B.Pharm_BPHC804T_ Unit 4_Hormones

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Thyroid and Antithyroid Drugs

THYROID HORMONES

The thyroid gland secretes 2 types of hormones

1 Follicular cells of thyroid gland secrete Iodine containing amino acids (are important for growth, development and metabolism) and these are:

Triodothyronine, (T_3)

Tetraiodothyronine, (T_4)

2 Calcitonin is important in the regulation of calcium level it is secreted by parafollicular cells of thyroid.

BIOSYNTHESIS OF THYROID HORMONES

- The iodine is necessary for the synthesis of T3 & T4 is derived from food or iodine supplement.

- Iodine uptake is an active process. Once taken up by the thyroid gland, iodine undergoes a series of enzymatic reactions that convert it into active hormone.

1st step : Transport of the iodine into the gland by intrinsic follicle cell basement membrane protein called sodium iodine symporter(NIS).

2nd step: Iodine trapped by follicle cell is carried across apical membrane by another transporter ‘Pendrin’ . Iodide is oxidized by thyroid peroxidase to iodinium or hypoiodous acid (HOI) , or enzyme linked hypoiodate (E-OI) with the help of H_2O_2.

3rd step: Iodination of tyrosine residues within the thyroglobulin molecule to form monoiodotyrosine (MIT) & diodotyrosine (DIT) this process is called iodide organifaction.

4th step: Two molecules of DIT combine within the thyroglobulinto form L-thyroxine (T_4)

- One molecule of MIT & one molecule of DIT combine to form T_3.

5th step:

- T4, T3, MIT & DIT are released form thyroglobulin by exocytosis & proteolysis of thyroglobulin.
- The DIT & MIT are deiodinated within the gland & the iodine is reutilized. This process of proteolysis is blocked by high levels of intrathyroidal iodide.

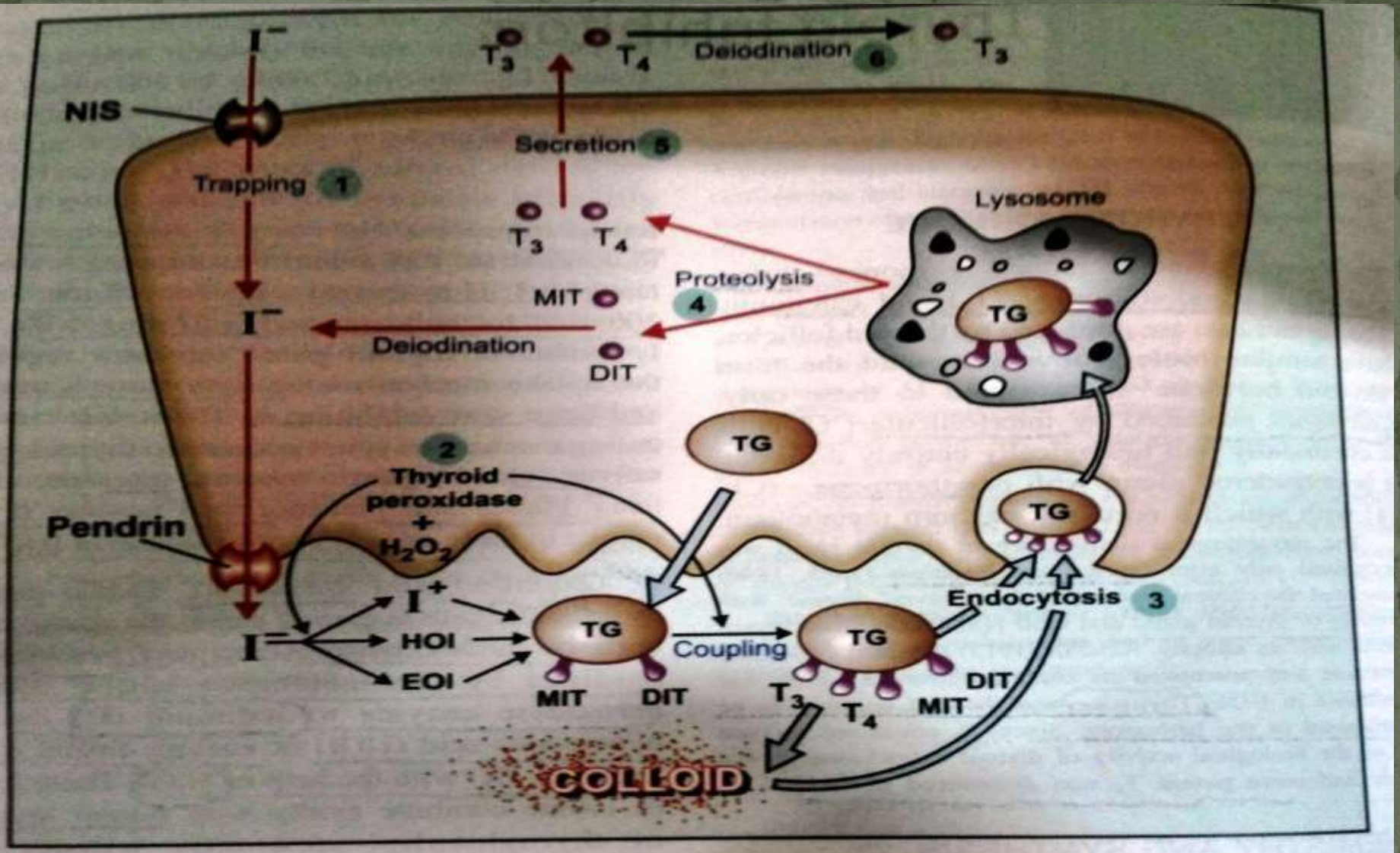


Fig. 18.1: Synthesis, storage and secretion of thyroid hormone

TG—Thyroglobulin; MIT—Monoiodotyrosine; DIT—Diiodotyrosine; T_3—Triiodothyronine; T_4—Thyroxine (Tetraiodothyronine); HOI—Hypoiodous acid; EOI—Enzyme linked hypoiodate; NIS—Na^+-iodide symporter; Thyroid-stimulating hormone (TSH) activates steps 1, 2, 3, 4, and 5; Ionic inhibitors block step 1; Excess iodide interferes with steps 1, 2, 3 and 5 with primary action on step 3 and 5; Propylthiouracil inhibits steps 2 and 6; Carbimazole inhibits step 2 only

- The ratio of T4 to T3 within the thyroglobulin is 5:1 so that most of the hormone released is thyroxine.
- Most of circulating T3 in the blood is derived from peripheral metabolism of thyroxine.

TRANSPORT

- Thyroid hormones are avidly bound to plasma proteins.
- Only 0.03-0.08% of T4 and 0.2-0.5% of T3 are in free form.
- Binding occurs to 3 plasma proteins in following decreasing order
  - Thyroxine binding globulin(TBG)
  - Thyroxine binding prealbumin(Transthyretin)
  - Albumin

PERIPHERAL METABOLISM

- Primary pathway of peripheral metabolism is deiodination. Deiodination of T4 may occur by removal of iodine from the outer ring producing 3,5,3’ triiodothyronine (T3).

- Alternatively deiodination of the inner ring produces 3,3’,5’ triiodothyronine (reverse T3or rT3) which is inactive.

- Drugs such as ipodate, beta-blockers & corticosteroids and severe illness or starvation inhibit the 5-deiodinase necessary for the conversion of T4 to T3 resulting in low T3 & high rT3.

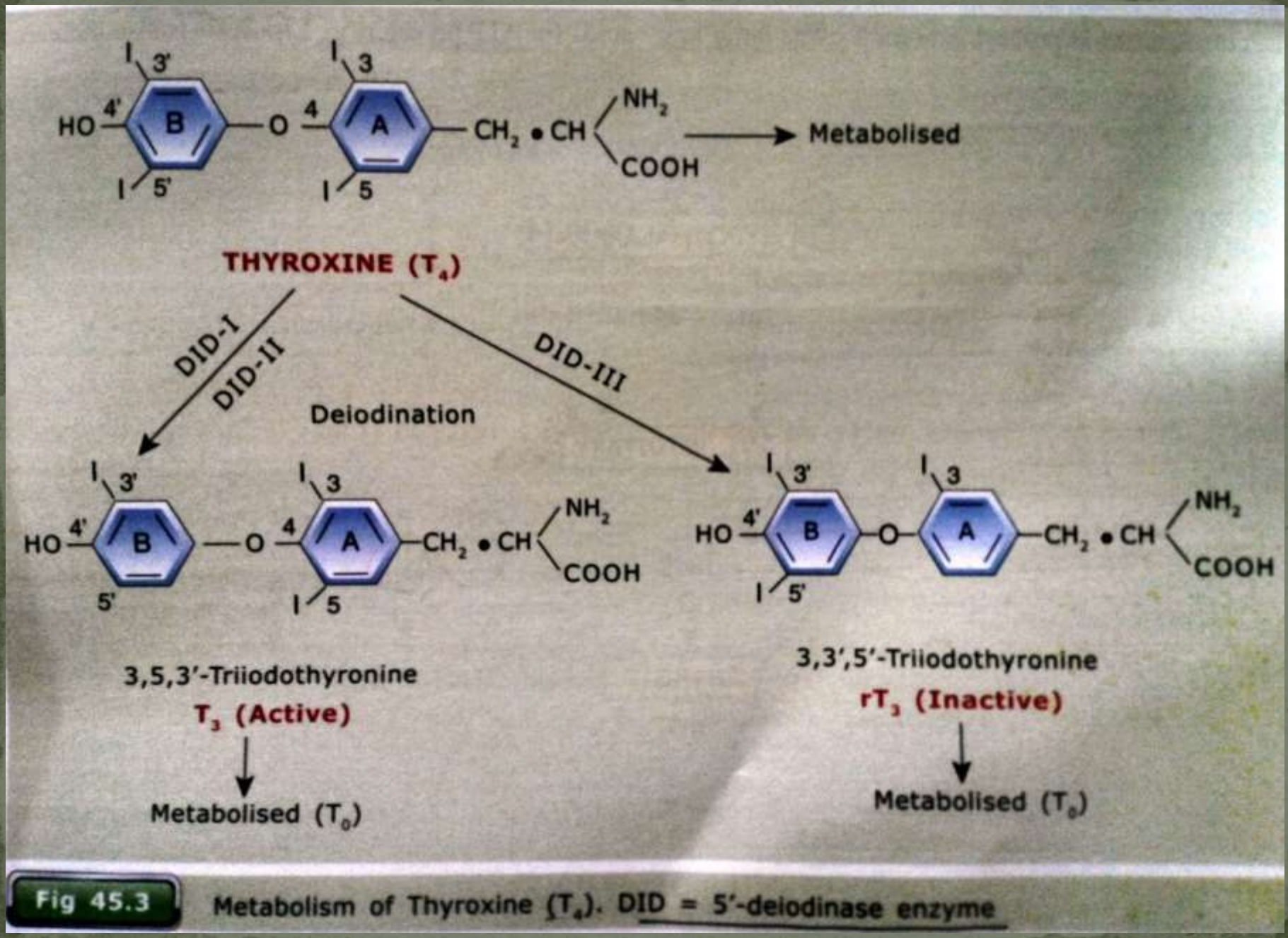


Fig 45.3 Metabolism of Thyroxine (T_4). DID = 5′-deiodinase enzyme

REGULATION OF THYROID FUNCTION

- Hypothalamic cells secrete thyrotropin releasing hormone (TRH) into the capillaries of the pituitary portal system. TRH stimulates the synthesis & release of thyroid stimulating hormone (TSH). TSH stimulates an adenylyl cyclase-mediated mechanism in the thyroid gland to increase the synthesis& release of T_4 & T_3

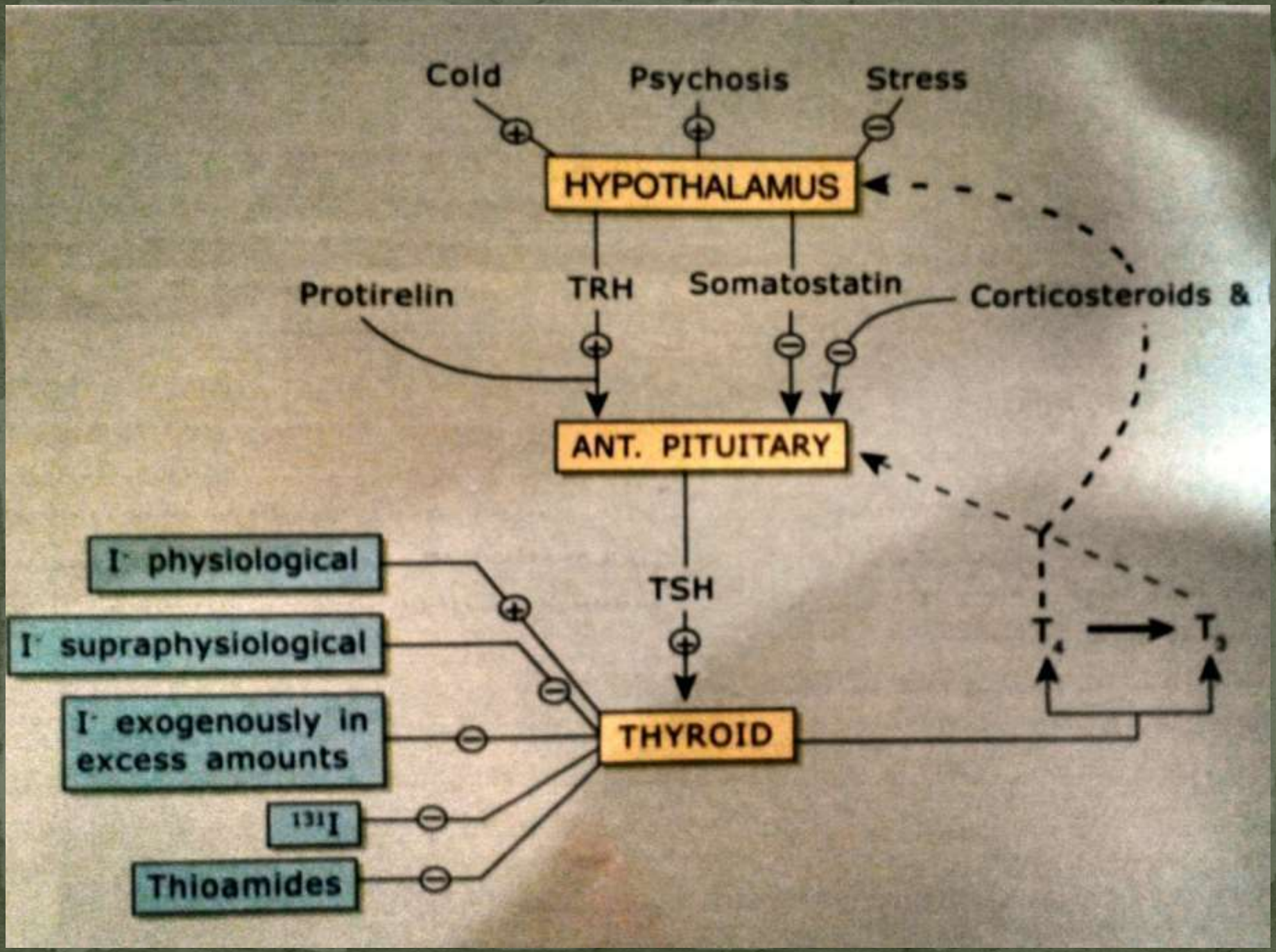
- T_4 & T_3 act in a negative feedback fashion (mechanism) to block the action of TRH on the pituitary gland & on the hypothalamus to inhibit the synthesis & release of TRH.

- The thyroid gland also regulates its uptake of iodide & thyroid hormone synthesis by intrathyroidal mechanism that are independent of TSH.

- These mechanisms primarily related to the level of iodine in the blood.

- High concentration of iodide inhibits iodide organification, and effect that is useful in the treatment of thyroiddisease.

- Inadequate iodine intake results in diffuse enlargement of the thyroid (Goitre).


