

Treatment of Diabetes Mellitus

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Goal of Therapy

Normoglycemia

The target HbA1c should be as close to normal as can be obtained without causing severe and/or frequent hypoglycemia.

ADA guidelines

ACE guidelines

HbA _{1c}	< 7%	≤ 6.5%
FPG	90–130 mg/dl (5–7.2 mmol/l)	< 110 mg/dl (< 6.1 mmol/l)
PPG	< 180 mg/dl (< 10 mmol/l)	< 140 mg/dl (< 7.8 mmol/l)

Based on data from the American Diabetes Association (ADA)⁵ and the American College of Endocrinology (ACE)⁶ (with mmol/l equivalents in parentheses)

HbA_{1c} = glycosylated hemoglobin; FPG = fasting plasma glucose; PPG = post-prandial glucose

In comparing the results of glucose testing, note that capillary blood glucose values can be variable, and venous blood glucose values are approximately 15% lower than plasma or serum glucose values

Treatment of Diabetes Mellitus

1

- **Patient Education**

2

- **Therapeutic Life style modifications**

3

- **Pharmacotherapy**

Patient education

- **The mission for improved glycaemic control has made it clear that whatever the technical expertise applied, the outcome depends on willing cooperation by the patient.**
- **Patient education can translate to increased self-management skills**

The Diabetic who knows the most lives the longest

Joslin

Initial education

- The causes of diabetes
- Blood glucose measurements
- Acceptable blood glucose values
- Advice about hypo- and hyperglycaemic episodes
- Dietary advice
- Insulin management
- Injection technique

Later on, More comprehensive education programme

- Aetiology & pathology
- Injection devices and methods
- Blood-glucose monitoring
- Diet
- Insulin adjustments
- Hypoglycaemia
- Hyperglycaemia
- Sick-day management
- Sport
- Drug abuse
- Travelling
- Gynaecological issues
- Complications

Despite these favorable effects, only 35% of people with diabetes in the United States have attended a diabetes education class or course.

Therapeutic life style modifications

Diet

- **For children with Type 1 DM, a goal is to match diet to insulin requirements to ensure normal growth and development.**
- **By contrast, in obese type 2 diabetic patients, it is important to achieve and maintain a reasonable or realistic body weight.**



Diet Composition

- Dietary protein intake should constitute 10%-20% of total daily calories.
- Saturated and polyunsaturated fat should each be limited to <10% of total daily calories.
- The remaining 60%-70% of calories, composed of monounsaturated fat and carbohydrate, may be tailored to individual needs.
- Soluble and insoluble dietary fiber is healthy for all individuals, and daily consumption should be increased.
- Cholesterol should be limited to <300 mg daily.

- Despite prior dogma that sweets and refined sugars be replaced with complex carbohydrates, contending that they incur greater immediate postprandial hyperglycemia, a large body of literature shows no significant difference in glycemic control from sucrose or complex carbohydrate forms.
- What is important, however, is the total number of calories. Sucrose may replace other carbohydrates, but the diet should remain isocaloric. Also, other nutrients often consumed with sucrose, such as fat, must be considered.

Diet in special circumstances

- Dietary protein intake should constitute 10%-20% of total daily calories, **except** in the presence of **nephropathy**, when the recommended daily allowance (RDA) for protein is **0.8 g/kg body weight/day** or **<10% of total daily calories**

- Potential problems with a high-carbohydrate (60% of total calories) and low-fat (20%-25% of total calories) diet, at least short-term, include elevation of triglycerides and very low-density lipoprotein (VLDL) cholesterol and postprandial hyperglycemia
- In contrast, a diet higher in monounsaturated fat, comprising up to 20% of total calories, with a more moderate carbohydrate intake of 50%-60% of calories may offer advantages to the individual with elevated blood triglycerides and VLDL.

Small frequent meals

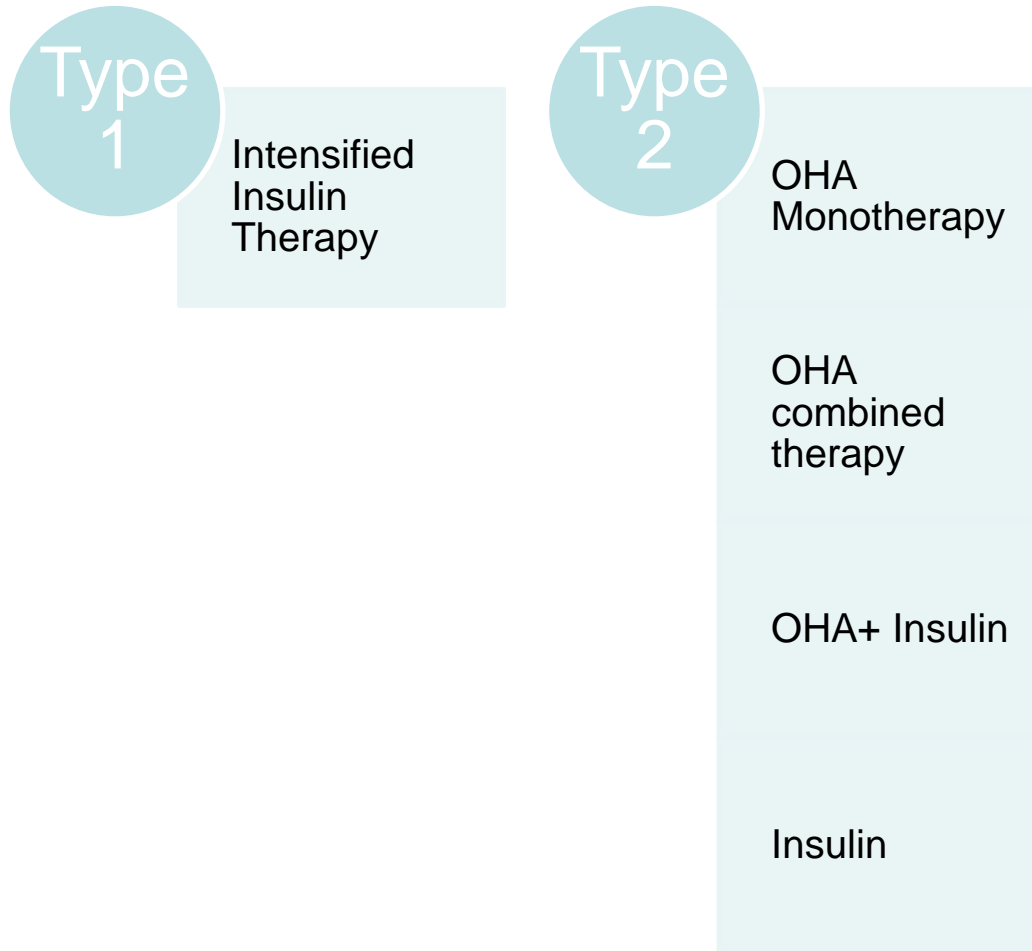
- Other useful strategies include spacing nutrient intake with more frequent meals as well as behavioral and attitude changes in the patient.

Exercise

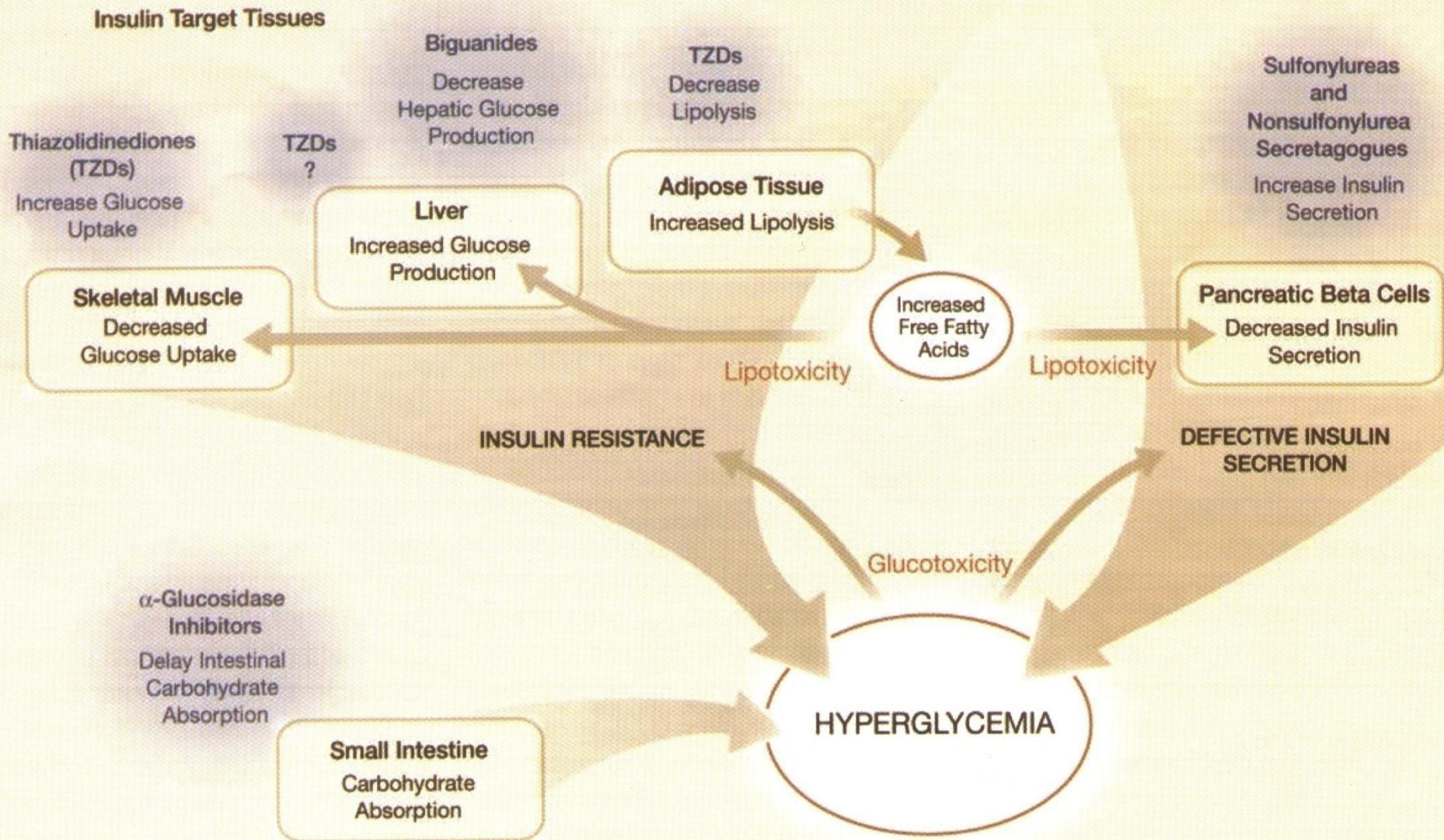
- Any increase in activity levels is to be encouraged, but participation in more formal exercise programmes is best.
- Both aerobic and resistance training improve insulin sensitivity and metabolic control in type 1 and type 2 diabetes.
- Patients on insulin or sulfonylureas should be warned that there is an increased risk of hypoglycaemia for up to 6–12 hours following heavy exertion.

