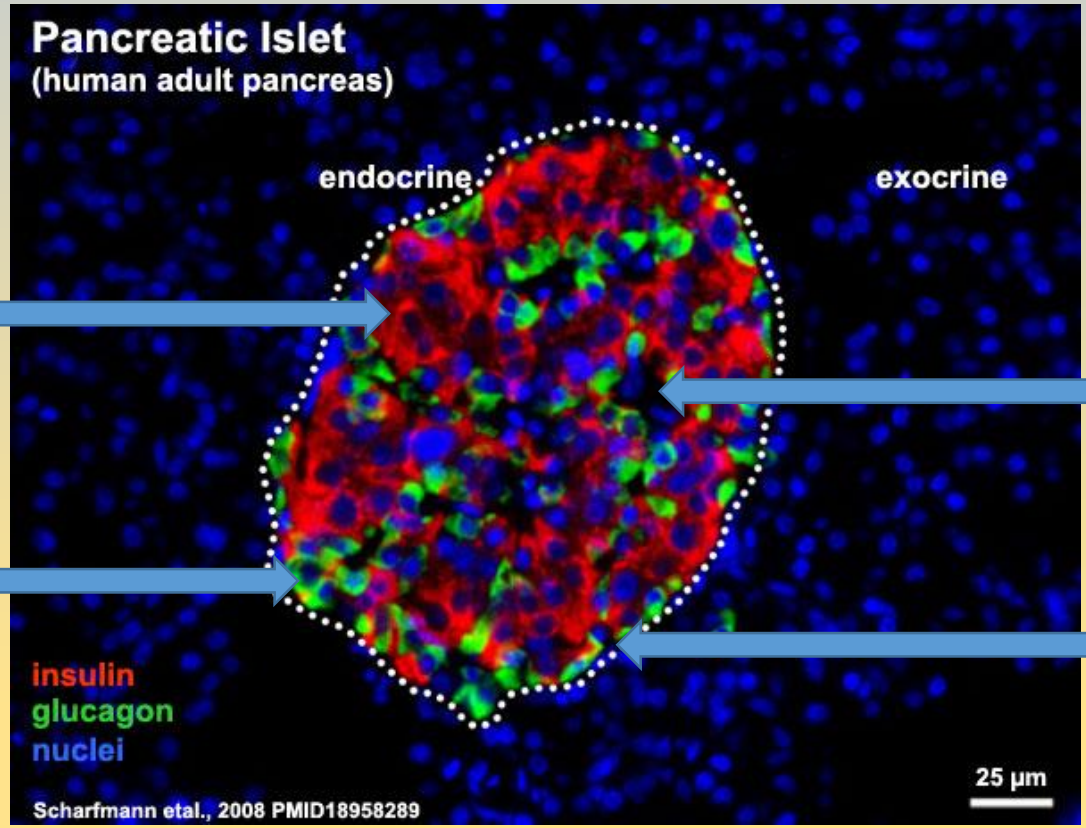
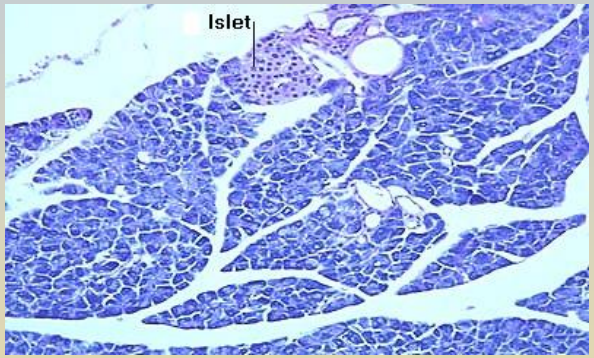
Endocrine versus exocrine pancreas





β cells
- Insulin
- Amylin
- TRH

α cells
- Glucagon
- GLP-1

δ cells
- somatostatin

PP cells
- Pancreatic polypeptide

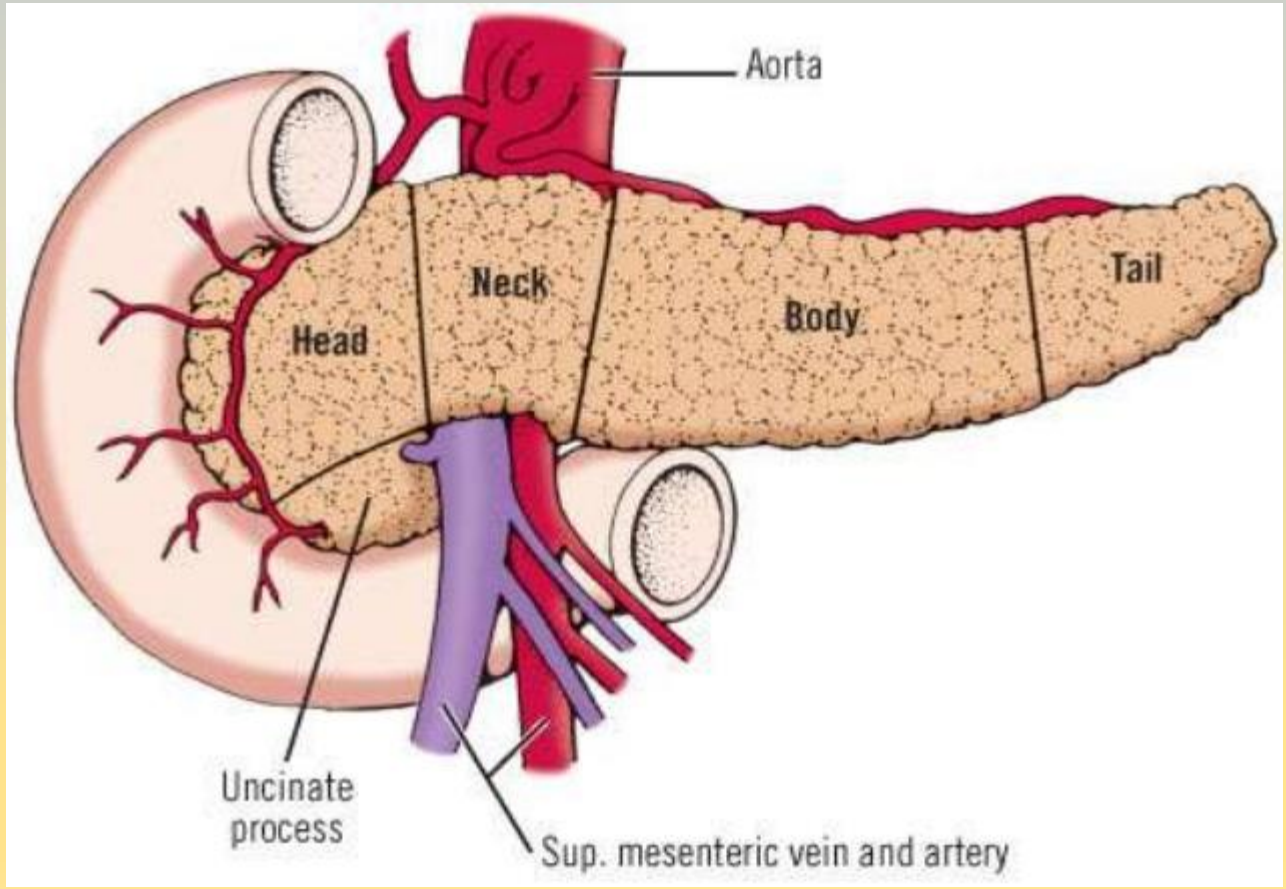
Pancreatic islets represent 1 – 2 % of pancreas, but blood flow through them represents 10 – 15 %.

Pancreas innervation

Acetylcholine
VIP
PACAP (pituitary adenylate cyclase-activating polypeptide)
GRP

CGRP
Substance P
(sensoric n.)