Cold
Psychosis
Stress
HYPOTHALAMUS
Protirelin
TRH
Somatostatin
Corticosteroids &
ANT. PITUITARY
TSH
I⁻ physiological
I⁻ supraphysiological
I⁻ exogenously in excess amounts
^{131}I
Thioamides
THYROID
T_4
T_3

MECHANISMS OF ACTION OF T_4 & T_3

- T3 is 10 times more potent than T4 and since T4 is converted to T3 in target cells(theliver & kidneys), most of the effect of circulating T4 is probably due to T3.
- Thyroid hormone binds to receptors in the nucleus that control the expression of genes responsible for many metabolic processes.
- These receptors when activated by T3 bind to DNA response elements & control synthesis of mRNA which codes for specific proteins that mediate the action of thyroid hormones.

- The proteins synthesized differ depending on the tissue involved. These proteins include Na+/K+ ATPase, specific contractile protein in smooth muscles & the heart, enzymesinvolved in lipid metabolism, important developmental components in the brain . etc.

EFFECTS OF THYROID HORMONE

- Includes normal growth & development of the nervous, skeletal & reproductive systems .
- Controls metabolism of fat, CHO, proteins & also metabolism of drugs.
- Thyroid deprivation in early life results in irreversible mental retardation & dwarfism (congenital cretinism), thyroid hyperactivity results in thyrotoxicosis.
- Decrease in thyroid activity results in hypothyroidism (myxedema).

PHARMACOKINETICS

- All of the naturally occurring T4 & T3 exist in Levo form (L-isomers), the Dextro form of Thyroxine has only 4% of the biological activity of the L-isomer.

- Thyroxine is well absorbed from the duodenum & ileum when taken orally; oral bioavailability of L-Thyroxine is about 80% absorbed while T3 is almost completely absorbed. T4 & T3 can also be given intravenously.

THYROID PREPARATIONS

These are synthetic compounds.

1. Levothyroxine (T_4).
2. Liothyronine (T_3).

- These synthetic compounds are identical to the natural hormones.

Levothyroxine (T4).

Absorption:

- 75-80% of drug is absorbed orally
- Absorption is reduced by
  - food,
  - alumunium containing antacids
  - Cholestyramine
  - Calcium carbonate
  - Proton pump inhibitor

Should be taken on emptystomach

Drug metabolism

- Metabolized mainly in liver
- Hepatic CYP3A4 induction reduces the plasma concentration of the drug.
- eg phenytoin, carbamazepine, rifampicin

Drug Excretion:

- Excreted partially in bile and in urine.
- Due to it's strong binding with plasma protein it protects the drug from metabolism and excretion and increases its $t_{1/2}$
- Due to longer $t_{1/2}$ (7 days) it takes longer time for clinical effects

Clinical uses

- Thyroid hormone replacement therapy in hypothyroid state, to replenish thyroid hormone lost due to illness eg .
  - Autoimmune thyroiditis
  - Suppression of TSH after thyroidectomy
  - radioiodine ablation in thyroid carcinoma.
- initially 50-100 µg administered orally increased 25-50 µg at 2weeks interval until the patient doesn't complain of ADR or until the serum TSH levels become normal.

Liothyronine (T3).

- Liothyronine (T3) has faster onset but shorter duration of action.
- It is costlier than levothyroxine
- Used only in acute emergencies

- eg
  - myxedema coma (100 µg is given I.V followed by 25 µg every 6 hrly I.V daily
  - Short term suppression of TSH in patients undergoing surgery of thyroid cancer
  - 5'- deiodinase defeciency

ANTI- THYROID DRUGS

- These are drugs used to lower the functional capacity of the hyperactive thyroid gland.

- Thyrotoxicosis is due to excessive secretion of thyroid hormones. Graves' disease(Autoimmune disorder) and toxic nodular goiter are two main causes.

Classification of Antithyroid Drugs

Thioamide derivatives

- Carbimazole
- Methimazole
- Propylthiouracil

Inhibitor of hormone release

- Iodine
- Iodides of Na, k
- Organic iodides

Iodinated contrast media

- Oral ipodate
- Ipanoic acid
- Diatrizoate (I.V)

Radioactive iodine

- ^{131}I (Radioactive iodine)

Ionic inhibitors

- Thiocynate(-SCN)
- Perchlorates(-ClO_4)
- Nitrates(NO_3)

THIOAMIDES

- Methimazole (carbimazole)
- Propyl thiouracil (PTU)

✓ These 2 are the major drugs used in the treatment of thyrotoxicosis (Carbimazoles converted to methimazole in vivo).

MOA: These drug inhibit thyroid hormone production by

a) inhibiting thyroid peroxidase which is required in intrathyroidal oxidation of Iodide.

b) by inhibiting the iodination of tyrosine

c) by inhibiting coupling of MIT and DIT to form thyroid hormones

d) propylthiouracil also inhibits peripheral conversion of T_4 TO T_3 by inhibiting DID -1 enzyme

Carbimazole

- More potent given in a single daily dose
-Completely absorbed & readily accumulated in thyroid gland
-Excreted in urine but slower than PTU.
-Has some immunosuppressive action leading to decrease in serum TSH receptor antibodies.
-Has little effect on conversion of T4 to T3
-Crosses placenta.
-It is excreted in breast milk.

Propyl thiouracil (PTU)

- Dose is 10 times that of Carbimazole given every 6-8 hrs.
- Rapidly absorbed with a bioavailability of 50-80 %
- Excreted in urine within 24 hrs
- Has no immunosuppressive effect
- It inhibits the peripheral conversion of T4 to T3
- Crosses placenta less readily, Preferable in pregnancy
- Not excreted in breast milk

Therapeutic uses of Thioamide derivatives

- These drugs controls thyrotoxicosis in both graves disease and toxic nodular goiter.
- Clinical improvement starts after 1-2 weeks
- Propylthiouracil : 50-150mg TDS followed by 25-50 mg BD-TDS for maintenance
- Carbimazole: 5-15 mg TDS initially
- Maintenance dose is 2.5-10mg daily in 1-2 divided doses

ADVERSE EFFECTS OF THIOAMIDES

- Occur in 3-12% of treated patients.
- Most reactions occur early. The most common adverse effect is maculopapular pruritic rash, sometimes accompanied by fever.

RARE ADVERSE EFFECTS INCLUDE:

Urticarial rash.
Vasculitis.
Hepatic failure
Arthralgia.
A lupus like reaction
Cholestatic jaundice.
Lymphadenopathy.
Hyperprothrombinemia, aplastic anemia
Agranutocytosis

IODIDE SALTS AND IODINE:

- Iodide salts inhibit organification (iodination of tyrosine) and thyroid hormone release.
- These salts also decrease the size & vascularity of the hyperplastic thyroid gland.
- Since iodide salts inhibit the release as well as the synthesis of the hormone, their onset of action occurs rapidly within 2-7 days.
- This effect is transient because the thyroid gland escapes from iodide block after several weeks of treatment.

- Iodide salts are used in thyroid storm(severe thyrotoxicosis) & to prepare the patient for surgical resections of the hyperactive thyroid.

- The usual forms of this drug are lugol's solution(iodine & potassium iodide) and saturated solution of potassium iodide.

- Lugols solution: 5% iodine in 10% KI solution : 5-10drops/day

- Iodide salts (sod/pot) 100-300 mg/day

Adverse effects

- Acute adverse effects occurs in individuals who are sensitive to iodine.
- Manifestations are
  - Swelling of lips,eyelids,
  - Angioedema of larynx
  - Fever
  - Joint pain
  - Petechial hemorrhage

- Chronic overdose (iodism)
  - Inflammation of mucous membrane
  - Salivation
  - Sneezing
  - Swelling of eyelids
  - G.i disturbance

IODINATED CONTRAST MEDIA (IPODATE):

- It suppresses the conversion of T4 to T3 via 5’ deiodinase in the liver, kidney and other peripheral tissues.

- Ipodate has proved very useful in rapidly reducing T3 concentration in thyrotoxicosis (in thyroid storm)

RADIOACTIVE IODINE

- Radioactive iodine is administered as sodium salt of ^{131}I dissolved in water and taken orally.
- ^{131}I emits x ray as well as β particles
- ^{131}I is concentrated by thyroid, incorporated in colloid- emits radiation from within the follicles.
- β particles penetrates around 0.5-2 mm of tissue
- Thyroid follicular cells are affected within undergoes pyknosis and necrosis followed by fibrosis when a large dose is given.

Uses

- Most common indication is hyperthyroidism due to Graves' disease or Toxic nodular goitre.
- Avg therapeutic dose is 3-6 milli curie
- Response is slow , it starts after 2 weeks and gradually increases reaching peak at 3 month.

Ionic inhibitors

- Certain monovalent anions inhibit iodide trapping by NIS into thyroid because of similar hydrates ionic size.
- T4 ,T3 synthesized is inhibited.
- They are very toxic so they are not used.
- eg: Thiocyanates, Perchlorates

β-blockers

- Propranolol is used to rapidly alleviate manifestations of thyrotoxicosis that are due to sympathetic overactivity

eg: Palpitation, tremor, nervousness and sweating,

- In addition they reduce peripheral conversion of T_4 to T_3

- β-blockers are used in hyperthyroidism in following situations:

a)while awaitng response to propylthiouracil/carbimazole

b)along with iodide for preoperative preparation before subtotal thyroidectomy

c) thyrotoxic crisis

- Propranolol 1-2mg slow I.V may be followed by 40-80 mg oral every 6 hrly.

Insulin and Oral Hypoglycemics

OBJECTIVE S

1. Understand the process of insulin synthesis and secretion by the β cell.
2. Understand the physiology of circulating insulin, C- peptide and proinsuli
3. Identify factors influencing insulin secretion.
4. Describe the metabolic effects of insulin and the major metabolic aberrations of insulin resistance.
5. Identify therapeutic problems encountered in insulin therapy.
6. Explain the limitations of oral hypoglycemics in management of diabetes
7. Explain the differences among commercially available insulin preparations.
8. Understand the different mechanisms of action between the commonly used oral hypoglycemic agents.

Prototype Drugs

Insulin and analogs

- Insulin (Humulin®)
- LisPro (Humalog®)
- Glargine (Lantus®)
- Insulin aspart (NovoLog®)
- Inhaled Insulin (Exubera®)

Somatostatin analogs

- Octreotide

Oral Hypoglycemic Agents:

Sulfonylureas

- Glimepiride
- Glipizide

Meglitinides

- Repaglinide

Biguanides

- Metformin

Thiazolidinediones

- Rosiglitazone
- Pioglitazone

Synthetic Incretin

- Exenatide

Dipeptidyl peptidase- 4 Inhibitors

- Sitagliptin

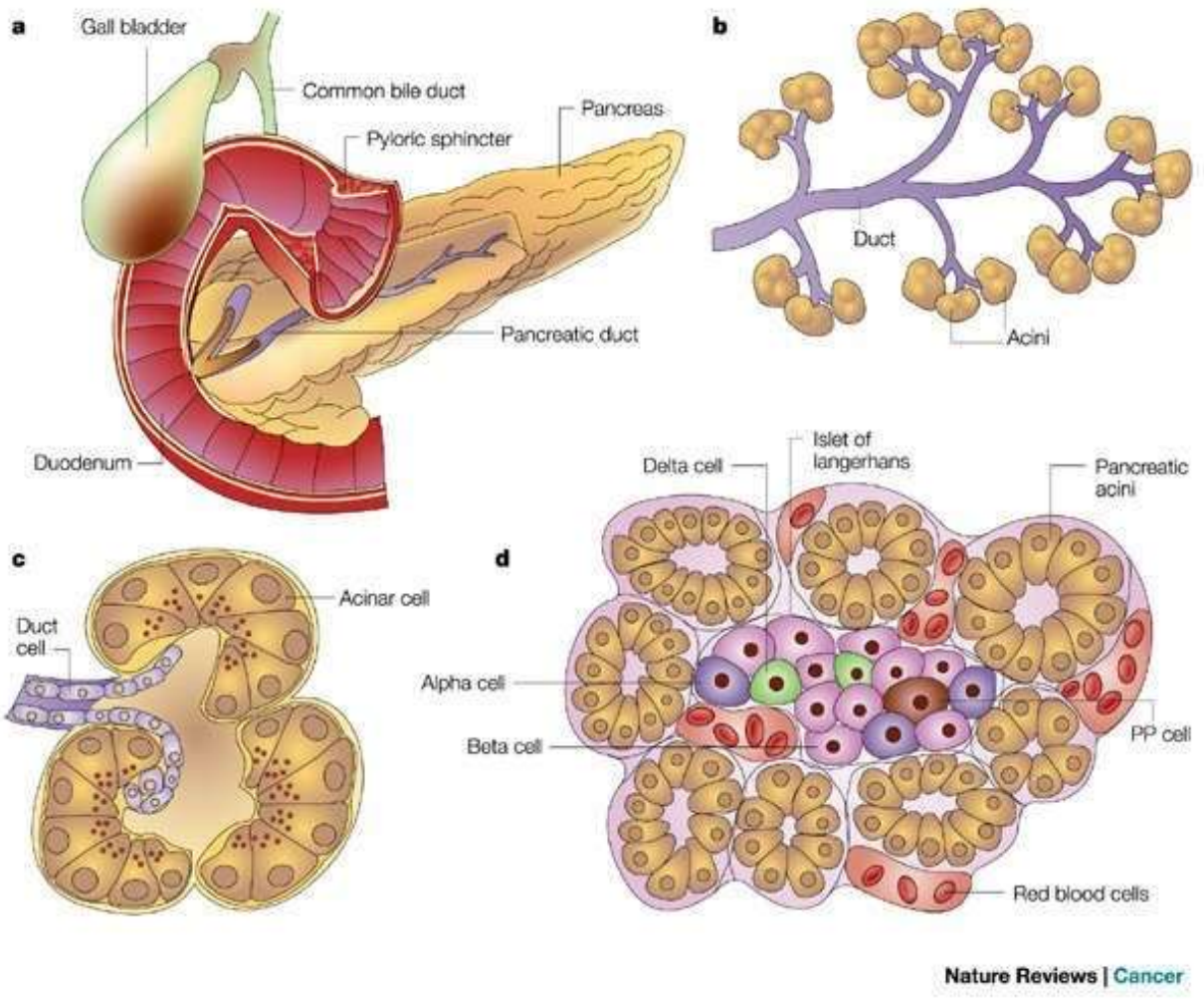
Hyperglycemic Agent

- Diazoxide

Insulin

Polypeptide hormone secreted by the pancreatic Islets of Langerhans

essential for the metabolism of carbohydrates and is used in the t



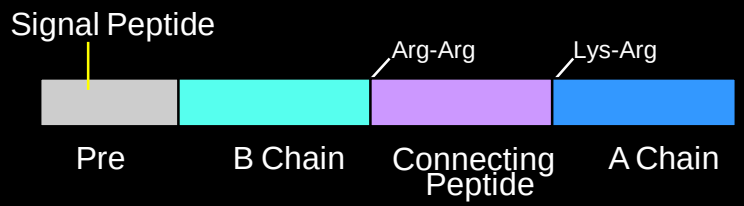
Insulin

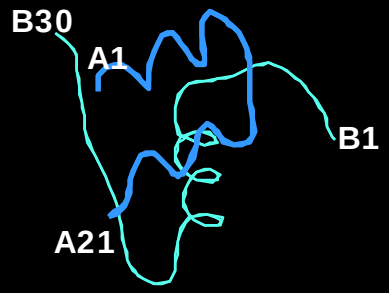
Consists of 2 polypeptide chains (A and B) connected by disulfide bonds

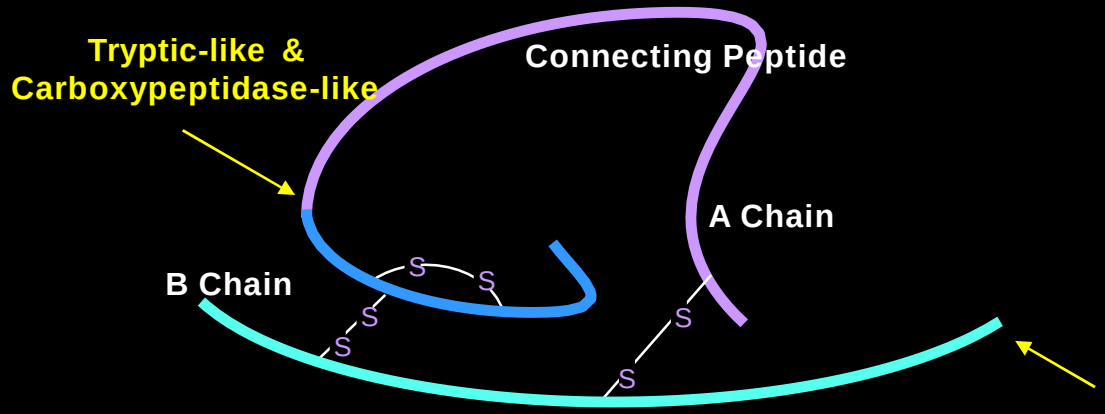
Positions B24 and B25 are important sites for receptor recognition; substitution at these sites is associated with a marked change in biological activity.

exists as a monomer, dimer or hexamer; each hexamer binds two molecules of Zn^{2+} which coordinates crystal formation within β granules.