Pharmacotherapy

Pharmacotherapy



Pharmacotherapy for type 2 Diabetes



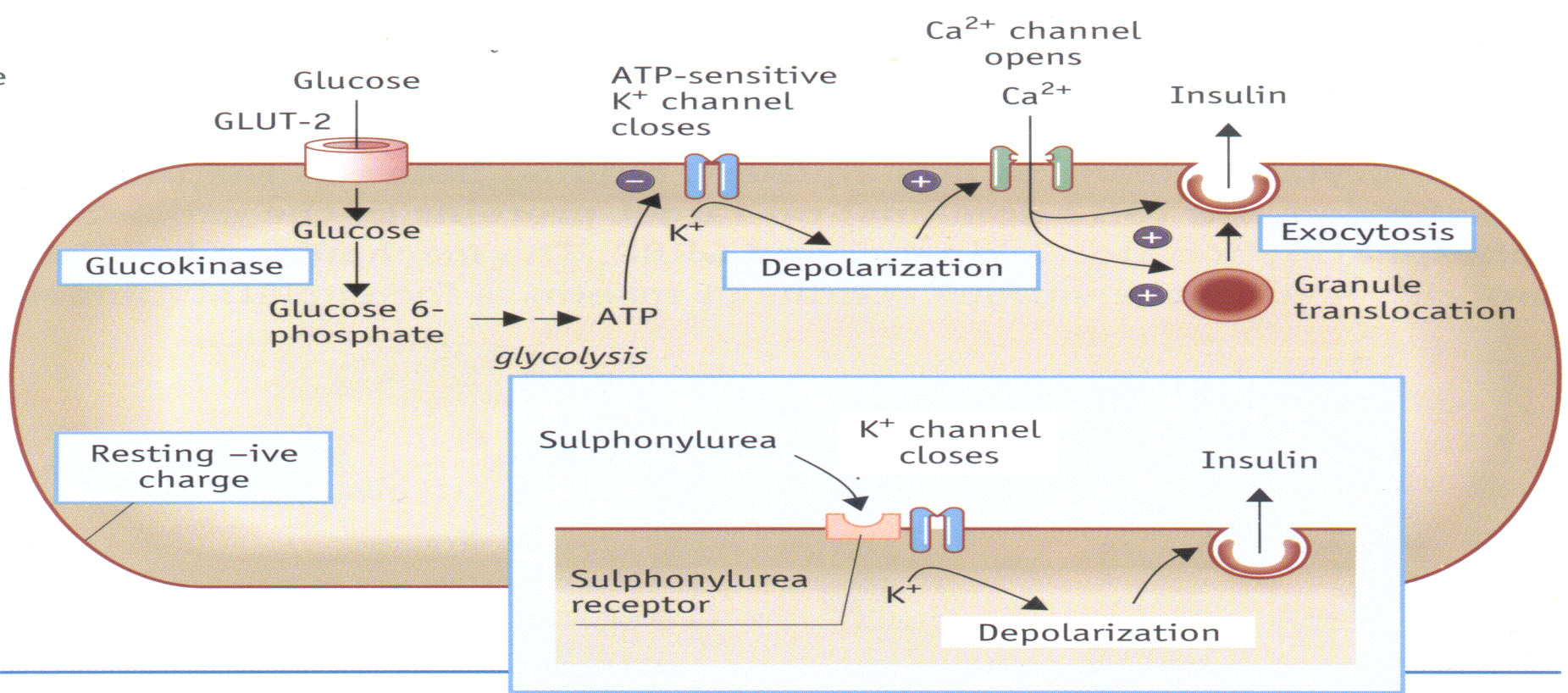
Pharmacological approaches to the major defects of type 2 diabetes.

Pharmacotherapy for type 2 Diabetes

1. **Sulfonylureas**
2. **Non- SU secretagogues**
3. **Biguanides**
4. **Thiazolidinediones**
5. **Incretins**
6. **Alpha glucosidase inhibitors**

Pharmacotherapy for type 2 Diabetes

1. **Sulfonylureas**
2. Non- SU secretagogues
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6. Alpha glucosidase inhibitors



- Sulphonylureas stimulate the production and release of insulin by binding to a receptor site on the membrane of the pancreatic beta cell. Binding blocks the opening of ATP-dependent potassium channels, which leads to a depolarization of the membrane, leading to an influx of calcium. These events result in an increased production of insulin by the beta cell.**

- **Different SU agents stimulate insulin secretion by attaching to the sulfonylurea receptor at different sites and for varying periods of time.**

Sulfonylureas

- **1st generation SUs** [chlorpropamide, acetohexamide and tolbutamide]: No longer used today
- **2nd generation SUs**: are more potent and safer than 1st generation SUs
 1. Glibenclamide
 2. Gliclazide
 3. Glipizide
 4. Glimeperide

Differences between SU agents

- **Current agents are equally effective**
- **Differences in their metabolism. Most agents are metabolized by the liver and cleared by the kidney. Therefore they must be used cautiously in patients with advanced liver or renal disease.**
- **Differences in duration of action.**

Side effect of the sulfonylureas

- Hypoglycemia is usually associated with reduced oral intake or prolonged exercise, and is more common with longer-acting sulfonylureas than with short-acting agents.

Exhaustion of B cell function by SUs

- Long term use of SUs may lead to exhaustion of B cell function .
- However, decline in B cell function may be an underlying characteristic of the diabetic state itself.

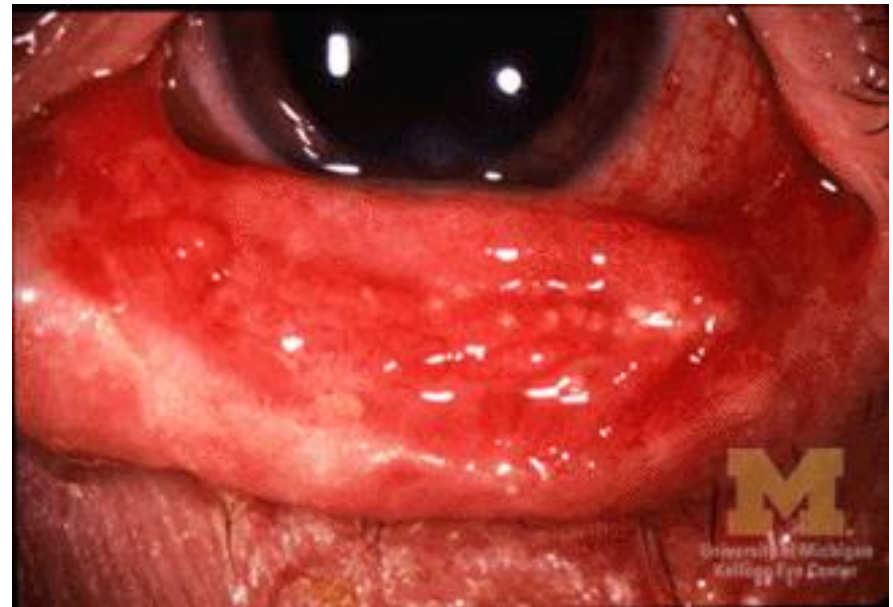
Weight gain

- **Weight gain with SU therapy may be a problem.**
- **Weight gain mediated by secretagogue therapy may be caused or exacerbated by frequent and severe hypoglycemia**

Dermatologic side effects include:

- Pruritus,
- Erythema multiform,
- Erythema nodosum,
- Urticaria,
- Morbilliform rash,
- Lichenoid eruptions,
- Photosensitivity.

