„Insulin“ history

- **Banting and Best – 1921 – described insulin (as the islet hormones was named)**
- **(an aqueous extracts of pancreas couls be lower blood glucose and prolong survival in a pancreatectomized dogs in experiment – laboratory in Department of Physiology, University of Toronto, Canada)**
- **End of 1923 insulin was being prepared from beef and pork pankreas on an industrial scale – patients from around the world were receiving effective treatment of their diabetes**
- **1924 Nobel price: Banting and MacLeod**

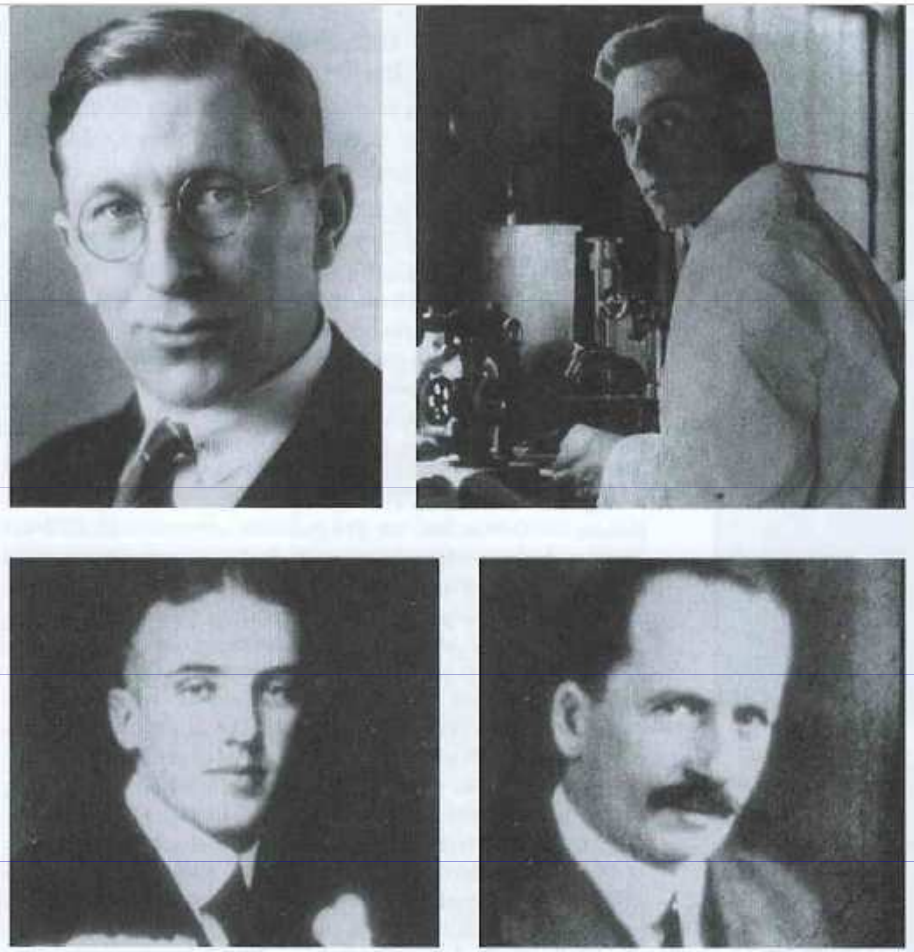


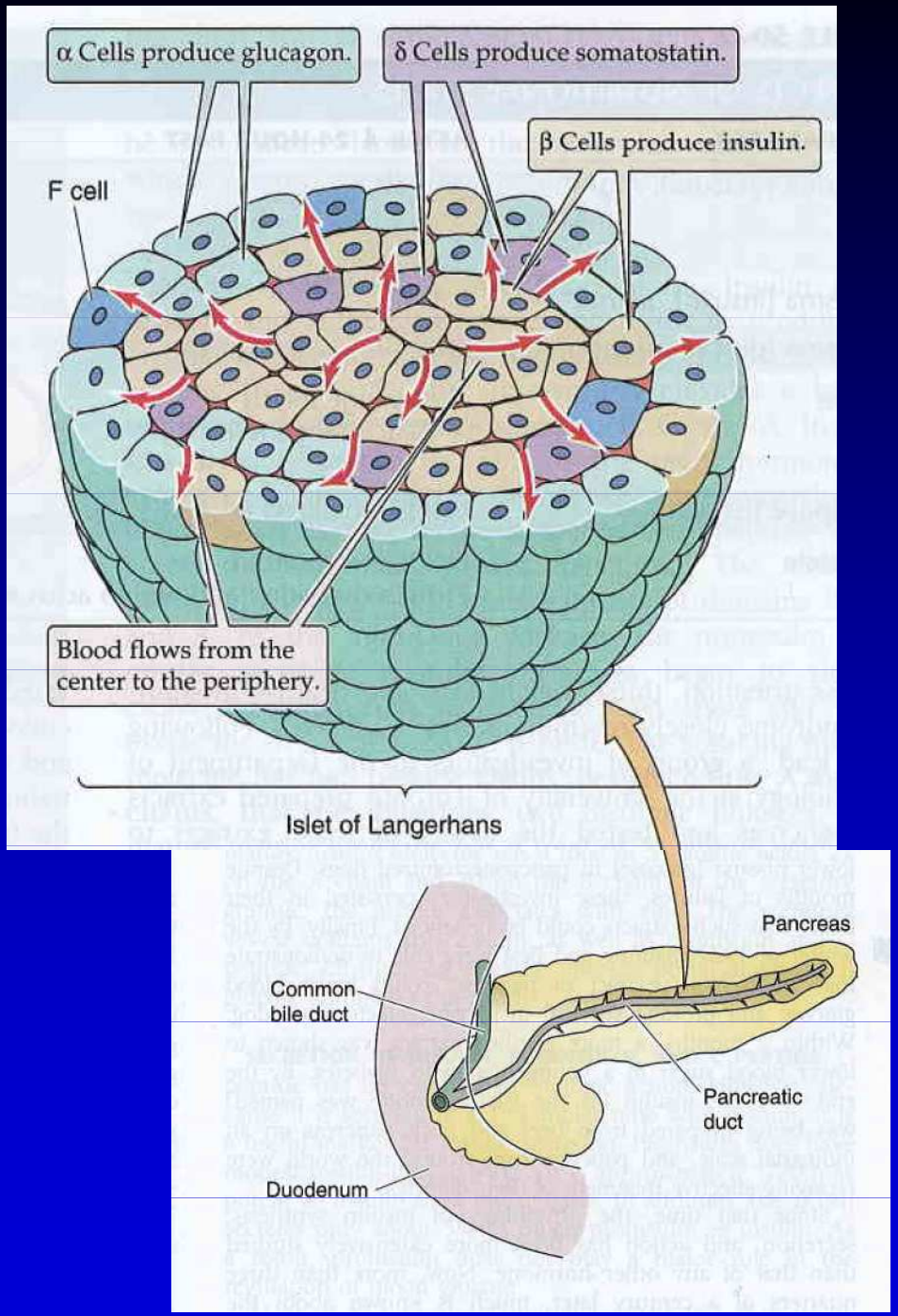
Figure 1.11 The discoverers of insulin. Clockwise from top left: Frederick G. Banting (1891–1941); James B. Collip (1892–1965); J.J.R. Macleod (1876–1935); and Charles H. Best (1899–1978). Courtesy of the Fisher Rare Book Library, University of Toronto.

Figure 1.12 Leonard Thompson, the first patient to receive insulin, in January 1922. Courtesy of the Fisher Rare Book Library, University of Toronto.

Beta cells of pancreas secrete:

- Insulin
- Proinsulin
- C peptide
- Amylin (new described protein, 37 aminoacid peptide co-secreted with insulin. It delays gastric emptying, suppresses post-prandial glucagon secretion, increases satiety)

- Alfa cells principally secrete glucagon
- Delta cells – somatostatin
- F cells – pancreatic polypeptide



Boron and Boulpaep, Medical Physiology, 2003

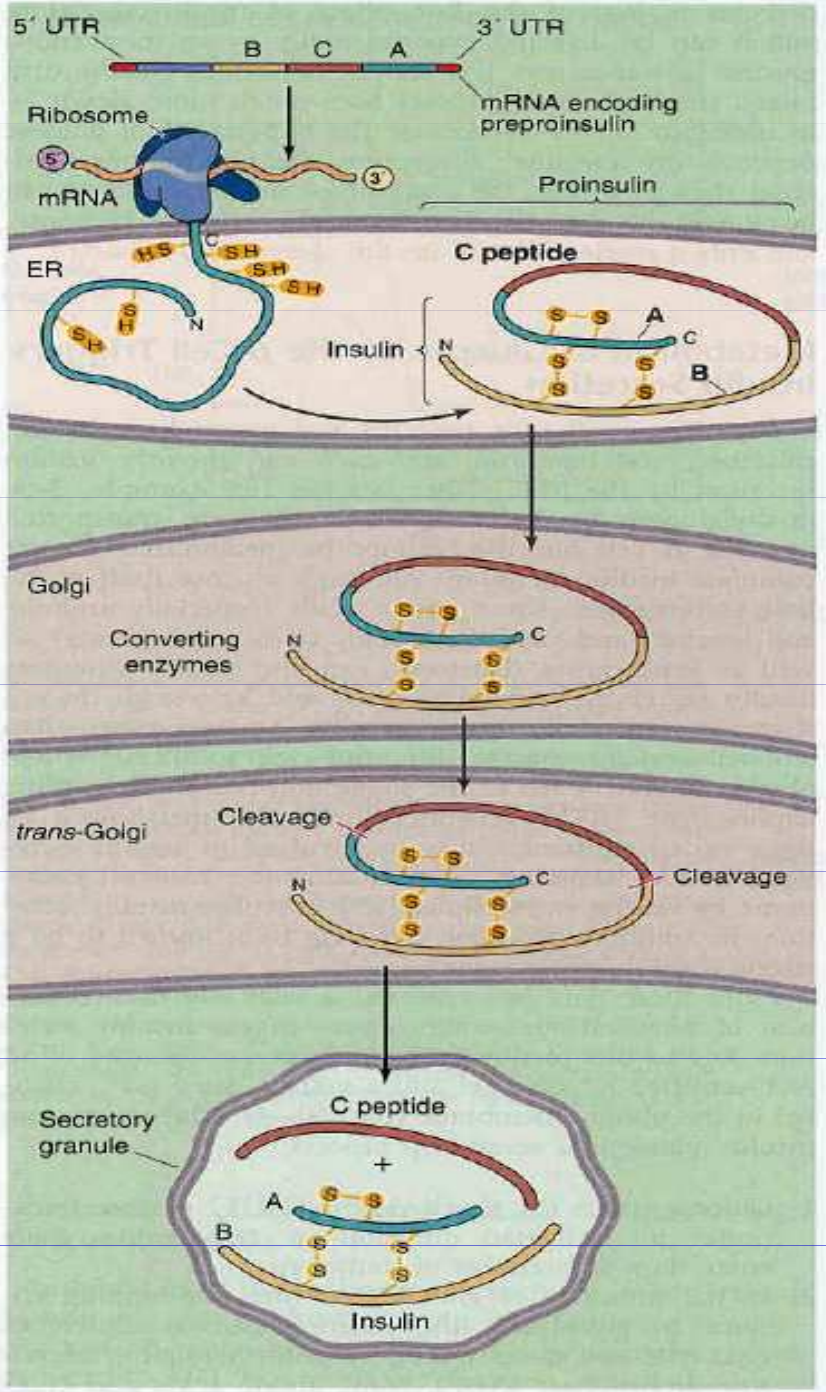


FIGURE 50–2. Synthesis and processing of the insulin molecule. The mature mRNA of the insulin gene product contains a 5′ untranslated region (UTR); nucleotide sequences that encode a 24-amino acid leader sequence, as well as B, C, and A peptide domains; and a 3′ UTR. Together, the leader plus the B, C, and A domains constitute preproinsulin. During translation of the mRNA, the leader sequence is cleaved in the lumen of the rough endoplasmic reticulum. What remains is proinsulin, which consists of the B, C, and A domains. Beginning in the *trans*-Golgi, proteases cleave the proinsulin at two sites, releasing the C peptide as well as the mature insulin molecule, which consists of the B and A chains that are connected by two disulfide bonds. The secretory granule contains equimolar amounts of insulin and the C peptide, as well as a small amount of proinsulin. These components all are released into the extracellular space during secretion. ER, endoplasmic reticulum; mRNA, messenger RNA.

