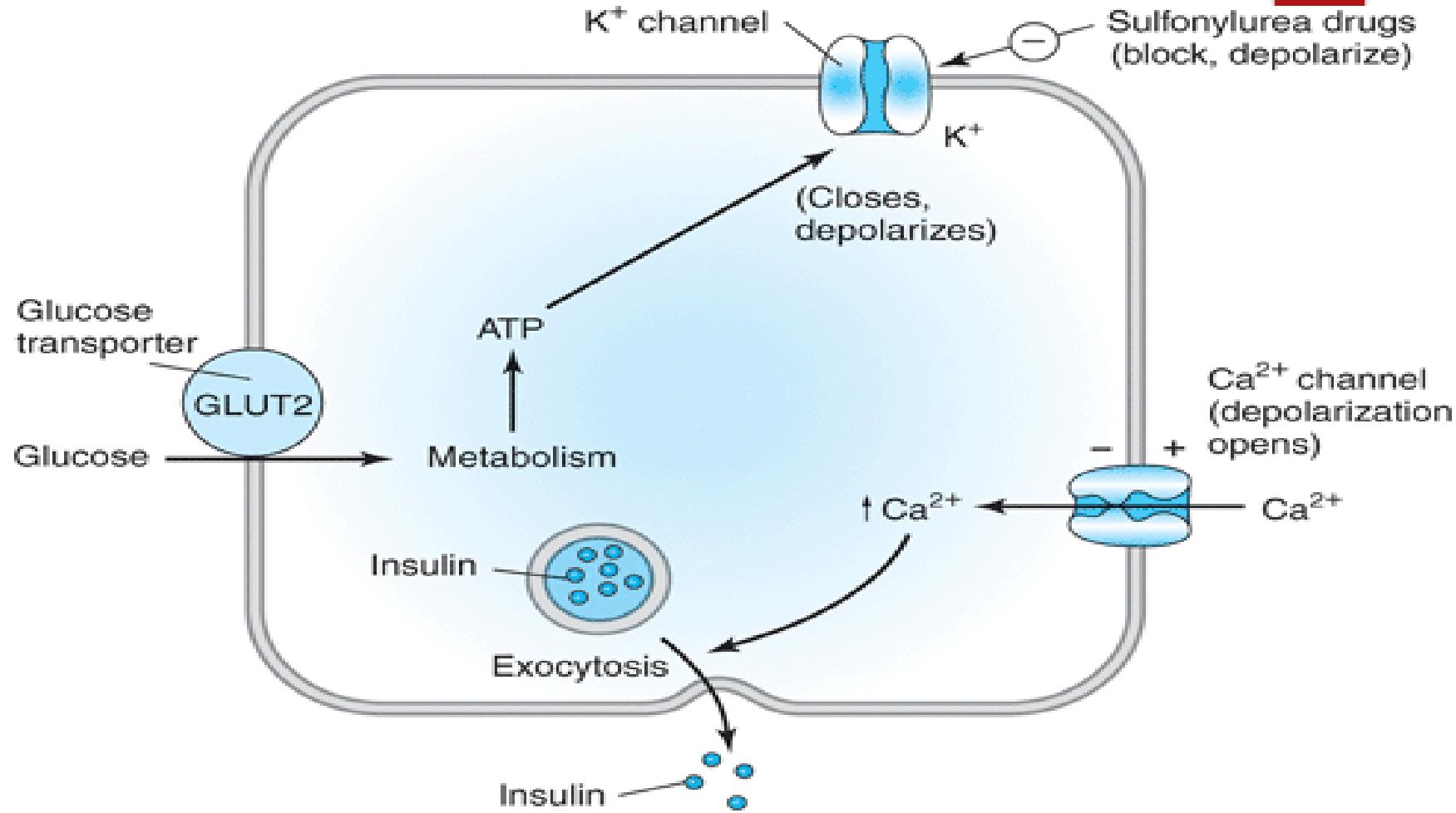
Peroral antidiabetic drugs



Peroral antidiabetic drugs (1)

Sulphonylureas

- ▶ Enhance the insulin release from the pancreatic beta-cell.
- ▶ The drug closes the ATP-dependent K channel in beta-cell, this is followed the depolarisation of the cell membrane followed by the opening of the Ca channel. The latter is the stimulus of insulin release.
- ▶ Hypoglycaemia can be induced by sulphonylureas.
- ▶ Primary and secondary sulphonylurea resistance: ~20 – 20%
- ▶ Only for treatment of T2DM
- ▶ Glibenclamid, glipizid, gliklazid, glimepirid
- ▶ Gilemal, Minidiab, Diaprel, Amaryl
- ▶ Newer very short acting drugs:
- ▶ glinides (Novonorm, Starlix) originating from the non-sulphonyl root of glibenclamid. = postprandial blood glucose regulators. To be taken at the start of the meal.



Generic and (Trade Names)	Tablet Size (mg)	Dosage (mg) Usual	Dosage (mg) Range	Daily Dose	Duration of Action (hrs)
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First Generation Drugs

1.	Tolbutamide (Orinase)	500	1500	500 - 2000	2 - 3	6 - 10
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Inactivated by liver through oxidation to carboxytolbutamide, excreted by kidney and may give false positive test for proteinuria.

2.	Acetohexamide (Dymelor)	250	750	250 - 1500	1 - 2	10 - 20
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Metabolites formed by hydroxylation in liver; L-hydroxyhexamide is most active component.

3.	Tolazamide (Tolinase)	100	500	100 - 1000	1 - 2	12 - 24
		250				
		500				

Metabolized by liver to six compounds, three of which have hypoglycemic activity and are excreted by the kidney.

SU- second gen.

Generic and (Trade Names)	Tablet Size (mg)	Dosage (mg.) Usual Range	Daily Dose	Duration of Action (hrs.)
Second Generation Drugs				
5. Glyburide (Micronase or Diabeta)	1.25, 2.5 5.0, 10	10 1.25 - 20	1 - 2	12 - 24
6. Glipizide (Glucotrol)	5 10	20 2.5 - 40	1 - 2	12 - 24

These compounds are metabolized by liver, partially excreted into bile, and the remainder excreted by the kidney.

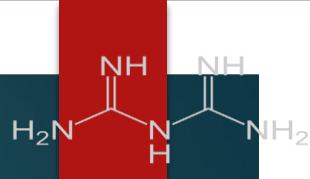
Glimepiride (AMARYL)

Adverse effects of SUs

- ▶ May cause hypoglycemia
 - ▶ alcohol
 - ▶ monoamine oxidase inhibitors, phenylbutazone, clofibrate, bishydroxycoumarin, sulfonamides
 - ▶ beta blockers - all lower blood sugar
 - ▶ all enhance effects
- ▶ Weight gain, allergic reactions, pruritus, rash, hepatotoxicity, and photosensitivity are possible
- ▶ Hyponatremia and water retention - non b cell effects

Meglitinides

- ▶ Meglitinides - Non-sulfonylurea oral hypoglycemic agents
- ▶ Repaglinide (Prandin®/NovoNorm®)
 - ▶ an insulinotropic agent stimulates insulin secretion by pancreatic beta cells
 - ▶ fast acting - short duration, administered before meals - from 30 min prior, right up to meal time - unlike sulfonylureas (30 min)
 - ▶ for type 2 diabetics for
 - ▶ use in controlling postprandial
 - ▶ glucose excursions.
 - ▶ mechanism of action:
 - ▶ causes closure of ATP-dependent K⁺-channels.
- ▶ In general, these are minimal, can cause hyperglycemia, hypoglycemia
- ▶ Repaglinide has recently been contraindicated in patients taking gemfibrozil due to the risk of severe/prolonged hypoglycemia
- ▶ Also can occur with Clarithromycin, itraconazole, ketoconazole, MAOIs



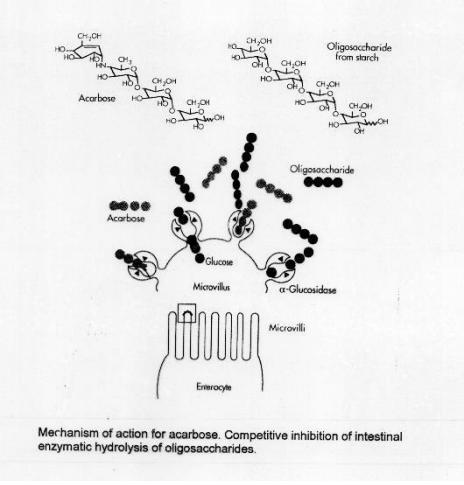
Biguanides

- ▶ Improve insulin sensitivity in the liver, enhance insulin independent glucose disposal (muscles)
- ▶ Hepatic gluconeogenesis is inhibited.
- ▶ Activates AMP-activated protein kinase (AMPK) → inhibitory effect on the production of glucose by liver cells
- ▶ Weight loss can be induced by biguanides.
- ▶ Beneficial effect on plasma lipids.
- ▶ Lactic acidosis can be induced (avoid alcohol, feverish diseases, renal-, liver insufficiency, left heart failure, x-ray with contrast material).
- ▶ No hypoglycaemia.
- ▶ Only in T2DM
- ▶ Contraindicated in MIDD (Maternally inherited diabetes and deafness).
- ▶ Only metformin (Merckformin, Adimet, Metfogamma)
- ▶ Riomet (liquid cherry flavored Metformin)

Peroral antidiabetic drugs

Alpha-glucosidase inhibitors.