Stevens-Johnson's syndrome



A disulfiram like reaction

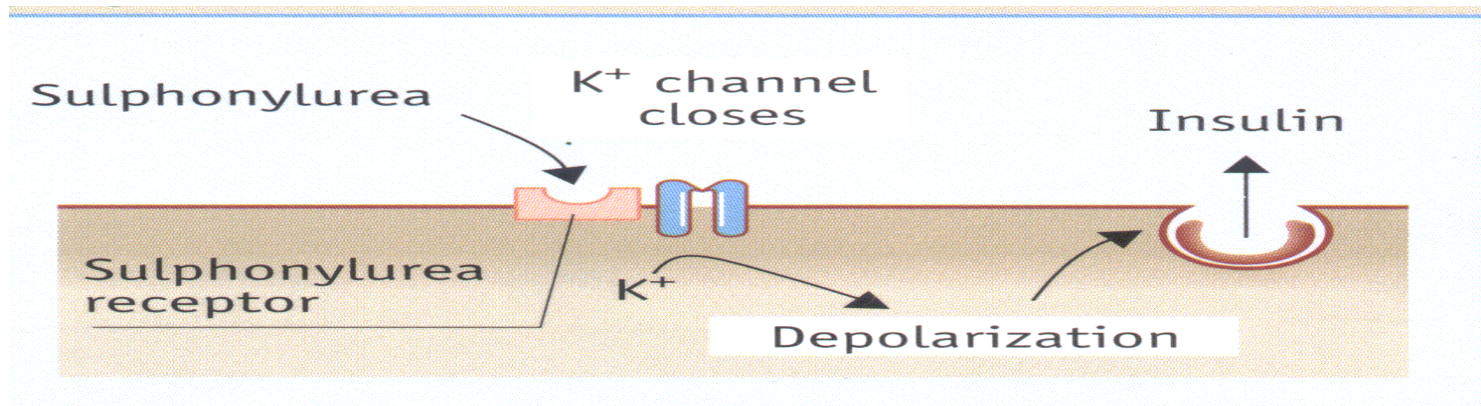
- A disulfiram like reaction may results from ingestion of alcohol in patients receiving 1st generation sulfonylurea agent.
- Chloropropamide is the most common offending agent.
- The reaction characterized by facial flushing, sensation of dizziness, tachycardia beginning 20 minutes after alcohol use.

Pharmacotherapy for type 2 Diabetes

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Non- SU secretagogues (meglitinides)

- Although not chemically sulfonylureas, they increase insulin production by a similar mechanism, at the ATP-dependent potassium channels.



- **They are much shorter-acting. Typically taken at the beginning of a meal, they induce an insulin surge, which fades rapidly, thus reducing the risk of later hypoglycemia.**
- **Examples: Repaglinide (benzoic acid derivative) and nateglinide (phenylalanine derivative).**
- **Repaglinide is more potent than nateglinide, but insulin response is more rapid in response to nateglinide.**

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Biguanides (Metformin)

- **It has been marketed in Europe for 30 years., but It was released in USA since 1995.**

- **The major mechanism of action of metformin is in the liver, where it decreases glucose production through suppression of gluconeogenesis.**
- **Metformin also reduces insulin resistance either by decreasing food intake and/or mediating weight loss or by the peripheral action of mobilizing glucose transporters in the myocyte or adipocyte.**
- **As a result, the primary action of metformin is reducing fasting glucose, and its less prominent effect is decreasing insulin resistance.**

- **lowering of LDL cholesterol, lipoprotein (a), triglyceride, PAI-1, and fibrin levels; decreasing clotting factors and platelet aggregation; improving endothelial function; and lowering C-reactive protein levels.**

- **Metformin does not encourage weight gain. In fact, some patients lose weight on metformin therapy.**
- **Dose: 2000 mg per day.**

Side effects of Metformin

- **A high incidence of gastrointestinal complaints. One out of 3 patients will experience problems ranging from mild heartburn to significant diarrhea. Patients do tend to become more tolerant of metformin with time, so that, in some cases, one can reduce the dose and achieve a lower level of gastrointestinal distress.**

- **The most serious complication of biguanide use is lactic acidosis, which can be fatal.**
- **Fortunately, the incidence of lactic acidosis with metformin use is low (1 case per 33,000 patient-years) and could be avoided if properly used.**

Contraindications to Biguanides

- A serum creatinine of 1.5 mg/dL is the suggested upper limit on use of this agent.
- Dehydration, surgery and with the use of radiologic contrast dye. Metformin should be stopped at the time of the radiographic contrast procedure and not restarted for 48 hours.
- Any acute illness.
- Metformin is contraindicated in hepatic dysfunction and congestive heart failure .

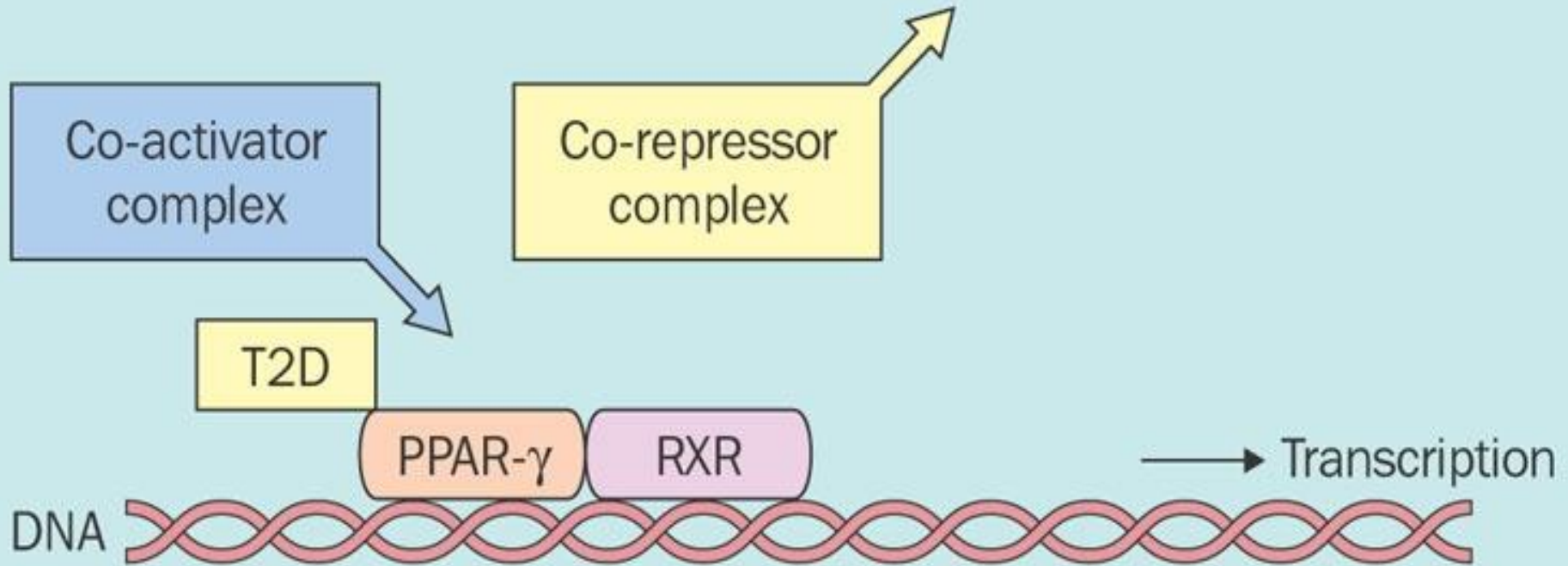
Pharmacotherapy for type 2 Diabetes

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Thiazolidinedione

- **Have a very slow onset of action. Although effects begin within 2 weeks, the maximal benefit of treatment is not seen for about 3 months.**
- **Rosiglitazone and pioglitazone followed troglitazone. Neither agent is toxic to the liver. However, Rosiglitazone was withdrawn for cardiac toxicity.**

Peroxisome-proliferation-activating receptor- γ pathway for activation of transcription



Comprehensive Clinical Endocrinology 3e: edited by Besser & Thorner
Elsevier Science Ltd

- The thiazolidinediones interact with peroxisome proliferator-activated receptor-gamma (PPAR-gamma), a nuclear receptor which regulates large numbers of genes including those involved in lipid metabolism and insulin action.

The main site of action

- **PPAR γ is most highly expressed in adipocytes, while expression in myocytes is minor.**
- **The main action of TZD is to increase glucose uptake by the muscles.**
- **The muscle is affected indirectly by the effect of TZD on fat cells through: FFA, leptin, TNF, adiponectin, resistin.**

Side effects of thiazolidinediones

- Weight gain (partially due to fluid retention).
- In some susceptible patients, fluid retention may trigger congestive heart failure. This phenomenon occurs far more frequently in insulin-treated patients receiving a thiazolidinedione.
- Rosiglitazone and pioglitazone should not be used in patients with heart failure