Effects of insulin

Carbohydrates

promotes glucose entry into cells

⇑ synthesis of glycogen

inhibits glycogenolysis

inhibits gluconeogenesis

Lipids

promotes lipids synthesis

inhibits lipolysis in adipose and muscle cells

proteins

promotes amino acid entry into liver,

muscle and adipose cells

has a direct effect on the ribosomes in increasing the translation of messenger RNA, thus forming a new proteins

(inhibits the catabolism of proteins)

Effects of insulin

Carbohydrates

promotes glucose entry into cells

⇑ synthesis of glycogen

inhibits glycogenolysis

inhibits gluconeogenesis

Lipids

promotes lipids synthesis

inhibits lipolysis in adipose and muscle cells

proteins

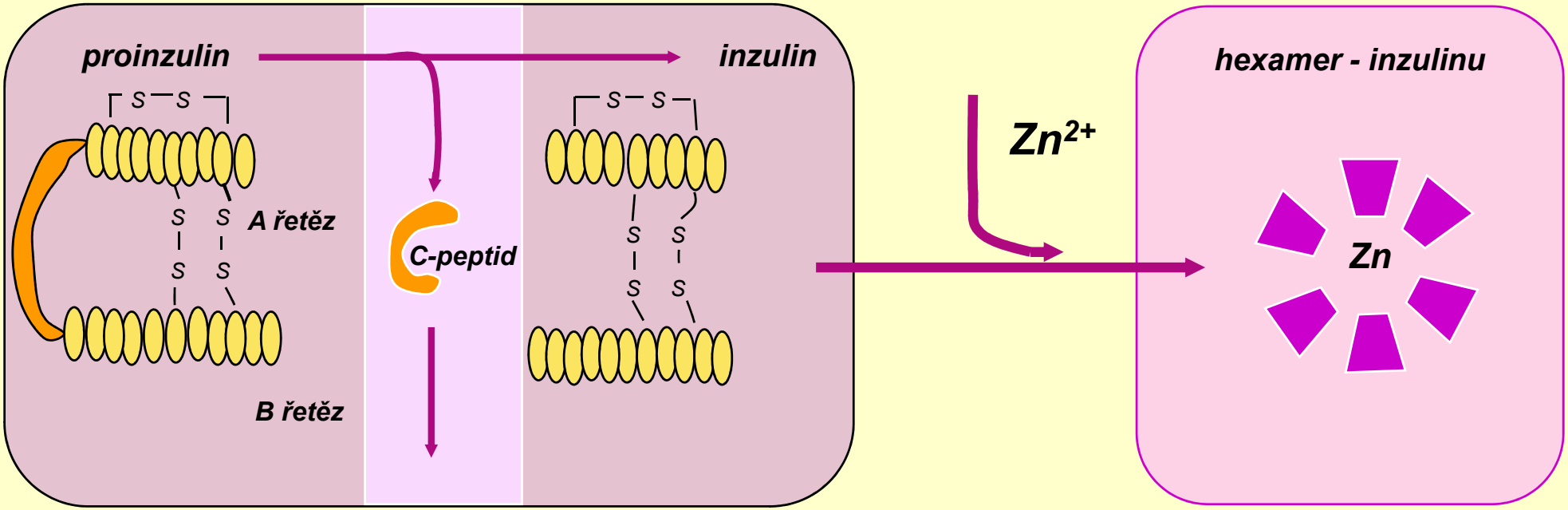
promotes amino acid entry into liver,

muscle and adipose cells

has a direct effect on the ribosomes in increasing the translation of messenger RNA, thus forming a new proteins

(inhibits the catabolism of proteins)

Beta cell

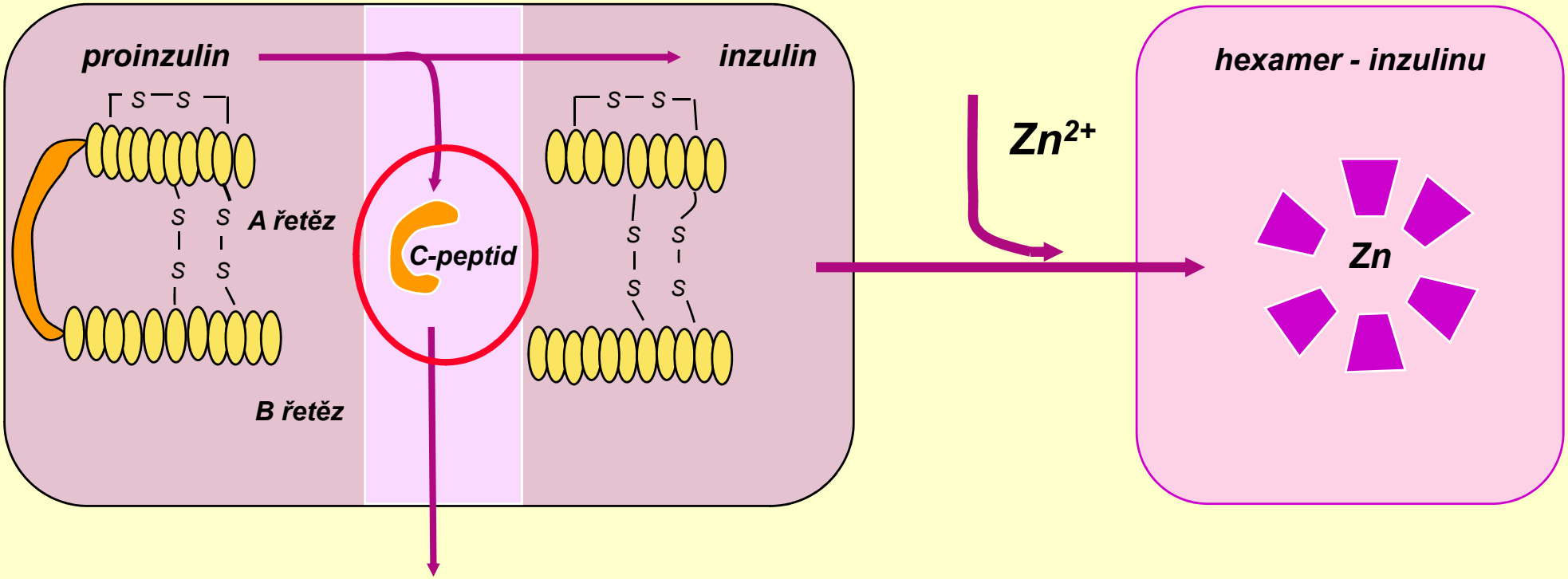


Golgiho aparát / Golgi Apparatus

Golgi vesicles / granula

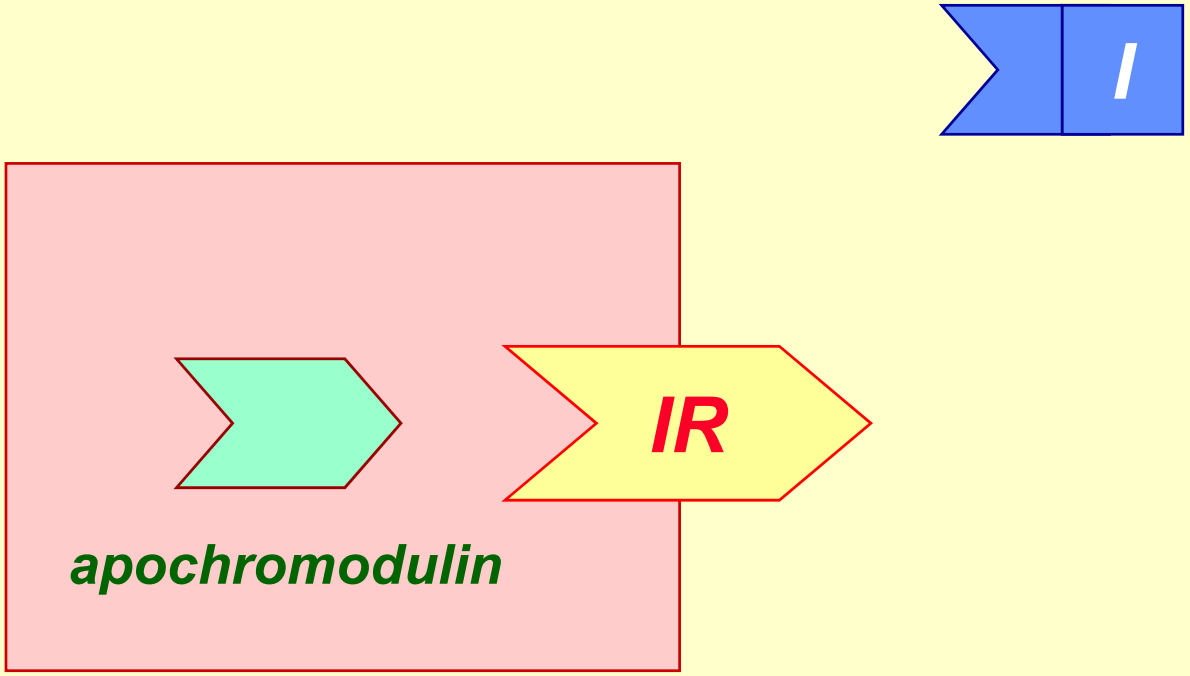
Endogenous insulin is formed by the cleavage of proinsulin to insulin and C peptid.
If a patient experiences hypoglycaemia in the presence of high insulin levels, C peptide measurements help to distinguish between excess endogenous insulin (e.g. insulinoma) and excess exogenous insulin (e.g.overdose).