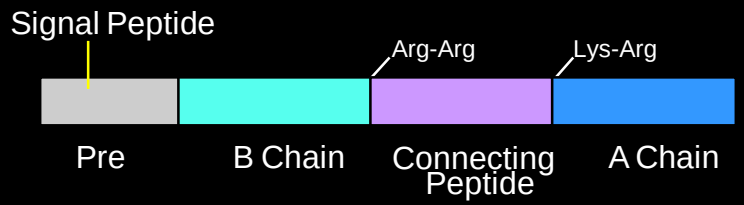
Processing of Proinsulin to Insulin and C-peptide

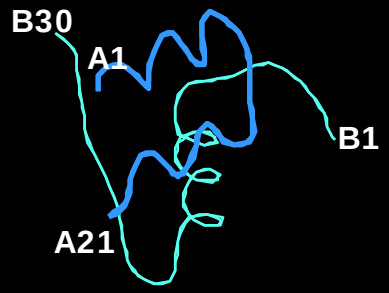


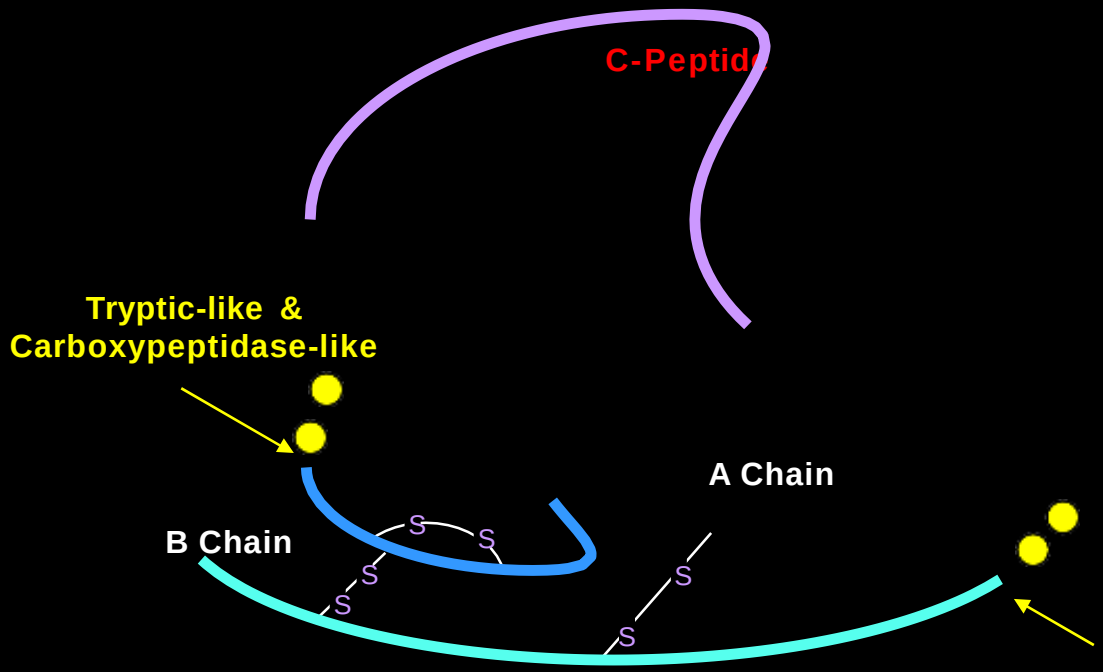




Processing of Proinsulin to Insulin and C-peptide







B. Insulin Biosynthesis and Secretion

1. Insulin gene is on chromosome 11

2. Synthesized by β cells of the Islets of Langerhans of the endocrine pancreas as a 12, 000 Dalton precursor (pre-proinsulin) which is processed to final secreted products (proinsulin, insulin, C-peptide).

3.Synthesis is regulated at the transcriptional and translational levels.

B. Insulin Biosynthesis and Secretion

4. Three Biosynthetic Products:

a. Proinsulin

- Released in small amounts (3- 4%)
  except in pathologic states*

-constitutes 10- 50% of circulating immunoreactive insulin content

- reduced biological action ~ 2% activity of insulin
- prolonged circulation time - $T_{1/2}$ = 17 min.

* insulinoma, familial hyperproinsulinemia
- diagnostic = 80%

B. Insulin Biosynthesis and Secretion

4. Three Biosynthetic Products

b. C- peptide

- connecting peptide (joins A and B chains)
- removed from proinsulin by proteases within secretory granules

- released in equimolar amounts with insulin
- not removed from the circulation by the liver - thus found in higher concentrations than insulin (4:1)

- Clinically important marker of insulin secretion

DIAGNOSTIC

B. Insulin Biosynthesis and Secretion

4. Three Biosynthetic Products

c. Insulin

- Released from the beta cell in a

rapid first phase and slower second phase

- represents release of insulin stored in granules and newly synthesized insulin, respectively.

-significant amount is removed during first pass through the liver, therefore hepatic insulin levels exceed peripheral level.

- $T_{1/2}$ = 5- 6 min

Factors Affecting Insulin Secretion

5. Factors Affecting Insulin Secretion

a. Stimulatory Factors

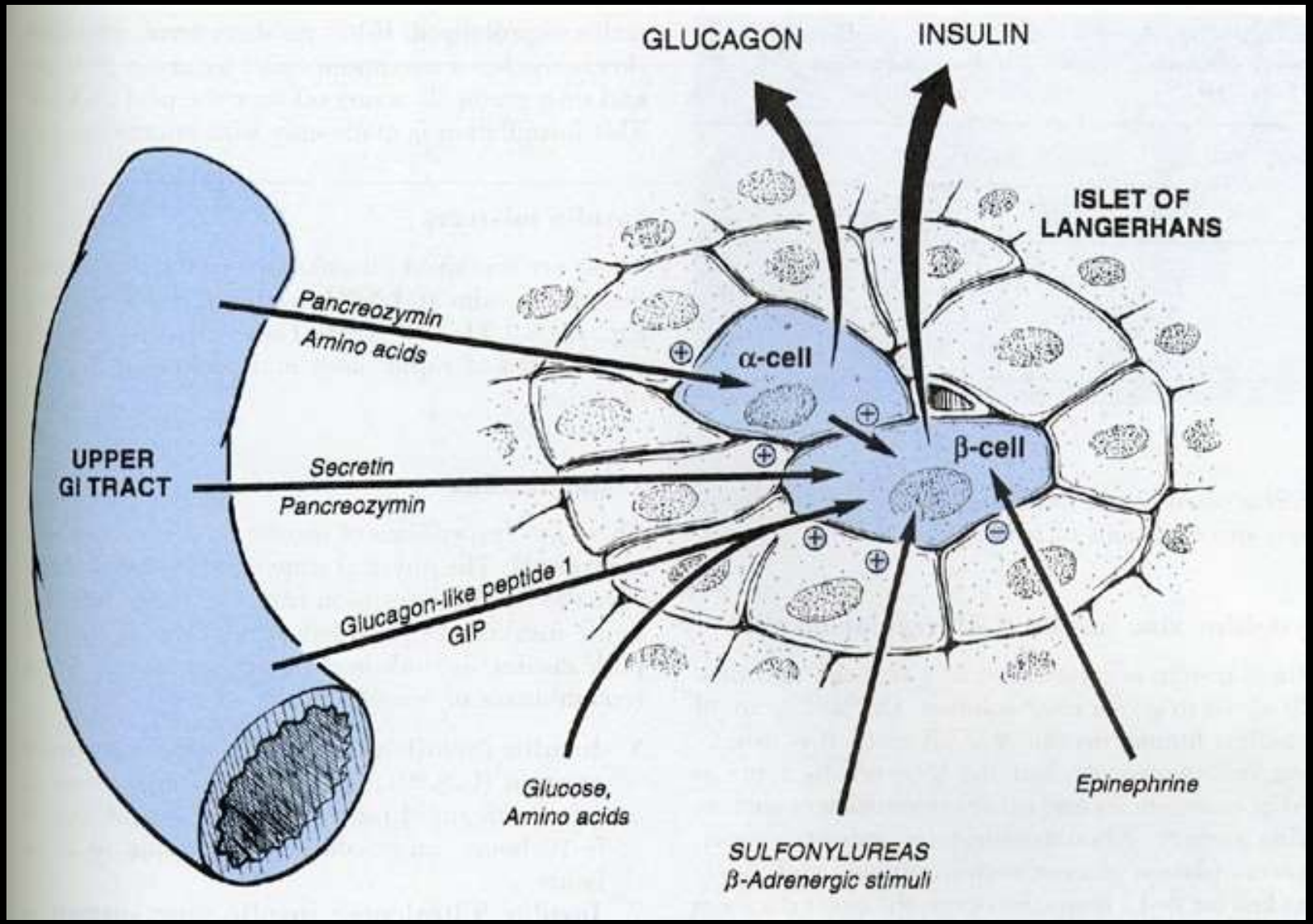
Metabolic components
glucose* / amino acids / fatty acids / ketones

Hormonal components - ↑ cAMP - ↑ Ca^{2+}
Growth Hormone / ACTH / Glucagon
Cholinergic and β_2-adrenergic stimulation
(propranolol ↓)

Intestinal nutrients via gastrin, secretin, enteroglucagon, CCK, GLP-1
- oral vs. iv glucose yields a larger response

b. Inhibitory Factors - Decrease cAMP Levels
insulin / epinephrine / adrenergic stimulation / serotonin

Factors Affecting Insulin Secretion



Glucose- induced Insulin Secretion

Glucose enters β cell by facilitated transport via Glut 2

It is phosphorylated by Glucokinase - (β cell and liver only)

The ability of sugars to be phosphorylated and undergo glycolysis correlates closely with their ability to stimulate insulin secretion

Glucose metabolism initiated by Glucokinase ↑ ↓

- **causes a change in the ATP/ADP ratio (ATP; MgADP)**
- **alters/closes ATP- sensitive potassium channels (K_{ATP} channel)**

Glucose- induced Insulin Secretion

The β cell depolarizes, leading to the compensatory activation of a Voltage- dependent Ca^{2+} channel and Ca^{2+} influx

Secretion is dependent upon intracellular Ca^{2+} levels

✔ Intracellular Ca^{2+} acts as the insulin secretagogue

cAMP increases intracellular Ca^{2+} levels-

e.g., glucagon and β-adrenergics

Glucose- induced Insulin Secretion

Recap:

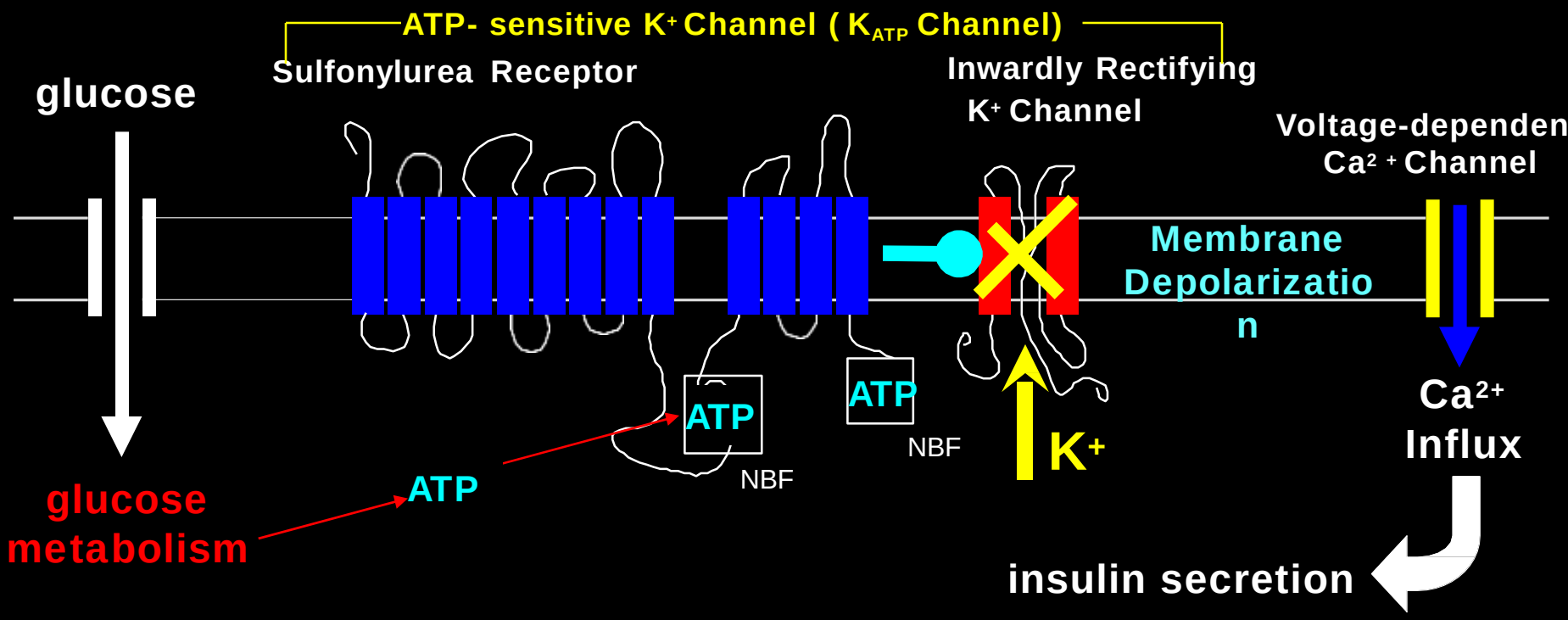
✔ **ATP- sensitive potassium channels (K_{ATP} channel) link the metabolic state of the cell to the membrane potential.**

✔ **Glucose transported into the β cell is metabolized, in turn increasing ATP and decreasing MgADP levels in the β cell.**

✔ **The increase in ATP:ADP ratio CLOSES the K_{ATP} channel depolarizing the β cell membrane leading to the opening of voltage- dependent Ca^{2+} channels allowing Ca^{2+} influx into the β cell.**

✔ **The rise in intracellular Ca^{2+} triggers insulin secretion.**

K_{ATP} Channel Structure and Function



NBF

Nucleotide Binding Fold = site of ATP/ ADP binding

Four copies of each subunit combine to form an active K_{ATP} channel

Mechanism of Insulin Action

1. **Insulin binds to an α subunit of the Insulin Receptor activating the tyrosine kinase domain on its β subunits**

- Receptor autophosphorylation leads to activation of cellular effectors and a biologic response

A key response is recruitment of glucose transporters to the cell surface in skeletal muscle and adipose tissue