- ▶ Inhibition and delay of the digestion of disaccharides, dextrin, starches in the gut.
- ▶ inhibit the intestinal α -glucosidase
- ▶ Decrease postprandial hyperglycaemia.
- ▶ Bacterial decomposition of undigested carbohydrates causes the side effects: flatulence, abdominal distension, diarrhoea.
- ▶ Mainly in T2DM but can be used in T1DM, too.
- ▶ Glukobay (Acarbose)



Peroral antidiabetic drugs 4. Insulin sensitizers

- ▶ Peroxisoma proliferator activated receptor agonists (PPAR-gamma agonists)
- ▶ Thiazolidindions or glitazons
- ▶ They decrease glucose and insulin levels, that is improve insulin sensitivity.
- ▶ They decrease triglyceride level in the serum and hepatic and adipose tissue NEFA production.
- ▶ Side effects:
 - ▶ haemodilution, oedema formation, liver failure, heart failure, ischemic heart disease
- ▶ Rosiglitazon (Avandia) (withdrawn, heart attack), Pioglitazon (Actos), Rivotril

Dual PPAR agonists (α , γ)

- ▶ GLITAZARS
- ▶ Aleglitazar (phase III clinical trials)
- ▶ Muraglitazar (Pargluva) – discontinued
- ▶ Tesaglitazar – discontinued
- ▶ Saroglitazar (Lipaglyn)
- ▶ Agonist action at PPAR α lowers high blood triglycerides, and agonist action on PPAR γ improves insulin resistance and consequently lowers blood sugar
- ▶ Reduce fasting plasma glucose and HBA1c
- ▶ approved for use in India

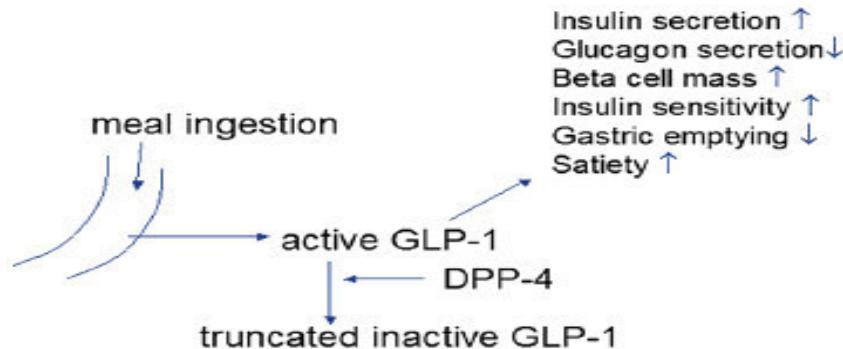
Incretins

GIP: glucose-dependent insulinotropic polypeptide

42 AA, produced by the K cells in duodenum

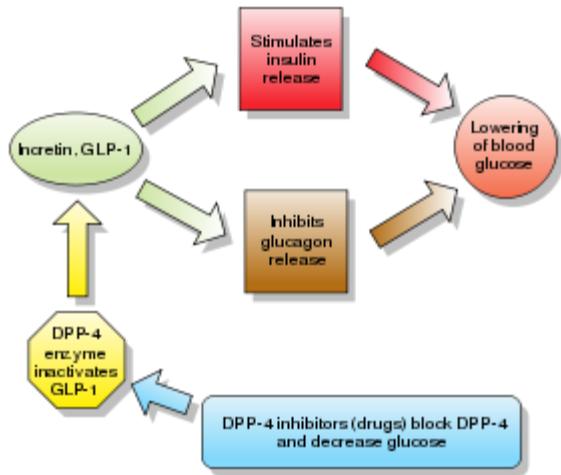
GLP-1: glucagon-like peptide 1

produced by the L cells in the distal part of small intestine



Incretin effect

Incretins



Functions of GLP-1

- ▶ Decreases glucagon secretion from the pancreas
- ▶ Increases insulin secretion from the pancreas
- ▶ Increases Beta cell mass and insulin gene expression
- ▶ Reduces apoptosis of Beta cells
- ▶ Increases satiety – decreases food intake
- ▶ Inhibits acid secretion and gastric emptying
- ▶ Activates hepatic vagal afferents
- ▶ Improves myocardial and endothelial function
- ▶ Reduce high blood pressure!!!
- ▶ Evokes Preconditioning!!!
- ▶ Improves pump function of the heart!
- ▶ Neuroprotection (e.g. in Parkinson's disease)

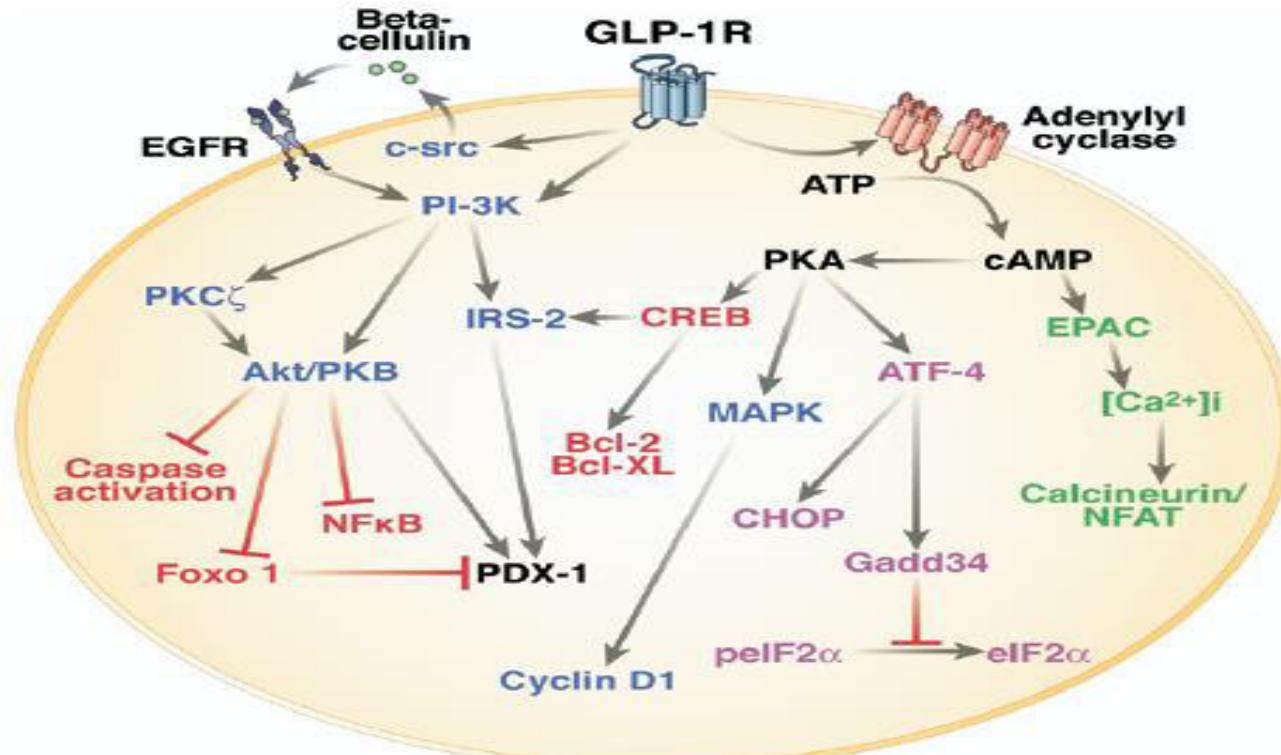
GLP-1 receptor activation in beta cells

β -cell proliferation
and neogenesis

(PK: protein kinase)

Inhibition of
apoptosis

(CREBP:
cAMP response
element binding
protein)



Insulin
Biosynthesis

(EPAC: ex –
change pro-
tein activa-
ted by cAMP)

Glucagon-like peptide-1 (GLP-1) receptor agonists – GLP-1 analogues

- ▶ Exenatide (BYETTA, BYDUREON)
- ▶ Liraglutide (VICTOZA)
- ▶ Lixisenatide (LYXUMIA)
- ▶ Albiglutide (EPEZAN) discontinued
- ▶ Dulaglutide (TRULICITY)

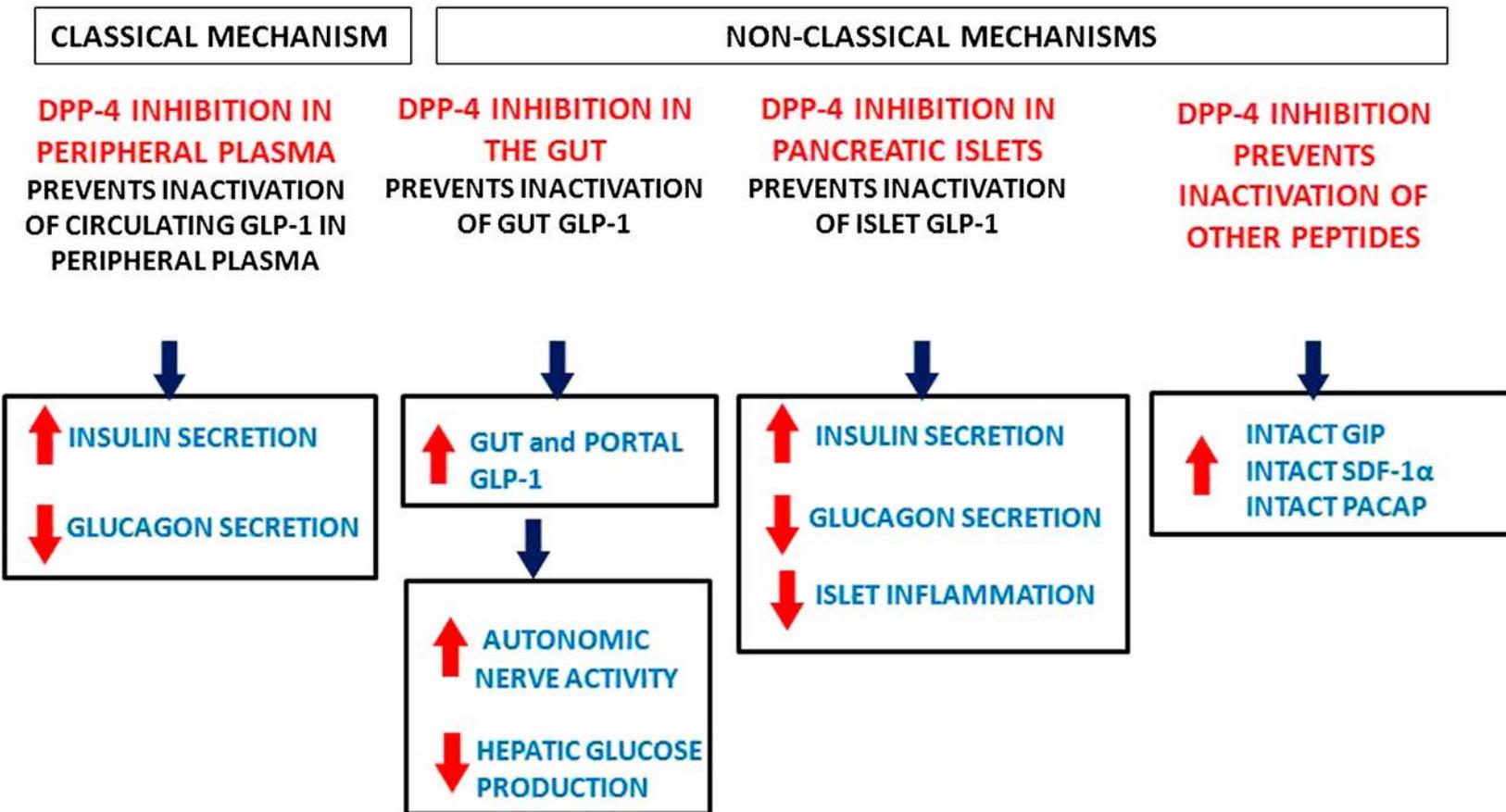
Exenatide - (Byetta®)