beta cell

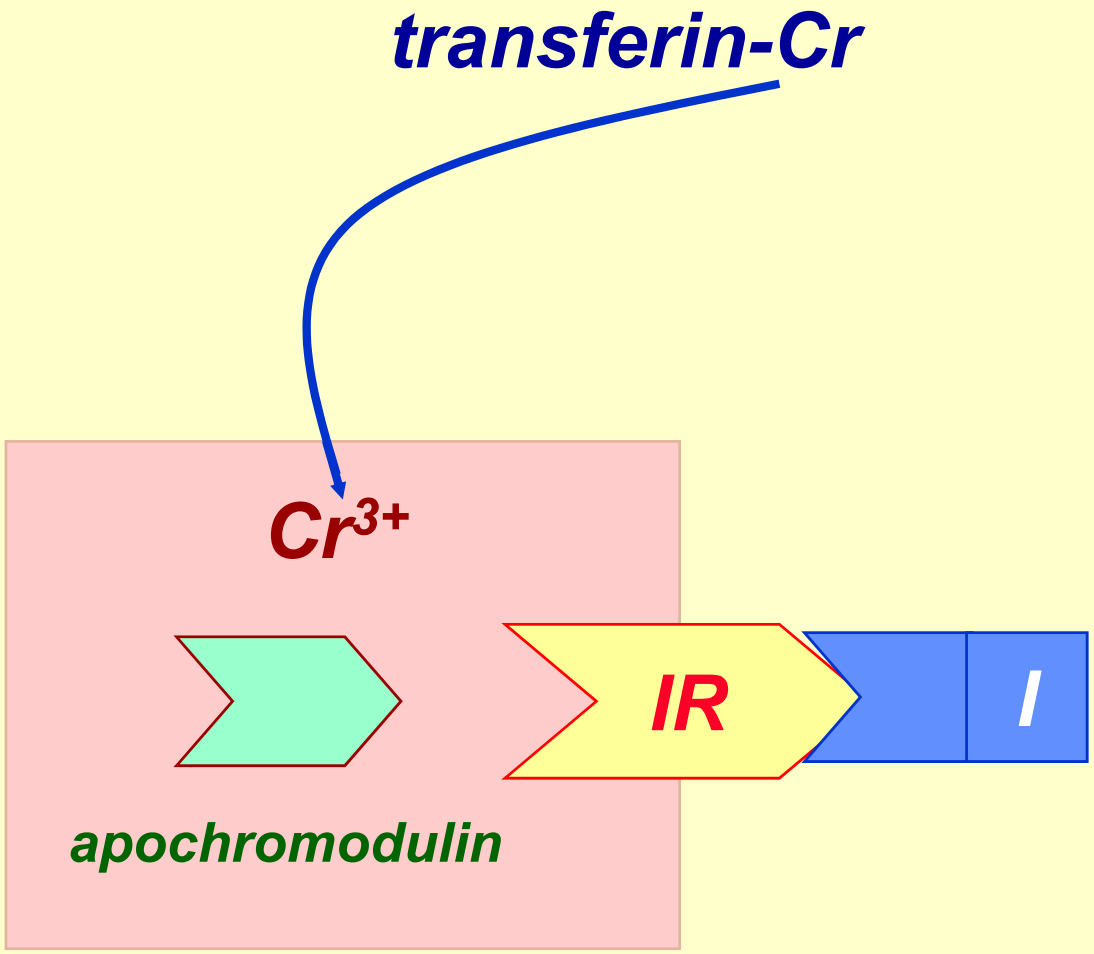


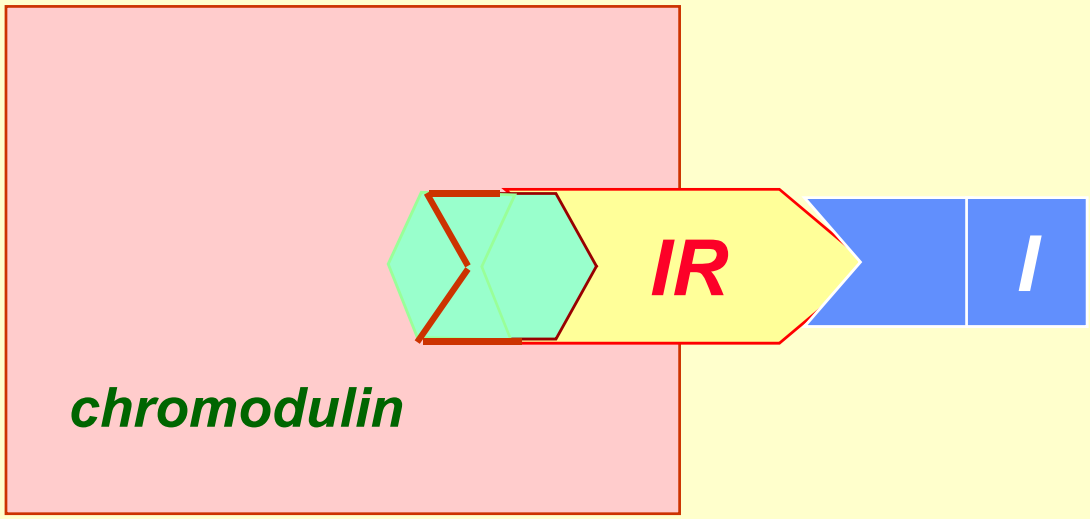
- ⇑ perfusion
-- ⇑ difusion in capillary region
-- ⇑ intake of oxygen and glucose into the cells