No competitive antagonists
or
partial agonists of insulin exis..t.yet

Oral insulin- mimetic has been described

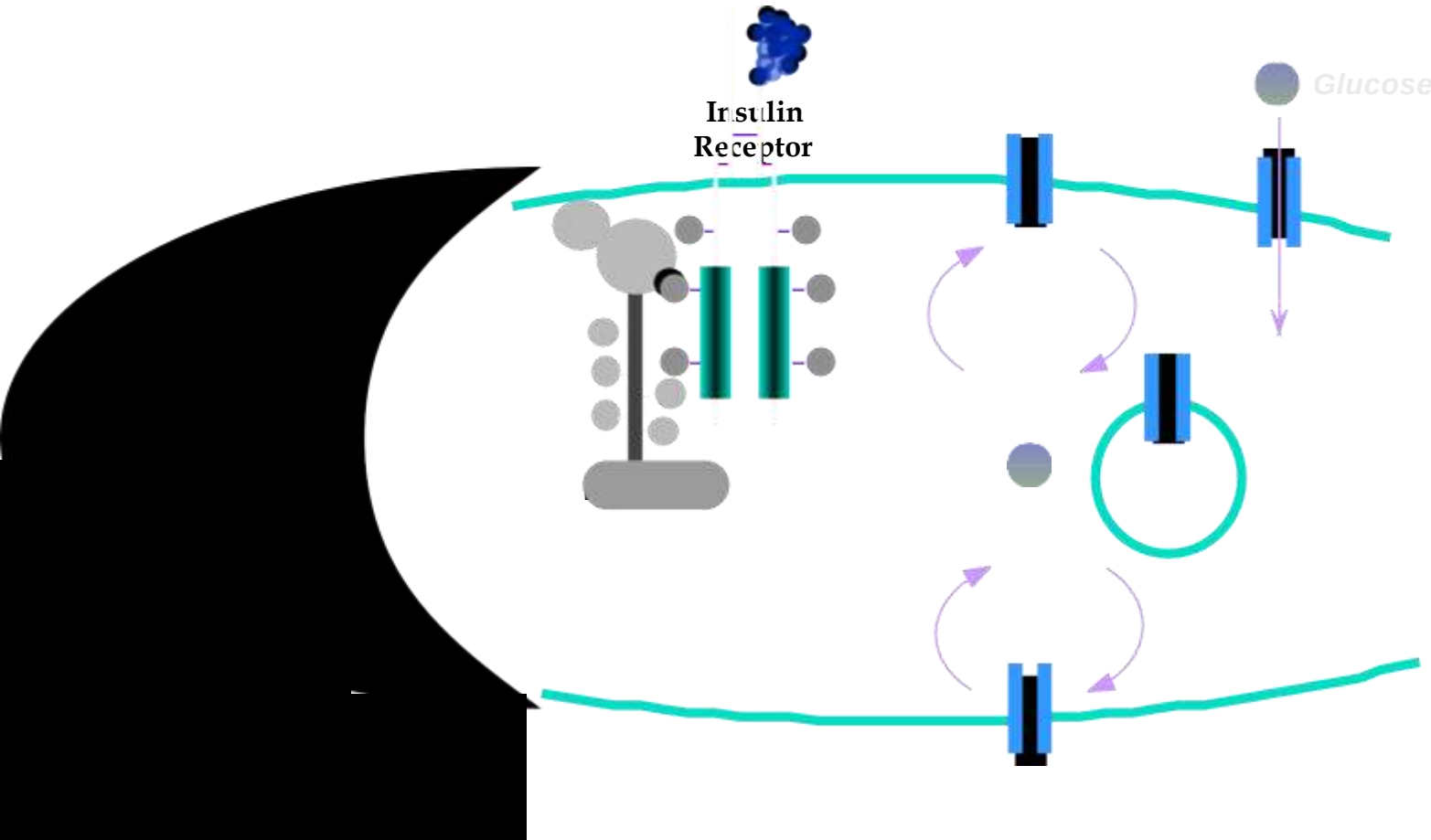
Recruitment of Effectors

Protein:Protein Interactions

Signal Transduction Networks

Activation of Phosphorylation Cascades

Skeletal muscle
Adipose Tissue



Insulin Action (cont'd.)

Facilitated diffusion along a downhill gradient is assured by the phosphorylation of glucose to G- 6- P.

2. **The extent of insulin action is dependent upon:**

   a. Level of circulating "free" insulin

   - β-cell secretory activity

   - Clearance from circulation - degradation - "insulinases"

   b. Number of cell surface insulin receptors

   - Down regulation phenomenon - affinity and number

   c. Presence of anti-receptor antibodies

3. **"Post-receptor" cellular events may also regulate insulin action**

   a. Counter-regulatory hormone action on the cell:

   - catecholamines / glucagon / cortisol / growth hormone

Metabolic Effects of Insulin - A Review

Major regulator of overall body fuel metabolism

Effect on liver:

- **Anabolic action**
  - **Promotes glucose storage as glycogen**
    - **induces glucokinase and glycogen synthase,**
    - **inhibits phosphorylase.**
  - **Increases triglyceride synthesis.**
  - **Increases very low density lipoprotein formation.**

Metabolic Effects of Insulin - A Review

Effect on muscle:

- **Increased protein synthesis**
  - Increases amino acid transport
  - Increases ribosomal protein synthesis

- **Increased glycogen synthesis**
  - Increases glucose transport
  - Induces glycogen synthase and inhibits phosphorylase

Metabolic Effects of Insulin - A Review

Effect on adipose tissue:

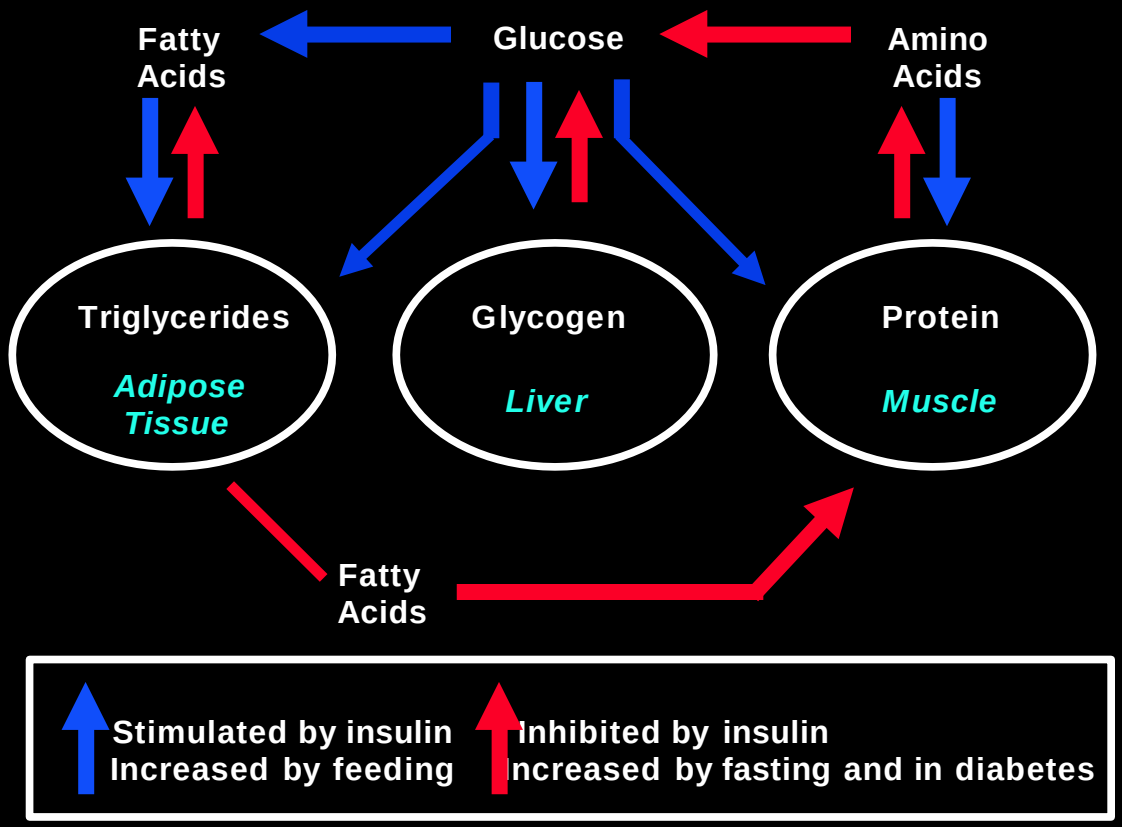
- Increased triglyceride storage

Insulin induces and activates Lipoprotein Lipase to hydrolyze triglycerides from lipoproteins.

Glucose transport provides glycerol phosphate for esterification of fatty acids supplied by lipoprotein transport.

Hormone- sensitive lipase is inhibited by insulin

Metabolic Effects of Insulin - *OVERVIEW* (cont'd)

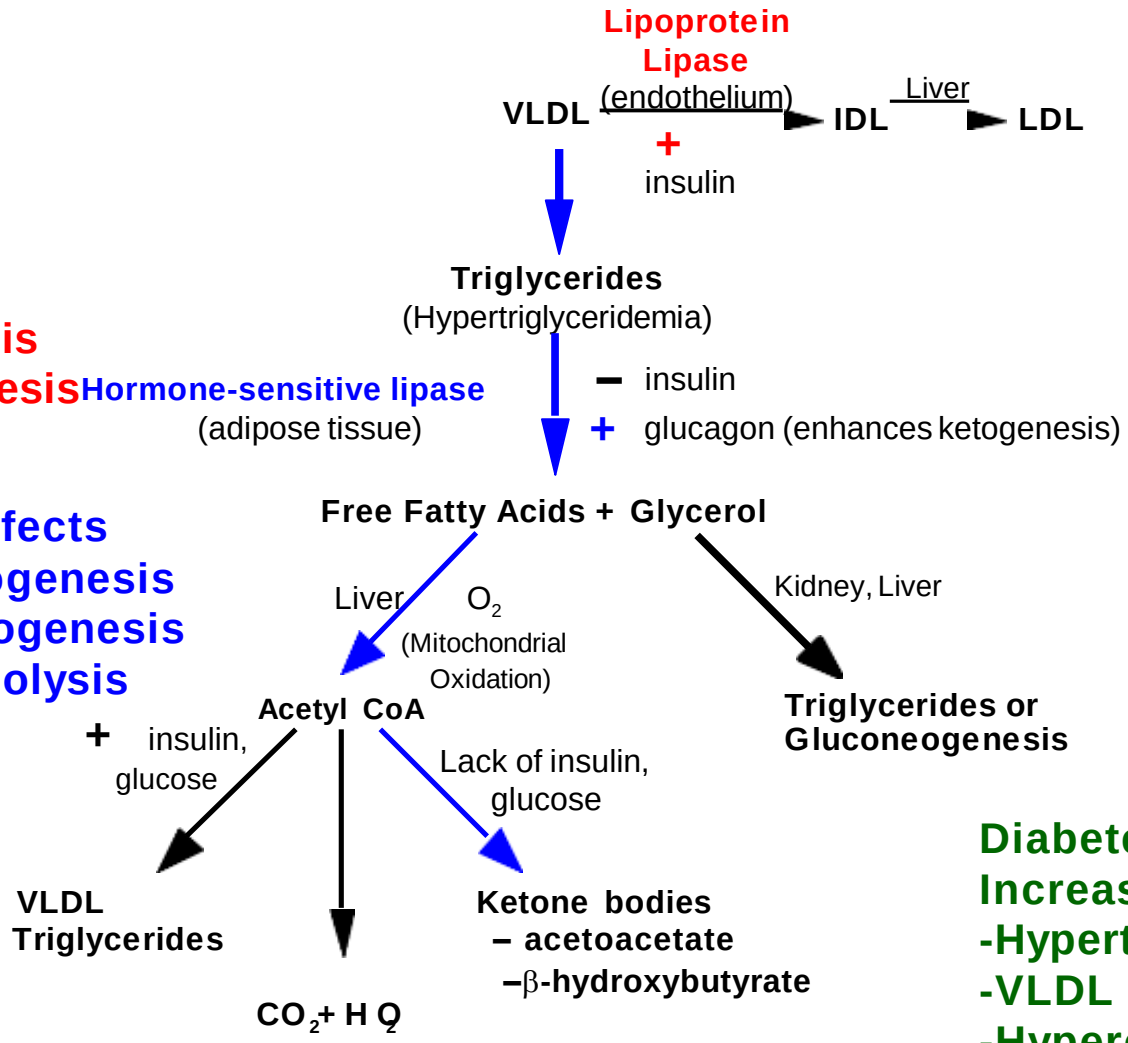


Impact of Reduced Insulin Effectiveness

1. Marked reduction in rate of glucose transport across cell membranes - fat/muscle
   (exceptions: liver, brain, erythrocytes, leukocyte, renal medulla)
2. Marked reduction in conversion of glucose to glycogen
3. Marked increase in converting protein to glucose (gluconeogenesis)
4. Marked increase in mobilization of fatty acids from peripheral fat deposits (lipolysis)
5. Abnormally high production of ketone bodies (ketoacidosis)
6. Increased production and excretion of urea and ammonia (azoturia)

Insulin Deficiency:
- A. Hyperglycemia
- B. Hyperlipemia
- C. Ketosis-acidosis
- D. Protein wasting
- E. Hyperkalemia

Ketogenesis Pathway



Insulin
- inhibits lipolysis
- stim. FA synthesis

Glucagon
-has reverse effects
-enhances ketogenesis
-stim. Gluconeogenesis
-stim. glycogenolysis

Diabetes:
Increased
-Hypertriglyceridemia
-VLDL
-Hypercholesterolemia

Diabetes Mellitus

1.A group of syndromes characterized by hyperglycemia, altered metabolism of lipids, carbohydrates and proteins and increased risk of complications from vascular disease.

Associated with a relative or absolute insufficiency of insulin secretion with various degrees of insulin resistance.

Clinical Characteristics:

fasting hyperglycemia

atherosclerotic and microangiopathic vascular disease, neuropathy = complications of diabetes

2. Previous Classification of Diabetes Mellitus:

Insulin Dependent Diabetes Mellitus (IDDM) = Type 1 Diabetes

Non-Insulin Dependent Diabetes Mellitus (NIDDM) = Type 2 Diabetes

Diabetes Classification (cont'd)

In July 1997, The American Diabetes Association adopted the following guidelines
for the classification of diabetes types, based on etiology.

Type 1 - results from an autoimmune response to pancreatic ß-cell component(s)
triggered by viral infection

Type 2 - hyperglycemia may be due to:

a. Increased hepatic glucose production
b. Impaired insulin secretion
c. Receptor and post receptor defects (insulin resistance)

Definition:

A group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both.

The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart and blood vessels.