parasympathetic



Basal secretion I
Glu-stimulated secretion I
(α-AR)
Somatostatin

sympathic

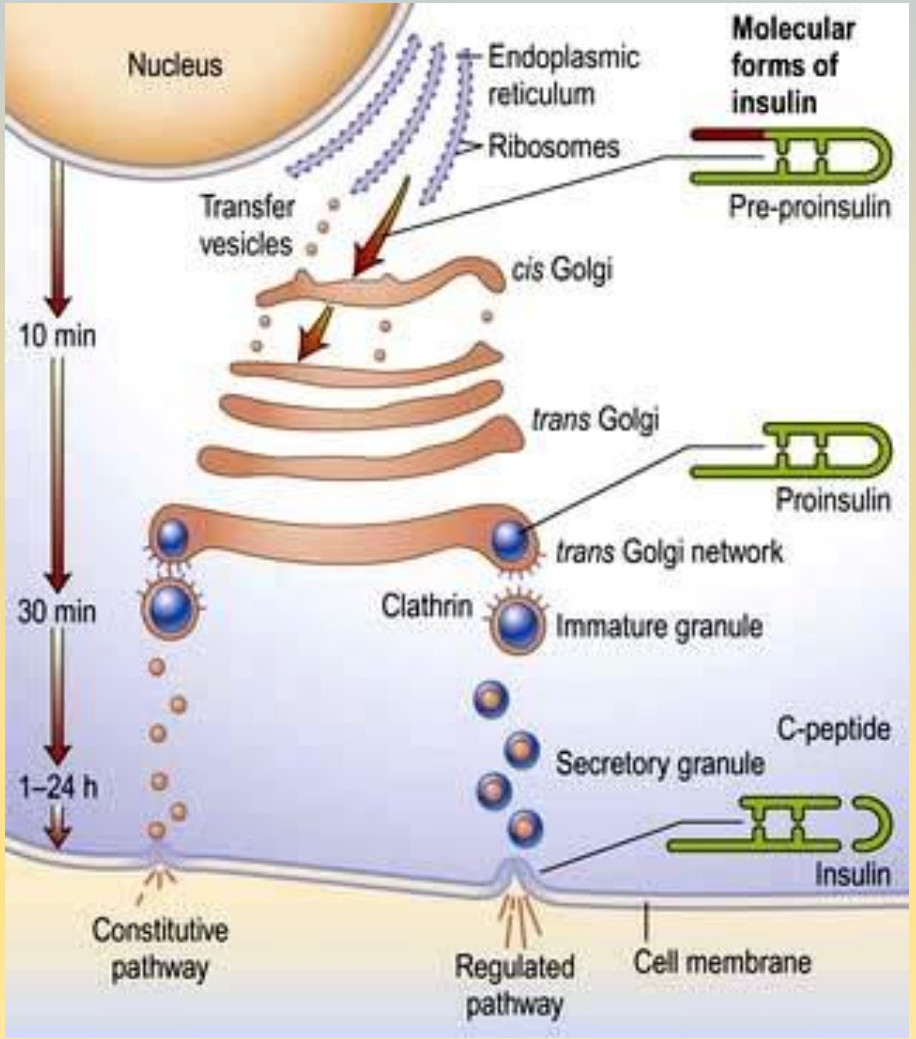
Noradrenaline
Galanin
Neuropeptide Y

Glucagon
PP

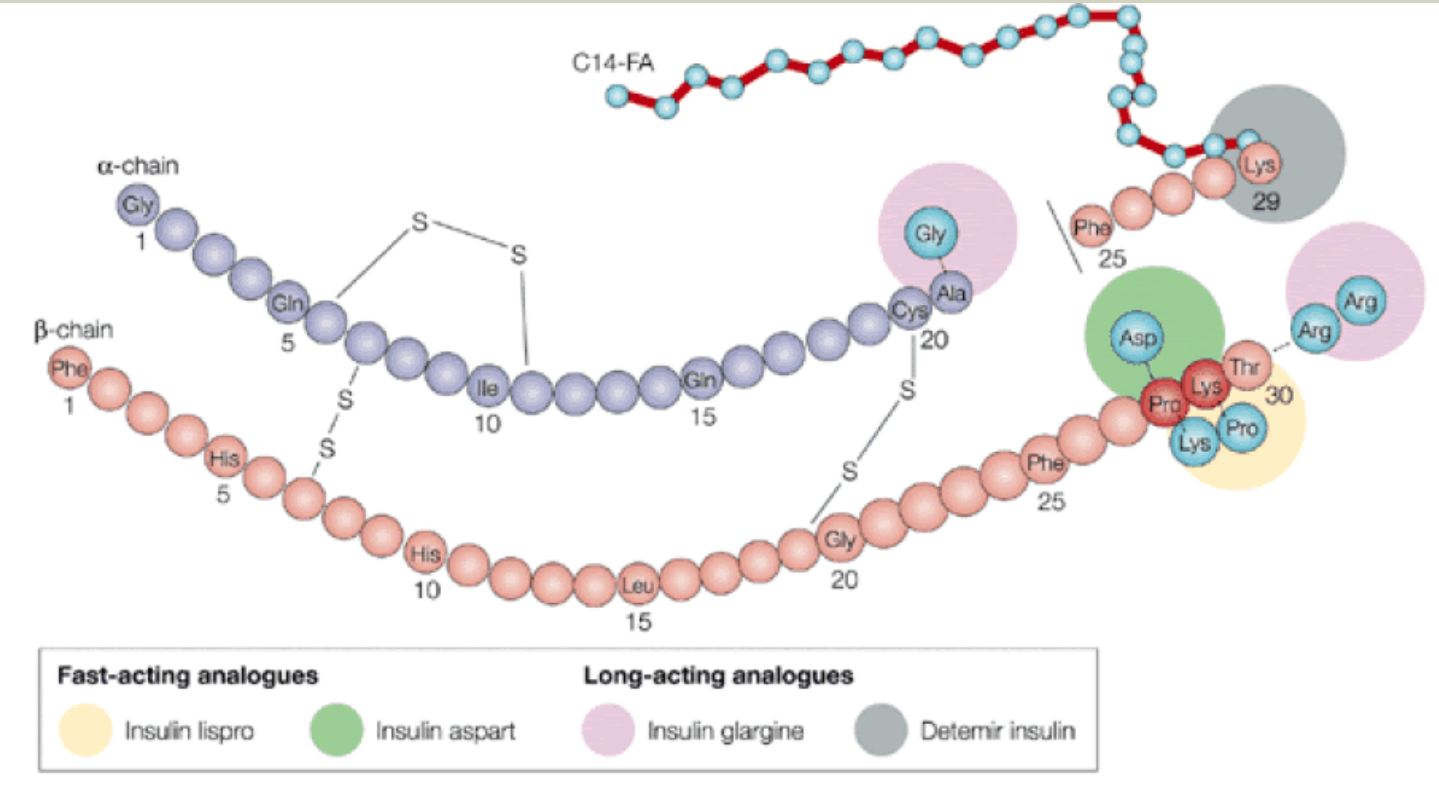
Insulin

Characteristics
- Polypeptide
- Secretory granules – free insulin and C-peptide
- Two types of secretory granules:
  - Quickly secretable (5 %)
  - Reserve pool (95 %)
- Half-time 3 – 8 min
- Degradation - liver (up to 50 %), kidneys, target tissues (insulin proteases)

Insulin secretion
- Insulin and C-peptide (approx. 1:1)
- C-peptide = sign of pancreatic secretory capacity (half-life approx. 35 min)
  - Possible biologic activity
  - Regulation of renal functions
  - Potential role in nervous system



Clinical relevance – insulin structure and analogues



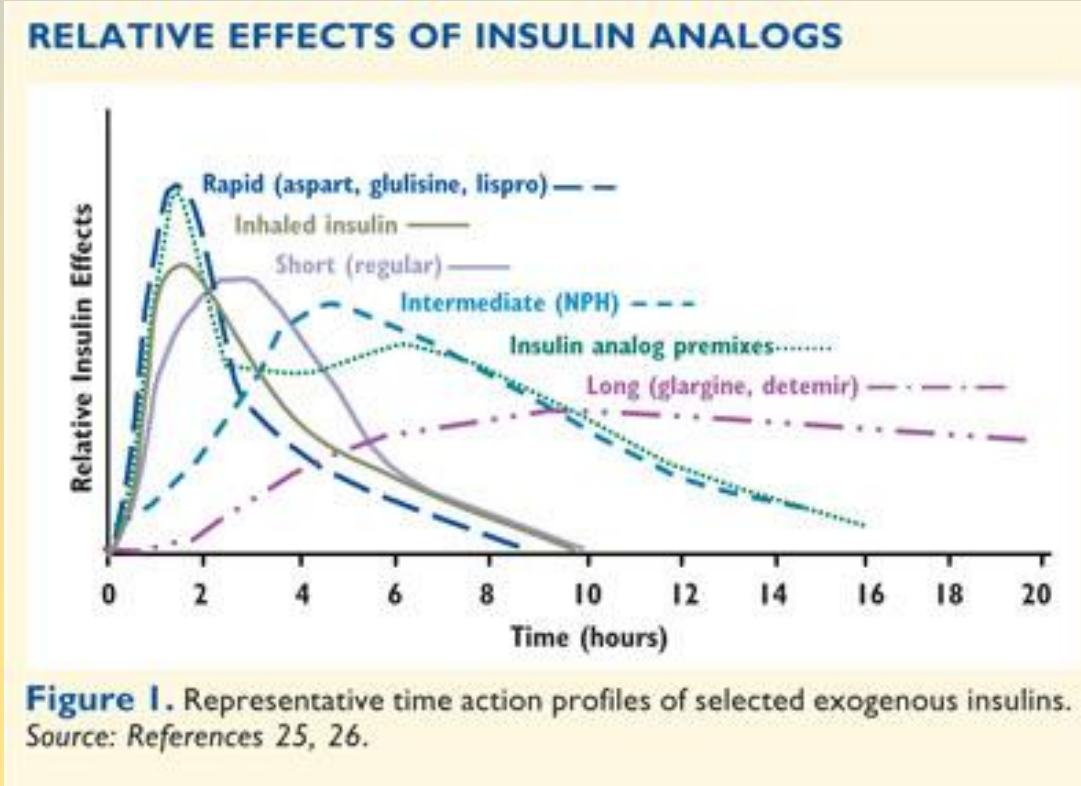
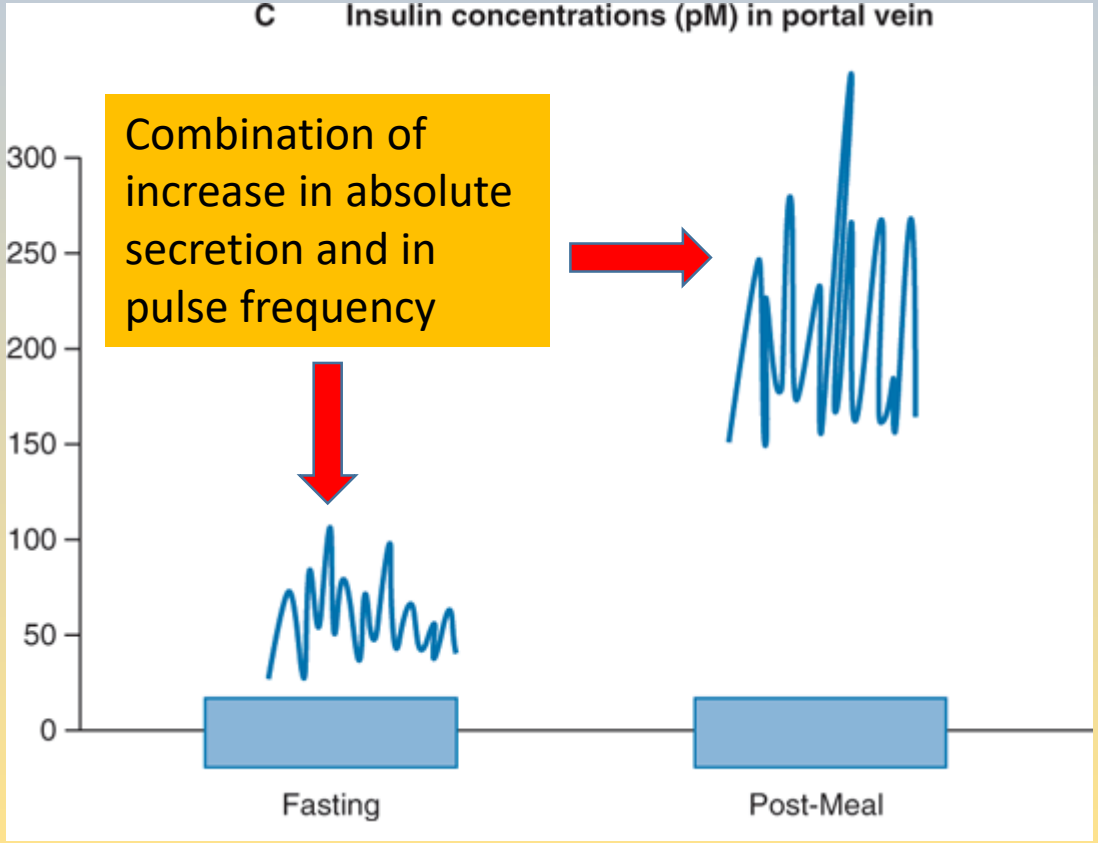
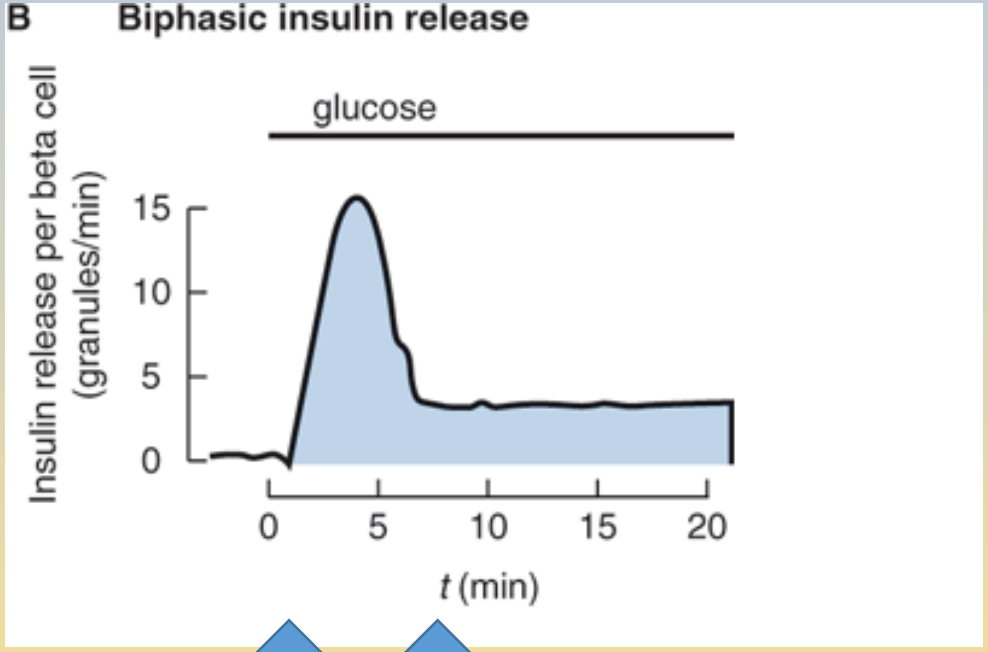