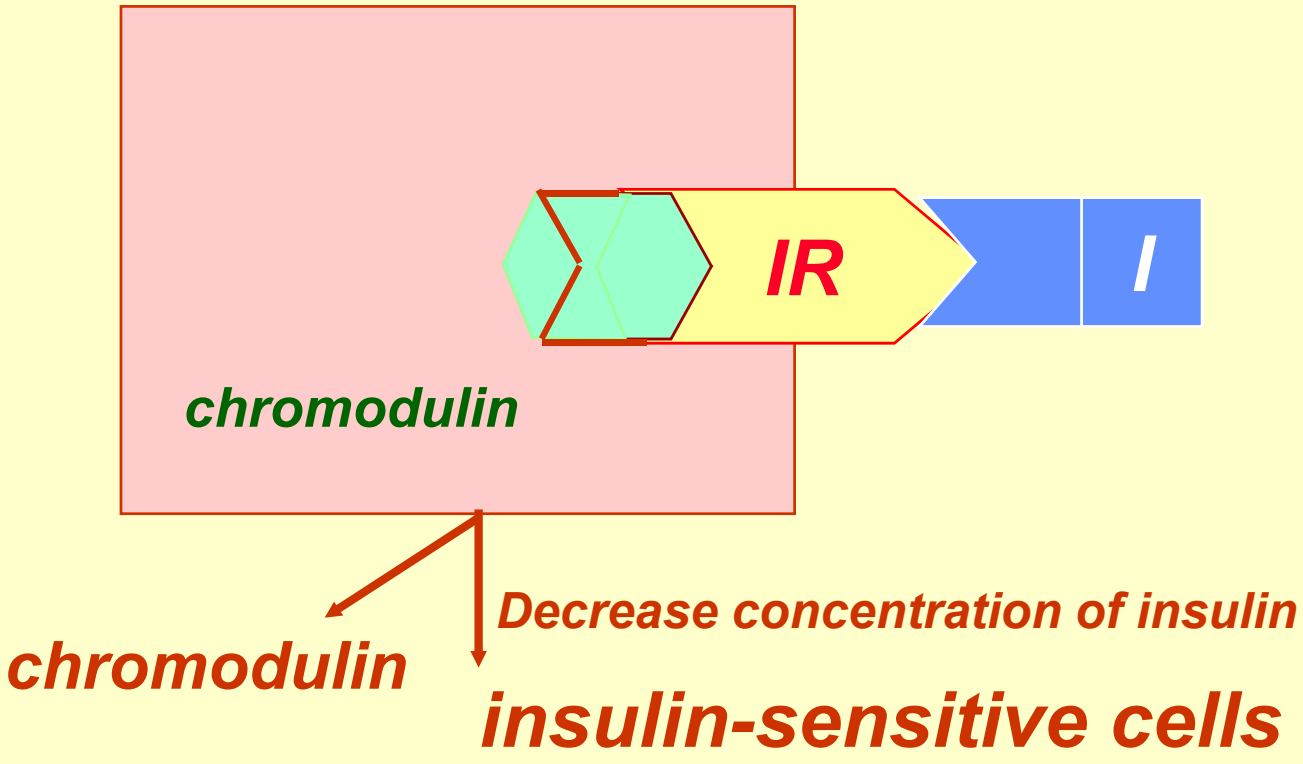
half-time decomposition: 25 min

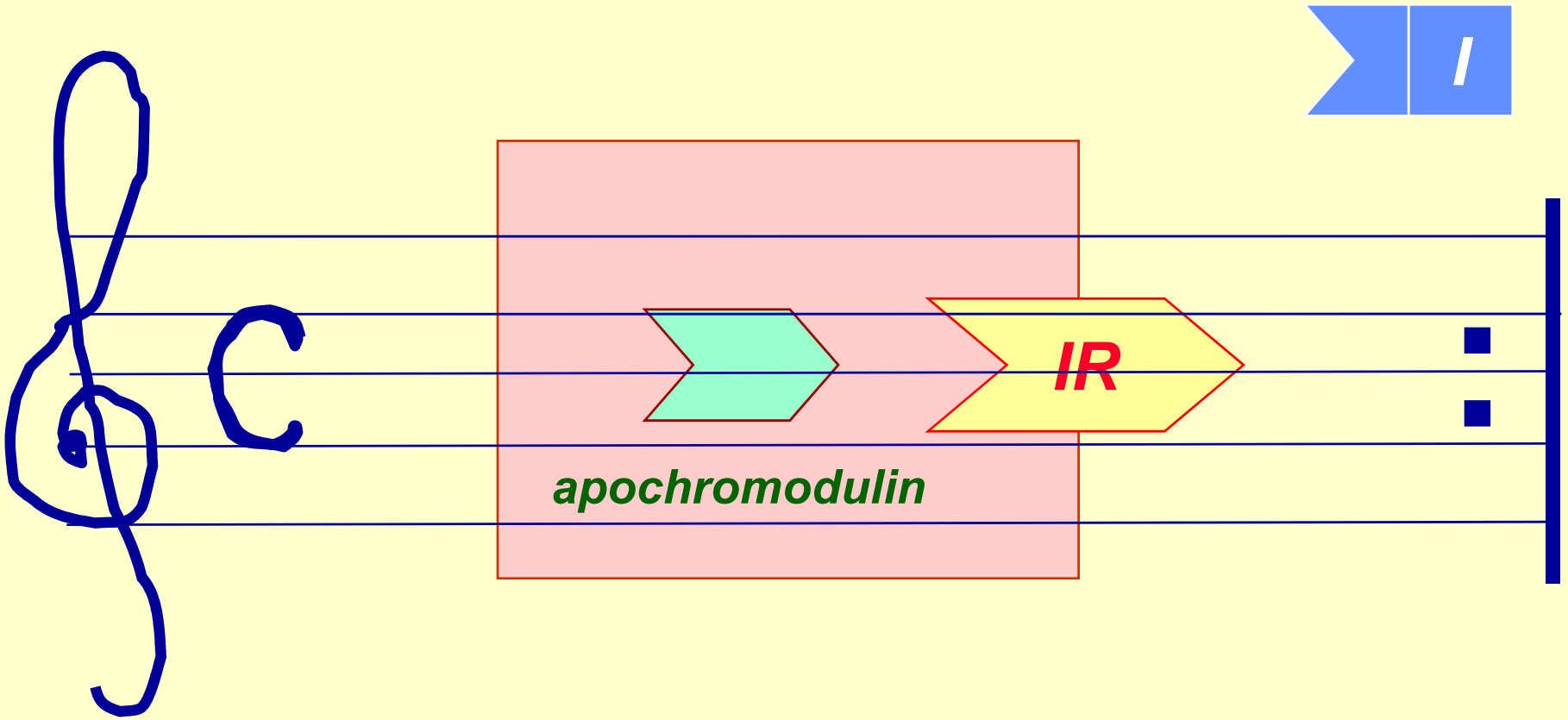


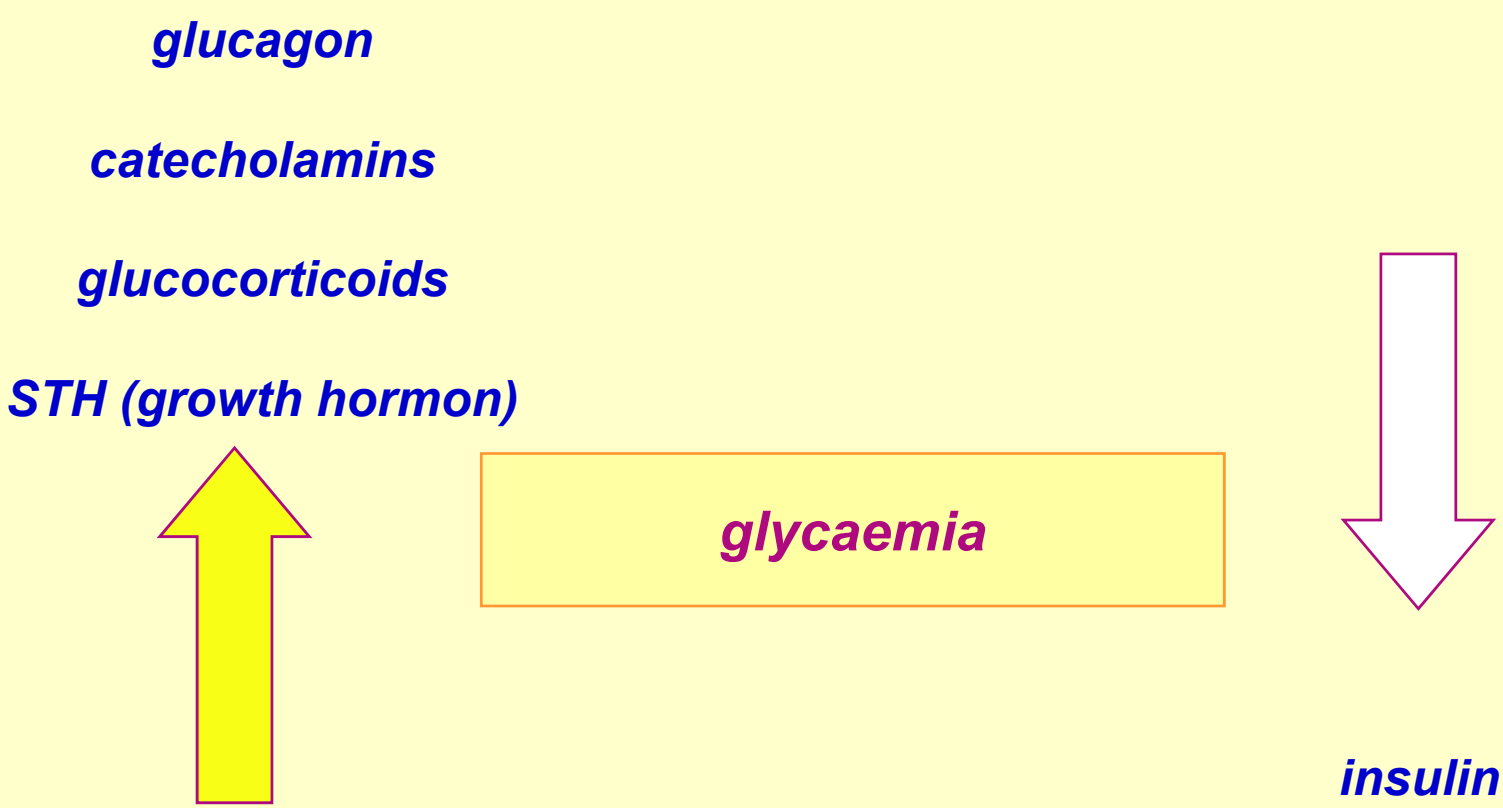
Vincent J. B.: J. Nutr. 130: 715 – 718, 2000

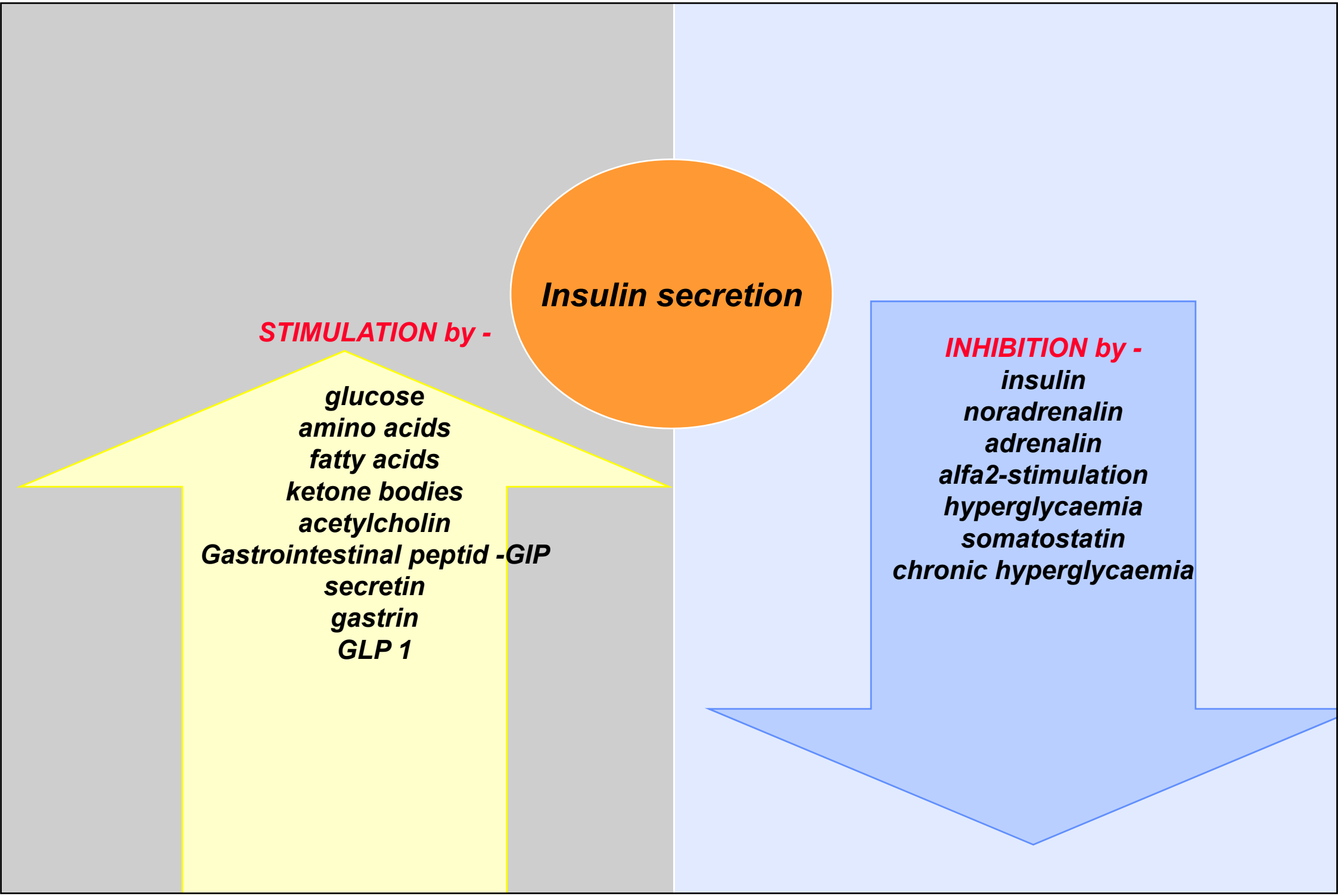

transferin-Cr
Cr3+
IR
I
apochromodulin

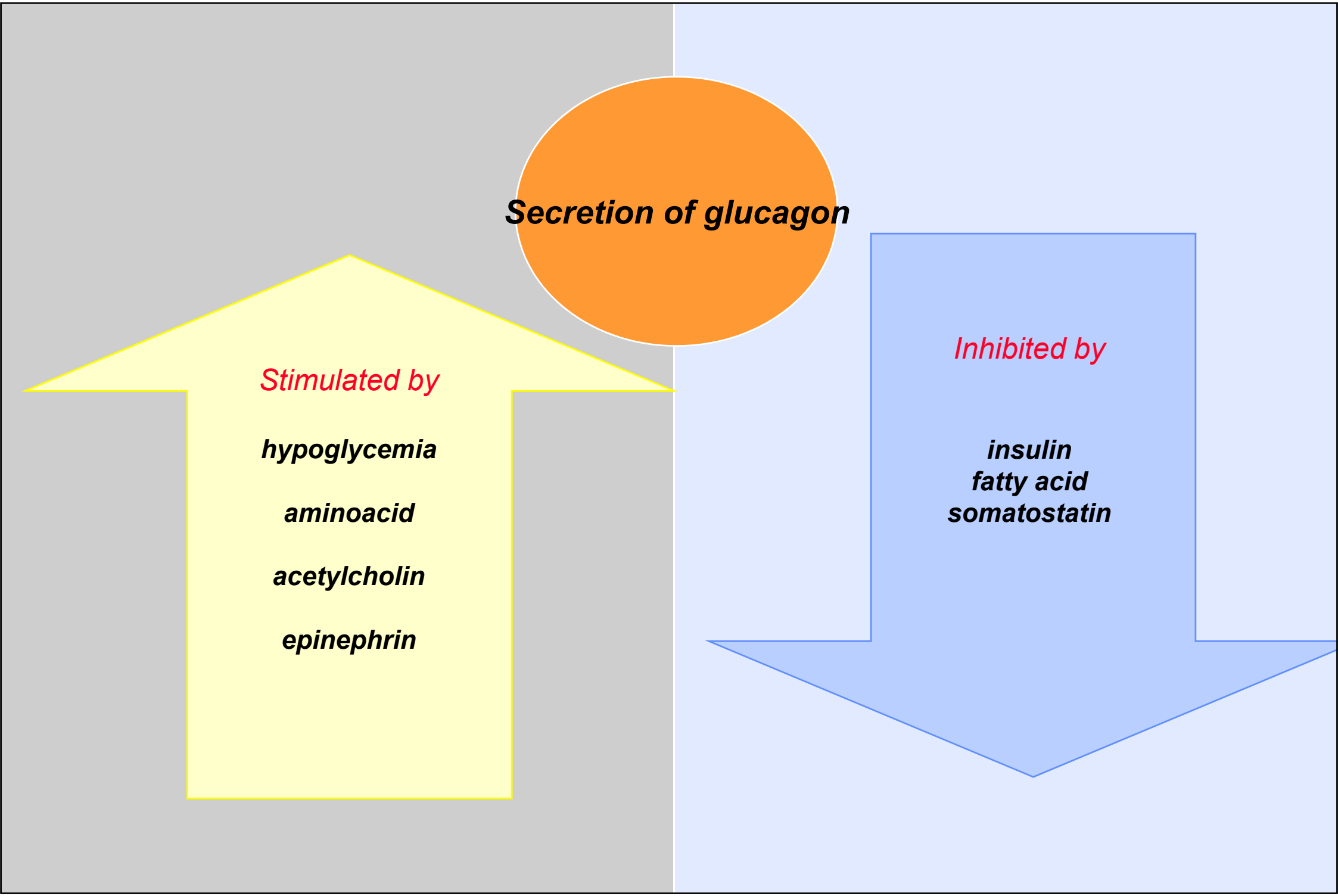

IR
I
chromodulin


IR
I
chromodulin
chromodulin
Decrease concentration of insulin
insulin-sensitive cells