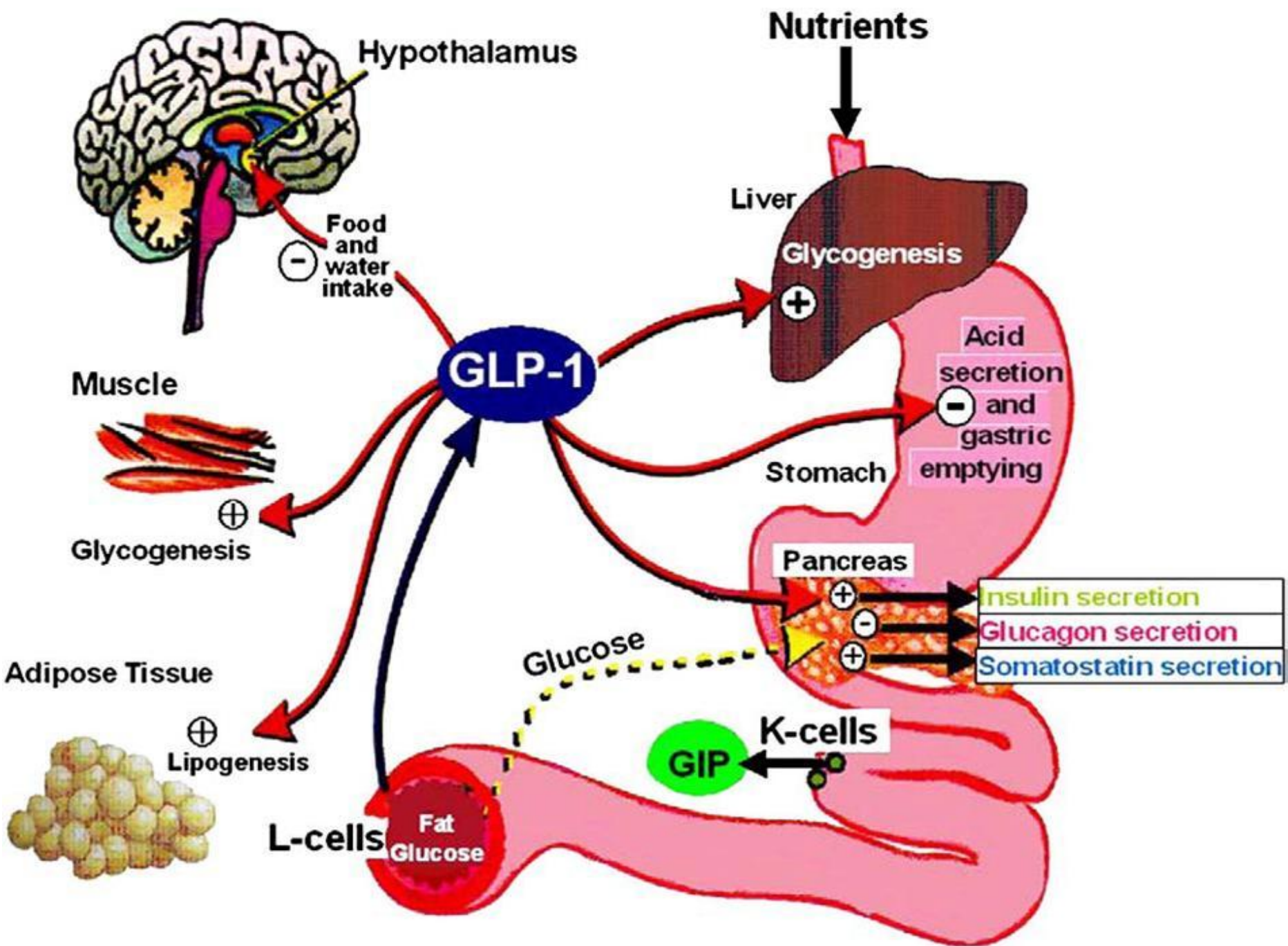
- **Osteoporosis especially in postmenopausal women**
- **Increased bladder cancer had been reported and more studies are needed to prove or disprove.**

Pharmacotherapy for type 2 Diabetes

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6. Alpha glucosidase inhibitors

Incretins

- It has long been known that the insulin response to oral glucose is greater than the response to intravenous glucose.
- This is known as the incretin effect, and is due to release of two peptide hormones, glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1) from the L cells in the intestine.
- The incretin effect is diminished in type 2 diabetes.



Hypothalamus

Nutrients

Food and water intake (-)

Liver

Glycogenesis (+)

Muscle

Glycogenesis (+)

Acid secretion and gastric emptying (-)

Stomach

Pancreas

Insulin secretion
Glucagon secretion
Somatostatin secretion

Adipose Tissue

Lipogenesis (+)

Glucose

GIP

K-cells

L-cells Fat Glucose

- GLP-1 has a very short half-life, and exenatide and liraglutide, longer-acting analogues, are now available.
- Exenatide, which must be given by twice-daily subcutaneous injection, promotes insulin release, inhibits glucagon release, reduces appetite and delays gastric emptying, thus blunting the postprandial rise in plasma glucose.
- Its main clinical disadvantage is the need for injection, and its advantage is that it improves glucose control whilst inducing useful weight reduction.

- Side-effects include nausea, and acute pancreatitis has been reported.
- A new long-acting preparation is now available and can be given once-weekly

DDP4 inhibition

- The enzyme dipeptidyl peptidase 4 (DPP4) rapidly inactivates GLP-1 as this is released into the circulation, and inhibition of this enzyme thus potentiates the effect of endogenous GLP-1 secretion.
- DDP4 inhibition is an alternative approach to incretin-based therapy.
- The two agents currently available, sitagliptin (Januvia) and vildagliptin (Galvus), are moderately effective in lowering blood glucose but do not induce weight loss.
- They are likely to be most effective in the early stages of type 2 diabetes when insulin secretion is relatively preserved.
- The main side-effect is nausea.

Pharmacotherapy for type 2 Diabetes

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6. **Alpha glucosidase inhibitors**

Disaccharidase Inhibitors

- Absorption of carbohydrates requires the eventual breakdown of disaccharides to form single sugars by the enzymes in the brush border of the small intestine.
- Disaccharidase inhibitors, such as acarbose and miglitol, effectively compensate for defective early-phase insulin release by inhibiting the breakdown of disaccharides to monosaccharides in the intestinal epithelium. Consequently, there is delayed and decreased absorption of these sugars.

- The [alpha]-glucosidase inhibitors are minimally absorbed from the GI tract, and the kidneys rapidly excrete this small amount. However, with renal decompensation, the serum levels of these drugs may rise to hepatotoxic levels. Therefore, these agents should not be used when serum creatinine levels are >2 mg/dL.
- Therefore, if hypoglycemia occurs when [alpha]-glucosidase inhibitors are being used, glucose tablets (not sucrose) should be employed.

- Adverse reactions: the large amount of nonabsorbed disaccharides in the intestinal tract lead to flatulence, abdominal discomfort, and diarrhea.
- Increased disaccharide concentration leads to the induction of disaccharidases in the jejunum and ileum. Eventually, this induction of new enzymes results in a slower, smoother absorption of disaccharides.