Figure 1. Representative time action profiles of selected exogenous insulins.
Source: References 25, 26.

Insulin secretion





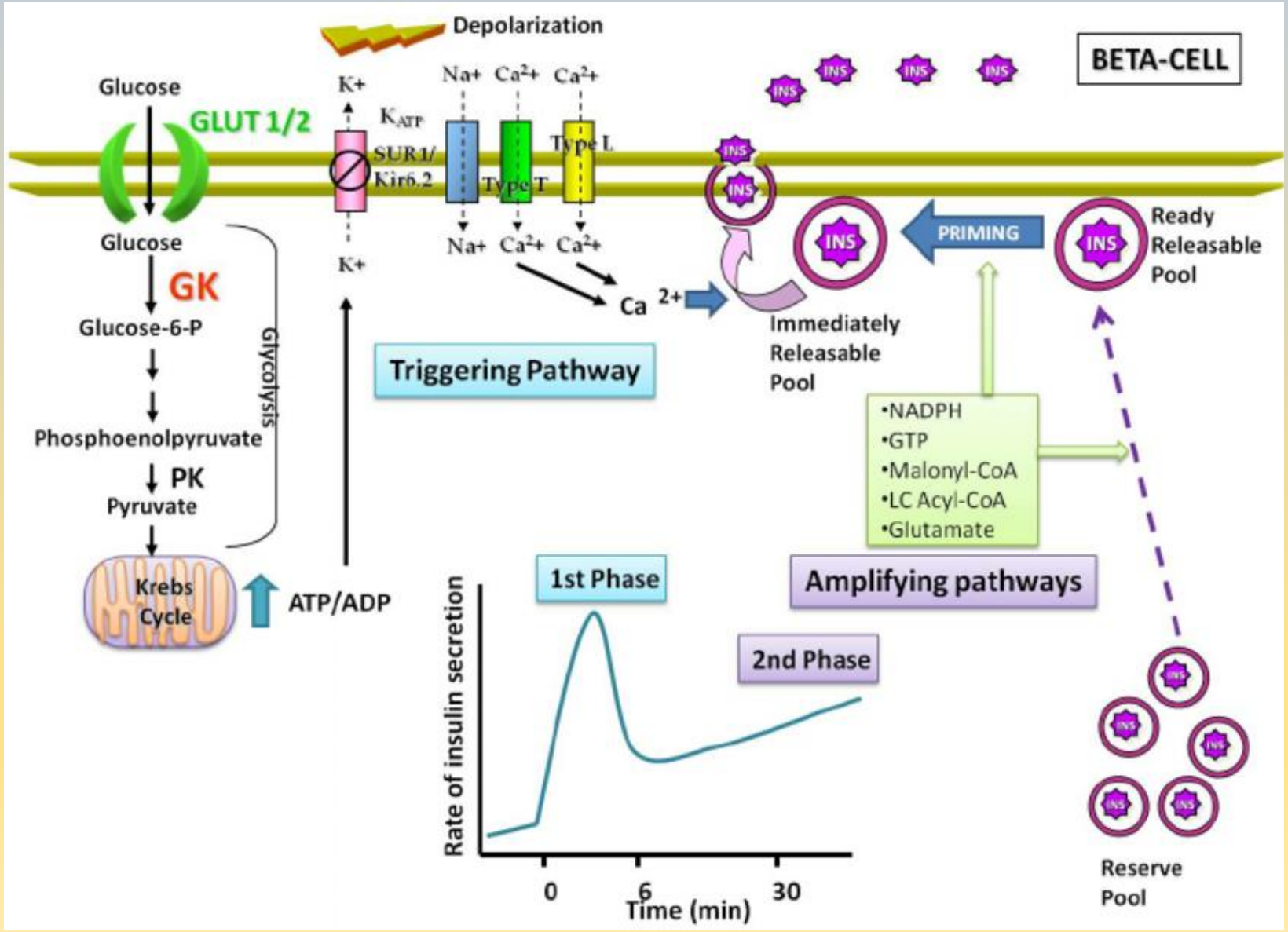
1. pool 2. pool

Pulsatile secretion
- Maintaining maximal biological response
- Suppression of liver gluconeogenesis
- Uptake adipocytes

Secretion of insulin by individual β cells is synchronized

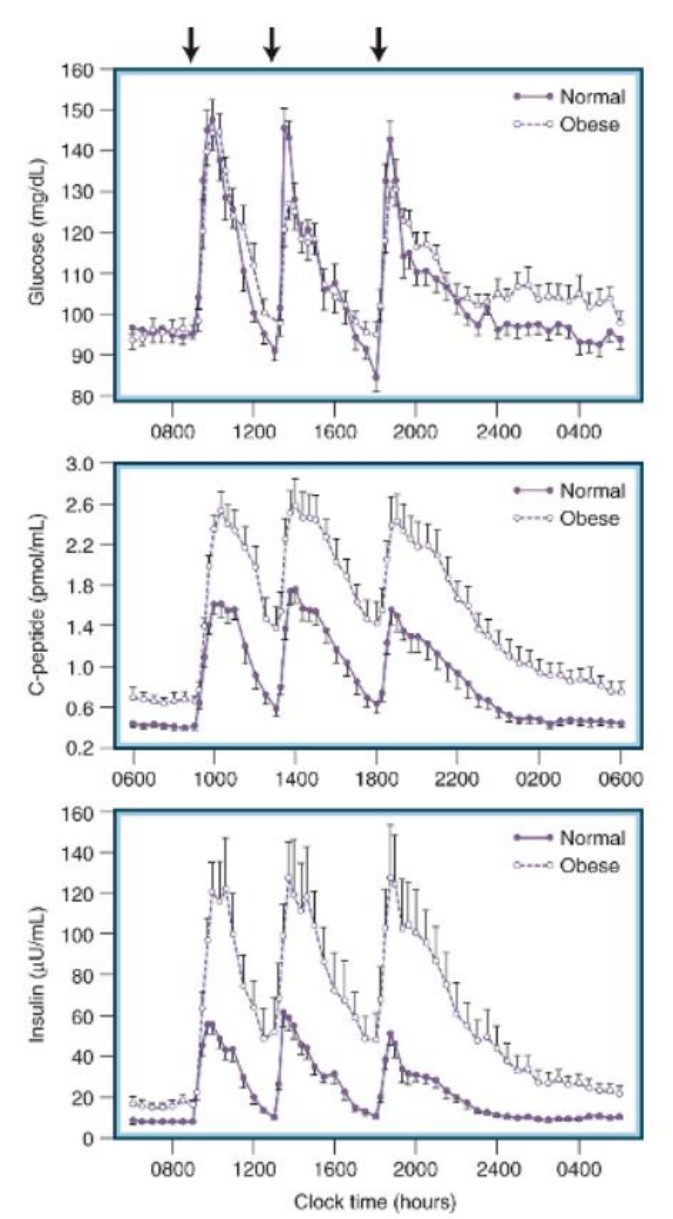
Secretion of insulin is pulsatile and shows rhytmicity. Stimulation of insulin secretion by glucose is biphasic. Glucose exhibits incretin effect.