I
IR
apochromodulin


glucagon
catecholamins
glucocorticoids
STH (growth hormon)
glycaemia
insulin


Insulin secretion
STIMULATION by -
glucose
amino acids
fatty acids
ketone bodies
acetylcholin
Gastrointestinal peptid -GIP
secretin
gastrin
GLP 1
INHIBITION by -
insulin
noradrenalin
adrenalin
alfa2-stimulation
hyperglycaemia
somatostatin
chronic hyperglycaemia


Secretion of glucagon
Stimulated by
hypoglycemia
aminoacid
acetylcholin
epinephrin
Inhibited by
insulin
fatty acid
somatostatin

DIABETES MELLITUS

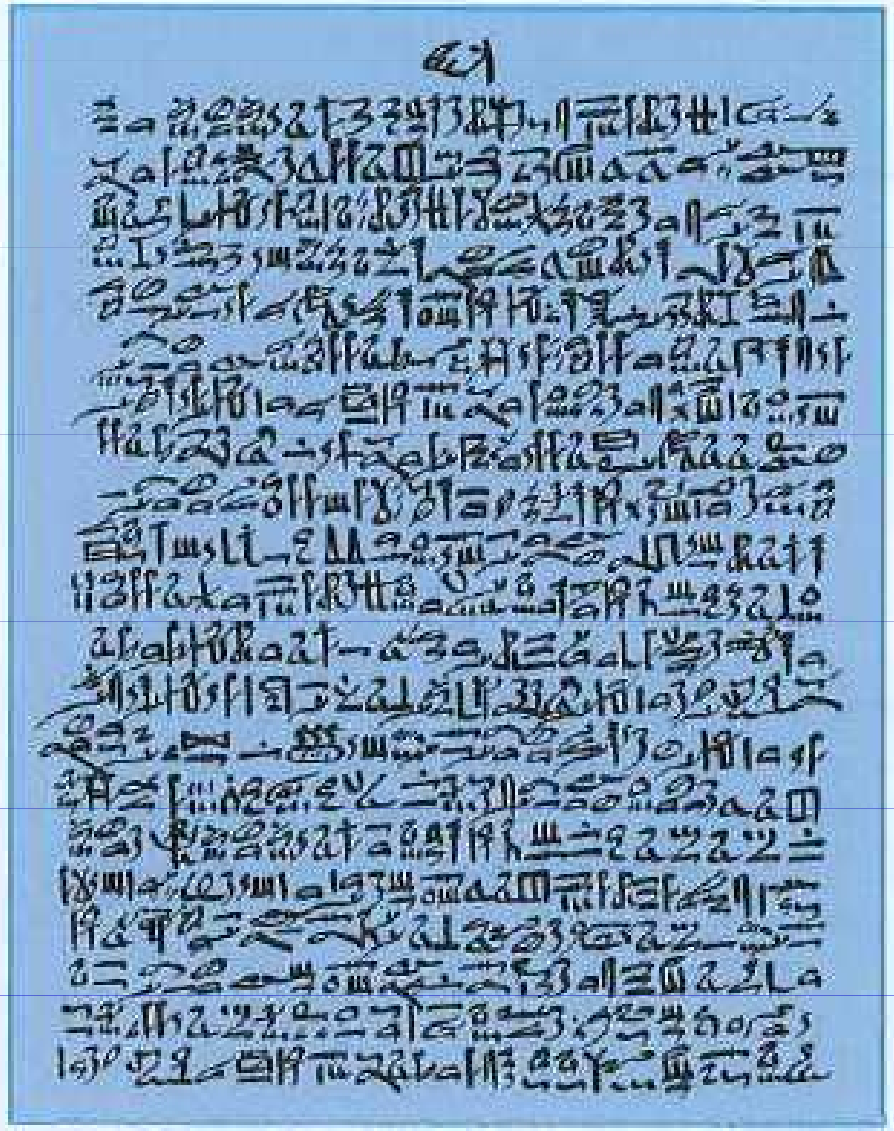
„Epidemic of the 21st century“

„Chronic progressive disease“

„Vessels - vascular disease“

Table 1.1 Milestones in the clinical descriptions of diabetes and its complications.

Clinical features of diabetes	
Ebers papyrus (Egypt, 1500 BC)	Polyuric state
Sushrut and Charak (India, 5th century BC)	Sugary urine; thin and obese patients distinguished
Aretaeus (Cappadocia, 2nd century AD)	Polyuric state named "diabetes"
Chen Chuan (China, 7th century)	Sugary urine
Avicenna (Arabia, 10th century AD)	Sugary urine; gangrene and impotence as complications
Diabetic ketoacidosis	
William Prout (England, 1810–1820)	Diabetic coma
Adolf Kussmaul (Germany, 1874)	Acidotic breathing
Hyperlipidemia	
Albert Heyl (Philadelphia, 1880)	Lipemia retinalis
Retinopathy	
Eduard von Jaeger (Germany, 1855)	General features
Stephen Mackenzie and Edward Nettleship (England, 1879)	Microaneurysms
Edward Nettleship (England, 1888)	New vessels, beading of retinal veins
Julius Hirschberg (Germany, 1890)	Classification of lesions; specific to diabetes
Neuropathy and foot disease	
John Rollo (England, 1797)	Neuropathic symptoms
Marchal de Calvi (France, 1864)	Neuropathy is a complication of diabetes
William Ogle (England, 1866)	Ocular nerve palsies in diabetes
Frederick Pavy (England, 1885)	Peripheral neuropathy
Julius Althaus (Germany, 1890)	Mononeuropathy
Thomas Davies Pryce (England, 1887)	Perforating foot ulcers
Nephropathy	
Wilhelm Griesinger (Germany, 1859)	Renal disease in patients with diabetes
Paul Kimmelstiel and Clifford Wilson (USA, 1936)	Glomerulosclerosis associated with heavy proteinuria



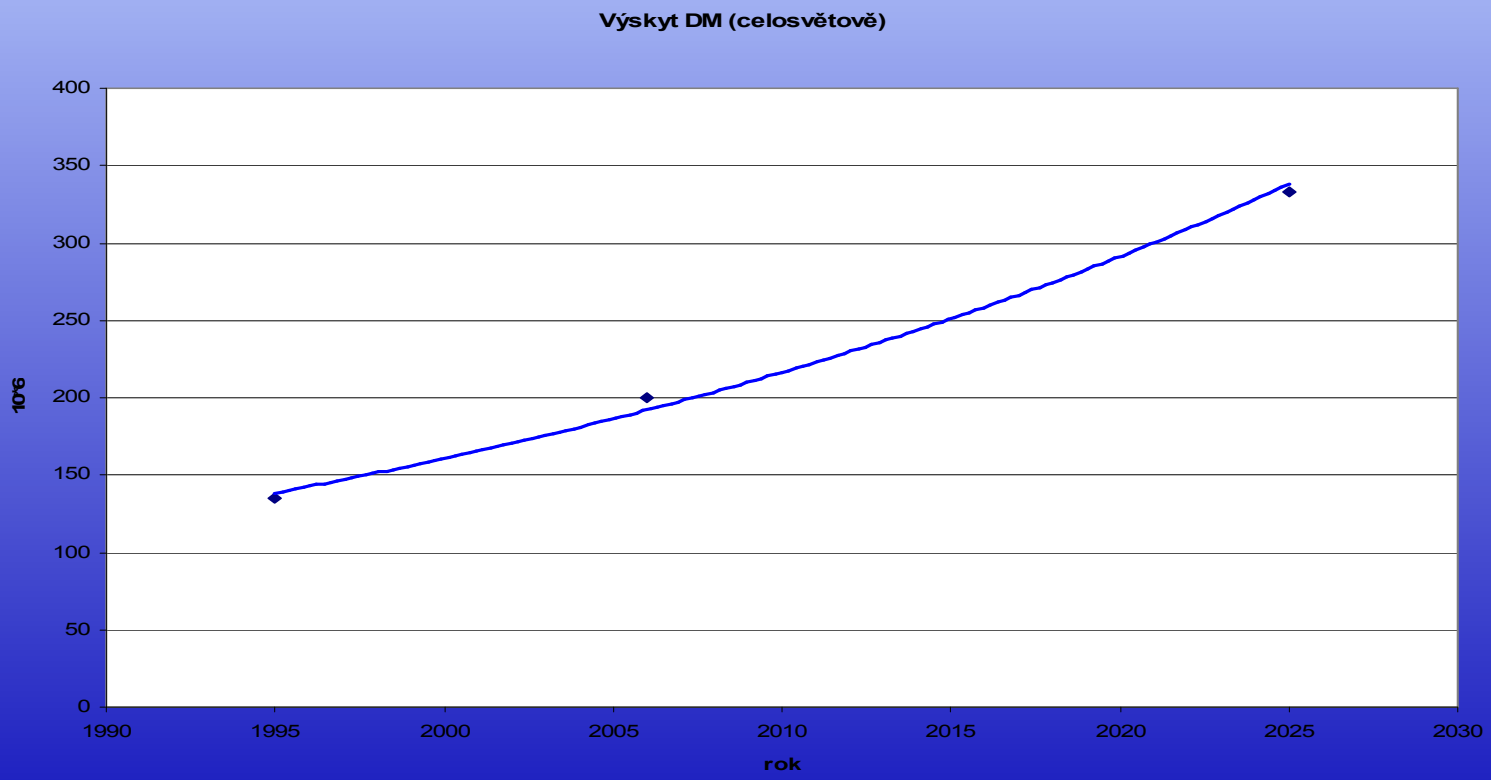
ure 1.1 The Ebers papyrus. Courtesy of the Wellcome Library, London.

Diabetes is the common term for several metabolic disorders in which the body no longer produces insulin or uses the insulin it produces ineffectively.
It is a common condition and is characterised by abnormally high blood sugar levels.
Diabetes is known as "diabetes mellitus" - where diabetes comes from the Greek word for siphon, which describes the excessive thirst and urination of this condition, and mellitus is the Latin word for honey, because diabetic urine is filled with sugar and is sweet.

The key to the problem is insulin - as insulin's role in the body is to help glucose get into the body cells where it is used to make energy.

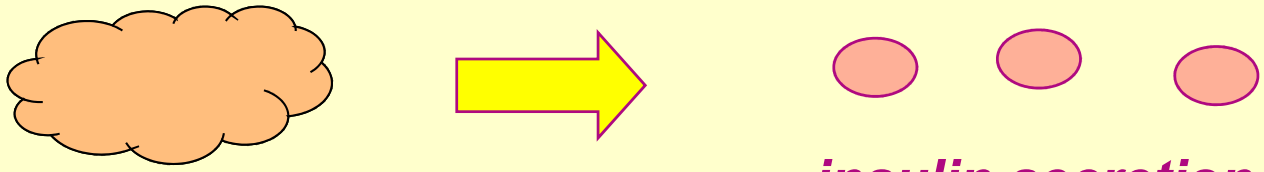
Diabetes is characterized by a partial or complete lack of insulin production by the body.
The most common forms of diabetes are:
Prediabetes – increase glycemia morning, oGTT disapear
Type 1 diabetes
Type 2 diabetes
(In both types of diabetes, people have little or no ability to move sugar out of the blood stream and into the cells, where it is used as the body's primary fuel)

DIABETES MELLITUS - *incidence worldwide*



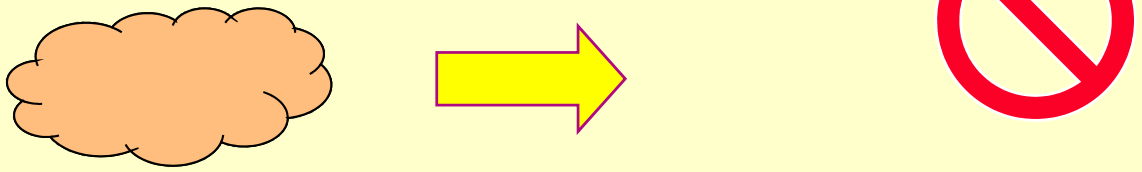
Czech Republic – year: 2000 – 654 000….year: 2013 - 861 000,
new patients with DM - 72 600 during 13 years
☺ promising field in your decision for the future ☺ as good job ♡
USA – 320 million people – 30 million have diabetes
100 million do not know their illness - prediabetes!!!!!