- ▶ glucagon-like peptide-1 (GLP-1), a member of the incretin family
- ▶ exendin-4 derivative is a 39 amino acid peptide in salivary secretions of Gila monster
- ▶ exhibits 53% sequence similarity to GLP-1; protease (DPP-4) resistant
- ▶ enhances glucose-dependent insulin secretion
- ▶ suppresses elevated glucagon secretion and slows gastric emptying
- ▶ improves glycemic control by reducing fasting and postprandial glucose concentrations in patients with type 2 diabetes
- ▶ Weight loss in the range of 2–3 kg
- ▶ administered twice daily, (subcutaneously) alone or in combination with metformin, a sulfonylurea or both - significantly reduces HbA1c
- ▶ Side Effects:
 - ▶ hypoglycemia, when taken in conjunction with a sulfonylurea,
 - ▶ GI disturbances – nausea, vomiting, diarrhea

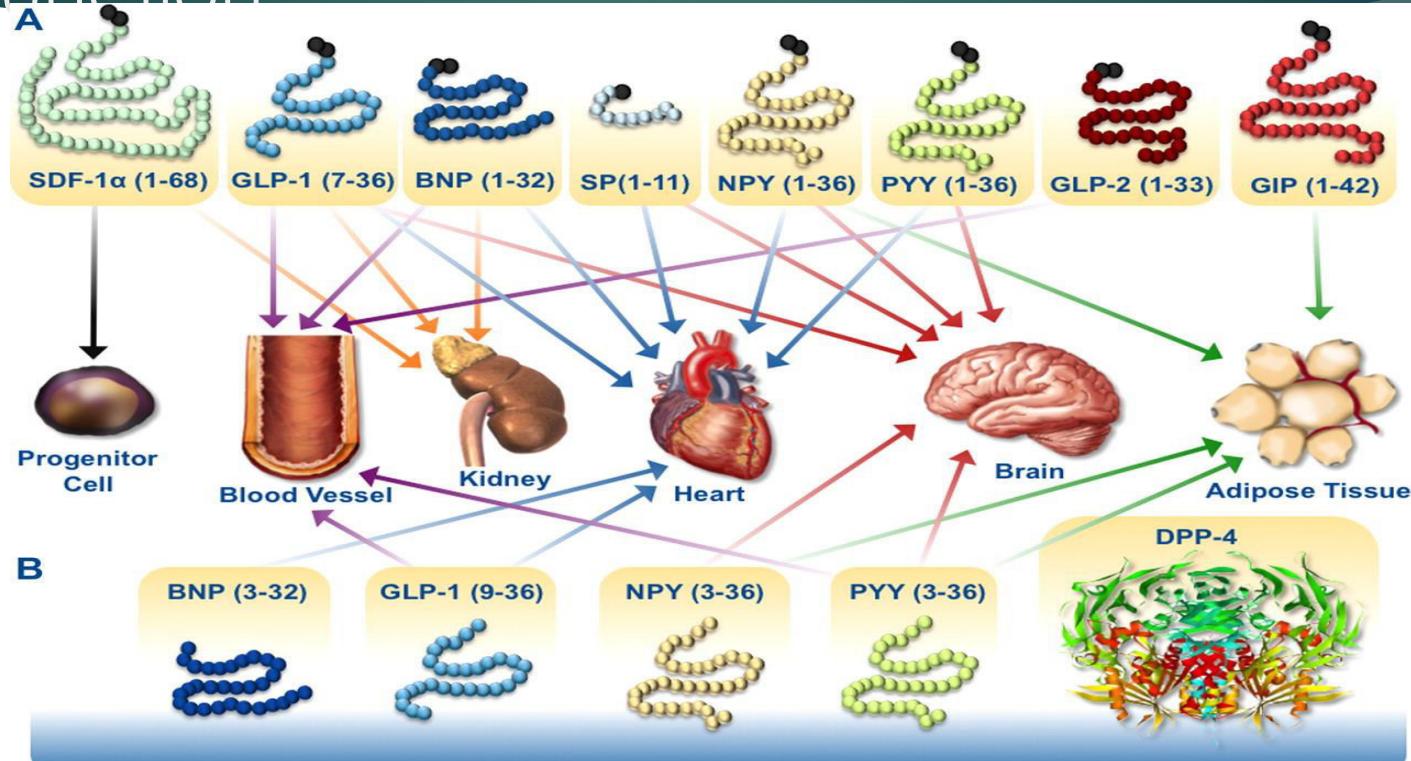
Glucagon-like peptide-1 (GLP-1) receptor agonists – GLP-1 analogues

- ▶ Liraglutide
- ▶ a soluble fatty acid-acylated GLP-1 analog.
- ▶ T1/2 ~ 12 hours, once-daily dosing
- ▶ ↓ HbA1c (0.8–1.5%) and weight loss from none to 3.2 kg.
- ▶ Dulaglutide
- ▶ two GLP-1 analog molecules covalently linked to an Fc fragment of human IgG4. The GLP-1 molecule has amino acid substitutions that resist DPP-4 action.
- ▶ The half-life of dulaglutide is about 5 days
- ▶ maximum recommended dose is 1.5 mg weekly
- ▶ Lixisenatide
- ▶ 44 amino acids, des-38-proline-exendin-4
- ▶ an autoinjector containing fourteen doses and is injected subcutaneously

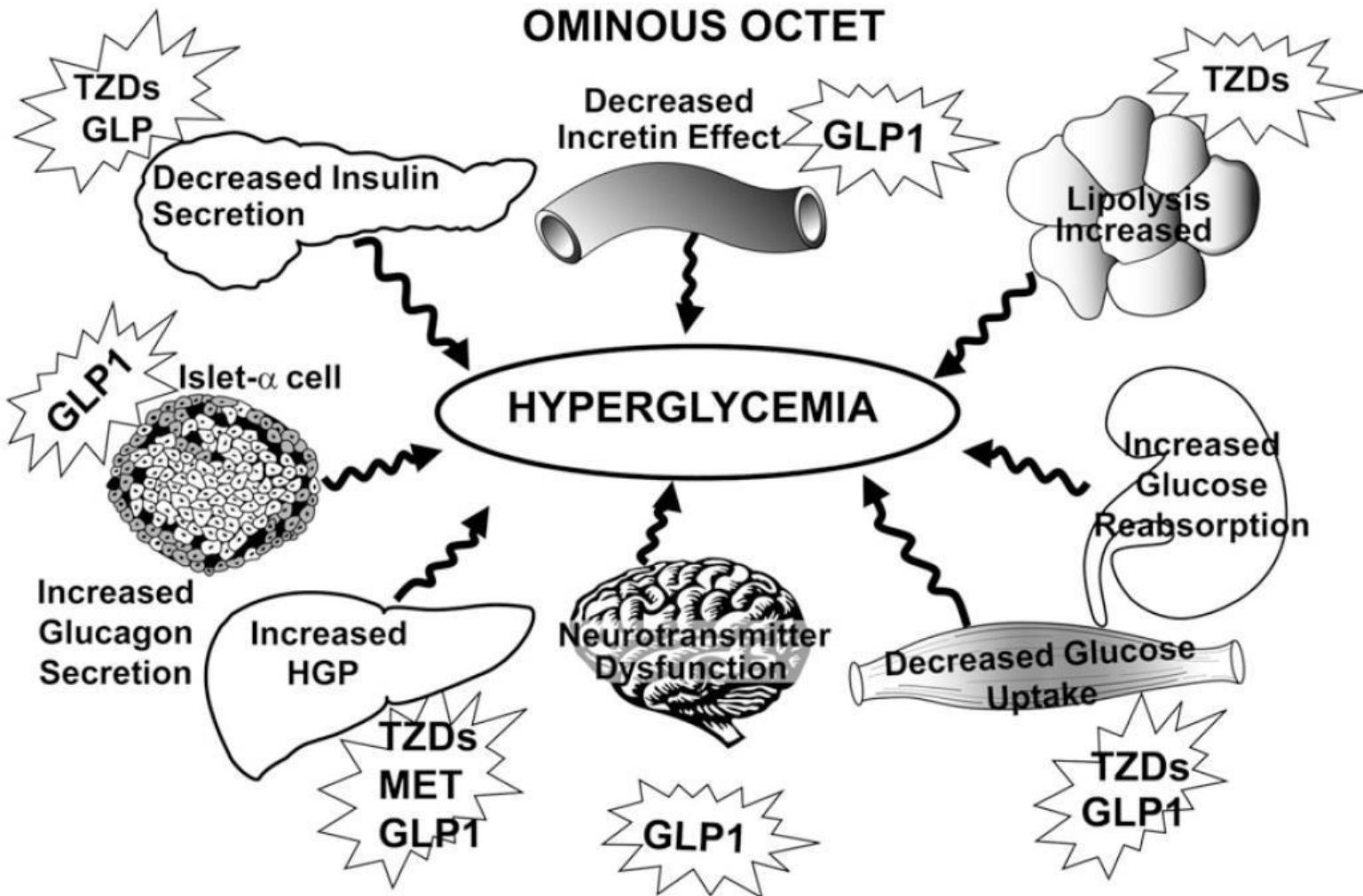
The pleiotropic mechanisms of DPP-4 inhibition