Biphasic insuline secretion

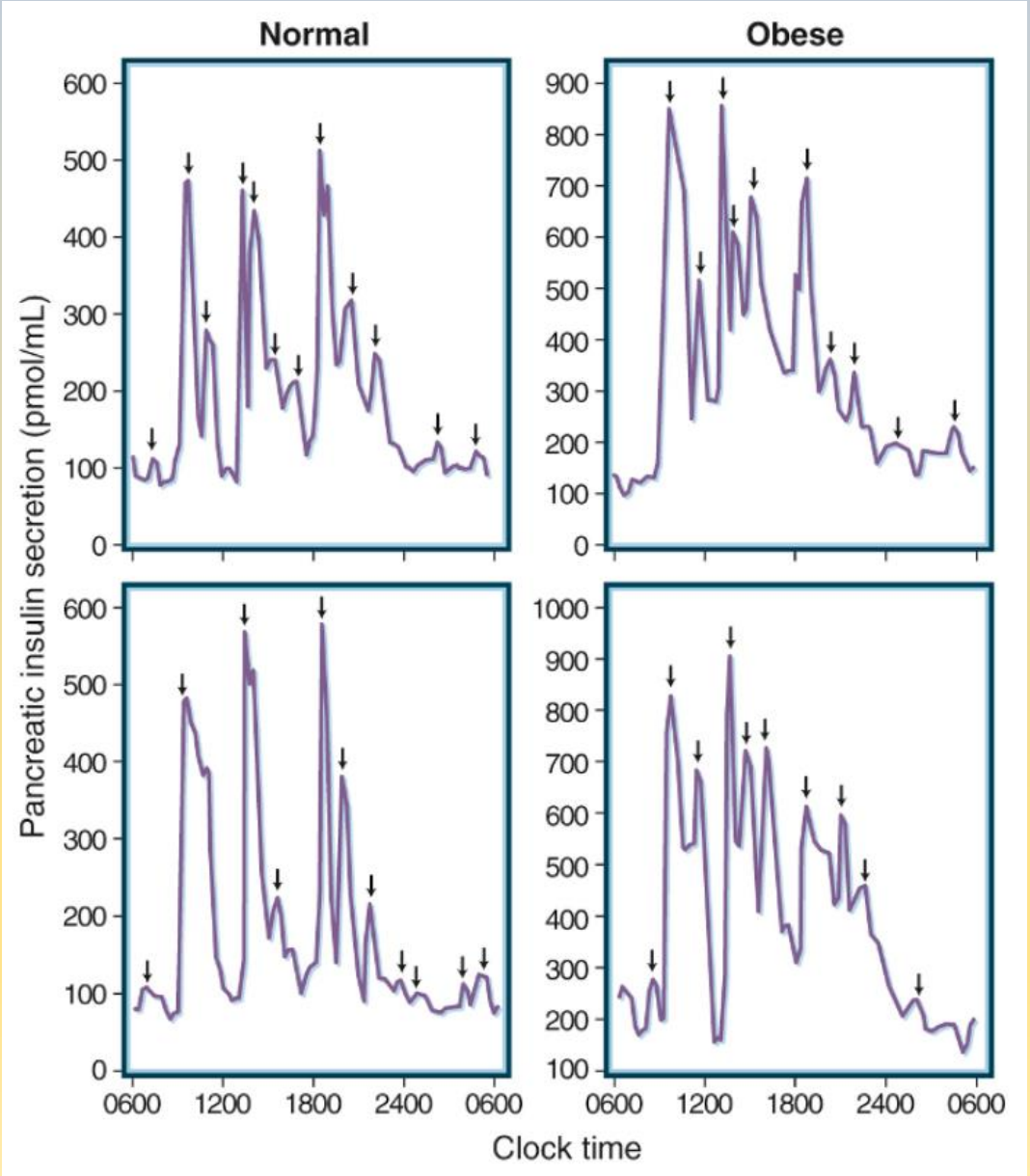


Insulin secretion – „normal“ and obese

Glycemia, insulinemia and C-peptide concentration



Pulsatile insulin secretion and its rhytmicity – ultradian



Regulation of insulin secretion

β cells = neuroendocrine integrator, response to:
- Plasmatic concentrations of substrates (AA, Glu)
- PC of hormones (insulin, GLP-1, somatostatin, adrenaline)
- PC of neurotransmitters (noradrenaline, acetylcholine)

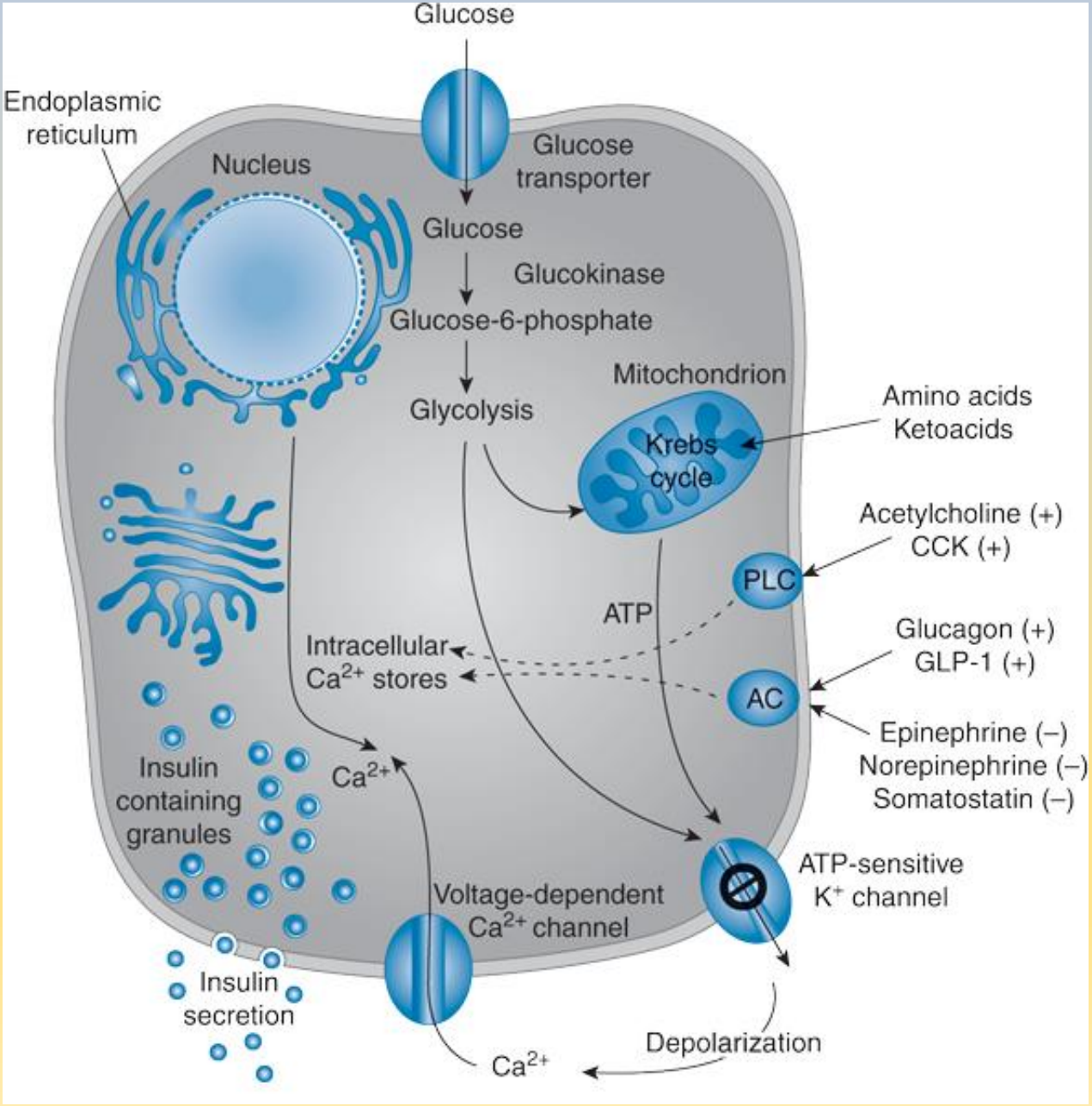
Glu
- Production of ATP – change in ATP/ADP ratio – closure of ATP-sensitive K^+ IC – inhibition of K^+ efflux - depolarization – opening of voltage-gated Ca^{2+} IC – exocytosis

AA – Leu, Arg, Lys
- Generation of ATP
- Direct depolarization of plasmatic membrane

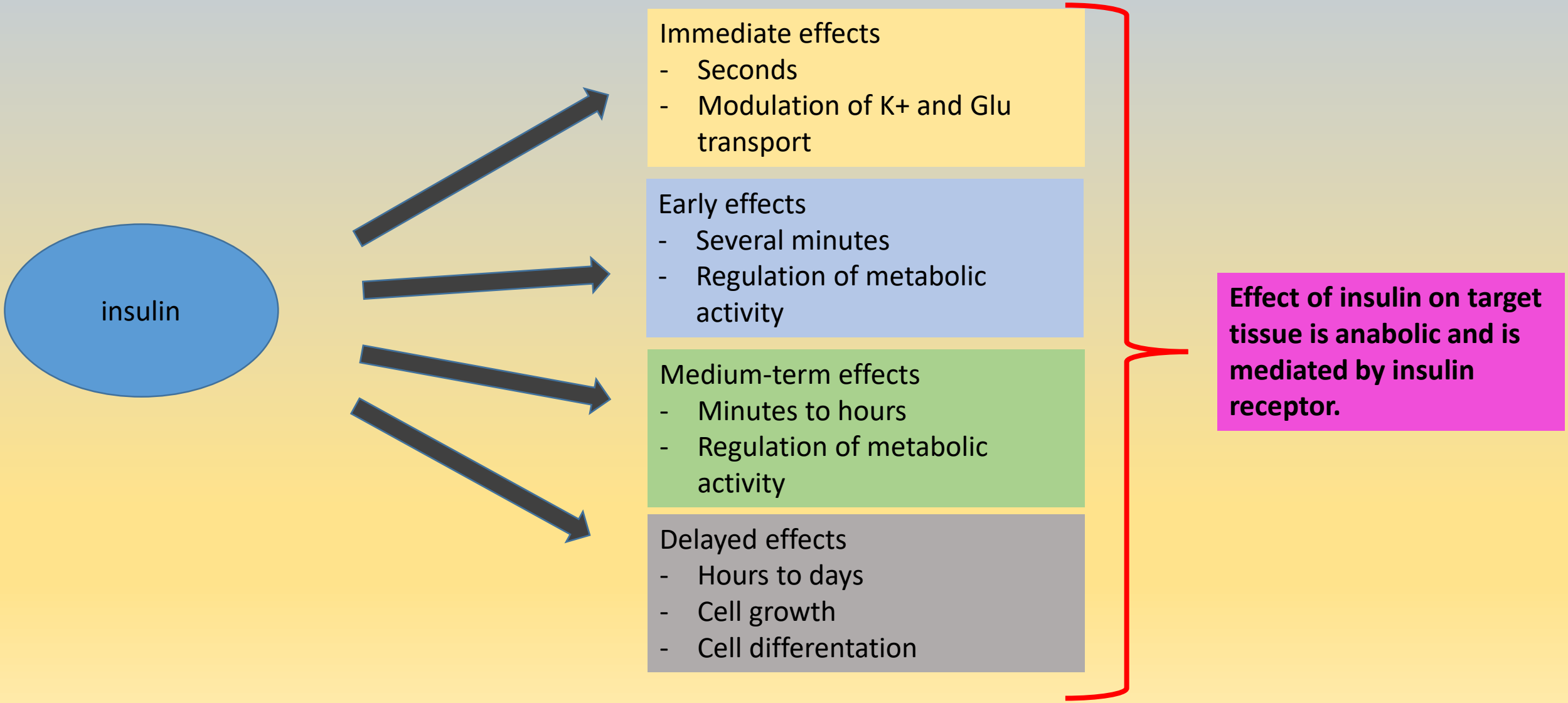
Modification of mRNA translation
- Glu – (+) mRNA

Other: - GH, VIP, secretin, gastrin, glucocorticoids, prolactin, placental lactogene, sex hormones

Glucose is the main stimulus for insulin secretion. Glucose has a permissive effect on secretion of other insulin secretion modulators.