Insulin Therapy

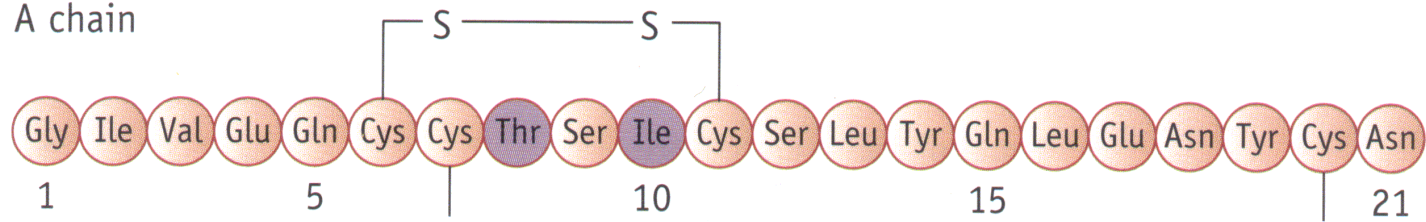


**Insulin
Discovery in
1921**

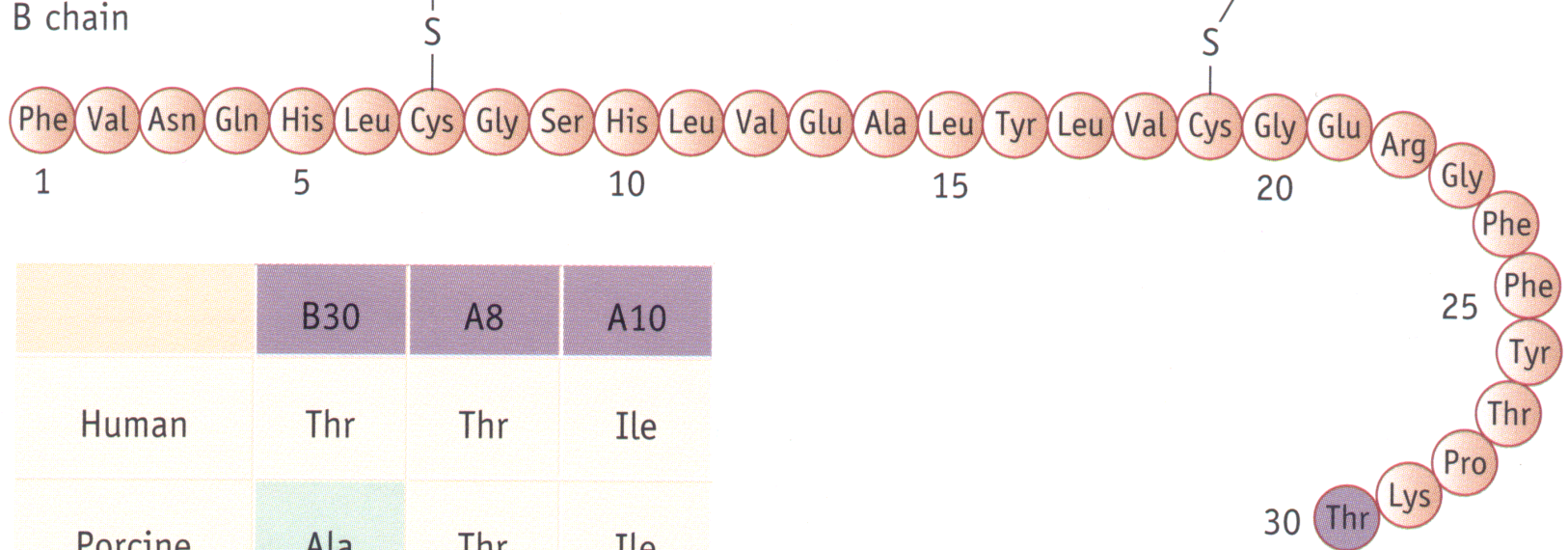
Insulin production



A chain

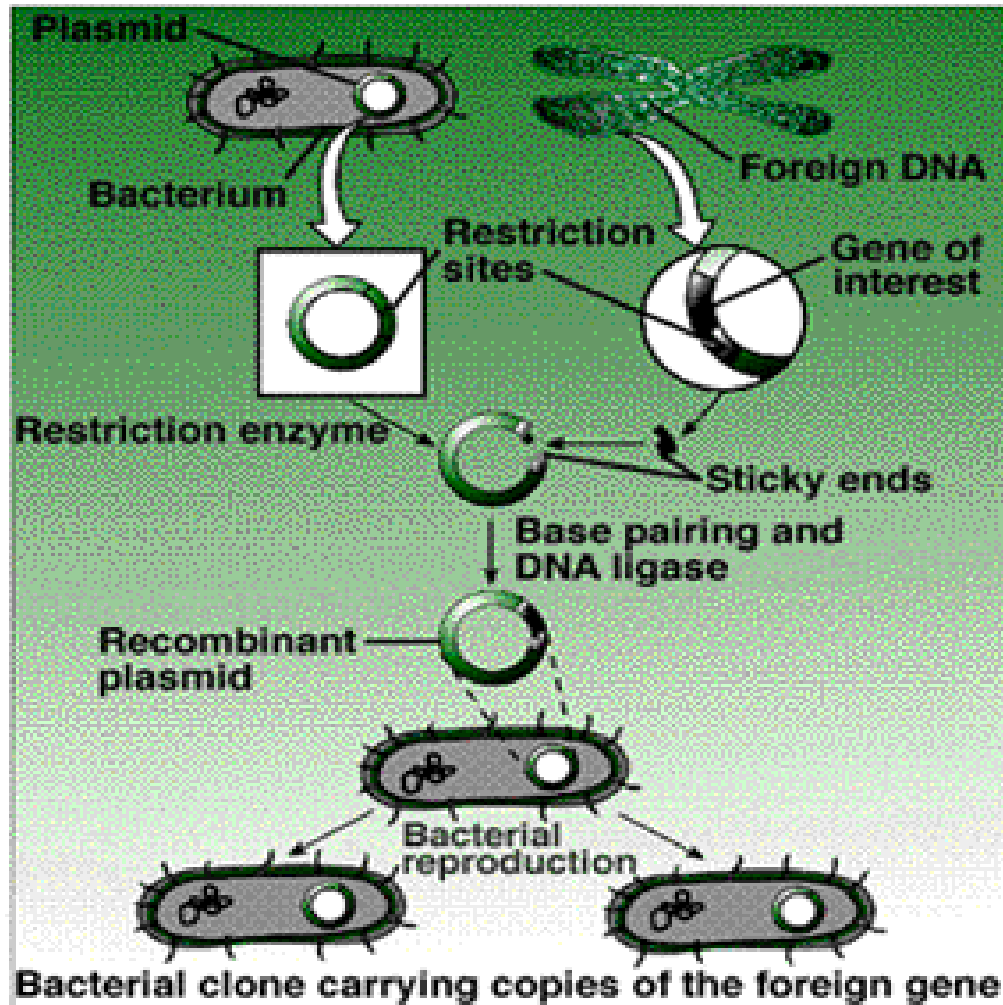


B chain



	B30	A8	A10
Human	Thr	Thr	Ile
Porcine	Ala	Thr	Ile

Recombinant DNA technology



Types of Insulin

Human Insulin

- Short acting
- Intermediate acting
- Mixed

Insulin analogues

- Rapid acting
- Basal
- mixed

Types of Insulin

Human Insulin

- Short acting
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Insulin analogues

- Rapid acting
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Types of Insulin

Human Insulin

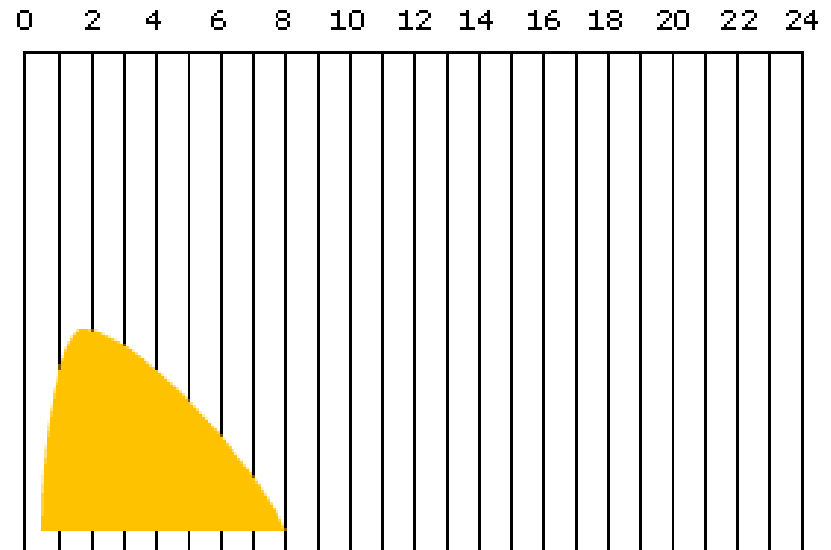
- **Short acting**
- Intermediate acting
- Mixed

Insulin analogues

- Rapid acting
- Basal
- mixed

Short acting Insulin

- **Clear solution**
- **Onset of action: 30 min**
- **Peak action: 1-3 hours**
- **Maximal duration: 6 hours**



Types of Insulin

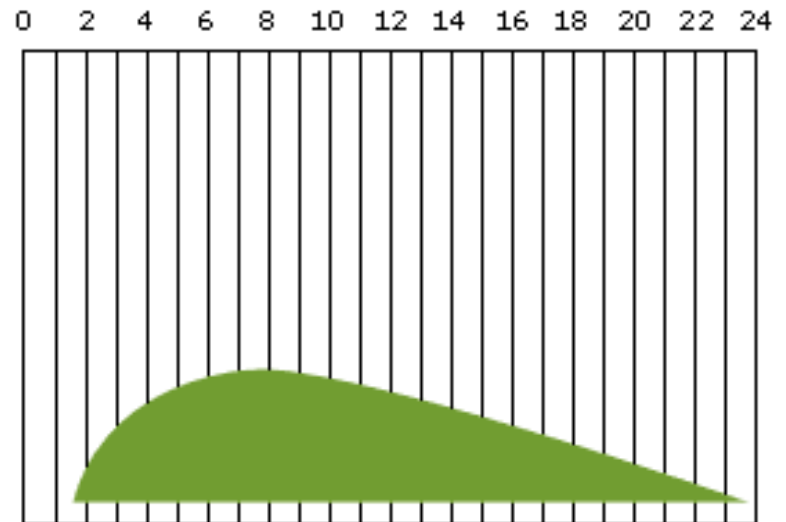
Human Insulin

- Short acting
- **Intermediate acting**
- Mixed

Insulin analogues

- Rapid acting
- Basal
- mixed

- **Cloudy solution (should be thoroughly mixed before use)**
- **Onset of action: 1–2 hours**
- **Peak action: 4-6 hours**
- **Maximal duration: 12 hours**



Types of Insulin

Human Insulin

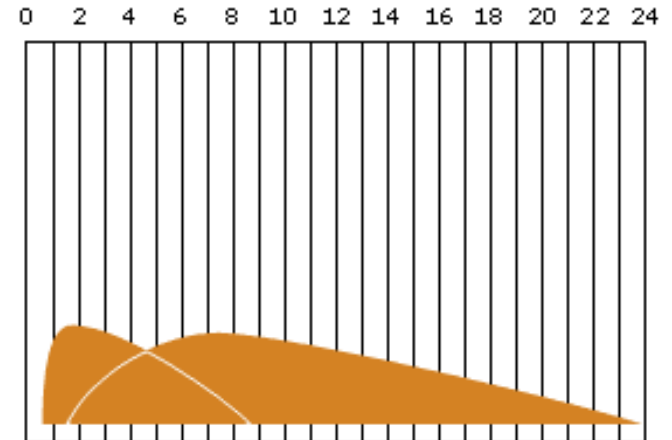
- Short acting
- Intermediate acting
- **Mixed**

Insulin analogues

- Rapid acting
- Basal
- mixed

Mixed (short+ Intermediate)

- Different formulas e.g. 30/70, 50/50
- Cloudy solution (should be thoroughly mixed before use)
- Onset of action: 1/2–1 hours
- Peak action: 4-5 hours
- Maximal duration: 12 hours