Classification of Diabetes (Traditional)

Characteristic	Type 1 (Juvenile form)	Type 2 (Maturity-onset)
Onset (age)	Under 30 years	Approximately 40 years
Type of onset	Abrupt	Gradual
Nutritional status at onset	Usually undernourished	Often none
Clinical symptoms	Polydipsia, polyphagia and polyuria	Often none
Ketosis	Frequent, unless diet, insulin and exercise are properly coordinated	Infrequent (except in the case of infection or stress)
Endogenous insulin	Negligible	Present, but relatively ineffective due to obesity; insulin resistance
Related lipid abnormalities	Hypercholesterolemia frequent, particularly when control is sub- optimal; all lipid fractions elevated in ketoacidosis	Cholesterol and triglycerides often elevated; carbohydrate- induced hypertriglyceridemia common
Insulin therapy	Required	Required in only 20-30 percent of patients
Hypoglycemic drugs	Should not be used	Clinically indicated
Diet	Mandatory along with insulin for blood glucose control	Diet alone frequently sufficient to blood glucose control

Diabetes Classification (cont'd)

1. **Type 1 diabetes - ~ 10% of all patients**

   β- cell destruction leading to absolute insulin deficiency

   A. Immune mediated

   B. Idiopathic

2. **Type 2 diabetes - ~ 90% of all patients**

   May range from predominantly insulin resistant with relative insulin deficiency to a predominantly secretory defect with insulin resistance. Larger genetic component than type 1

3. **Other specific types**

   Includes genetic defects of β-cell function, genetic defects of insulin action, exocrine pancreatic disease, endocrinopathies, drug- or chemical induced forms, infections, and other genetic defects sometimes associated with diabetes mellitus.

e. g., Maturity Onset Diabetes of Youth = Glucokinase mutation - increased threshold for insulin secretion, causing mild, persistent hyperglycemia

Causes of Insulin Resistance

- **Abnormal ß- 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:

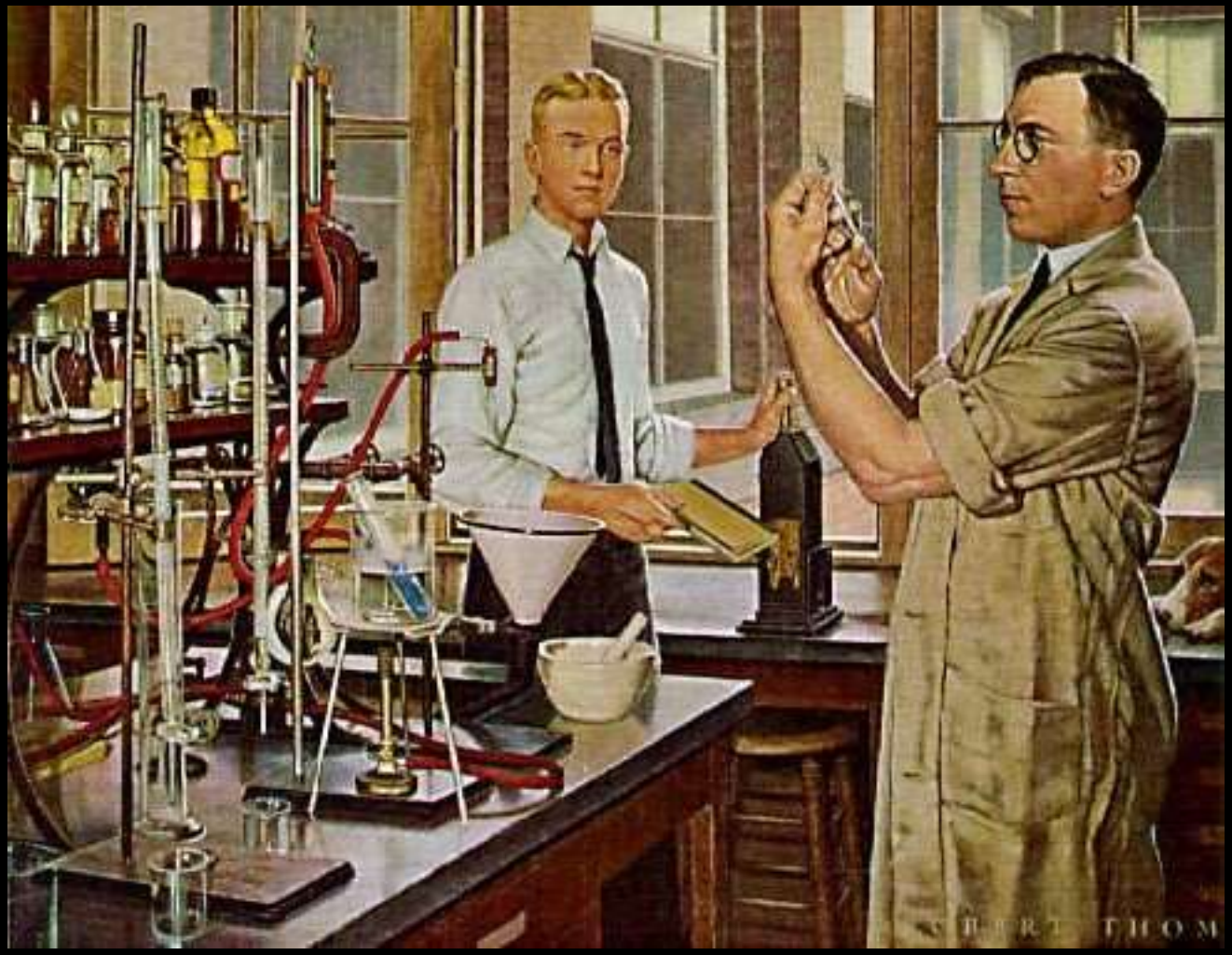
- **Impaired glucose tolerance (IGT)**
- **Gestational diabetes mellitus (GDM)**
- **Previous abnormality of glucose tolerance (Prev AGT)**
- **Potential abnormality of glucose tolerance (Pot AGT)**
- **(latent diabetes)**
- **Steroid diabetes**

Nonketotic Hyperosmolar Coma (Type 2 = iatrogenic)

- **glucocorticoids most common cause**
- **also induced by drugs that inhibit insulin secretion**

  e.g., β - blockers, diazoxide

Banting and Best



The birth of an idea

In October, 1920 Frederick Banting, a young surgeon in London, Ontario, Canada, first conceived the idea that led to the discovery of insulin.

One evening, after delivering a lecture on the pancreas to medical students, he was struck by an idea:

Could the internal secretions of the pancreas be isolated from the external secretions to keep dogs with diabetes alive?

- tie-off pancreatic ducts to cause acinar tissue degeneration, thereby removing proteases which were destroying the anti-diabetic principle during its extraction.

The discovery of insulin

Banting began his research on May 19, 1921, with Macleod as formal supervisor and Charles Banting as his assistant.

In August of 1921 after numerous failures, Banting and Best prepared a new extract from the atrophied pancreas of one of the dogs.

They then isolated two other dogs with diabetes, administering the extract to one and leaving the second untreated.

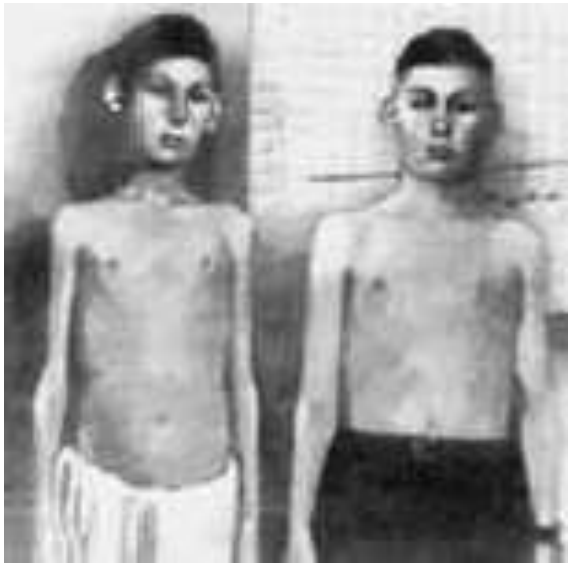
Four days later, the untreated dog died of severe diabetes.

The dog that received the extract lived for three more weeks, dying only when the extract was used up - Marjorie.

Banting and Best

Marjorie

First Human Patient



On Jan. 11, 1922, 14-year-old Leonard Thompson was the first human patient to receive insulin made by Banting and Best.

The initial test failed, causing only slight reductions in blood glucose levels.

A second series of "purified" insulin injections, produced by J. B. Collip, achieved the desired results.

Leonard's blood glucose dropped to normal, and he began to gain weight.

Insulin Therapy

Prior to 1972 , the purity of commercial insulin preparations was low and insulin contained as much as 5- 10% impurities, proinsulin being the major contaminant. Insulin preparations are now recombinant and lack proinsulin and other contaminants.

The clinical significance of purified insulin preparations has been a reduction in side effects thought to be caused by immunological issues including:

a. **lipodistrophy**
b. **insulin allergy**
c. **antibody- related insulin resistance**
d. **prolonged circulation of injected insulin may contribute to hypoglycemia**
e. **immune complex deposition**

Therapeutic Preparations

For clinical treatment insulin is formulated as **soluble crystalline insulin** which is absorbed rapidly from the subcutaneous depot.

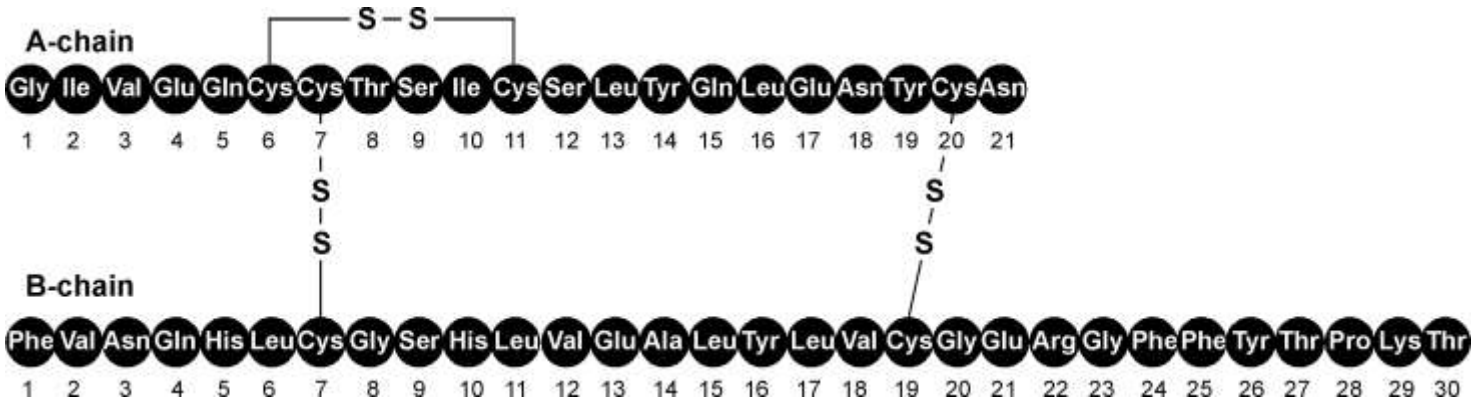
Alternatively, insulin may be **aggregated/complexed to protein, structurally mutated or chemically modified**, to slow absorption and prolong its duration of action.

The latter preparations are <u>only for subcutaneous injection</u>.

Insulin Preparations - Regular Insulin

Regular insulin - crystalline zinc insulin; 1 mg = 27. 5 units

Crystalline (uncomplexed) insulin may be given intravenously

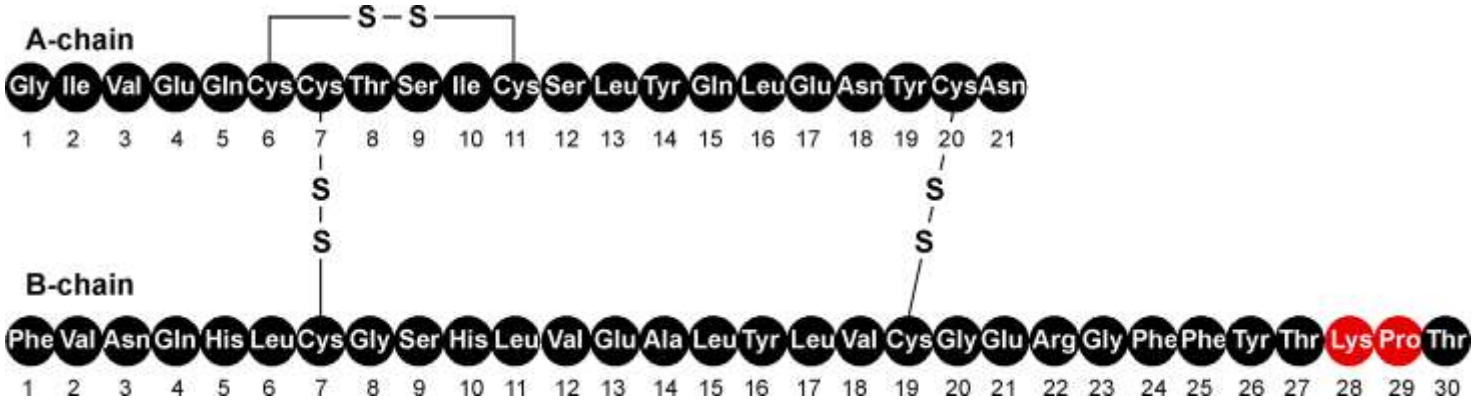


Insulin hexamers crystallize around 2 zinc molecules

Insulin Preparations - Lispro Insulin

Lispro insulin

- 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

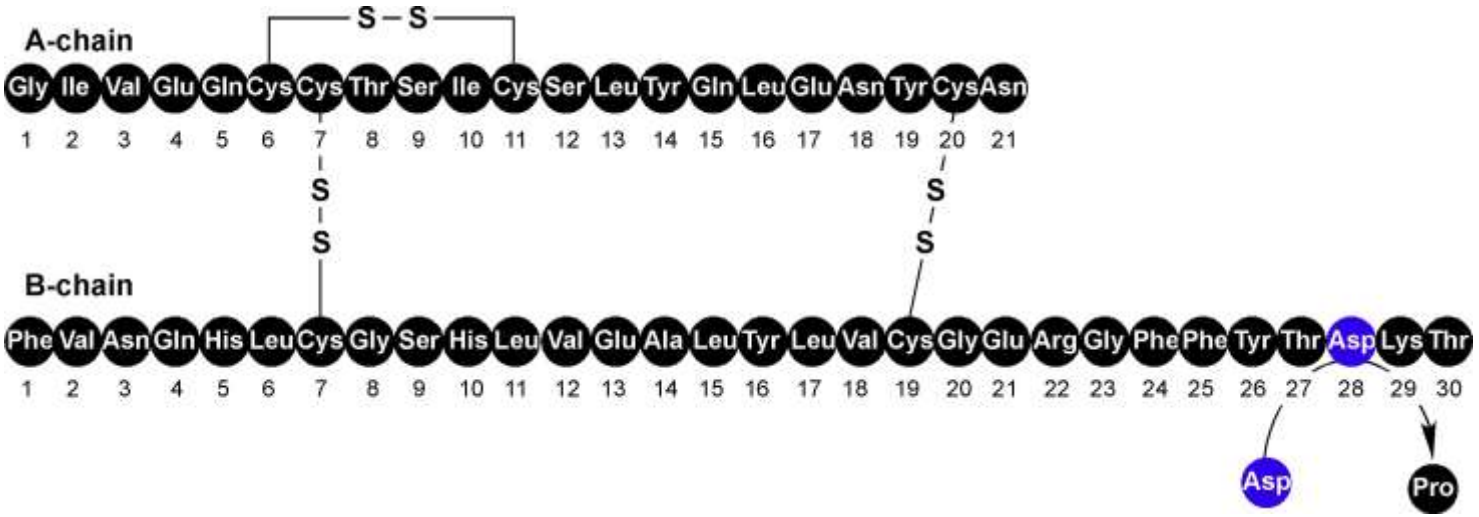


Administer	Maximum Effect
Insulin	**Peak**
30 - 45 min	1.5 - 2 h
LisPro	**Peak**
0 - 15 min	0.5 - 1 h

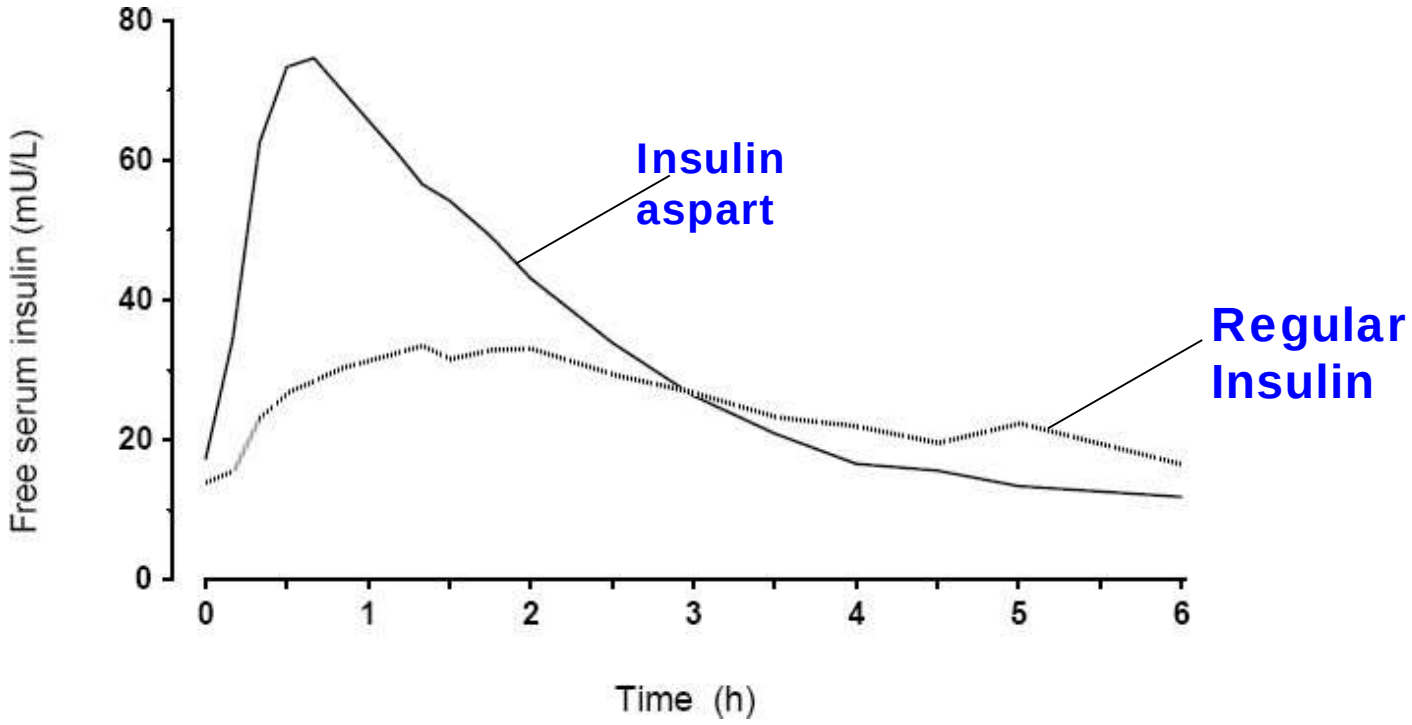
Insulin Preparations - Insulin Aspart

Insulin Aspart

- structurally modified human recombinant insulin
- change eliminates the ability to dimerize/hexamerize
- results in faster absorption rates - similar to Lispro



Insulin Preparations - Insulin Aspart



Serial mean serum free insulin concentration collected up to 6h following a single pre-meal dose of insulin aspart (NovoLog®) or regular human insulin injected immediately before a meal in 22 patients with type 1 diabetes.