Physiologic effects of insulin



Insulin receptor

Number of available IR is influenced by exercise, diet, insulin itself and by other hormones. Obesity and chronic hyperinsulinemia causes significant decrease in number of IR, exercise and starvation significant increase in number of IR.

Characteristics
- 2 α and 2 β subunits
- TK activity
- Phosphorylation of IRS 1-4 (insulin receptor substrate)
- Interaction with other cell substrates
- PI3K (phosphatydylinositol-3-kinase)
- MAPK (mitogen-activated protein kinase)

α subunits = Ligand binding

β subunits = TK activity

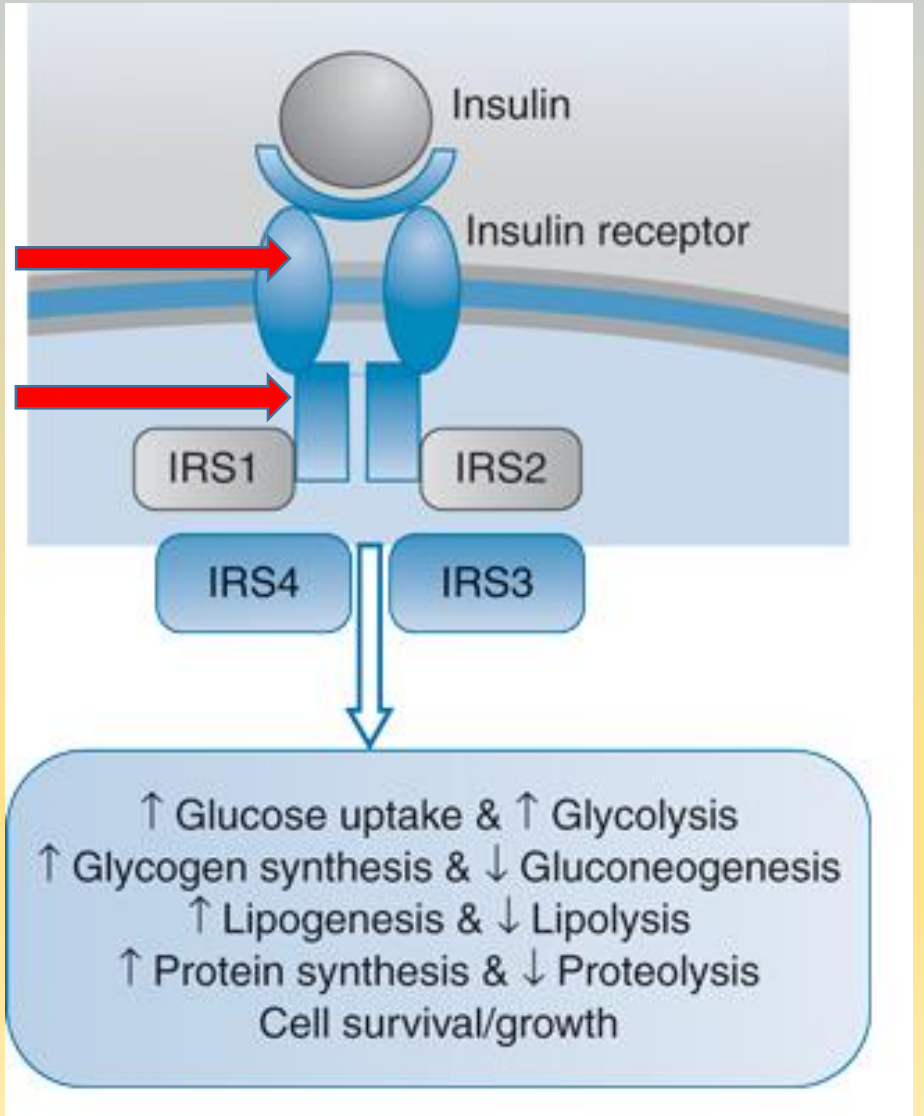
PI3K → PI3P PI2P → PI-dependent kinase Proteinkinase B

- Metabolic effects – transport of Glu, glycolysis, glycogen synthesis, proteosynthesis regulation
- Cell growth, strong antiapoptotic signal

MAPK → Pro-proliferative effects of insulin and cell differentiation

Endocytosis of IR → Endosome acidification → Insulin dissociation → Phosphoryl-ation

Insulin dissociation → Degradation of insulin



Immediate effects of insulin of target tissues

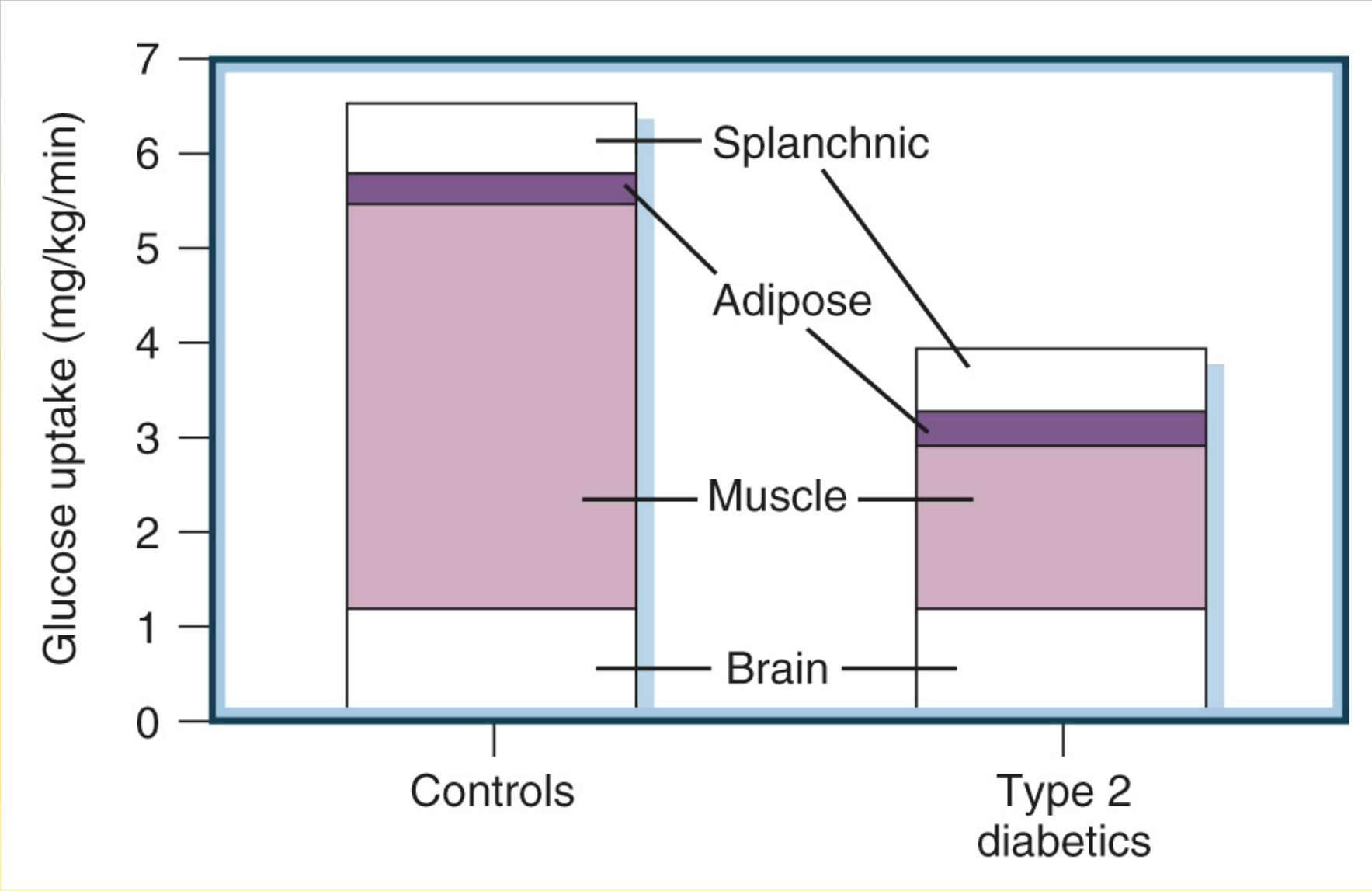
Utilization of glucose
- Approx. 40 % of glucose in body
- Approx. 80 – 90 % skeletal muscles
- Adipose tissue - adipocytes
- **GLUT4**

While **GLUT1** is responsible for basal uptake of glucose by skeletal muscles and adipocytes, **GLUT4** is stimulated by insulin and is responsible for insulin-stimulated uptake of glucose.

Transporter	Expression	Function
GLUT1	- Ubiquitous - Ery, endothelial cells (CNS), placenta, kidneys, colon - Skeletal muscles and adipocytes	- Basal uptake of Glu
GLUT2	– β cells of pancreas - Liver, small intestine, kidneys	- Glu sensor - Uptake of Glu during high concentrations of circulating Glu
GLUT3	- Primarily neurons - Placenta, liver, epithelial cells of GIT	- Basal uptake of Glu - Essential role in CNS
GLUT4	- Skeletal muscles and adipocytes - Vesicles!	- Insulin-stimulated uptake of Glu
GLUT5	- Jejunum, sperms	- Transport of Fru

Utilization of glucose is the main immediate effect of insulin.