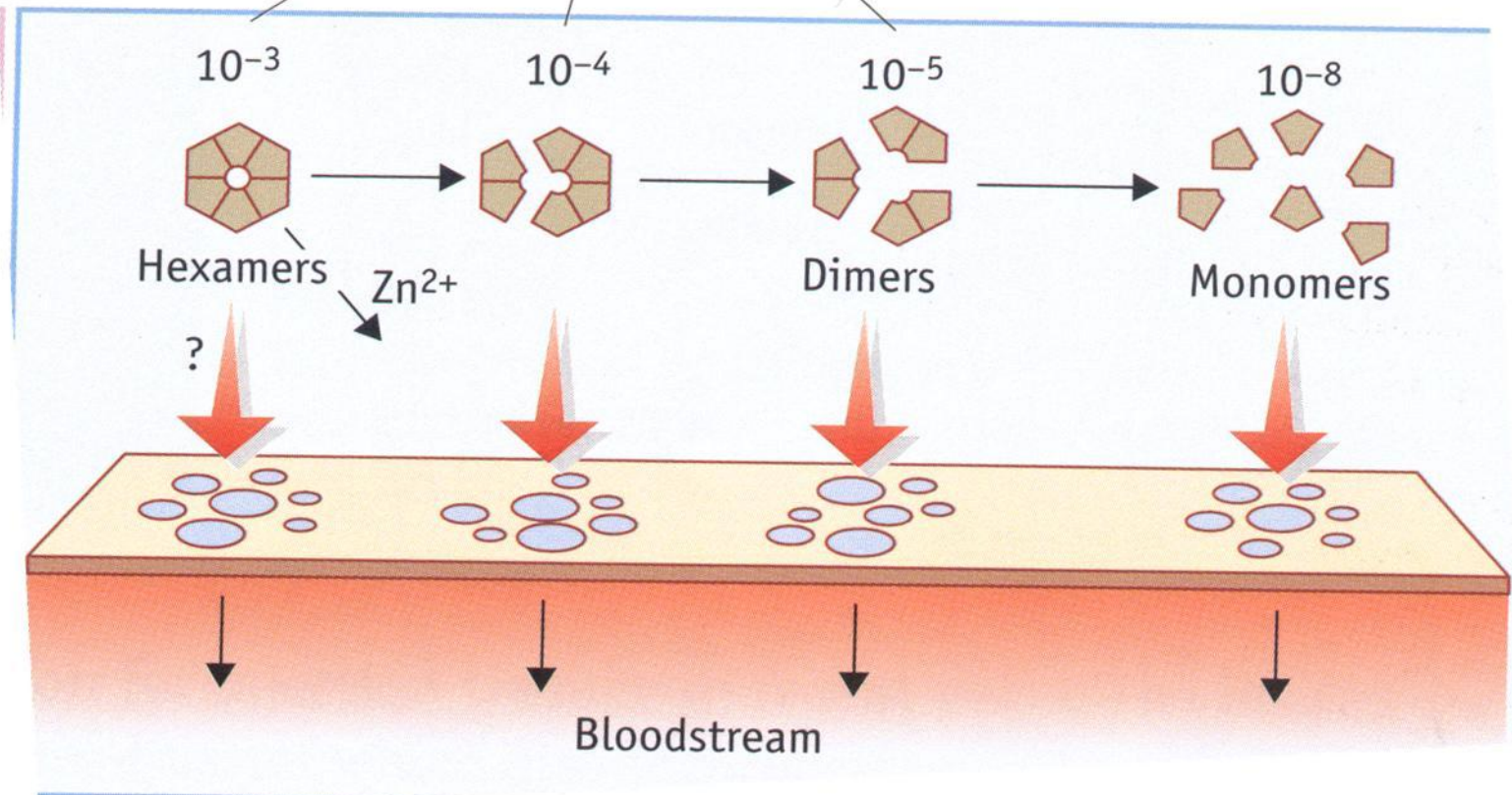
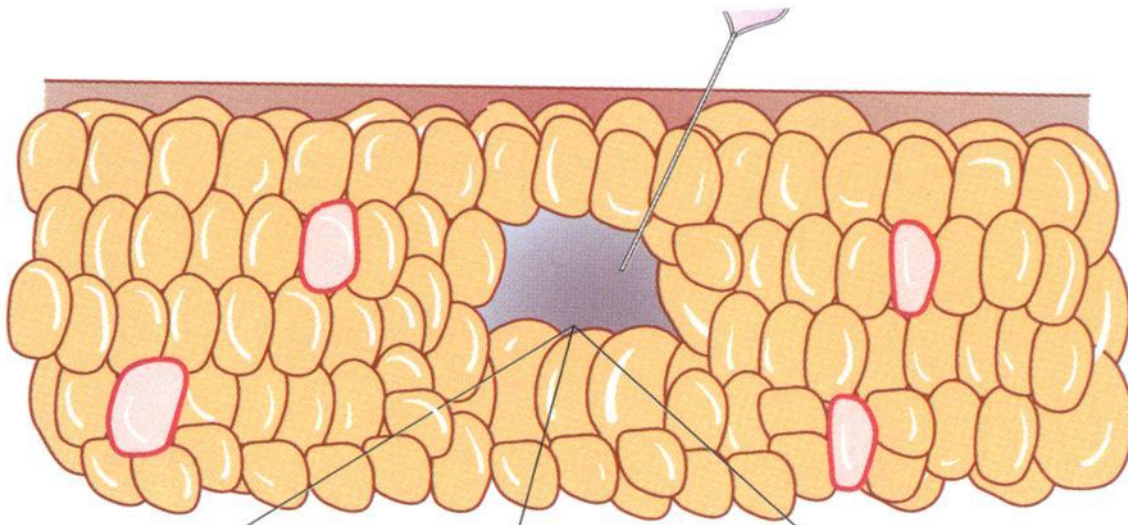
Types of Insulin

Human Insulin

- Short acting
- Intermediate acting
- Mixed

Insulin analogues

- Rapid acting
- Basal
- mixed



Types of Insulin

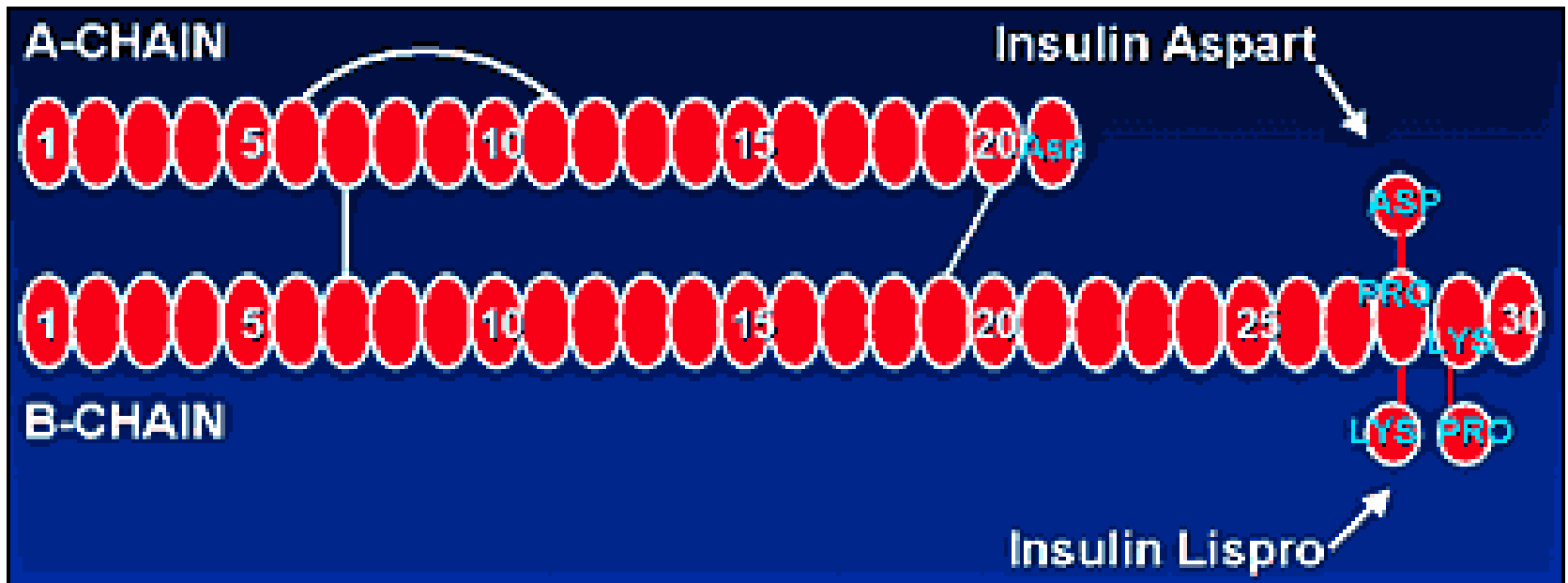
Human Insulin

- Short acting
- Intermediate acting
- Mixed

Insulin analogues

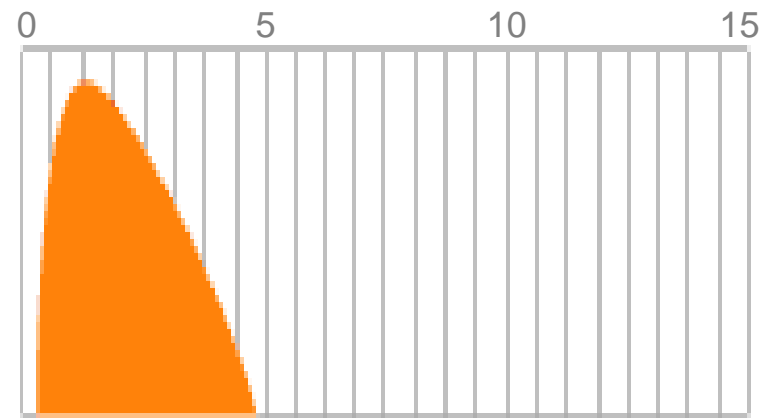
- Rapid acting
- Basal
- mixed

- Insulin lispro (Humalog): Reversal of the sequence of amino acids 28 and 29 (Lysine and Proline)
- Insulin aspart (Novorapid): substitution of the amino acid, B28, which is normally Proline, by Aspartic acid.