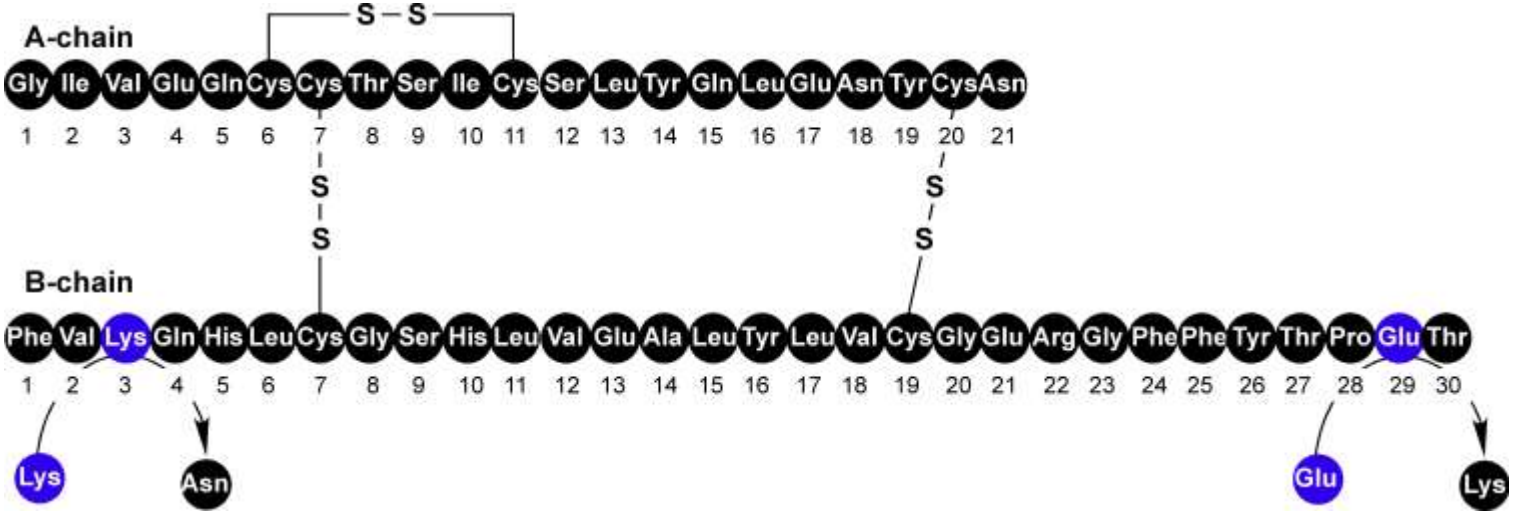
Insulin Preparations - Glulisine Insulin

Glulisine Insulin

- **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**

obese patients had faster onset kinetics than seen with other rapid-acting insulins

-early trial results indicate less “clumping” - may be insulin of choice for use in insulin pumps due to less clogging – requires validation



Insulin Preparations - Inhaled Insulin

Inhaled Insulin

- rapid acting can be taken 10 min before meals
- for type 1 and type 2 diabetics
- some patients may require additional meds to manage blood glucose

Contraindicated

- Smokers or those who have quit smoking less than 6 months prior

- Patients with unstable or poorly controlled lung disease (such as unstable or poorly controlled asthma, chronic obstructive pulmonary disease, or emphysema)

-Children and teenagers should not use Exubera, because it has not been tested enough in individuals under 18 years of age.

Side effects:

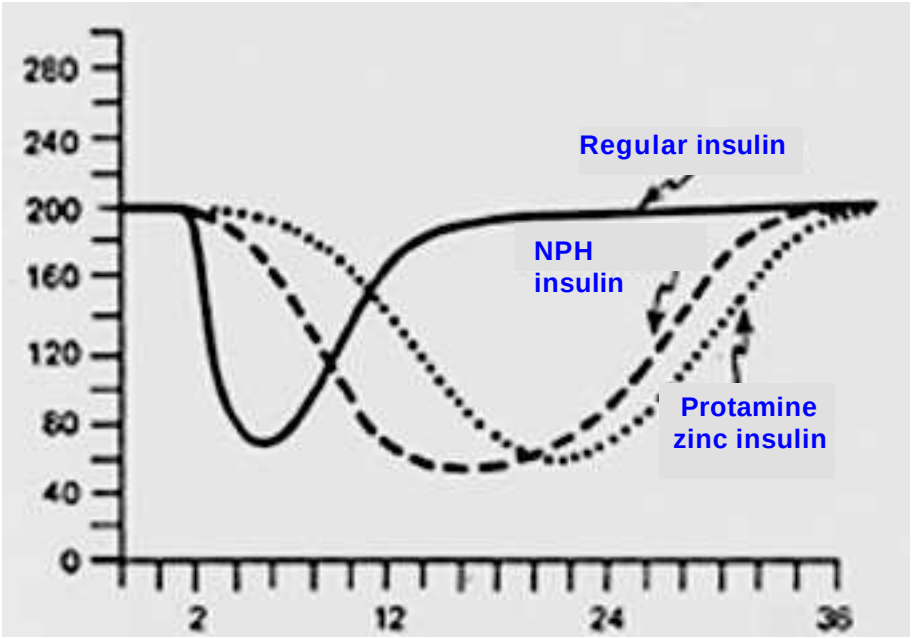
-reduced lung function, Cough, dry mouth, chest discomfort, hypoglycemia

Insulin Preparations - NPH Insulin - intermediate

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

Extent and Duration of Various Insulins in a Fasting Diabetic



Counter-regulatory hormones restore plasma glucose to baseline

Insulin Preparations - Lente Insulins

- suspensions of insulin in acetate buffer at neutral pH
- physical state and crystal size influences the rate of absorption from the site of injection

Lente insulin

- insulin zinc suspension

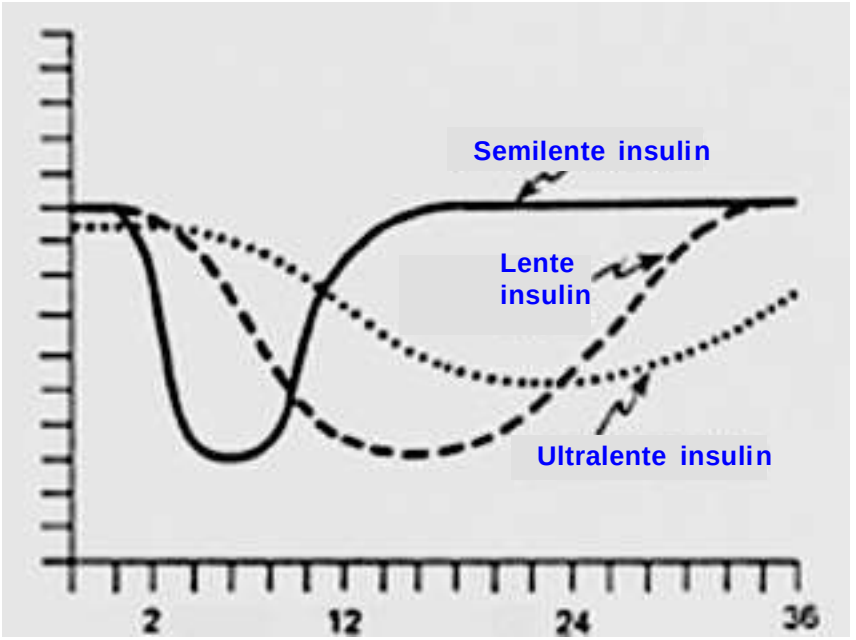
-consists of a mixture of two forms of insulin zinc suspension: 1. amorphous form - dissolves rapidly

2. crystalline form - less soluble, slowly absorbed

- similar in duration to NPH insulin
  i. e., intermediate-acting

Ultralente insulin

- first long- acting prep.
- crystalline insulin zinc particles
- large crystals
- slow absorption
- used to provide a basal level of insulin



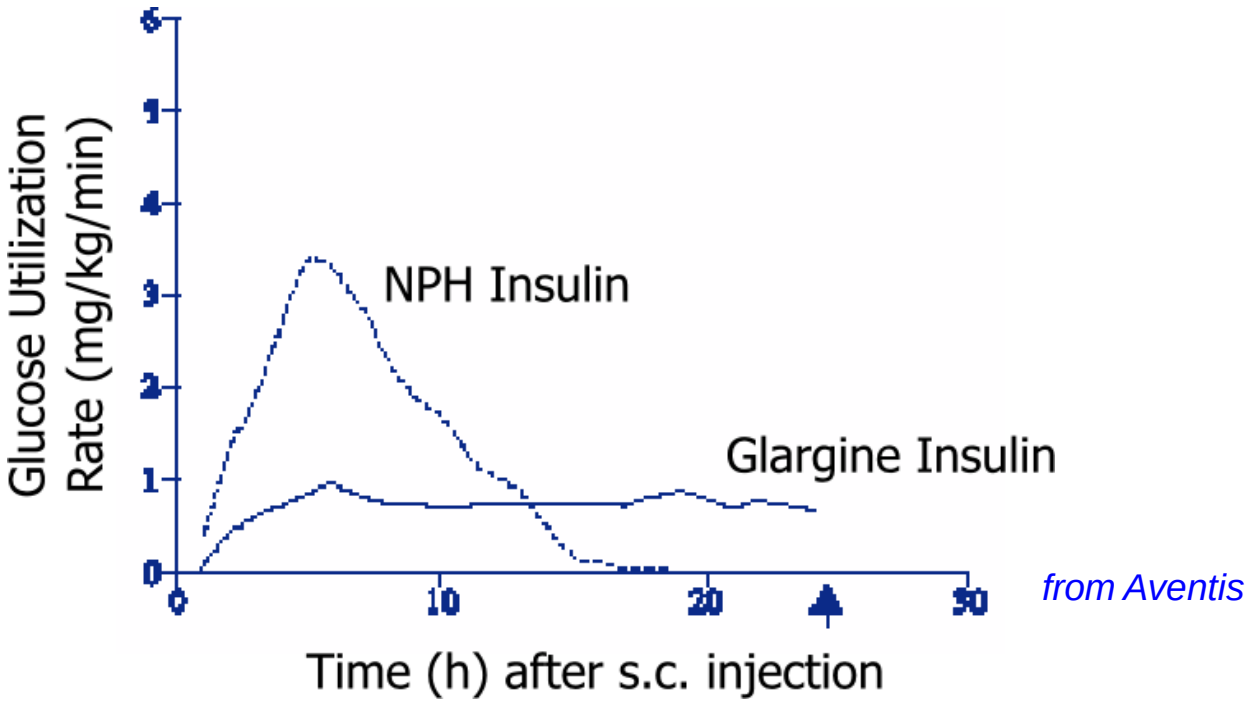
Insulin Preparations - Glargine Insulin

Long- Acting Insulin

Glargine Insulin (Lantus®)

- pH 4 solution
- A substituted form of insulin in which Asn 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 *slooowww* release over 24 h with no pronounced peak
- can be used as basal insulin injection on a once daily injection basis

Definitions Reviewed - Glargine Insulin



from Aventis

Side effects - hypoglycemia; injection site pain due to acidity

Insulin Preparations - Detemir Insulin

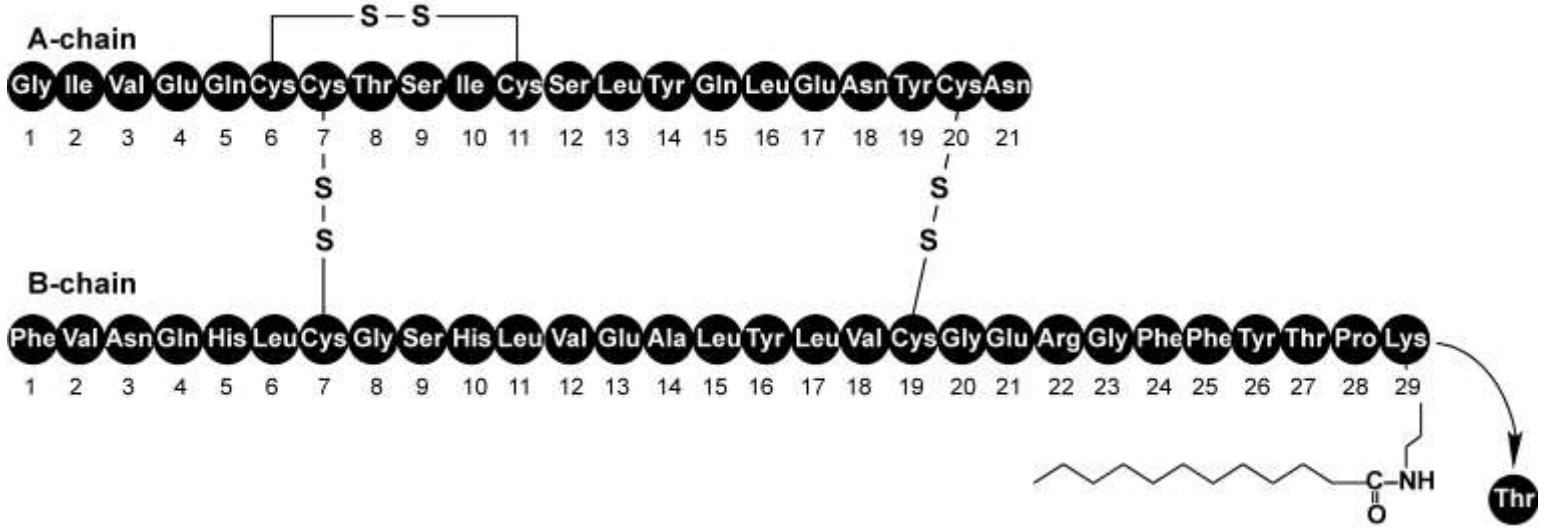
Detemir Insulin (Levimir®) fatty acid derivatized, long- acting