DPP-4 substrates that directly or indirectly regulate cardiovascular function



OMINOUS OCTET



DPP-4 inhibitors (gliptins)

- ▶ Sitagliptin (JANUVIA)
- ▶ Saxagliptin (ONGLYZA)
- ▶ Alogliptin (NESINA)
- ▶ Vildagliptin (GALVUS) (vildagliptin+metformin (Eucreas))
- ▶ Gemigliptin (ZEMIGO (South-Korea))
- ▶ Linagliptin (TRADJENTA/TRAJENTA)

Dipeptidyl Peptidase-4 (DPP-4) Inhibitors Sitagliptin - (Januvia®, Xelevia®)

- ▶ blocks DDP-4, a cell surface peptidase that cleaves a wide range of protein/peptide substrates
- ▶ This results in elevated levels of endogenous GLP-1 and GIP
 - ▶ Increases insulin and decreases glucagon secretion,
 - ▶ leading to better glycemic control.
- ▶ It is used as an adjunct monotherapy to diet and exercise, to improve glycemic control in patients with type 2 diabetes mellitus
- ▶ May be used in combination with metformin or a thiazolidinedione (TZD).
- ▶ Sitagliptin should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.
- ▶ Recommended dose is 100 mg once daily, with or without food, as monotherapy
- ▶ as combination therapy with metformin or a TZD or as an adjunct to diet and exercise.
- ▶ Side effects include respiratory tract infection, nasopharyngitis (cold symptoms) and headache
- ▶ Should be immediately discontinued if pancreatitis or allergic and hypersensitivity reactions occur

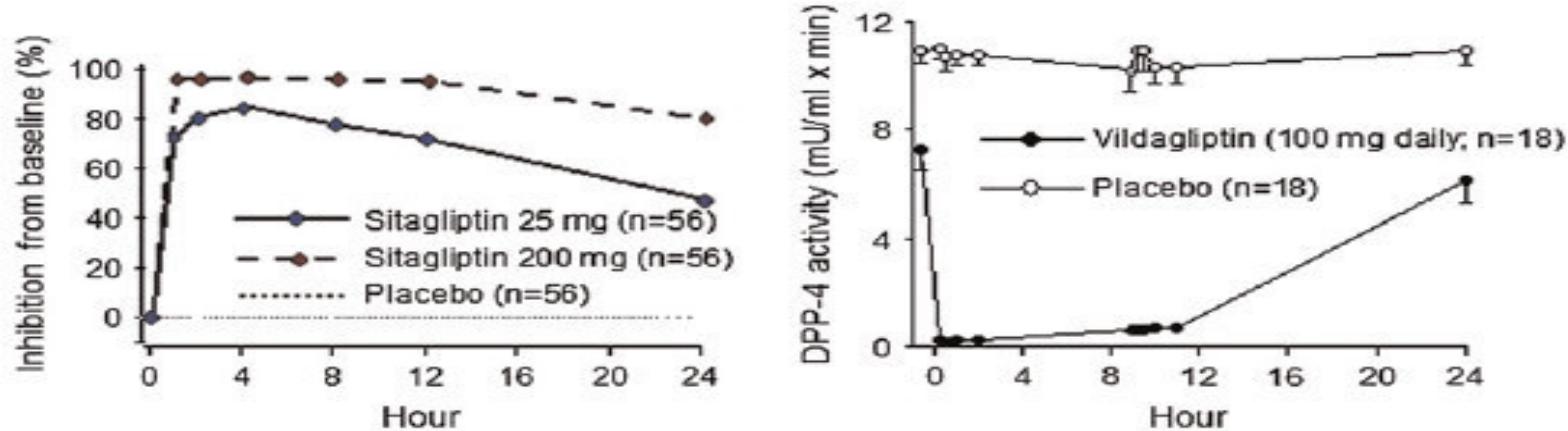


Figure 2. Inhibition by sitagliptin (left panel) and vildagliptin (right panel) on plasma dipeptidyl peptidase 4 (DPP-4) activity. Left panel shows percentage inhibition of plasma DPP-4 activity after administration of a single oral dose of sitagliptin at 25 or 200 mg or placebo in subjects with type-2 diabetes. Reproduced from Herman et al (2006, *Journal of Clinical and Endocrinological Metabolism* 91: 4612–4619) with permission. Right panel shows plasma DPP-4 activity after 4 weeks' treatment with vildagliptin or placebo in subjects with type-2 diabetes. Reproduced from Ahrén et al (2004, *Journal of Clinical and Endocrinological Metabolism* 89: 2078–2084) with permission.

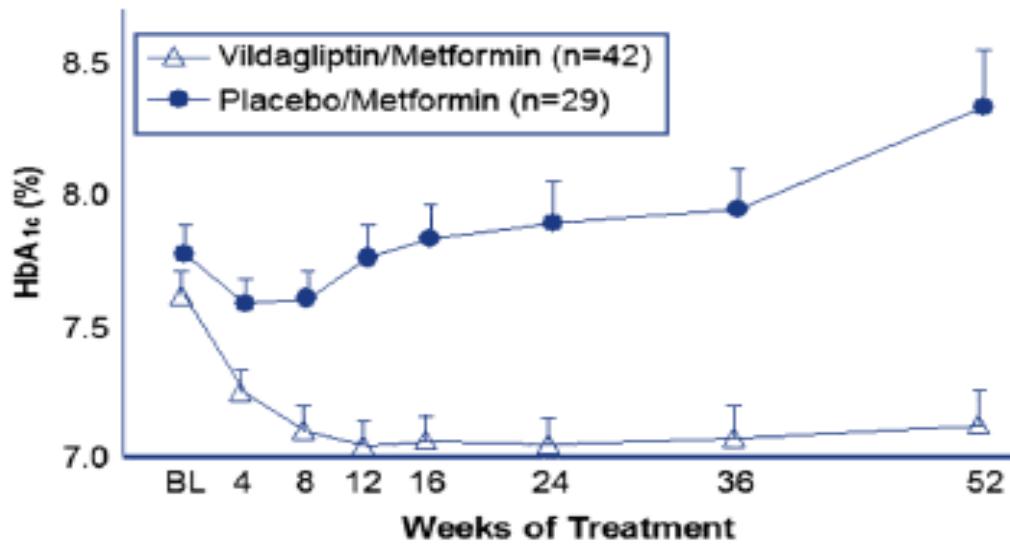
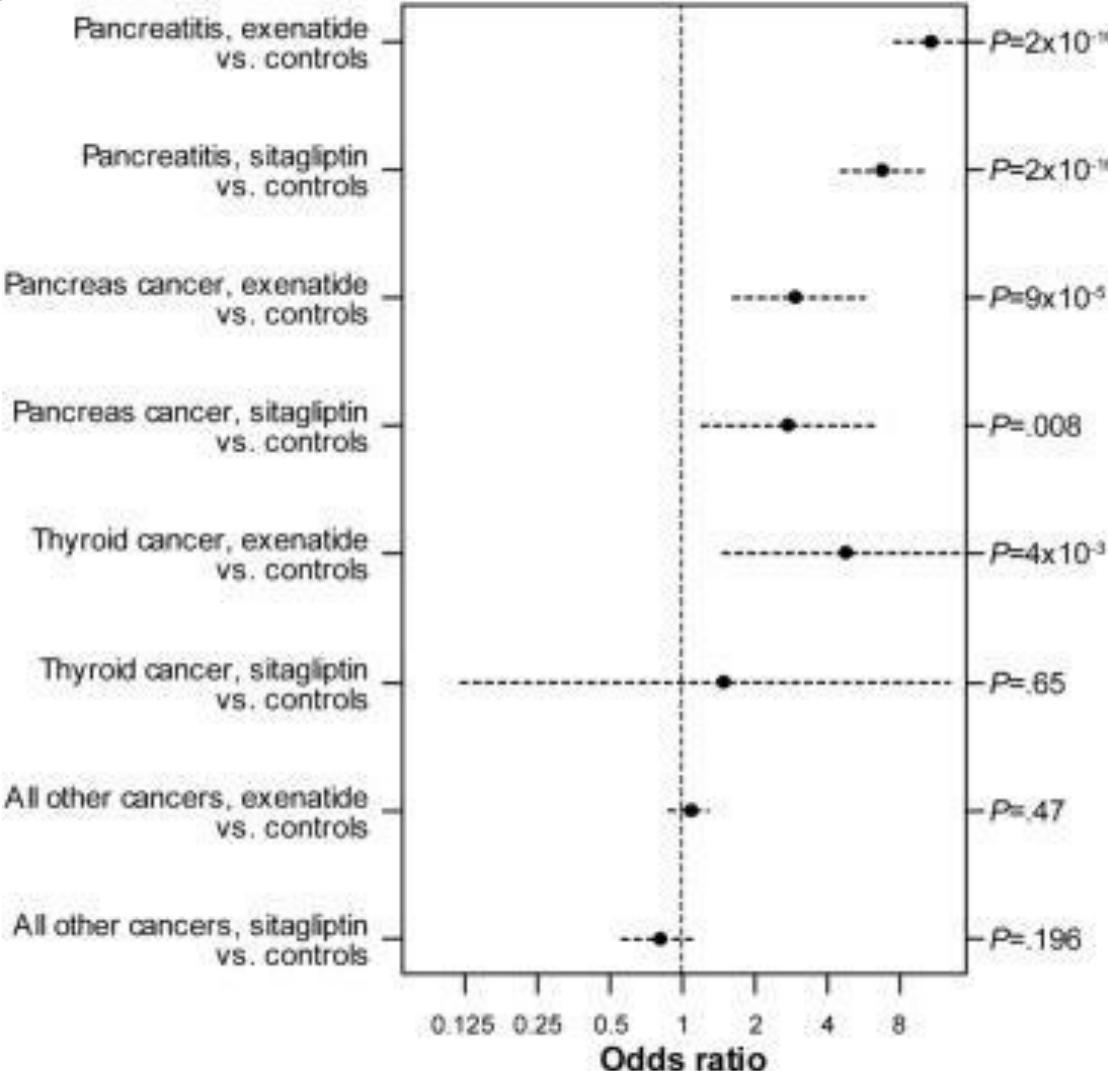