Rapid acting insulin analogues

- **Clear solution**
- **Onset of action: 10 min**
- **Peak action: 1-2 hours**
- **Maximal duration: 3-4 hours**



Types of Insulin

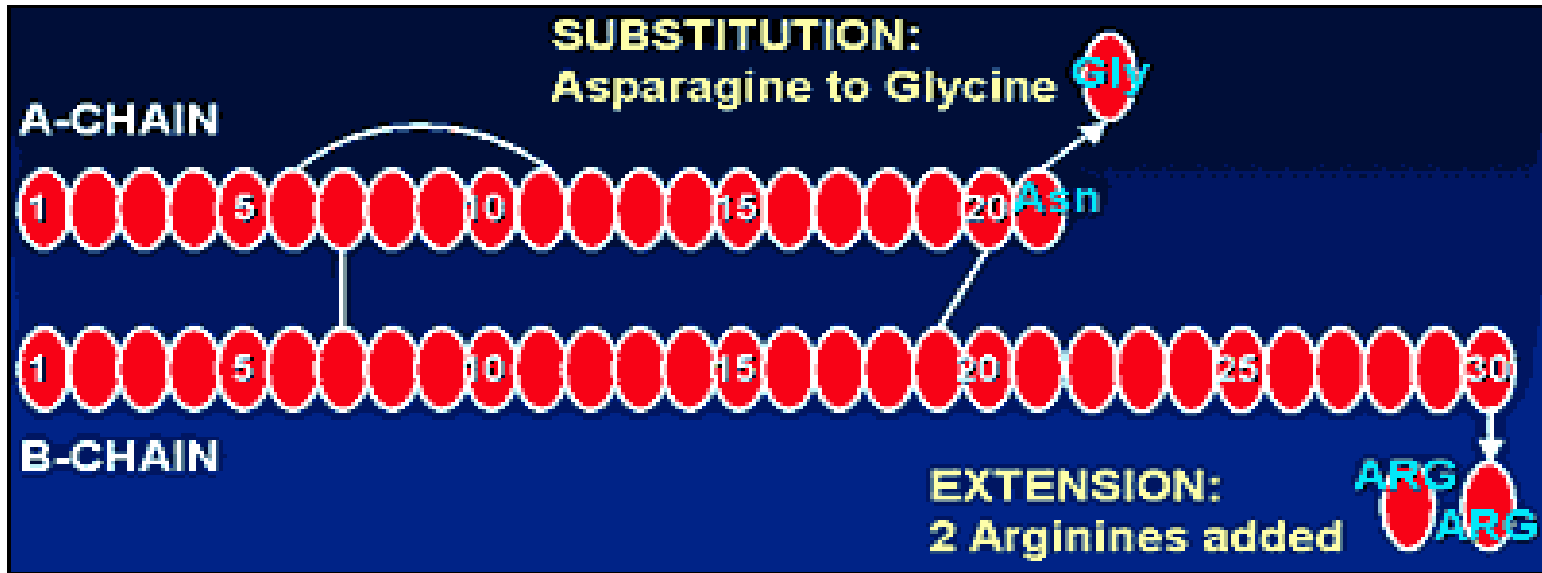
Human Insulin

- Short acting
- Intermediate acting
- Mixed

Insulin analogues

- Rapid acting
- **Basal**
- mixed

Insulin Glargine (Lantus)

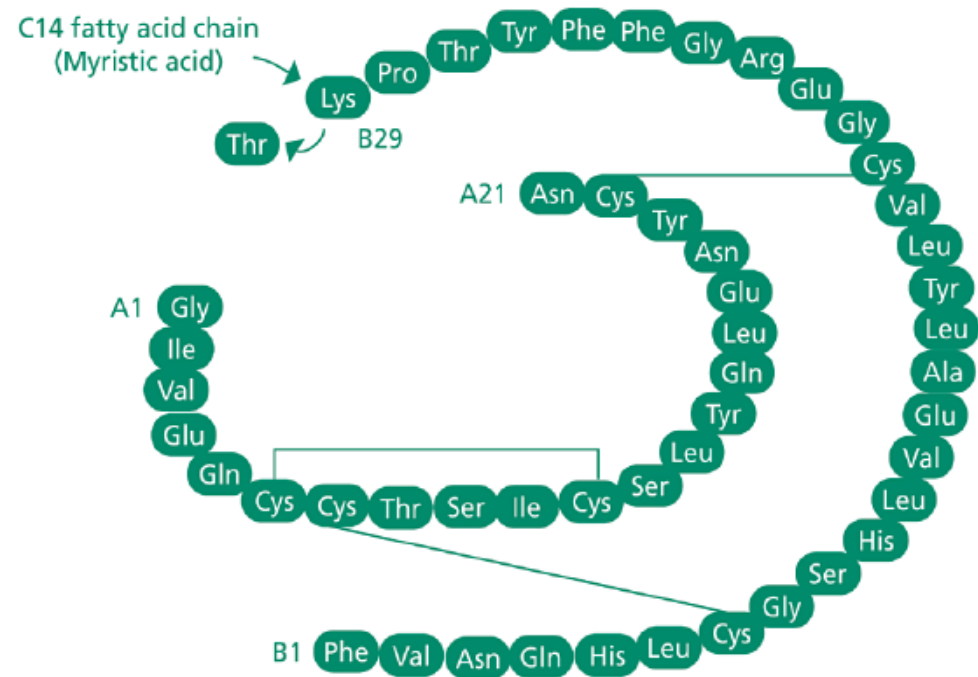


2 modifications: A21 (asparagine replaced by glycine) & arginines added to C-terminus of the B-chain .

These changes make the agent most soluble at a slightly acidic pH and less soluble under neutral conditions. Upon injection, insulin glargine precipitates into stable hexamers within the physiologically pH-neutral environment, thereby prolonging its dissociation and subsequent absorption .

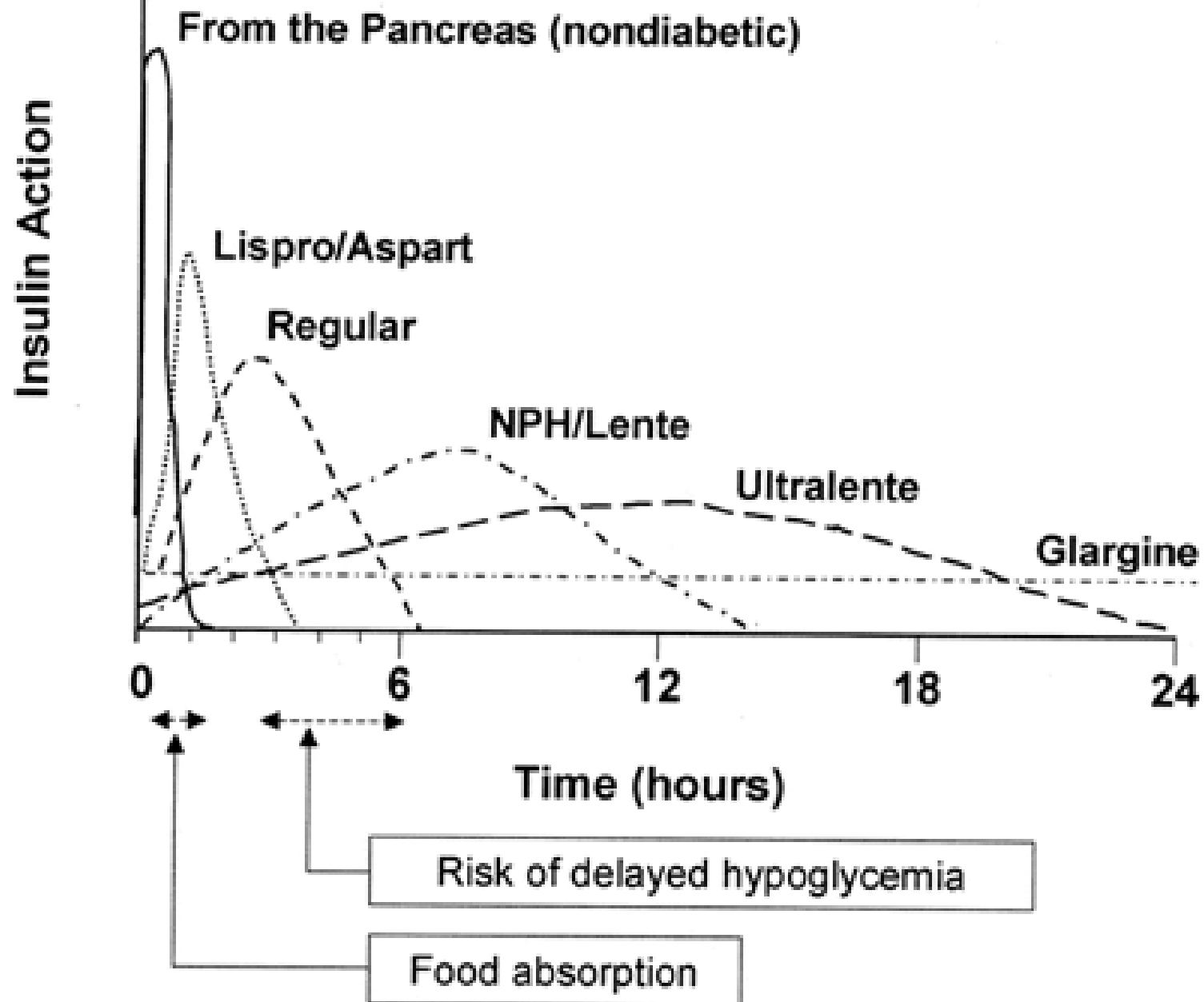
Insulin Detemir (Levemir)

- Addition of a C14 fatty acid side chain at position B29.
- Lead to hexamer and reversible albumin binding within SC tissue.