Healthy people



insulin secretion

Diabetes mellitus 1



without insulin secretion

Diabetes mellitus 2

⇓insulin secretion

(resistence)
⇓receptors:down regulation

Type 1 diabetes develops when an "autoimmune reaction" destroys beta cells in the pancreas.

Autoimmune reaction means that the body creates antibodies against its own cells. As a result, the pancreas stops producing insulin or cannot produce enough insulin on its own.

Treatment involves daily insulin injections, in conjunction with healthy eating and regular exercise.

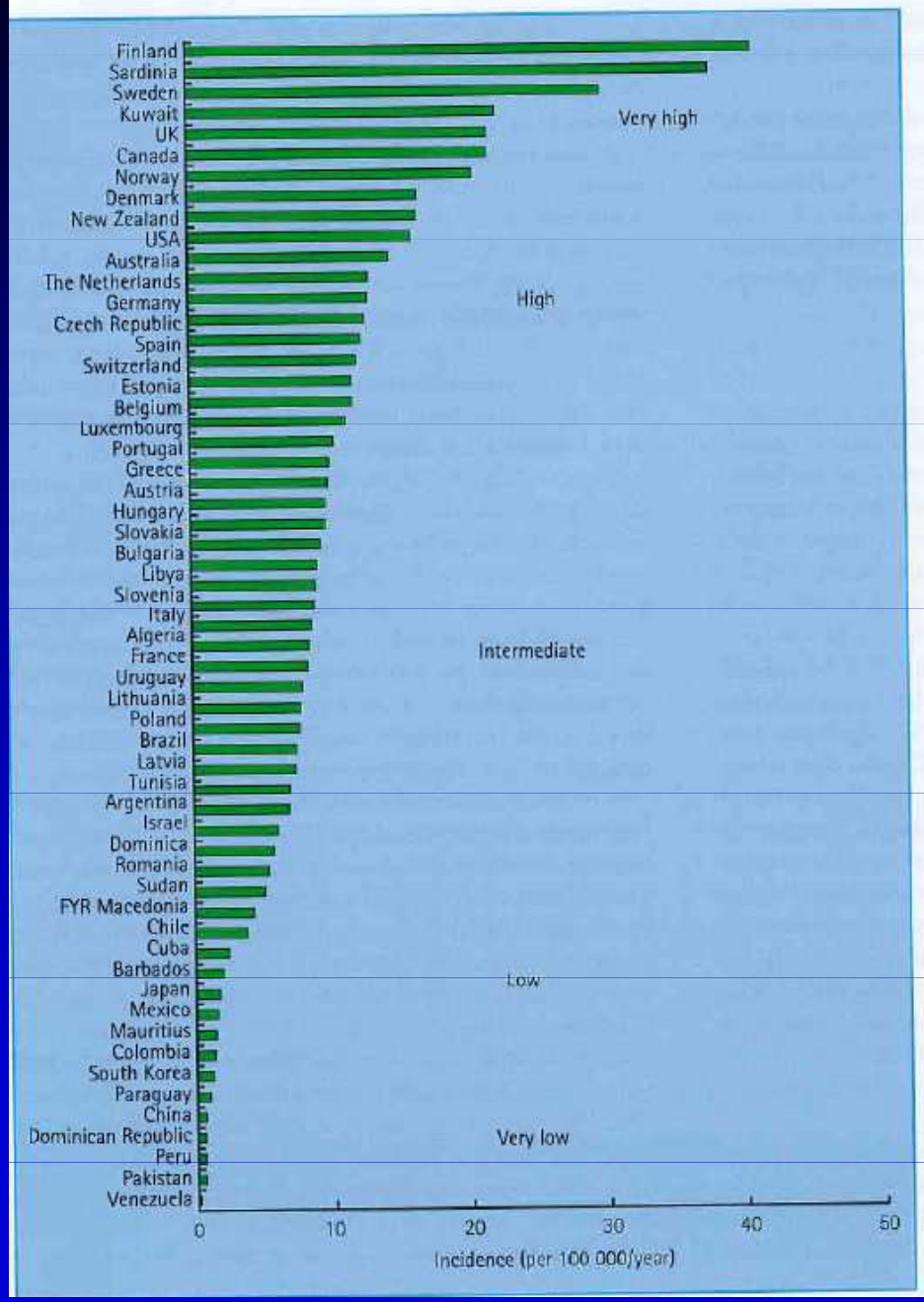


Figure 3.2 Geographic variation in childhood onset type 1 diabetes incidence rates, 1990–1999. Note that most registries were not nationwide and that several countries display within-country variation. Reproduced from the Diamond Project Group [6] with permission from John Wiley & Sons Ltd, Chichester.

Clinical specialities of DM type 1

Type 1 diabetes most often affects people under 20 years of age. It was previously called juvenile-onset diabetes or Insulin-Dependent Diabetes Mellitus (IDDM).

polyuria (excessive elimination of urine - frequent urination)
polydipsia (excessive drinking of water-extreme thirst and/or hunger)

weight loss
fatigue

- ***An acetone-like smell around the body***
- ***Fatigue, weakness, drowsiness***

DM 2

reccurents infections
metabolic syndrom

Risk factors of type 2 diabetes include:

- *Age (being over 45 years old)*
- *Being overweight or obese*
- *Having a family history of diabetes*
- *Ethnic background or race (Native/Indigenous, African, Hispanic or Asian descent)*
- *Having given birth to a large baby (over 4 kg or 9 lbs)*
- *Impaired glucose intolerance*

The symptoms of type 2 diabetes are the same as type 1 diabetes. Some people may also experience slow healing cuts and bruises, recurring gum or bladder infections, or tingling in their hands or feet.

Other terms previously used for type 2 diabetes are adult-onset diabetes and Non-Insulin Dependent Diabetes Mellitus (NIDDM).

Risk factors in patients with DM

Artery damage:

diabetic retinopathy (among adults, diabetes is the leading causes of blindness)

hypertension

stroke

myocardial infarction

diabetic nephropathy (kidney disease - failure)

Nerve damage:

diabetic neuropathy

Complication of DM

acute

<u>hypoglycemia < 3,3 mmol/l</u>

sweat, starvation, vertigo, headache, heart palpitation, tremor, double vission, tiredness, sleepiness, spasmus, unconsciousness

<u>hyperglycemia > 15 mmol/l</u>

be thirsty, starvation, sleeepiness, spasm in down extremities, unconsciousness

Complication of DM

chronic

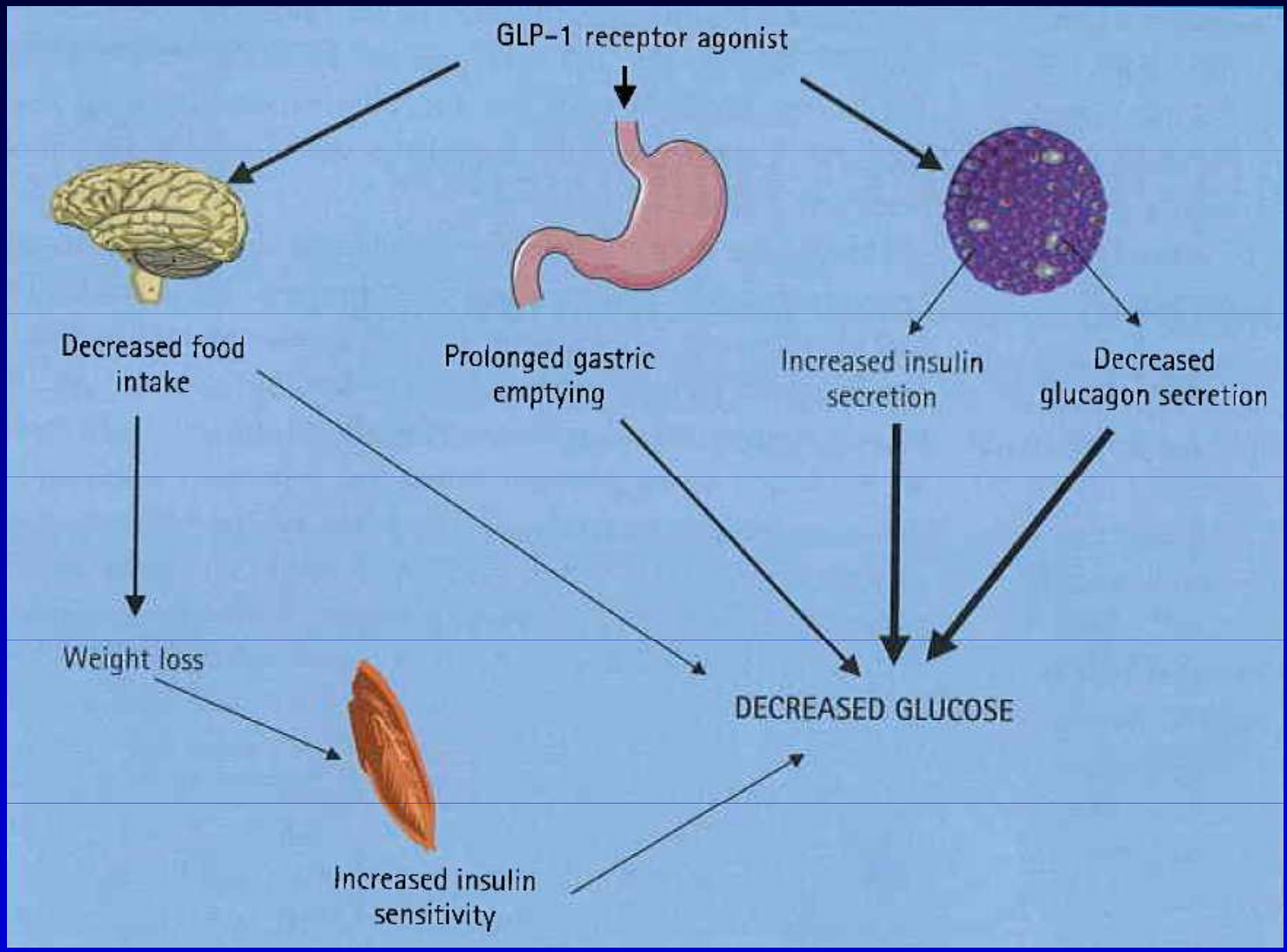
- ***specific***
  retinopathy, neuropathy, nephropathy