Effect of insulin on glucose uptake



Early and medium-term effects of insulin

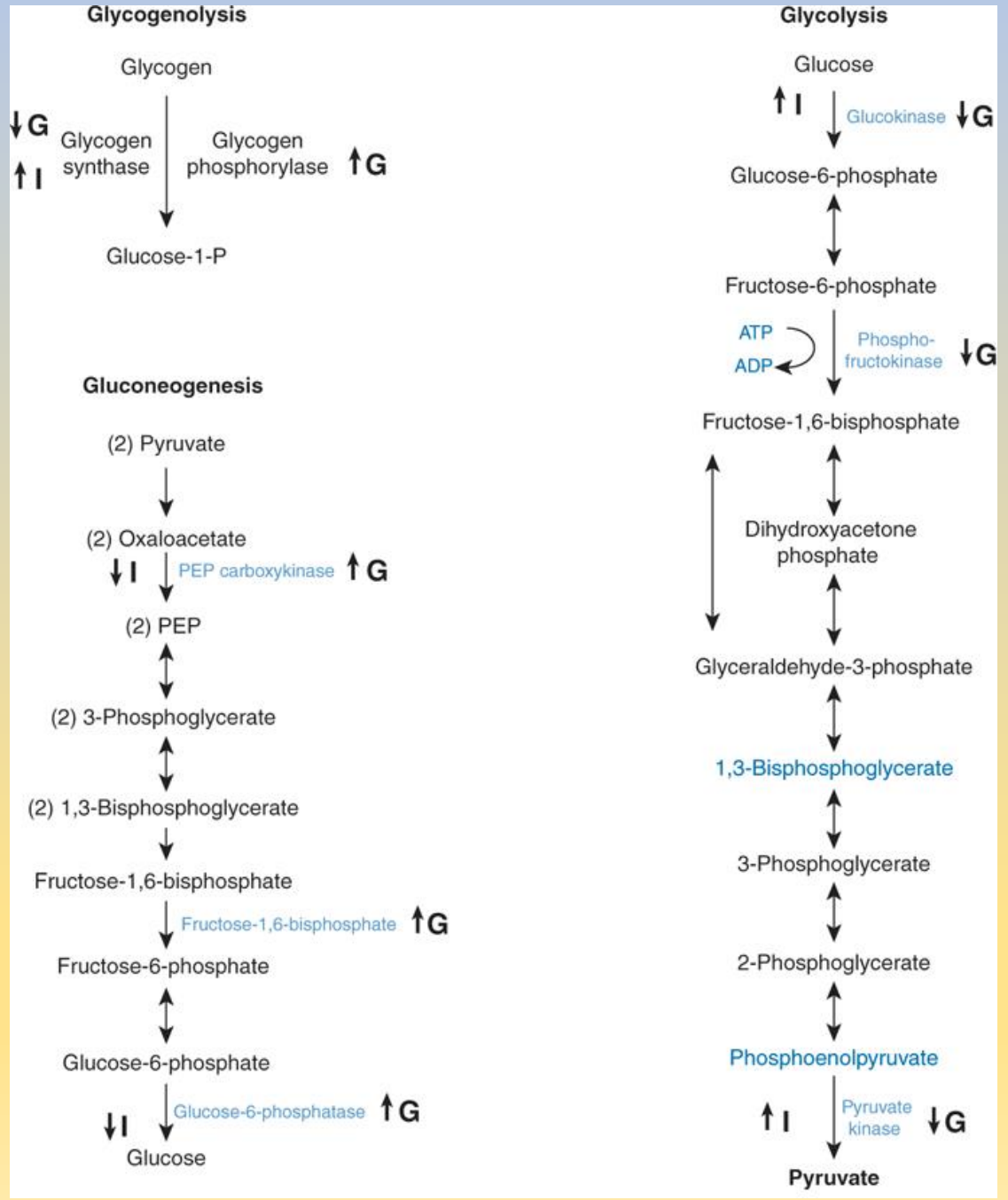
- Determined by phosphorylation of enzyme connected to metabolic pathways.
- Skeletal muscles, adipose tissue, liver

Production of ketone bodies (-)

- Dephosphorylation of hormone-sensitive lipase (inhibition of triglyceride utilization and cleavage to FFA and glycerol)
- Activation of acetylcoenzyme A carboxylase (lipogenesis)
- Antagonization of catecholamines effect on lypolysis (phosphorylation and activation of phosphodiesterase = decreased intracellular cAMP)

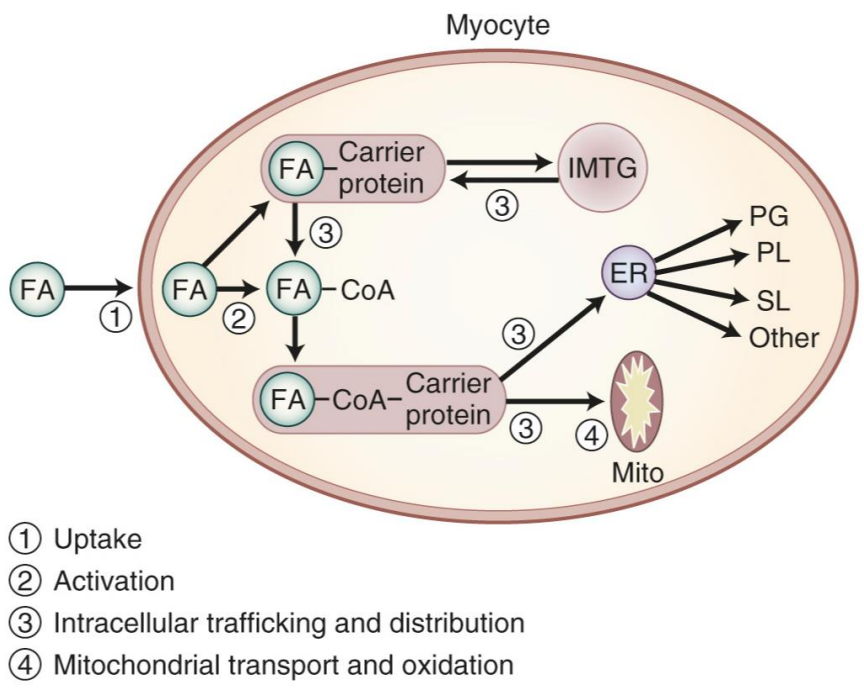
Utilization of glucose

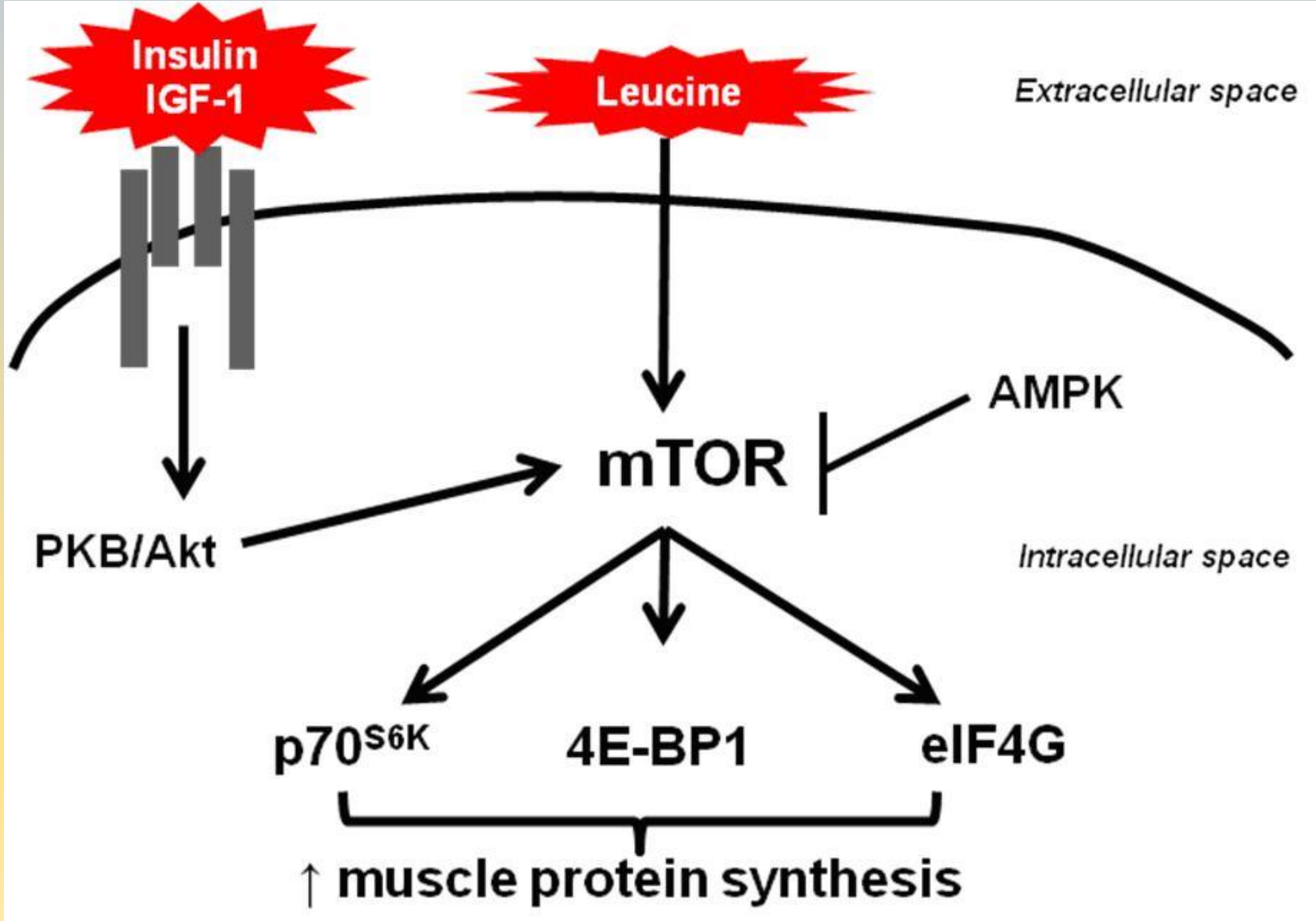
- liver
- Stimulation of expression of enzymes connected to Glu utilization (glucokinase, pyruvate kinase) and lipogenic enzymes
- Inhibition of enzymes connected to Glu production (phosphoenolpyruvate carboxykinase, glucose-6-phosphatase)
- Stimulation of glycogen synthesis
- Stimulation of malonylcoenzyme A synthesis – inhibition of ketone bodies synthesis