-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



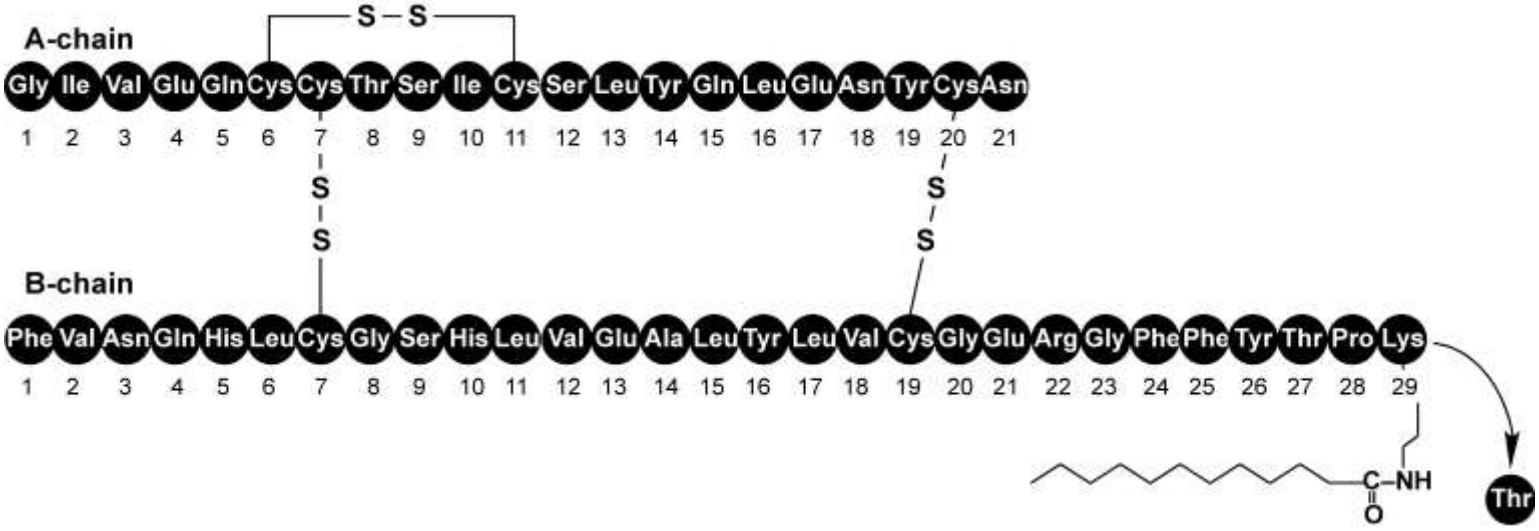
Insulin Preparations - Detemir Insulin

- 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

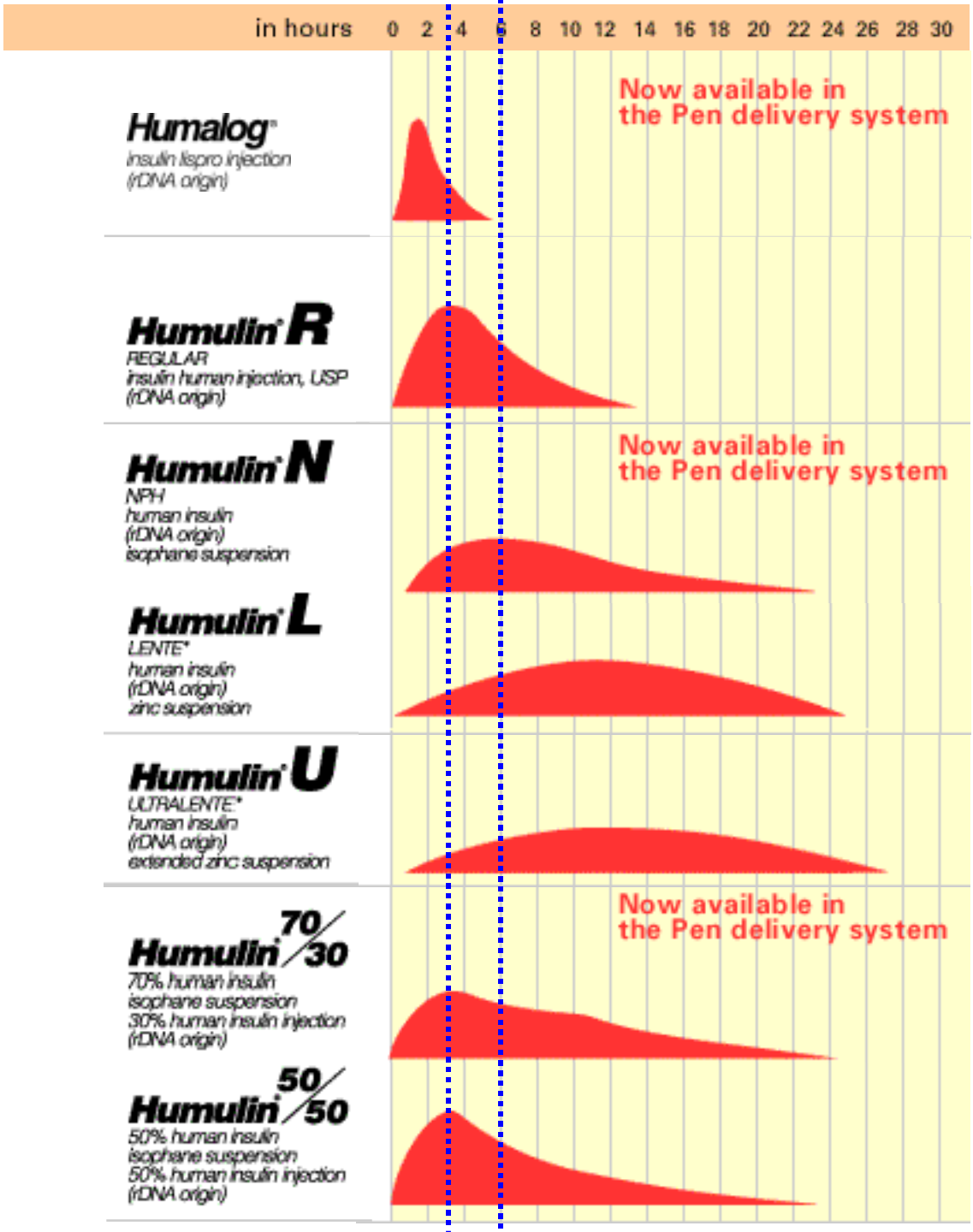


Insulin Mixtures

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.

and may reduce the effectiveness of the regular insulin.


in hours
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30
Humalog®
insulin lispro injection
(rDNA origin)
Now available in
the Pen delivery system
Humulin® R
REGULAR
insulin human injection, USP
(rDNA origin)
Humulin® N
NPH
human insulin
(rDNA origin)
isophane suspension
Now available in
the Pen delivery system
Humulin® L
LENTE®
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)
Now available in
the Pen delivery system
Humulin® 50/50
50% human insulin
isophane suspension
50% human insulin injection
(rDNA origin)

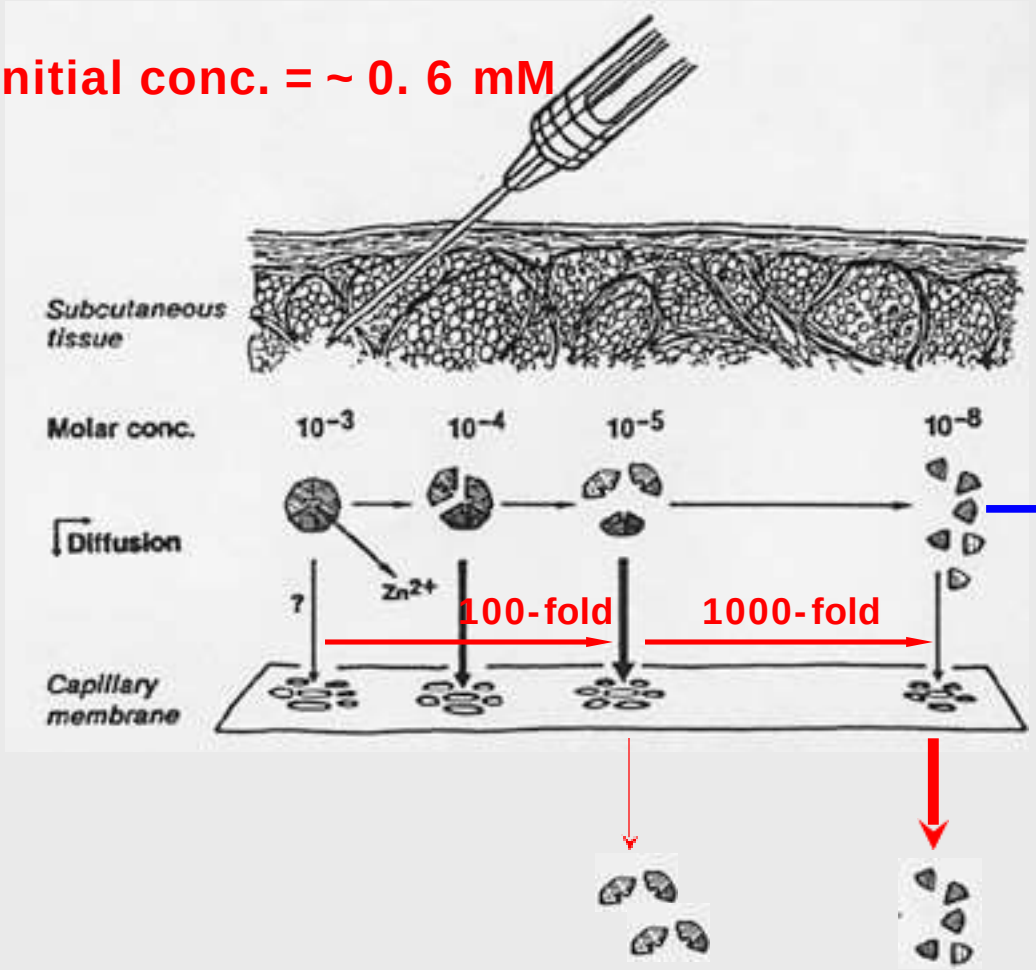
Routes of Administration

a. Intravenous - **bolus or infusion of regular or uncomplexed insulin only:**

This route is used when a rapid onset of action is needed or when subcutaneous absorption is inadequate;
close- loop delivery system.

b. Subcutaneous
- **bolus: regular, intermediate, long- acting or mixture**
- **infusion: regular; open- loop delivery system**
- **controlled (glucose level) system.**

Subcutaneous Injection of Regular Insulin



Passage of hexamers and dimers through capillary membrane is believed to be restricted by steric hindrance.

Routes of Administration

c. Experimental

- inhaled - FDA approved, 2006 **Exubera**
- oral
- intraperitoneal
- mucous membranes: nasal and rectal
- lectin-bound, microencapsulated insulin
- islet transplantation, engineered cell lines with natural glucose- sensor
- oral tolerance induction with AI- 410 insulin
- INGAP - induction of beta cells
- C- peptide

Factors Affecting Subcutaneous Absorption

a. site of injection: abdomen > arm > buttocks > thigh

b. exercise = blood flow at site

c. depth of injection

d. concentration and dose of insulin

e. insulin degrading activity in subcutaneous tissue

Problems Associated with Insulin Replacement

a. Insulin resistance

-physiologic diurnal resistance
-resistance associated with uncontrolled diabetic state
-acute stress
-immune mediated: insulin antibodies, insulin receptor antibodies
-obesity

b. Diabetic ketoacidosis occurs when an absolute or severe relative insulin deficiency is accompanied by increased counter-regulatory hormone action.

This can lead to marked hyperglycemia, lipemia, ketoacidemia, glycosuria and dehydration.

This is an acute medical emergency

Problems Associated with Insulin Replacement

c. Hypoglycemia results in a hyperadrenergic state

- Characterized by tachycardia, sweating and anxiety

& symptoms of neuroglycopenia, e. g. confusion, psychosis, seizure, coma.

- Mild episodes may occur regularly in well controlled patients

- Severe episodes should be avoided

-Patients who have inadequate counter- regulatory hormone responses are prone to severe hypoglycemia

- Beta-adrenergic receptor antagonists reduce symptoms and block compensatory gluconeogenesis and glycogenolysis

Problems Associated with Insulin Replacement

-Hypoglycemia can induce a rebound hyperglycemia:

- Somogyi or “dawn phenomenon”
  - due to counter-regulatory hormone release
    - glucagon, cortisol, GH

Problems Associated with Insulin Replacement

d. Insulin allergy
denatured insulin
protamine or Zn^{++} sensitivity

e. Lipodystrophy -
Lipohypertrophy - lipogenic action of insulin
Lipoatrophy - contaminant causing immune complex deposition?

f. Insulin edema - following ketoacidosis or hyperglycemia
controlled with insulin:
Insulin- dependent Na^{+} retention and capillary permeability

Diabetes Control and Complications Trial (9/93)

OBJECTIVE Compare conventional vs. intensive insulin therapy for prevention of long- term microvascular and neurologic complications.

METHODS:

Conventional
- ~ 2 injections of insulin/day
- decrease catabolic state
- decrease glycosuria
- try to minimize hypoglycemic events

Intensive
- multiple injections of insulin or insulin pump
- constant glucose monitoring to maintain normal glucose

PATIENT POPULATION:

1441 type 1 diabetics

726 without evidence of retinopathy — 1° cohort

715 with mild retinopathy — 2° cohort

randomized to conventional or intensive therapy

- patients followed for an average of 6. 5 years

RESULTS: Intensive vs. Conventional Therapies

	[glucose]	HbA1c (glycated hemoglobin)
Intensive	~150 mg/dl	7%
Conventional	~225 mg/dl	9%

	Retinopathy	Microalbuminuria	Albuminuria	Neuropathy
1° cohort	⇩76%	⇩39%	⇩54%	⇩60%

Side Effects

- 3X increase in severe hypoglycemic events
- Significant increase in cost of supervision associated with intensive treatment.

Conclusion:

Intensive insulin therapy delayed onset and slowed progression of retinopathy, nephropathy and neuropathy in Type 1 diabetes.

Glucagon

29 amino acid peptide, synthesized in pancreatic islet α (A) cells (also stomach).

Actions:

Opposite to those of insulin:

- glucose inhibits glucagon secretion
- glucagon stimulates adenylyl cyclase to increase cAMP formation in target tissues.
- glucagon increases glycogenolysis, lipolysis and gluconeogenesis and inhibits glycogen synthesis and glucose oxidation. Glucagon may increase ketogenesis.

Observations with no known mechanism

- Glucagon inhibits gastric acid secretion and relaxes guinea pig ileum (anti- ulcer, spasmolytic).

Glucagon

Therapeutic uses

-Glucagon may be used to treat insulin- induced hypoglycemia (instead of glucose).

-A major use of glucagon is to relax the gut in preparation for radiographic exams

-may be of benefit in treating G.I. disorders associated with spasm, e.g. acute diverticulitis and esophageal impaction.

- diagnosis of pheochromocytoma

Administration

- By injection (i.v., i.m. or s.c.)

Somatostatin

Somatostatin/Growth- hormone- release inhibiting hormone- somatotrophin-release inhibiting hormone (SRIH/GHRIH)

14 residue peptide found in pancreatic islet δ (D) cells, in gastric mucosa and in hypothalamic neurons.