Figure 4. Time course of HbA_{1c} over 52 weeks in subjects with type-2 diabetes treated with vildagliptin (50 mg once daily) in combination with metformin ($n = 42$) versus metformin alone ($n = 29$). Reproduced from Ahrén et al (2004, Diabetes Care 27: 2874–2880) with permission.

Cancers with GLP-1's/DPP4's

With known risk for pancreatitis in Exenatide & Sitagliptin, a review also found an increased risk for pancreatic cancer with these medicines

Also thyroid cancer in Exenatide



SODIUM-GLUCOSE CO-TRANSPORTER 2 (SGLT2) INHIBITORS

- ▶ Dapagliflozin (FORXIGA)
- ▶ Sergliflozin (GSK, halted)
- ▶ Remogliflozin (GSK, halted)
- ▶ Canagliflozin (INVOCANA)
- ▶ Empagliflozin
- ▶ Tofogliflozin (CSG452)
- ▶ SGLT1
 - ▶ Located in the S3 segment of the proximal tubule.
 - ▶ Has a 2Na⁺:1Glucose co-transport ratio and is responsible for 2% of glucose reabsorption
- ▶ SGLT2
 - ▶ Is predominately located in the S1 and S2 segments of the proximal tubule.
 - ▶ Has a 1Na⁺:1Glucose co-transport ratio and is responsible for 98% of glucose reabsorption.

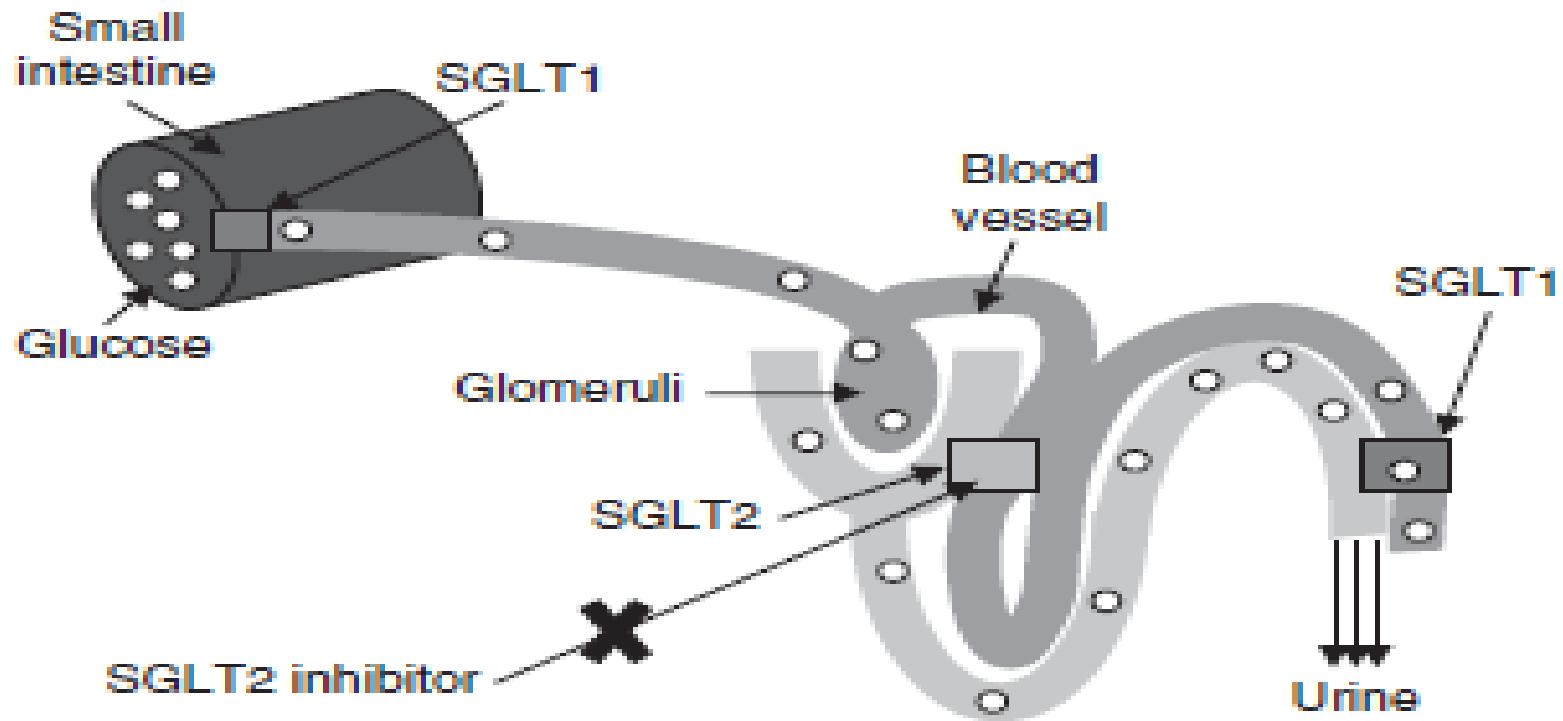
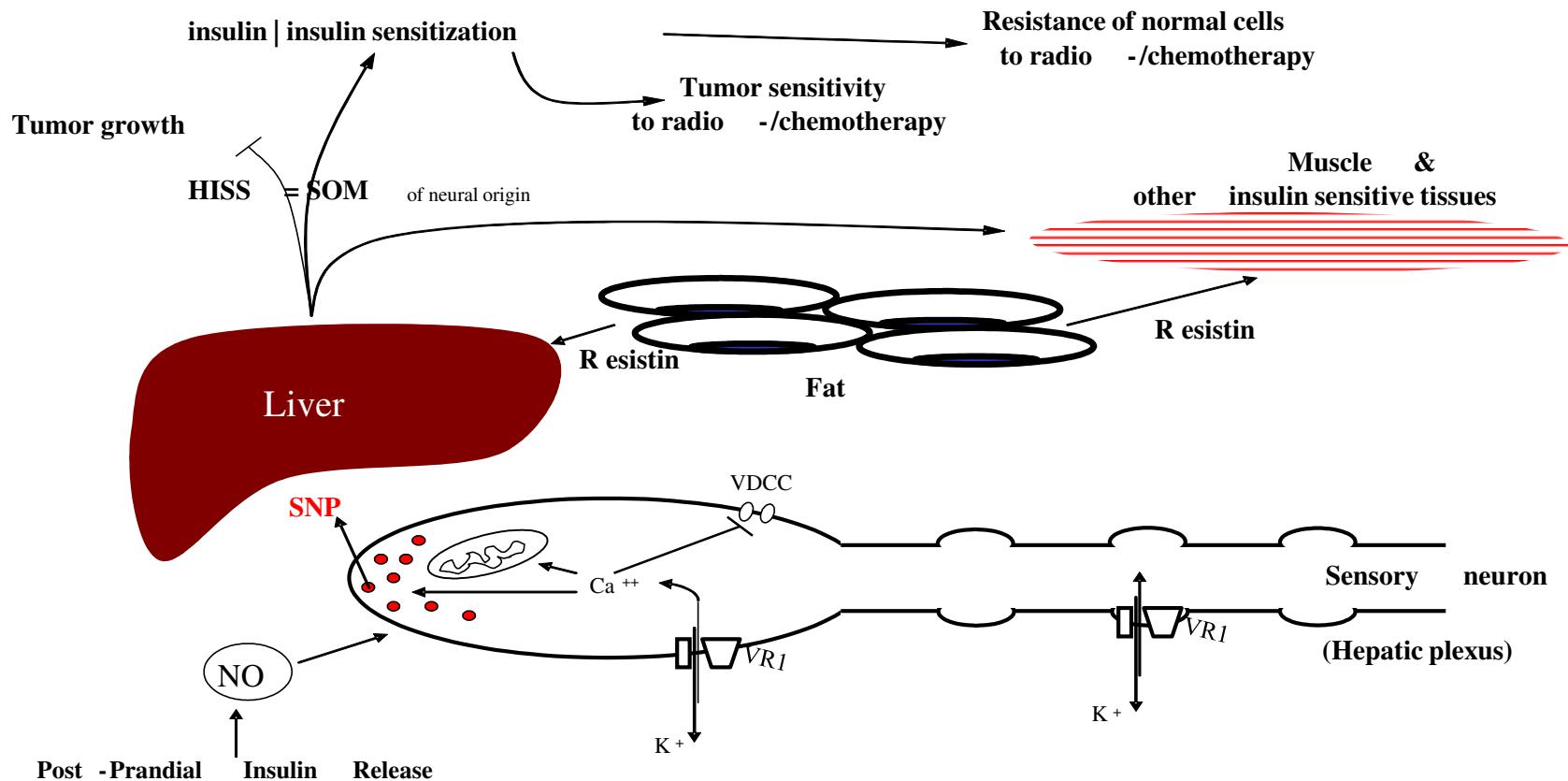


Fig. 1. Mechanism of action of sodium-glucose co-transporter 2 (SGLT2) inhibitors in type 2 diabetes mellitus.^[32] SGLT2 is responsible for 90% of the reabsorption of filtered glucose in the early proximal tubule of the nephron. Inhibition of SGLT2 transporters in the proximal tubule inhibits the reabsorption of filtered glucose, which, in turn, leads to the excretion of glucose via the urine.