Insulin and skeletal muscles

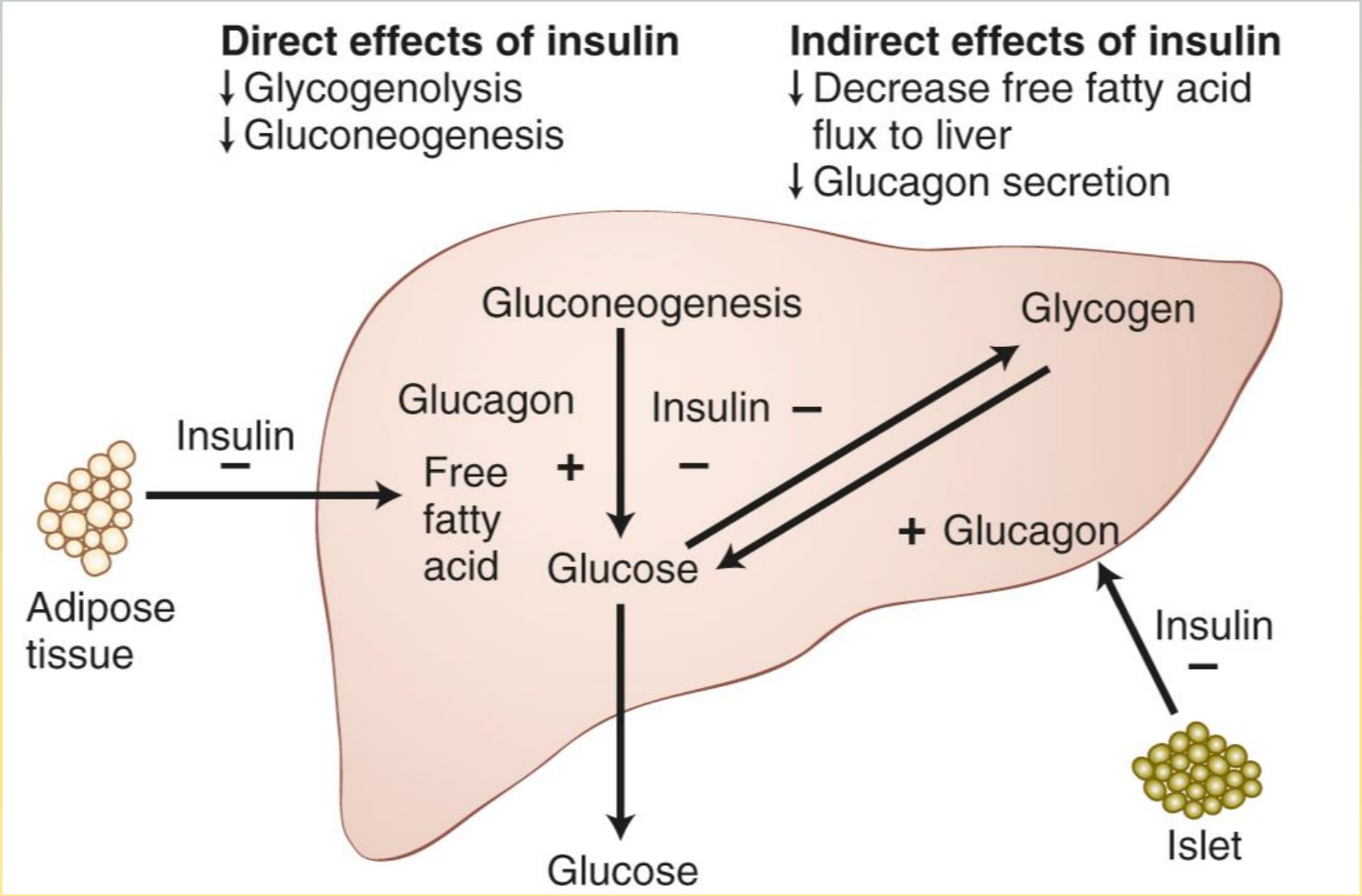
- (+) uptake of glucose (GLUT4)
- (+) glycogen synthesis
- (+) transport of AA
- (+) translation of mRNA
- (-) degradation of proteins
- (+) preference of fat reserves
- mechanism – mTOR phosphorylation



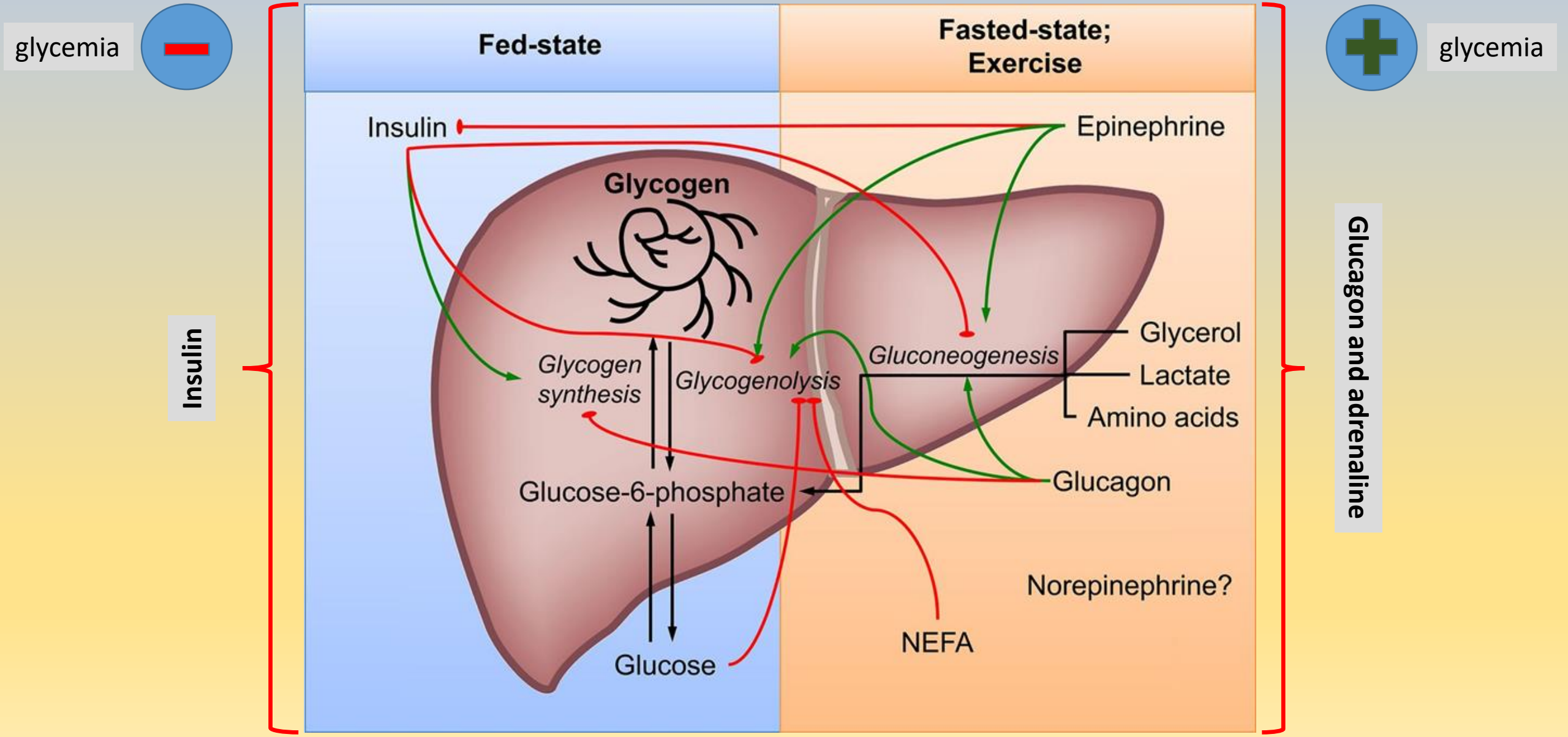


Insulin and liver

- **GLUT2** = Glu entry in hepatocytes
- Role of hexokinase – production of Glu-6-P and maintaining Glu gradient
- (+) lipid synthesis
- (+) proteosynthesis
- (-) ketogenesis



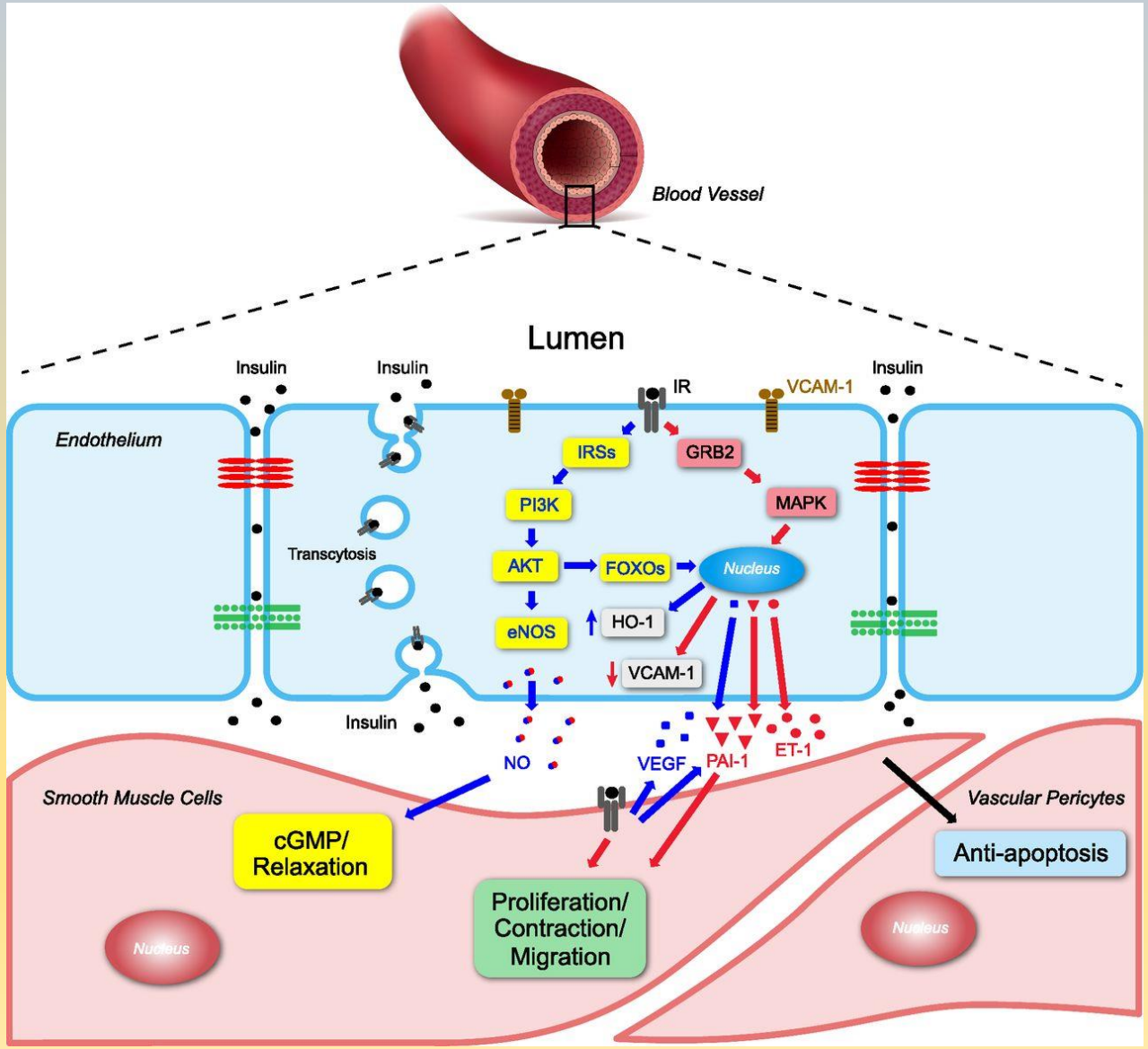
Fed-state versus fasted-state



Delayed insulin effects

- Synthesis of lipogenic enzymes
- Inhibition of gluconeogenesis enzymes
- MAPK cascade
  - Pro-growth effect – (+) cell growth
  - Mitogenic effect