Actions:

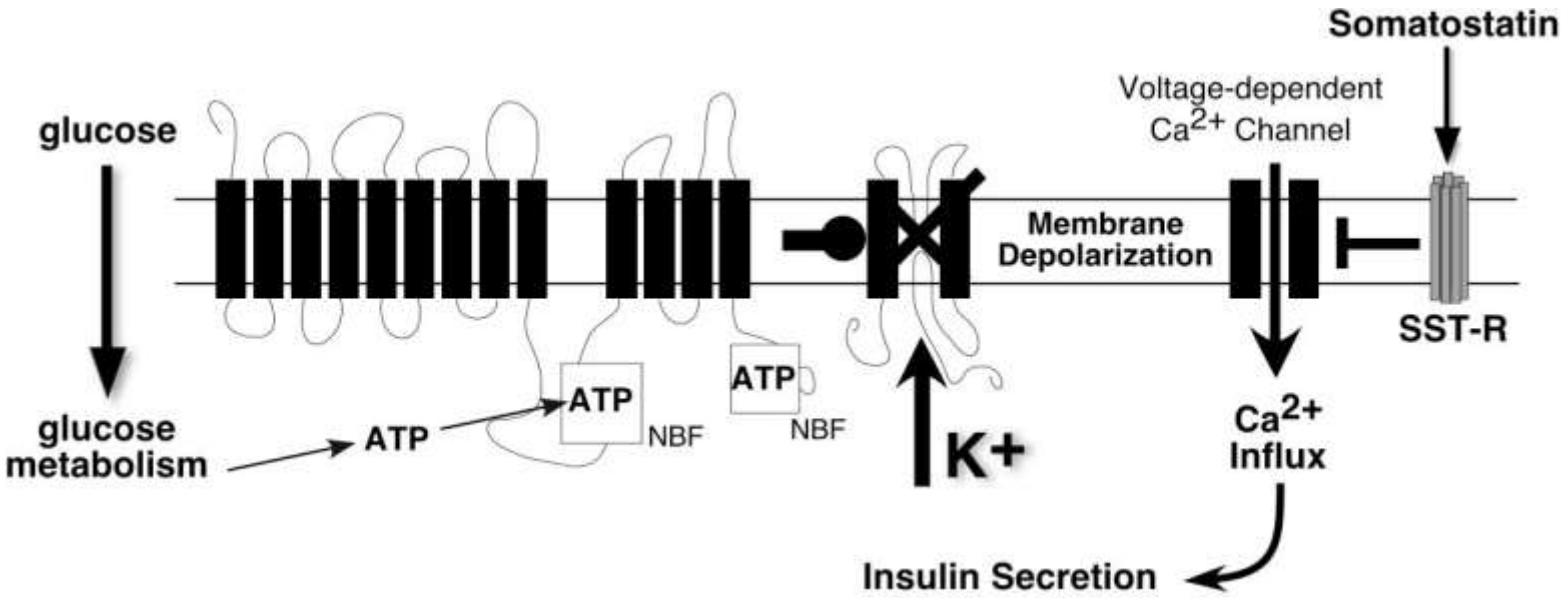
Inhibits growth hormone, insulin and glucagon secretion.

Reduces fasting hyperglycemia in insulin deficient type 1 diabetics

Somatostatin

Mechanism of Action:

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



Somatostatin

Therapeutic indications:

Management of acromegaly, pancreatic islet cell tumors and diabetes mellitus.

- (ameliorates fasting and postprandial hyperglycemia in type 1 patients by suppressing glucagon secretion).

May prevent diabetic retinopathy by suppressing growth hormone release and the concomitant increase in IGF- 1 production.

However, somatostatin (natural and synthetic) is very labile in circulation with a half life of only a few minutes.

Octreotide (Sandostatin®)

- long- acting form of somatostatin - i.e., longer half-life

Oral Hypoglycemic Agents

A. SULFONYLUREAS -

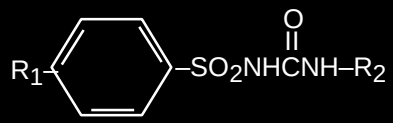
Accidentally discovered following the observation that sulfa antibiotics (sulfonamides) caused hypoglycemia in experimental animals.

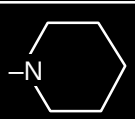
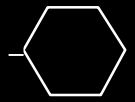
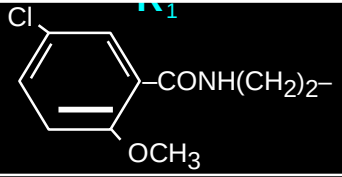
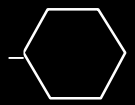
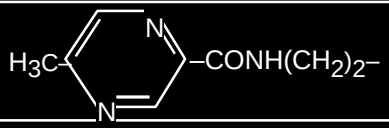
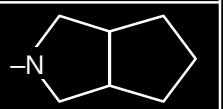
They are divided into two groups or generations of agents.

The second generation is considerably more potent than the first.

Structural Formulas of the Sulfonylureas

General Formula:



First Generation	R_1	R_2
Tolbutamide	$H_3C–$	$–C_4H_9$
Tolazamide	H_3C	
Acetohexamide	$H_3COO–$	
Second Generation	R_1	R_2
Glyburide		
Glipizide		
Gliclazide	$H_3C–$	

Mechanism of Sulfonylurea Action

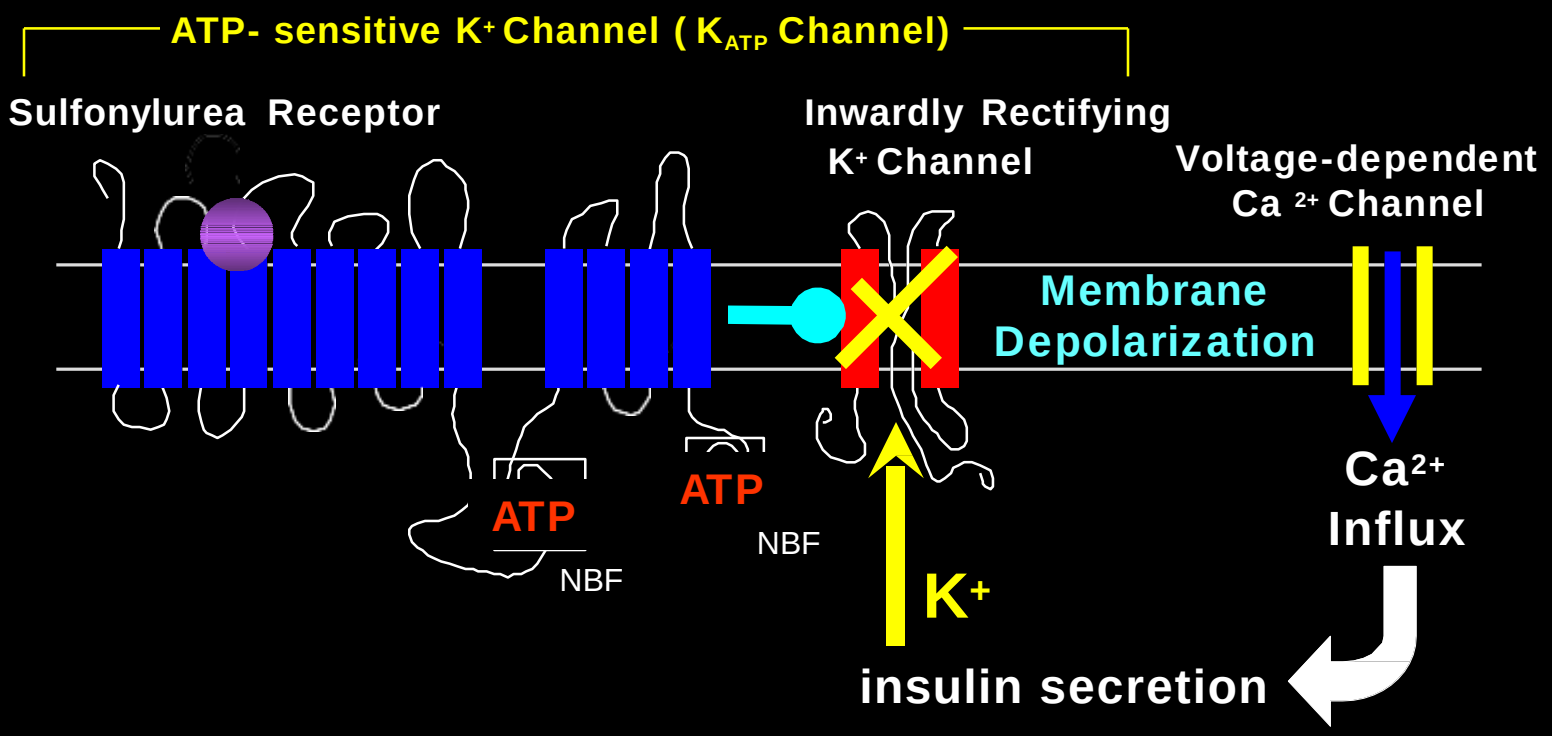
a.Stimulate the release of insulin from pancreatic β cells.

Sulfonylureas bind to SUR and block ATP-dependent K^+ channels

- This reduces K^+ efflux leading to: β cell depolarization, calcium influx and secretion of insulin.

b.May also increase the sensitivity of peripheral tissues to insulin.

Mechanism of Sulfonylurea Action



http://www.musc.edu/~rosenzsa

Therapeutic Uses of Sulfonylureas

1.Of value only in the management of type 2 diabetic patients that have not demonstrated ketosis and have not responded adequately to dietary therapy and weight control.

- must have functional beta cells -

2.Therapeutic effect may be antagonized by thiazide diuretics, estrogens or any agents that inhibit insulin release or antagonize peripheral action.

During periods of increased physical or emotional stress insulin therapy is often needed.

Side Effects of Oral Hypoglycemics (*Sulfonylureas*)

1. **May cause hypoglycemia**
   alcohol
   monoamine oxidase inhibitors, phenylbutazone, clofibrate, bishydroxycoumarin, sulfonamides
   beta blockers - all lower blood sugar
   - all enhance effects

7. **Weight gain, allergic reactions, pruritus, rash, hepatotoxicity, and photosensitivity are possible**

3. **Hyponatremia and water retention - non β cell effects**

Side Effects of Oral Hypoglycemics (*Sulfonylureas*)

Tolbutamide has minimal antidiuretic effect and the other agents have mild diuretic effects.

This may be an advantage of the second- generation agents.

Reported increase in cardiovascular mortality
Skin disorders
Hypothyroidism

MINIMAL ADVERSE REACTIONS
Associated with
- 2nd generation

Other Hypoglycemic Agents - 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

- mechanism of action:
  causes closure of ATP- dependent K^+- channels.

Side Effects - Meglitinides

Repaglinide (cont'd)

-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

-Due to CYP2C8 and CYP3A4 interactions

Other Hypoglycemic Agents - Biguanides

Biguanides - not marketed in US from 1977- 1994*

1. * Phenformin was associated with lactic acidosis
2. Metformin introduced in the US in 1994
   Indicated for use in type 2 diabetics

Several mechanisms of action have been proposed:

- increases liver, muscle and fat cell sensitivity to insulin
  - enhances peripheral glucose uptake and utilization

- reduces hepatic glucose output
- increased muscle glycogen synthesis

- particularly useful in patients with refractory obesity

- reduces a number of cardiac risk factors

Metformin Side Effects

G.I. Disturbances - nausea, diarrhea, and flatulence,

lactic acidosis (rare) - risk where clearance of metformin is reduced i.e., patients with renal or hepatic impairment

*** No significant hypoglycemia - does not stimulate insulin secretion**

should be avoided in patients with alcohol abuse, severe hepatic impairment, and severe congestive heart failure

Co- administered with a sulfonylurea, it can lower HbA1c values by 1 % to 2%

Exenatide

- glucagon- like peptide- 1 (GLP-1), a member of the incretin family

- exendin- 4 is a 39 amino acid peptide in salivary secretions of Gila monster

- exhibits 53 % sequence similarity to GLP- 1; protease 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

Exenatide

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

Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

Sitagliptin -

.Sitagliptin (Januvia®) 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. The

•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).

Dipeptidyl peptidase-4 (DPP-4) Inhibitors
Sitagliptin

-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

Other Hypoglycemic Agents - Acarbose

Intestinal Disaccharidase Inhibitors - Acarbose

- **α-glucosidase inhibitor -**
  taken preprandially, delays (low dose) or inhibits (high dose) carbohydrate absorption.

- **is an effective adjunct to sulfonylurea or insulin treatment**

Examples of Combined Therapies

Sulfonylurea with Biguanide - glyburide & metformin

or

Sulfonylurea with insulin augmentation (bedtime supplement)

or

Sulfonylurea with Acarbose

Thiazolidinediones - "Insulin Resistance Reducers"

First drugs developed to target insulin resistance
-"Glitazones"
Rosiglitazone)

Mechanism of Action

- lower blood glucose levels by improving target cell response to insulin.
  Adipose tissue and skeletal muscle

- alters the metabolism of fatty acids so that they don't compete with glucose for oxidative metabolism
- increases sensitivity of tissues to insulin by recruiting glucose transporters to the cell surface
- increases glucose uptake
- suppresses hepatic glucose output

i.e., favors carbohydrate metabolism/glucose utilization

and lipogenesis over lipid oxidation

Thiazolidinediones - "Insulin Resistance Reducers"

- Thiazolidinediones impact fatty acid metabolism by binding to:

  Peroxisome Proliferator- activated Receptors
  PPAR (γ isoform)

- members of the superfamily of ligand-activated transcription factors

- located in adipose tissue, skeletal muscle and large intestine

- target genes of PPAR γ include enzymes involved in lipid metabolism - results in decreased levels of FFAs

Only effective in the presence of insulin (endogenous or injected)

Thiazolidinediones (cont'd)

Therapeutic Use

- treatment of type 2 patients with inadequate control of hyperglycemia
- not used in type 1 patients

Potentially Hepatotoxic….

e.g., use of Troglitazone in the UK and the US was stopped
Newer agents with lower apparent hepatotoxicity:
Rosiglitazone
Pioglitazone
Accompanied with strong warnings and requirement of hepatic function tests before initiating therapy and continuing every 2 - 6 months
•Heart complications have been reported when combined with insulin therapy

Hyperglycemic Agent - Diazoxide

Diazoxide

– antihypertensive, antidiuretic, benzothiadiazine derivative

– also a potent oral hyperglycemic resulting from inhibition of insulin secretion.

Mechanism of Action

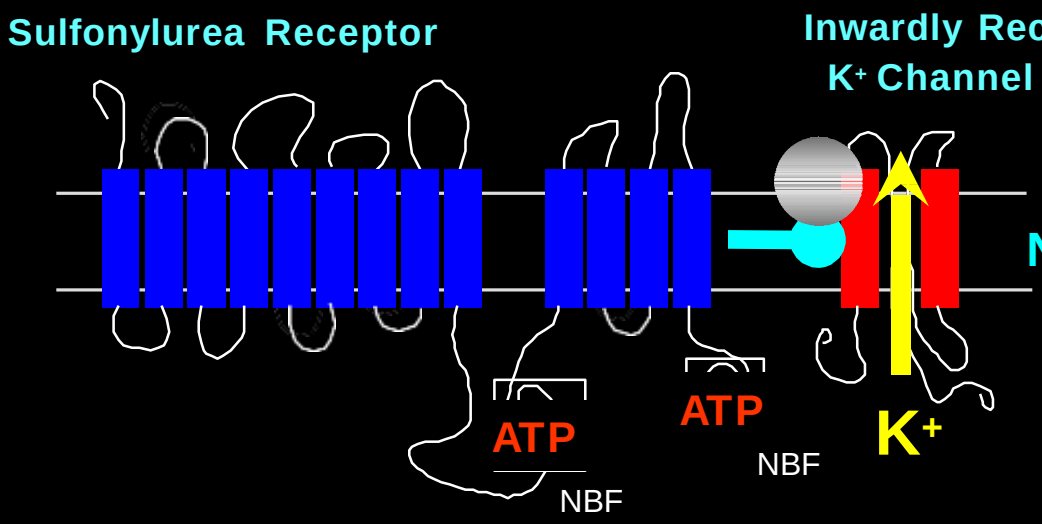
– binds to ATP- sensitive K^+ channels preventing their closing/prolongs open time.

This is opposite to the effect of sulfonylureas

Hyperglycemic Agent

Therapeutic Use

- treatment of hypoglycemia
- treatment of individuals with **inoperable insulinomas**



K^+ efflux maintained
No membrane depolarization
No Ca^+ influx

Insulin Secretion Inhibited

Persistent Hyperinsulinemic Hypoglycemia of Infancy - PHHI

- Neonatal disorder
- Due to a point mutation in the Sulfonylurea Receptor

- results in constitutive insulin secretion

- Early diagnosis and therapy are essential to prevent brain damage
- Treatment:

  Pancreatectomy

  Diazoxide - inhibits insulin secretion

  Somatostatin analogs - inhibit insulin secretion

Algorithm for managing type 2 diabetes