Treatment scheme of T2DM

- ▶ 1. step: diet and increase of physical activity
- ▶ 2. step: reinforce diet and physical exercise
- ▶ 3. step: reinforce diet and physical exercise
- ▶ 4. step: diet, physical exercise + metformin and/or alpha glucosidase inhibitor
- ▶ 5. step: as 4. step + PPAR-gamma agonist (?)
- ▶ 6. step: as 4. step + sulphonylurea
- ▶ 7. step: insulin



Animal models of diabetes



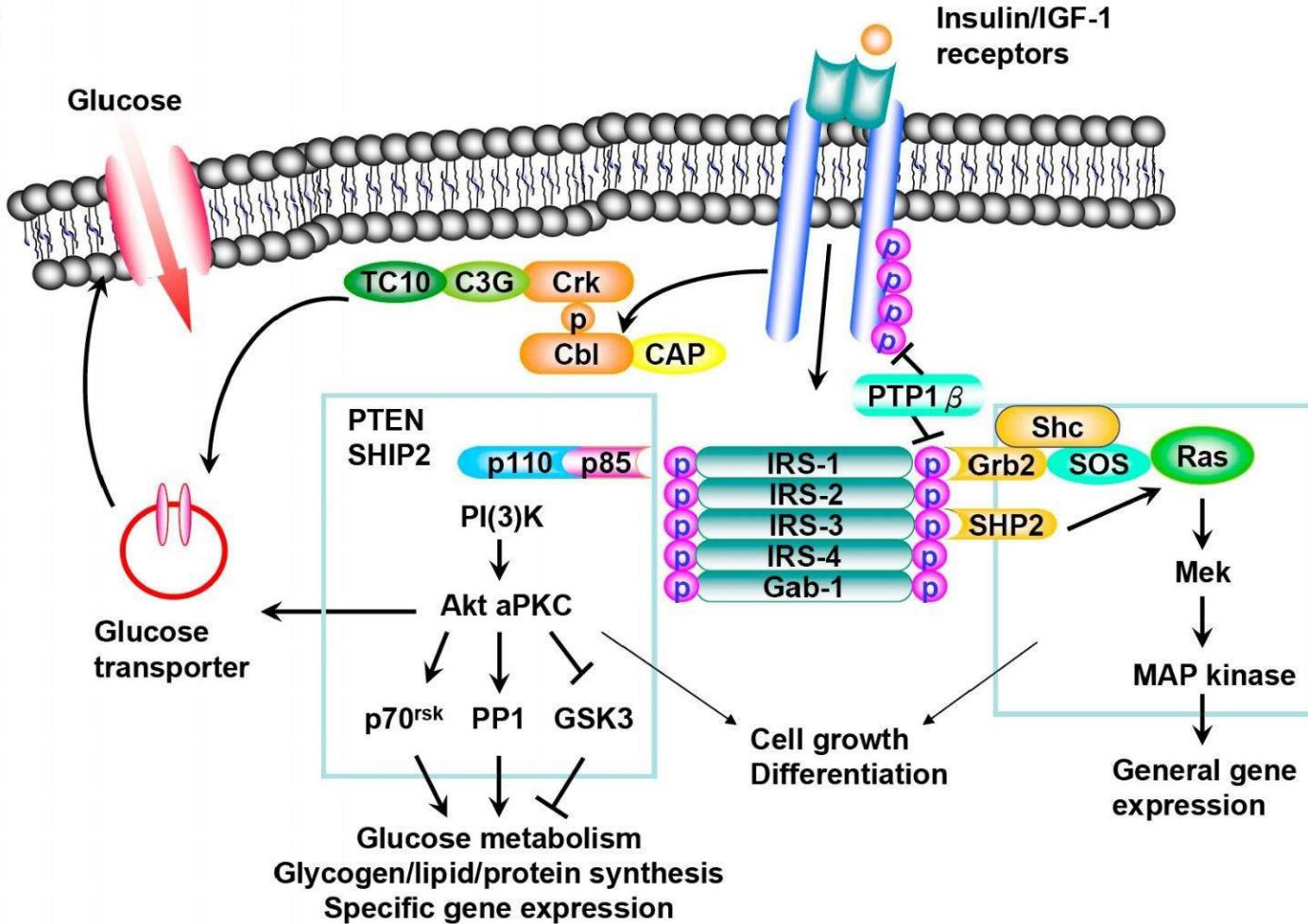
Zucker
Obese
Rat

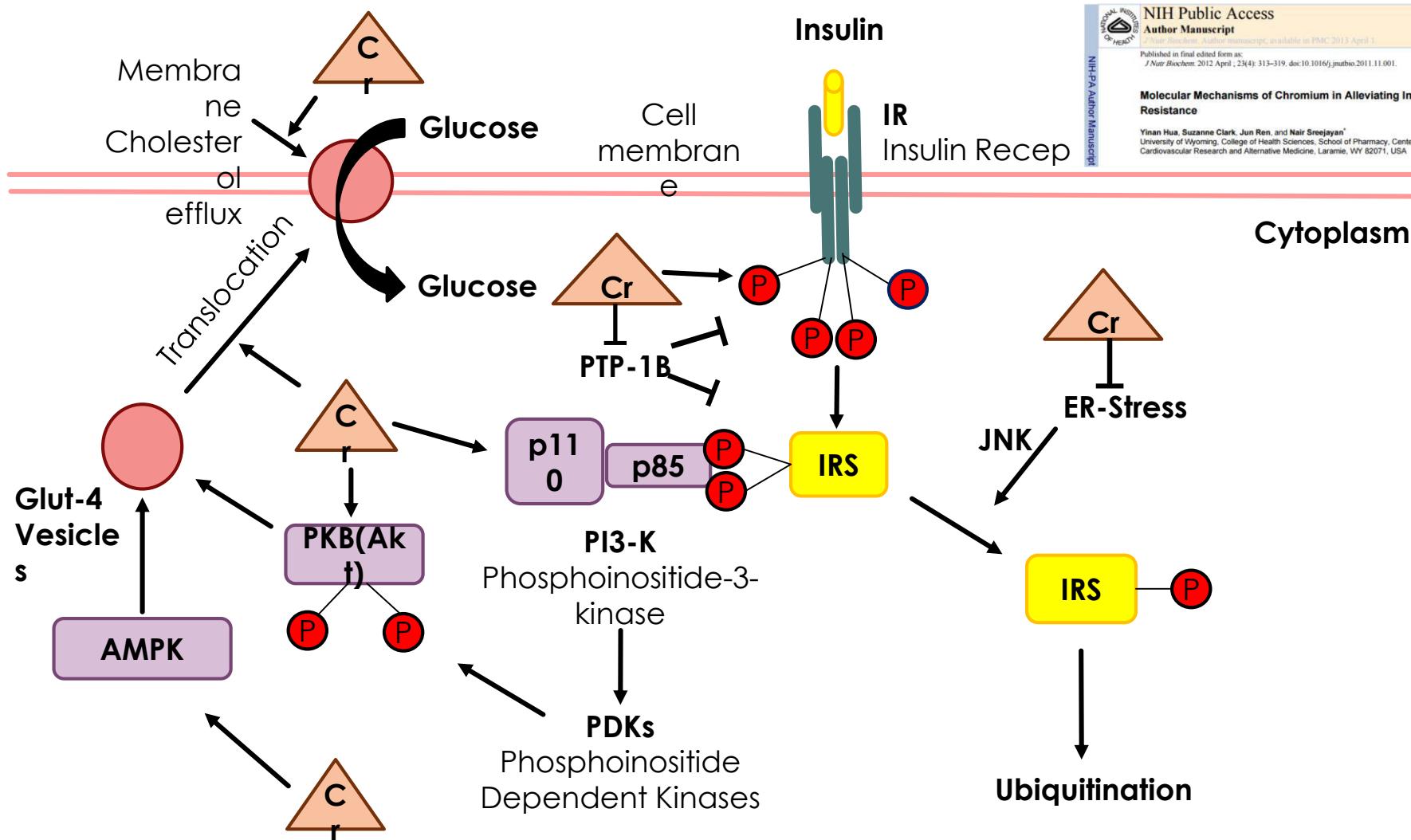


Goto-Kakizaki Rat



STZ
Rat





extracellular

insulin

Cr
channel

insulin-
receptor

apo-
chromoduline

intracellular

a

insulin



apo-
chromoduline

b

holo- /
chromoduline

c

activated
insulin-
receptor

d

Putative mechanisms by which chromium augments cellular glucose uptake

- ▶ Chromium has been shown to enhance the kinase activity of insulin receptor β , to increase the activity of downstream effectors of insulin signaling PI3-kinase and Akt and to enhance Glut4 translocation to the cell surface.
- ▶ Chromium also down-regulates PTP-1B, the negative regulator of insulin signaling and alleviates ER-stress within the cells, rescuing IRS from JNK-mediated serine phosphorylation and subsequent ubiquitination.
- ▶ Transient upregulation of AMPK by chromium leads to increased glucose uptake. Chromium mediates cholesterol efflux from the membranes causing glut4 translocation and glucose uptake.

PTP1B inhibitors as potential therapeutics in the treatment of type 2 diabetes and obesity.

Zhang ZY¹, Lee SY.