- ***non specific***
  atherosclerosis

mortality
cardiovascular diseases

„ The Incretin effect“

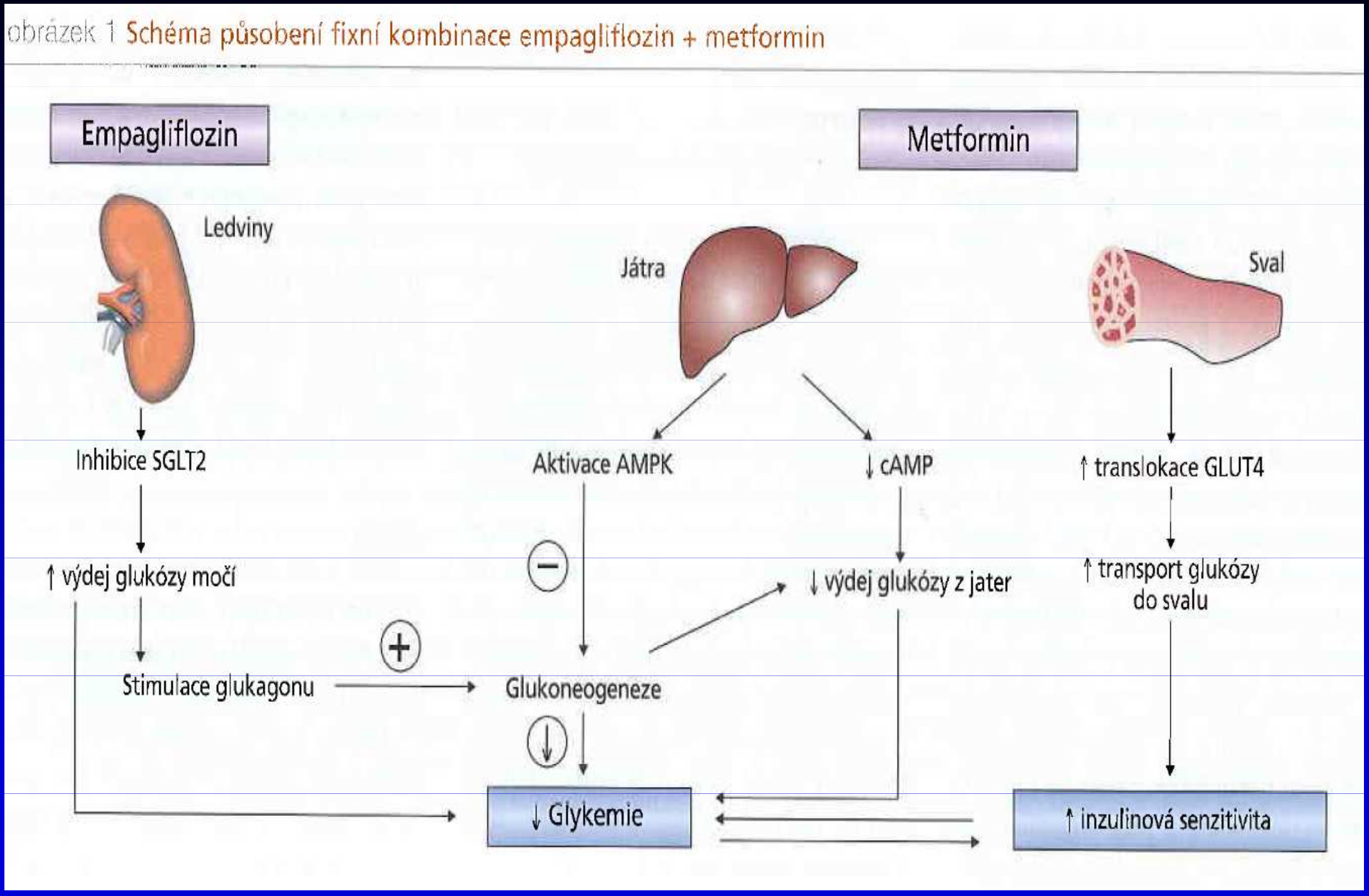
- Designates the amplification of insulin secretion elicited by hormones secreted from the gastrointestinal tract.
- In healthy subject the oral administration of glucose causes two- to threefold larger insulin response than the intravenous route as a results of the actions of the incretin hormones:
- glucose dependent insulinotropic polypeptide (GIP- previously named as gastric inhibitory polypeptid)
- Glucagon like peptid 1 (GLP 1)


GLP-1 receptor agonist
Decreased food intake
Prolonged gastric emptying
Increased insulin secretion
Decreased glucagon secretion
Weight loss
DECREASED GLUCOSE
Increased insulin sensitivity

sulfonylureas

- Enhance insulin secretion by beta cells by binding to and inhibiting ATP-sensitive K+channels, thereby decreasing the likelihood that these channels will be open. This action enhances glucose-stimulated insulin secretion (a proces in which this same channels is responsible for cell depolarization)
- By increasing insulin secretion and decreasing blood glucose-decresed the insulin resistance

obrázek 1 Schéma působení fixní kombinace empagliflozin + metformin



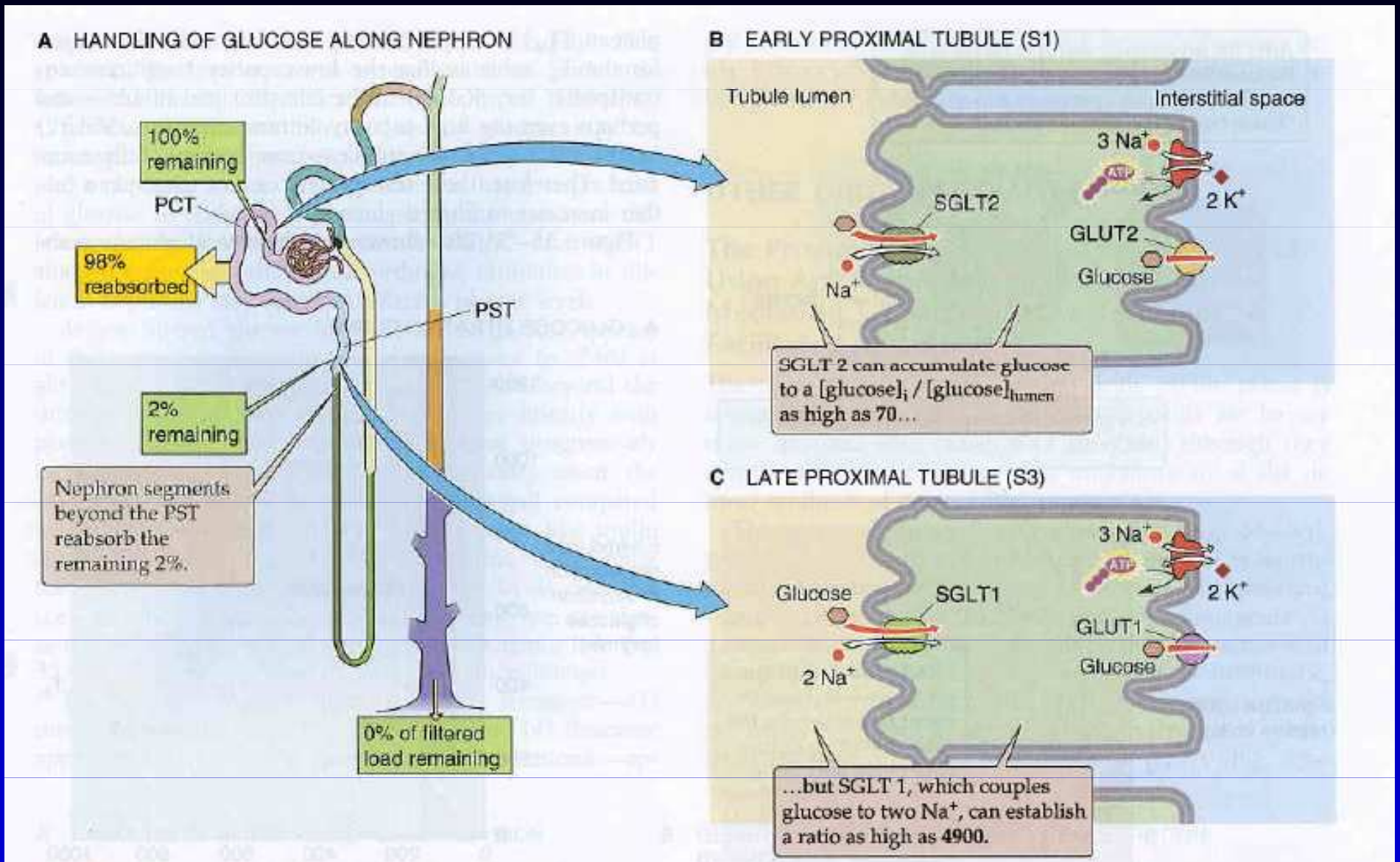


FIGURE 35–3. Glucose handling by the kidney. The *yellow box* indicates the fraction of the filtered load that the proximal tubule reabsorbs. The *green boxes* indicate the fraction of the filtered load that remains in the lumen at various sites. GLUT, glucose transporter (which mediates facilitated diffusion); PCT, proximal convoluted tubule; PST, proximal straight tubule; SGLT, Na/glucose cotransporter.

Ensure correct site of injection:
Abdomen for fast acting insuling
and thigh or buttock for prolonged acting insulin.
Rotate injection sites within a given body region.

How to inject?

The goal is to ensure injection in the subcutaneous tissue layer
(the fatty layer located immediately under the skin).
Pinch up the skin between two fingers to form a lifted skin-fold,
rotate gently to ensure that the underlying muscle is not also raised in
the skin-fold.
Insert the needle at a 90 degree angle to the lifted skin-fold.

- injection devices, with a range of designs and features. New devices use very thin needles and are virtually painless. They are easy, simple and convenient to use.

Hypoglycaemia – mild, moderate or severe type

- A hypo is a short term for hypoglycaemia which means low blood glucose. It can cause a wide spectrum of unpleasant symptoms, and if severe enough can lead to unconsciousness, coma or death.
- Hypos feel differently from person to person.

- Symptoms and signs
- Anxiety Blurred Vision Feeling cold
- Feeling weak Drowsiness Euphoria
- Headache Hunger Irritability
- Nervousness Pounding heart Restless sleep
- Sweating Trembling Unconsciousness

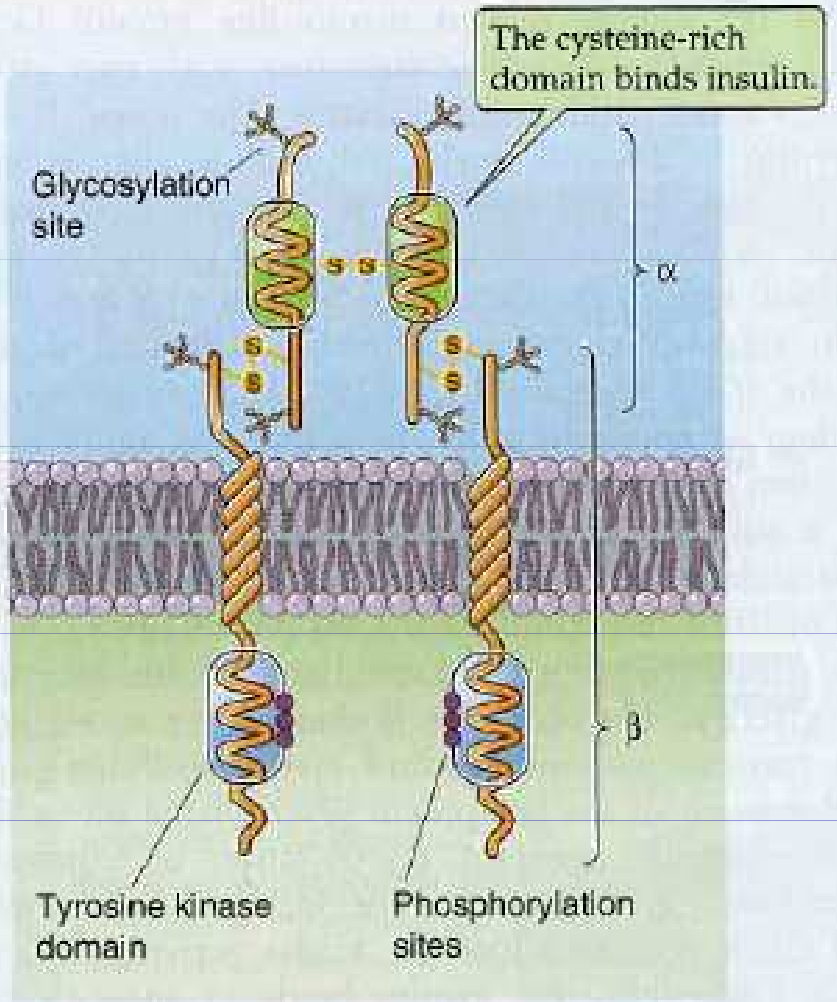


FIGURE 50–5. The insulin receptor. The insulin receptor is a heterotetramer that consists of two extracellular α chains and two membrane-spanning β chains. Insulin binding takes place on the cysteine-rich region of the α chains.