Basal Insulin analogues (Glargine, Detemir)

- Onset of action: 1-2 hrs
- Peak action: peakless
- Maximal duration: 20-24 hours



Types of Insulin

Human Insulin

- Short acting
- Intermediate acting
- Mixed

Insulin analogues

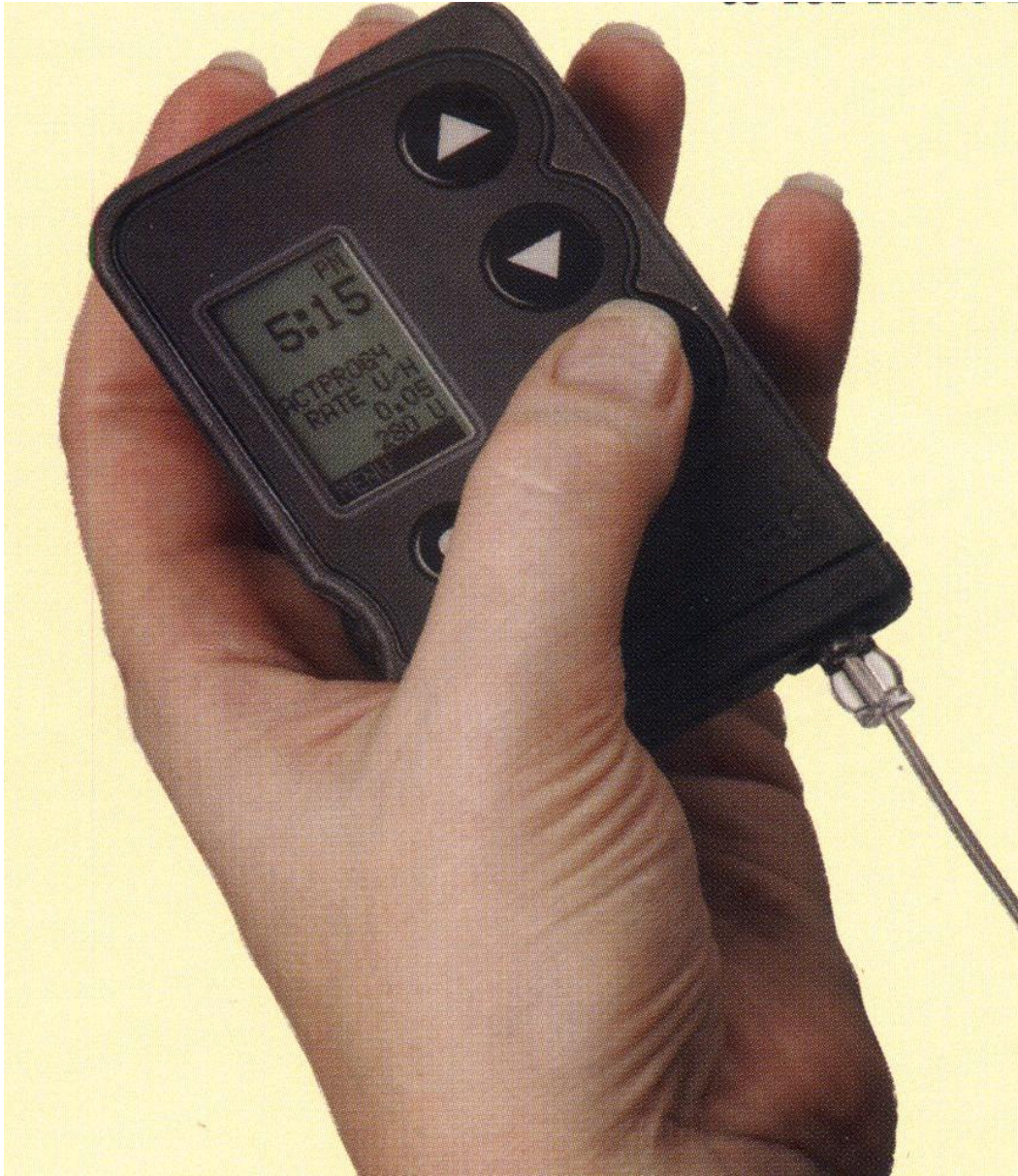
- Rapid acting
- Basal
- **mixed**

Insulin regimens

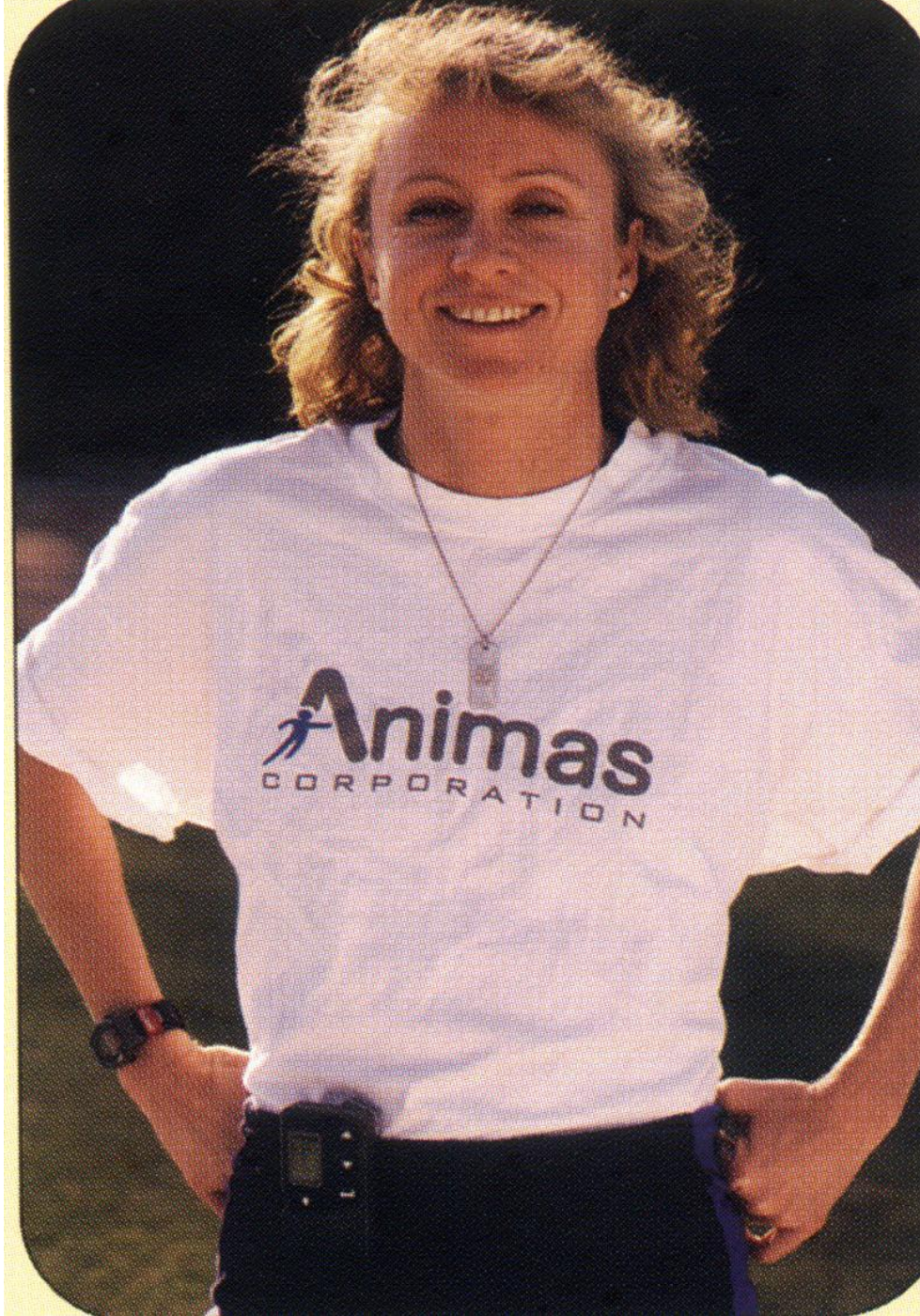
- **Most widely used insulin regimens:**
 - **Twice-daily injections, mixture short and intermediate, before breakfast and the evening meal**
 - **Three daily injections, mixture short and intermediate before breakfast, short-acting before the evening meal and intermediate-acting before bed**
 - **Short-acting insulin before main meals, intermediate before bed**







Insulin pumps



Complications of insulin therapy

Hypoglycemia:

- Mild
- Severe

Complications at the injection site

- **Shallow injections result in intradermal insulin delivery and painful, red lesions or even scarring.**
- **Local allergic responses rarely occur early in therapy and usually resolve spontaneously.**
- **Generalized allergic responses are very rare.**
- **Fatty lumps, known as lipohypertrophy, may occur as the result of overuse of a single injection site with any type of insulin.**
- **Lipoatrophy !!**
- **Injection site abscesses are extremely rare.**

Weight gain

- **Patients who are in poor control when insulin is started tend to gain most weight**
- **Many patients show weight gain on insulin treatment, especially if the insulin dose is increased inappropriately**

Whole pancreas and pancreatic islet transplantation

- **Whole pancreas transplantation has been performed for some 30 years, usually in diabetic patients who require immunosuppression for a kidney transplant.**

- **Islet transplantation is performed by harvesting pancreatic islets from cadavers (two or three pancreata are usually needed);**
- **These are then injected into the portal vein and seed themselves into the liver.**
- **This form of treatment was attempted for many years with poor results.**
- **The main indication is disabling hypoglycaemia, and the main disadvantage is the need for powerful immunosuppressive therapy, with associated costs and complications.**

Thank you