Author information

Abstract

Coordinated tyrosine phosphorylation is essential for signalling pathways regulated by insulin and leptin. Type 2 diabetes and obesity are characterised by resistance to hormones insulin and leptin, possibly due to attenuated or diminished signalling from the receptors. Pharmacological agents capable of inhibiting the negative regulator(s) of the signalling pathways are expected to potentiate the action of insulin and leptin and therefore be beneficial for the treatment of Type 2 diabetes and obesity. A large body of data from cellular, biochemical, mouse and human genetic and chemical inhibitor studies have identified protein tyrosine phosphatase 1B (PTP1B) as a major negative regulator of both insulin and leptin signalling. In addition, evidence suggests that insulin and leptin action can be enhanced by the inhibition of PTP1B. Consequently, PTP1B has emerged as an attractive novel target for the treatment of both Type 2 diabetes and obesity. The link between PTP1B and diabetes and obesity has led to an avalanche of research dedicated to finding inhibitors of this phosphatase. With the combined use of structure and medicinal chemistry, several groups have demonstrated that it is feasible to obtain small-molecule PTP1B inhibitors with the requisite potency and selectivity. The challenge for the future will be to transform potent and selective small molecule PTP1B inhibitors into orally available drugs with desirable physicochemical properties and in vivo efficacies.

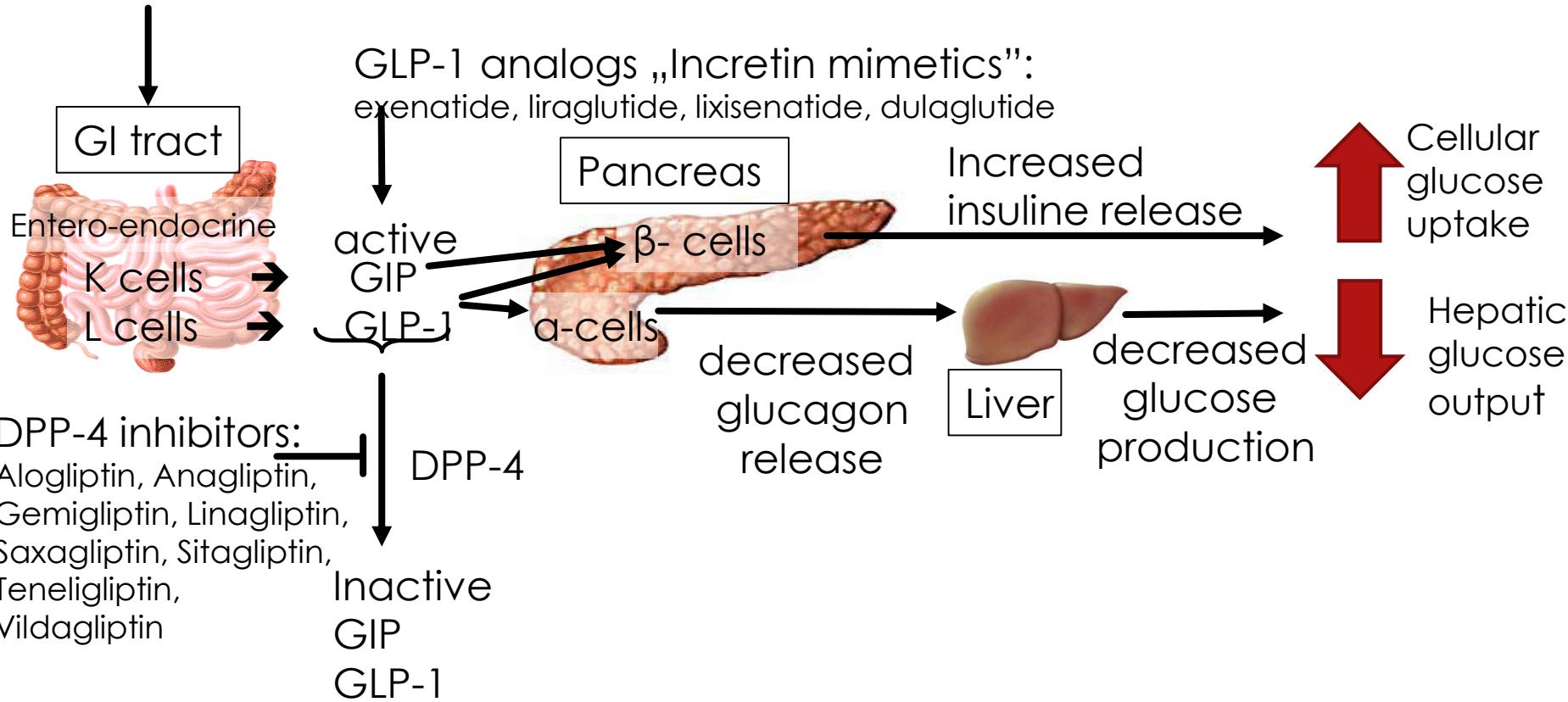
Meal ingestion



GIP = Glucose-dependent Insulinotropic Peptide

GLP-1 = Glucagon-Like Peptide 1

DPP-4 = DiPeptidyl Peptidase 4 (expressed on the surface of most cell types, **cleaves dipeptides from the end of polypeptides**)



- The entire GLP-1 molecule had no effect on insulin levels. Only one specific sequence of GLP-1 was found to have an insulinotropic effect: GLP-1 (7-36) amide.
 - It is rapidly inactivated to GLP-1 (9-36) by DPP-4 with a plasma half-life of only 1–2 minutes. GIP is also rapidly inactivated by DPP-4 to GIP (3-42).
- Thus, GLP-1 (7-36) amide is not very useful for treatment of **type 2 diabetes mellitus**, since it must be administered by continuous subcutaneous infusion.
- Several long-lasting analogs having insulinotropic activity have been developed, and three, **exenatide** (Byetta) and **liraglutide** (Victoza), plus exenatide extended-release (Bydureon), have been approved for use in the U.S.
- The main disadvantage of these **GLP-1 analogs** is they must be administered by subcutaneous injection.
- Another approach is to inhibit the enzyme that inactivates GLP-1 and GIP, DPP-4. Several **DPP-4 inhibitors** that can be taken orally as tablets have been developed.

Recently marketed

- ▶ DPP-4 inhibitors (sitagliptine, vildagliptine, saxagliptine)
 - ▶ They act primarily by blocking incretin degradation (GLP—1) and glucose-dependent insulinotropic peptide (GIP) leading to an increase in plasma concentrations of the same. This results in stimulation of insulin secretion, reduction in plasma glucose
- ▶ GLP-1 analogues (inj.) (exenatide, liraglutide)
 - ▶ Glucagon-like peptide (GLP) agonists bind to a membrane GLP receptor. As a consequence, insulin release from the pancreatic beta cells is increased
- ▶ Amylin analogues (inj.) (pramlitnide)
 - ▶ Amylin agonist analogues slow gastric emptying and suppress glucagon. They have all the incretins actions except stimulation of insulin secretion

New approaches

- ▶ SGLT-2 inhibitors (canagliflozin, empagliflozin, dapagliflozin)
 - ▶ Sodium-dependent glucose co-transporters (SGLT) are found in the intestinal mucosa of the small intestine and the proximal tubules of the nephrons.
 - ▶ SGLT2 inhibition enables us to reduce transcellular epithelial glucose reabsorption
- ▶ Dual PPAR agonists (glitazars) (aleglitazar, muraglitazar, tesaglitazar)
 - ▶ balanced dual PPAR α/γ agonists reduce hyperglycemia and improve the levels of HbA1C, HDL-C, LDL, and triglycerides with minimal PPAR-related adverse effects
 - ▶ In May 2006 development of two glitazar drugs was discontinued due to causing increased incidence of heart failure and decreased glomerular filtration

New approaches

- ▶ Glucokinase (hexokinase) activators
 - ▶ Glucokinase has an important glucose sensor role in pancreatic β-cells
 - ▶ Glucokinase activators (GKAs) stimulate insulin biosynthesis and secretion and augment glucose metabolism
- ▶ Monoclonal antibodies
 - ▶ Otelixizumab, an anti-CD3 monoclonal antibody, is known to stimulate C-peptide levels and reduce insulin requirement in type 1 diabetes
- ▶ Dopamine-2 receptor agonist
 - ▶ Timed bromocriptine is believed to act on circadian neuronal activities within the hypothalamus to reset abnormally elevated hypothalamic drive for increased plasma glucose, triglyceride, and free fatty acid levels
- ▶ PTP1B Inhibitors
 - ▶ Reversible protein tyrosine phosphorylation catalyzed by protein tyrosine phosphatases (PTPs) is important in the regulation of the signalling events of tyrosine-kinase pathways (insulin-R)
 - ▶ inhibitors of the PTPs are expected to have therapeutic value with novel modes of action in diabetes and obesity

Others

- ▶ Chromium
- ▶ β -Sitosterol has shown promising antidiabetic as well as antioxidant effects probably mediated via apoptosis induced by increased FAS levels and caspase 8 activity
- ▶ Allylcysteine (a natural constituent of fresh garlic) is shown to have significant antihyperglycemic effects along with lowering of tissue glycoprotein components (such as hexose, hexosamine, fucose and sialic acid)

Table 1—Properties of currently available glucose-lowering agents that may guide treatment choice in individual patients with type 2 diabetes mellitus