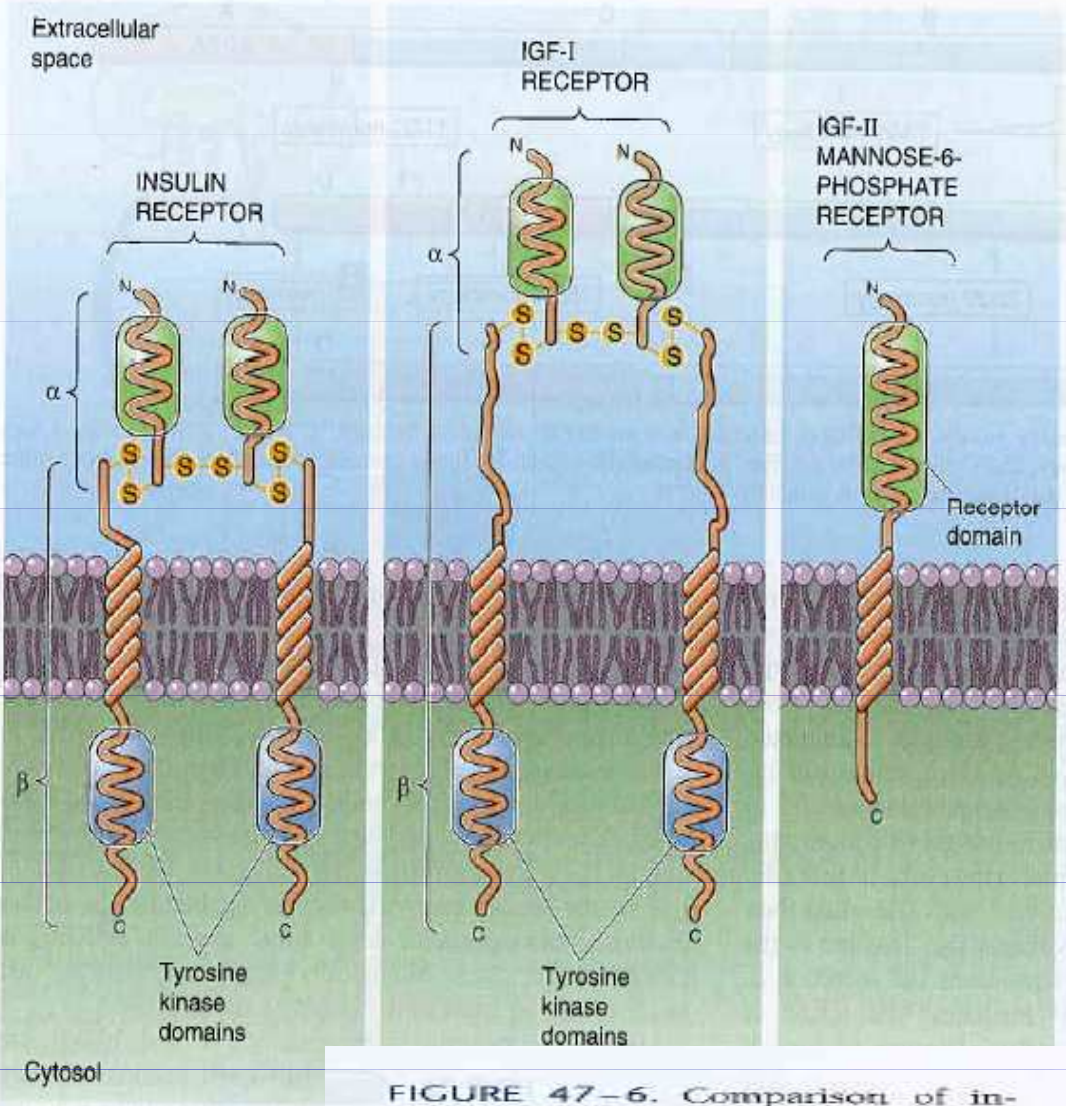


FIGURE 47–6. Comparison of insulin, insulin-like growth factor (IGF)-I, and IGF-II receptors. Both the insulin and IGF-I receptors are heterotetramers joined by disulfide bonds. For both, the cytoplasmic portion of the β subunits have tyrosine kinase domains as well as autophosphorylation sites. The IGF-II receptor (also called mannose-6-phosphate [M6P] receptor) is a single polypeptide chain with no kinase domain.

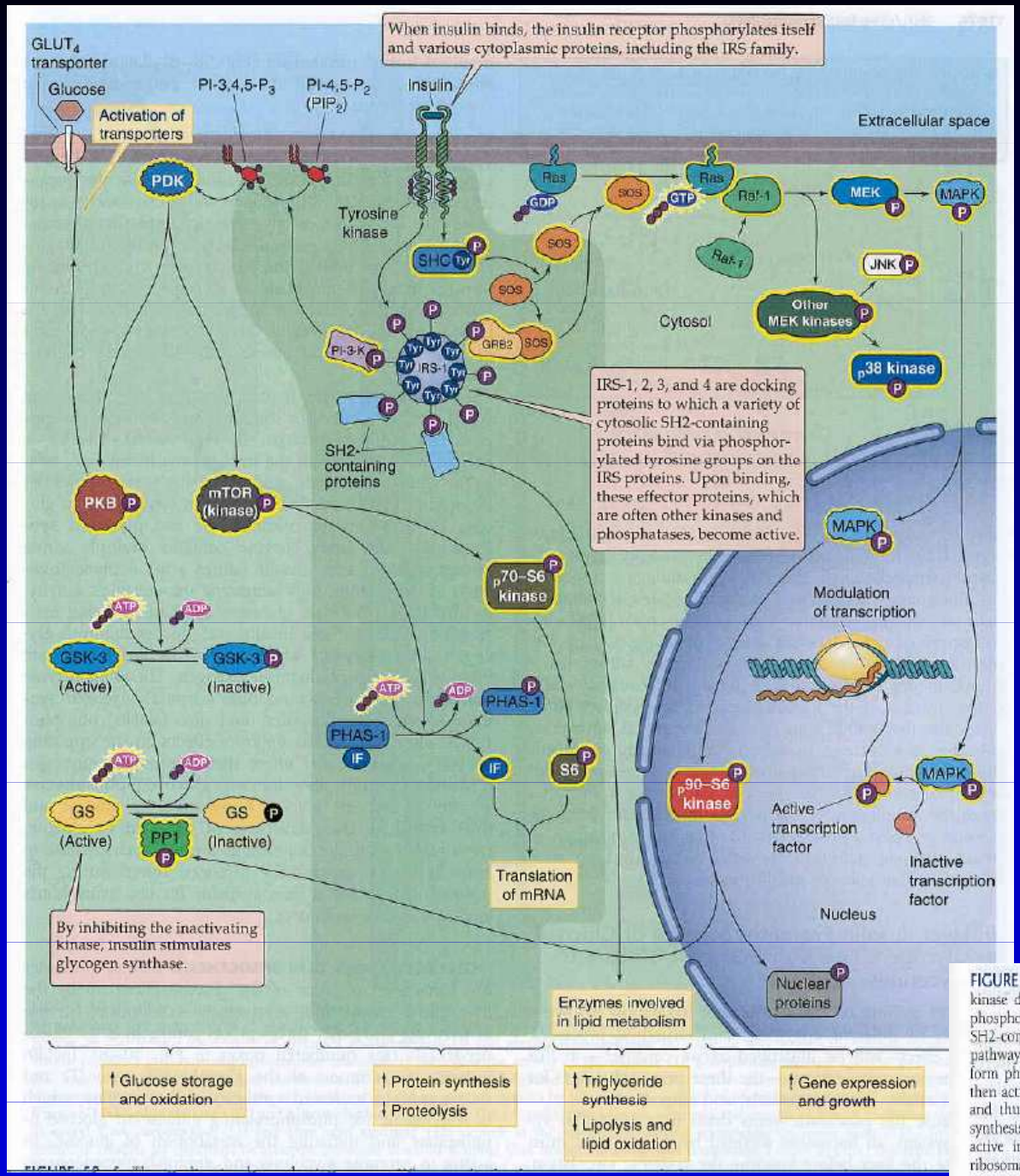


FIGURE 50–6. The insulin signal-transduction system. When insulin binds to its receptor—which is a receptor tyrosine kinase (RTK)—tyrosine kinase domains on the intracellular portion of the β chains become active. The activated receptor transduces its signals to downstream effectors by phosphorylating at tyrosine residues the receptor itself, the insulin-receptor substrate family (IRS-1, 2, 3, 4), and other cytosolic proteins (e.g., SHC). SH2-containing proteins dock onto certain phosphorylated tyrosine groups on the IRSs, and thus become activated. The figure shows two major pathways. In the first pathway, activation of phosphatidyl inositol 3-kinase (PI-3-K) phosphorylates phosphatidyl inositol-4,5-biphosphate (PIP_2), to form phosphatidyl inositol-3,4,5-triphosphate ($PI\text{-}3,4,5\text{-}P_3$), which in turn activates phosphatidyl inositol-dependent kinase (PDK). This Ser/Thr kinase then activates protein kinase B (PKB), which leads to the insertion of GLUT4 glucose transporters into the plasma membrane. PDK also phosphorylates and thus inactivates glycogen synthase kinase-3 (GSK-3); the net effect is reduced inactivation of glycogen synthase (GS) and enhanced glycogen synthesis. Finally PDK activates mTOR (target of rapamycin), a Ser/Thr kinase that phosphorylates the binding protein PHAS-1 and thus releases an active initiation factor (IF), promoting translation of mRNA into protein. mTOR also phosphorylates p70-S6 kinase, which phosphorylates the ribosomal S6 protein. In the second pathway, the insulin receptor phosphorylates SHC (Src homology, C terminus) at tyrosine residues, stimulating SOS. In addition, activation of GRB2 also stimulates SOS. The stimulated SOS activates the Ras pathway, as described in Fig. 5–15. The activated Raf-1, which is itself a MEK kinase, not only activates MEK, but other MEK kinases, which in turn activate JNK (a kinase) and p38 kinase. MAP kinase (MAPK) activates both a transcription factor and p90-S6 kinase. The activated p90-S6 kinase phosphorylates a variety of nuclear proteins as well as protein phosphatase 1 (PP1); the latter leads to activation of glycogen synthase.