Class	Compound(s)	Cellular mechanism	Primary physiological action(s)	Advantages	Disadvantages
Biguanides	• Metformin	Activates AMP-kinase	• ↓ Hepatic glucose production	• Extensive experience • No weight gain • No hypoglycemia • Likely ↓ CVD events (UKPDS)	• Gastrointestinal side effects (diarrhea, abdominal cramping) • Lactic acidosis risk (rare) • Vitamin B ₁₂ deficiency • Multiple contraindications: CKD, acidosis, hypoxia, dehydration, etc.
Sulfonylureas	2nd generation • Glyburide/glibenclamide • Glipizide • Gliclazide ^b • Glimepiride	Closes K _{ATP} channels on β-cell plasma membranes	• ↑ Insulin secretion	• Extensive experience • ↓ Microvascular risk (UKPDS)	• Hypoglycemia • Weight gain • ? Blunts myocardial ischemic preconditioning • Low durability
Meglitinides (glinides)	• Repaglinide • Nateglinide	Closes K _{ATP} channels on β-cell plasma membranes	• ↑ Insulin secretion	• ↓ Postprandial glucose excursions • Dosing flexibility	• Hypoglycemia • Weight gain • ? Blunts myocardial ischemic preconditioning • Frequent dosing schedule
Thiazolidinediones	• Pioglitazone • Rosiglitazone ^c	Activates the nuclear transcription factor PPAR-γ	• ↑ Insulin sensitivity	• No hypoglycemia • Durability • ↑ HDL-C • ↓ Triglycerides (pioglitazone) • ? ↓ CVD events (ProACTIVE, pioglitazone)	• Weight gain • Edema/heart failure • Bone fractures • ↑ LDL-C (rosiglitazone) • ? ↑ MI (meta-analyses, rosiglitazone) • ? ↑ Bladder cancer (pioglitazone)

Class	Compound(s)	Cellular mechanism	action(s)	Advantages	Disadvantages
Bile acid sequestrants ^a	• Colesevelam	Binds bile acids in intestinal tract, increasing hepatic bile acid production; ? activation of farnesoid X receptor (FXR) in liver	• Unknown • ? ↓ Hepatic glucose production • ? ↑ Incretin levels	• No hypoglycemia • ↓ LDL-C	• Generally modest HbA _{1c} efficacy • Constipation • ↑ Triglycerides • May ↓ absorption of other medications
Dopamine-2 agonists ^a	• Bromocriptine (quick-release) ^d	Activates dopaminergic receptors	• Modulates hypothalamic regulation of metabolism • ↑ Insulin sensitivity	• No hypoglycemia • ? ↓ CVD events (Cycloset Safety Trial)	• Generally modest HbA _{1c} efficacy • Dizziness/syncope • Nausea • Fatigue • Rhinitis
GLP-1 receptor agonists	• Exenatide • Exenatide extended release • Liraglutide	Activates GLP-1 receptors	• ↑ Insulin secretion (glucose-dependent) • ↓ Glucagon secretion (glucose-dependent) • Slows gastric emptying • ↑ Satiety	• No hypoglycemia • Weight reduction • ? Potential for improved β-cell mass/function • ? Cardiovascular protective actions	• Gastrointestinal side effects (nausea/vomiting) • ? Acute pancreatitis • C-cell hyperplasia/medullary thyroid tumors in animals • Injectable • Training requirements
α-Glucosidase inhibitors ^a	• Acarbose • Miglitol • Voglibose ^{b,d}	Inhibits intestinal α-glucosidase	• Slows intestinal carbohydrate digestion/absorption	• No hypoglycemia • ↓ Postprandial glucose excursions • ? ↓ CVD events (STOP-NIDDM) • Nonsystemic	• Generally modest HbA _{1c} efficacy • Gastrointestinal side effects (flatulence, diarrhea) • Frequent dosing schedule
DPP-4 inhibitors	• Sitagliptin ^a • Vildagliptin ^a • Saxagliptin • Linagliptin • Alogliptin ^{b,d}	Inhibits DPP-4 activity, increasing postprandial active incretin (GLP-1, GIP) concentrations	• ↑ Insulin secretion (glucose-dependent) • ↓ Glucagon secretion (glucose-dependent)	• No hypoglycemia • Well tolerated	• Generally modest HbA _{1c} efficacy • Urticaria/angioedema • ? Pancreatitis

Amylin mimetics ^a	<ul style="list-style-type: none"> • Pramlintide^d 	Activates amylin receptors	<ul style="list-style-type: none"> • ↓ Glucagon secretion • Slows gastric emptying • ↑ Satiety 	<ul style="list-style-type: none"> • ↓ Postprandial glucose excursions • Weight reduction 	<ul style="list-style-type: none"> • Generally modest HbA_{1c} efficacy • Gastrointestinal side effects (nausea/vomiting) • Hypoglycemia unless insulin dose is simultaneously reduced • Injectable • Frequent dosing schedule
Insulins	<ul style="list-style-type: none"> • Human NPH • Human Regular • Lispro • Aspart • Glulisine • Glargin • Detemir • Premixed (several types) 	Activates insulin receptors	<ul style="list-style-type: none"> • ↑ Glucose disposal • ↓ Hepatic glucose production 	<ul style="list-style-type: none"> • Universally effective • Theoretically unlimited efficacy • ↓ Microvascular risk (UKPDS) 	<ul style="list-style-type: none"> • Hypoglycemia • Weight gain • ? Mitogenic effects • Injectable • Training requirements • "Stigma" (for patients)

Effects of Diabetes Drug Action^a

	Met	GLP1RA	SGLT2I	DPP4I	TZD	AGI	Coles	BCR-QR	SU/Glinide	Insulin	Pram
FPG lowering	Moderate	Mild to moderate^b	Moderate	Mild	Moderate	Neutral	Mild	Neutral	SU: moderate Glinide: mild	Moderate to marked (basal insulin or premixed)	Mild
PPG lowering	Mild	Moderate to marked	Mild	Moderate	Mild	Moderate	Mild	Mild	Moderate	Moderate to marked (short/rapid-acting insulin or premixed)	Moderate to marked
NAFLD benefit	Mild	Mild	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
Hypoglycemia	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	<i>SU: moderate to severe Glinide: mild to moderate</i>	<i>Moderate to severe, especially with short/rapid-acting or premixed</i>	Neutral
Weight	Slight loss	Loss	Loss	Neutral	<i>Gain</i>	Neutral	Neutral	Neutral	<i>Gain</i>	<i>Gain</i>	Loss
Renal impairment/ GU	<i>Contraindicated in stage 3B, 4, 5 CKD</i>	<i>Exenatide contraindicated CrCl <30 mg/mL</i>	<i>GU infection risk</i>	<i>Dose adjustment may be necessary (except liraglutin)</i>	<i>May worsen fluid retention</i>	Neutral	Neutral	Neutral	<i>Increased hypoglycemia risk</i>	<i>Increased risks of hypoglycemia and fluid retention</i>	Neutral
GI adverse effects	Moderate	<i>Moderate (caution in PIs about pancreatitis)</i>	Neutral	<i>Neutral (caution in PIs about pancreatitis)</i>	Neutral	Moderate	Mild	Moderate	Neutral	Neutral	Moderate
CHF	Neutral	Neutral	Neutral	<i>Neutral (caution: possibly increased CHF hospitalization risk in CV safety trial)</i>	Moderate	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
CVD	Possible benefit	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Safe	?	Neutral	Neutral
Bone	Neutral	Neutral	<i>Bone loss</i>	Neutral	<i>Moderate bone loss</i>	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral

Abbreviations: AGI = α -glucosidase inhibitors; BCR-QR = bromocriptine quick release; CHF = congestive heart failure; CKD = chronic kidney disease; Coles = colesevelam; CrCl = creatinine clearance; CV = cardiovascular; DPP4I = dipeptidyl peptidase 4 inhibitors; FPG = fasting plasma glucose; GI = gastrointestinal; GLP1RA = glucagon-like peptide 1 receptor agonists; GU = genitourinary; Met = metformin; NAFLD = nonalcoholic fatty liver disease; PI = prescribing information; PPG = postprandial glucose; SGLT2I = sodium-glucose cotransporter 2 inhibitors; SU = sulfonylureas; TZD = thiazolidinediones.

^a Boldface type highlights a benefit or potential benefit; italic type highlights adverse effects.

^b Mild: albiglutide and exenatide; moderate: dulaglutide, exenatide extended release, and liraglutide.

Guideline

AMERICAN DIABETES ASSOCIATION

STANDARDS OF MEDICAL CARE IN

DIABETES – 2014

DIABETES CARE VOLUME 37, SUPPLEMENT 1, JANUARY 2014

Healthy eating, weight control, increased physical activity

Initial drug monotherapy

Efficacy ($\downarrow \text{HbA}_{1c}$)
Hypoglycemia
Weight
Side effects
Costs

Two-drug combinations

Efficacy ($\downarrow \text{HbA}_{1c}$)
Hypoglycemia
Weight
Major side effect(s)
Costs

Three-drug combinations

More complex insulin strategies

Metformin

high
low risk
neutral/loss
GI / lactic acidosis
low

If needed to reach individualized HbA_{1c} target after ~3 months, proceed to two-drug combination
(order not meant to denote any specific preference):

Metformin +	Metformin +	Metformin +	Metformin +	Metformin +
Sulfonylurea high moderate risk gain hypoglycemia low	Thiazolidinedione high low risk gain edema, HF, Fx's high	DPP-4 Inhibitor intermediate low risk neutral rare high	GLP-1 receptor agonist high low risk loss GI high	Insulin (usually basal) highest high risk gain hypoglycemia variable

If needed to reach individualized HbA_{1c} target after ~3 months, proceed to three-drug combination
(order not meant to denote any specific preference):

Metformin +	Metformin +	Metformin +	Metformin +	Metformin +
Sulfonylurea + TZD or DPP-4-i or GLP-1-RA or Insulin	Thiazolidinedione + SU or DPP-4-i or GLP-1-RA or Insulin	DPP-4 Inhibitor + SU or TZD or Insulin	GLP-1 receptor agonist + SU or TZD or Insulin	Insulin (usually basal) + TZD or DPP-4-i or GLP-1-RA

If combination therapy that includes basal insulin has failed to achieve HbA_{1c} target after 3-6 months,
proceed to a more complex insulin strategy, usually in combination with one or two noninsulin agents:

**Insulin
(multiple daily doses)**