Clinical relevance
- Hyperinsulinemia – DM2
- Increased risk of cancer
  - Endometrium
  - Breast
  - Colon
  - Kidney
- Proliferation of smooth muscle
  - Hypertension
  - Atherosclerosis
  - Dyslipidemia
  - Vascular diseases

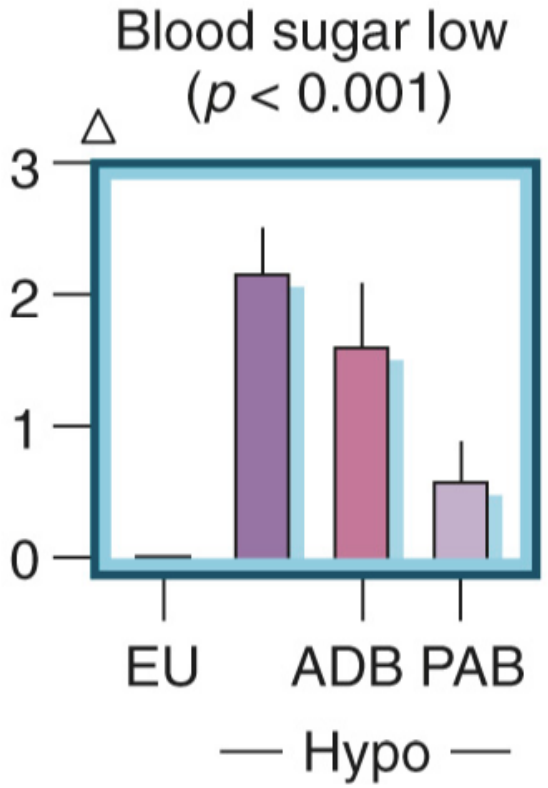


Hypoglycemia

- (-) insulin secretion
- (+) glucagon and adrenaline secretion (liver)
- (+) GH and cortisol (decreased utilization of Glu)

Neurogenic

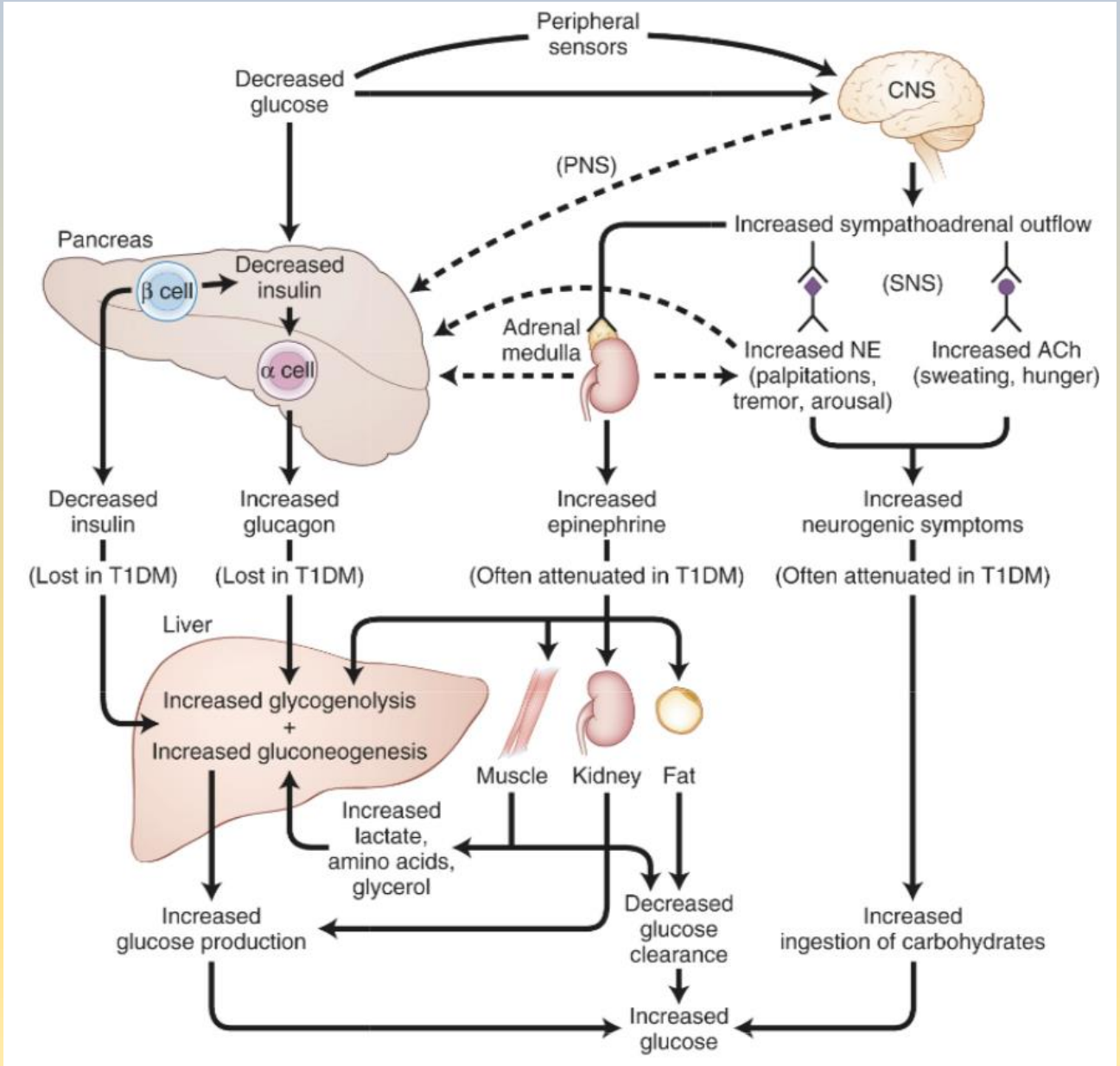
Sweaty
Hungry
Tingling
Shaky/tremulous
Heart pounding
Nervous/anxious



Neuroglycopenic

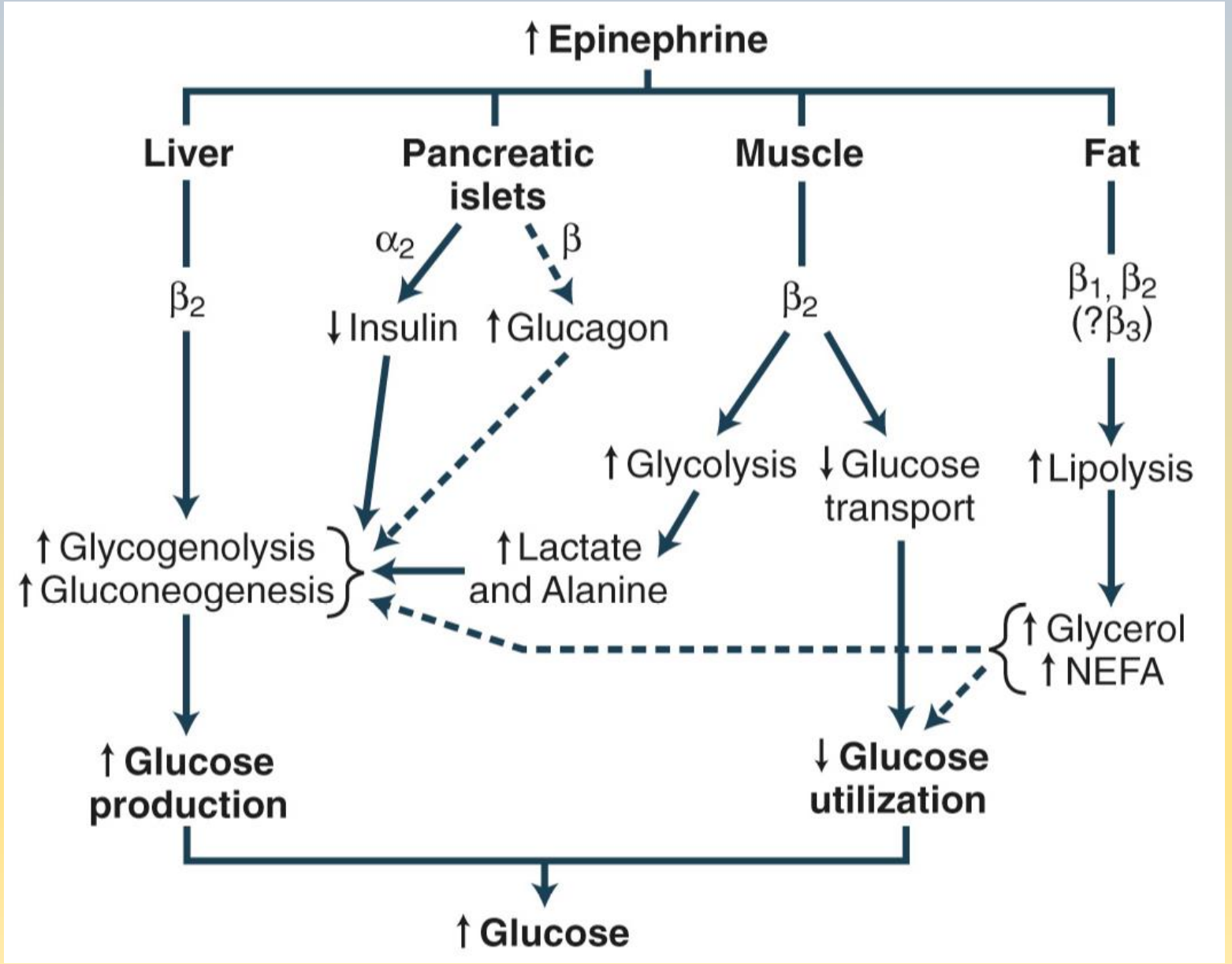
Warm
Weak
Difficulty thinking/confused
Tired/drowsy
Faint
Dizzy
Difficulty speaking
Blurred vision

Pgyziologic mechanisms preventing hypoglycemia



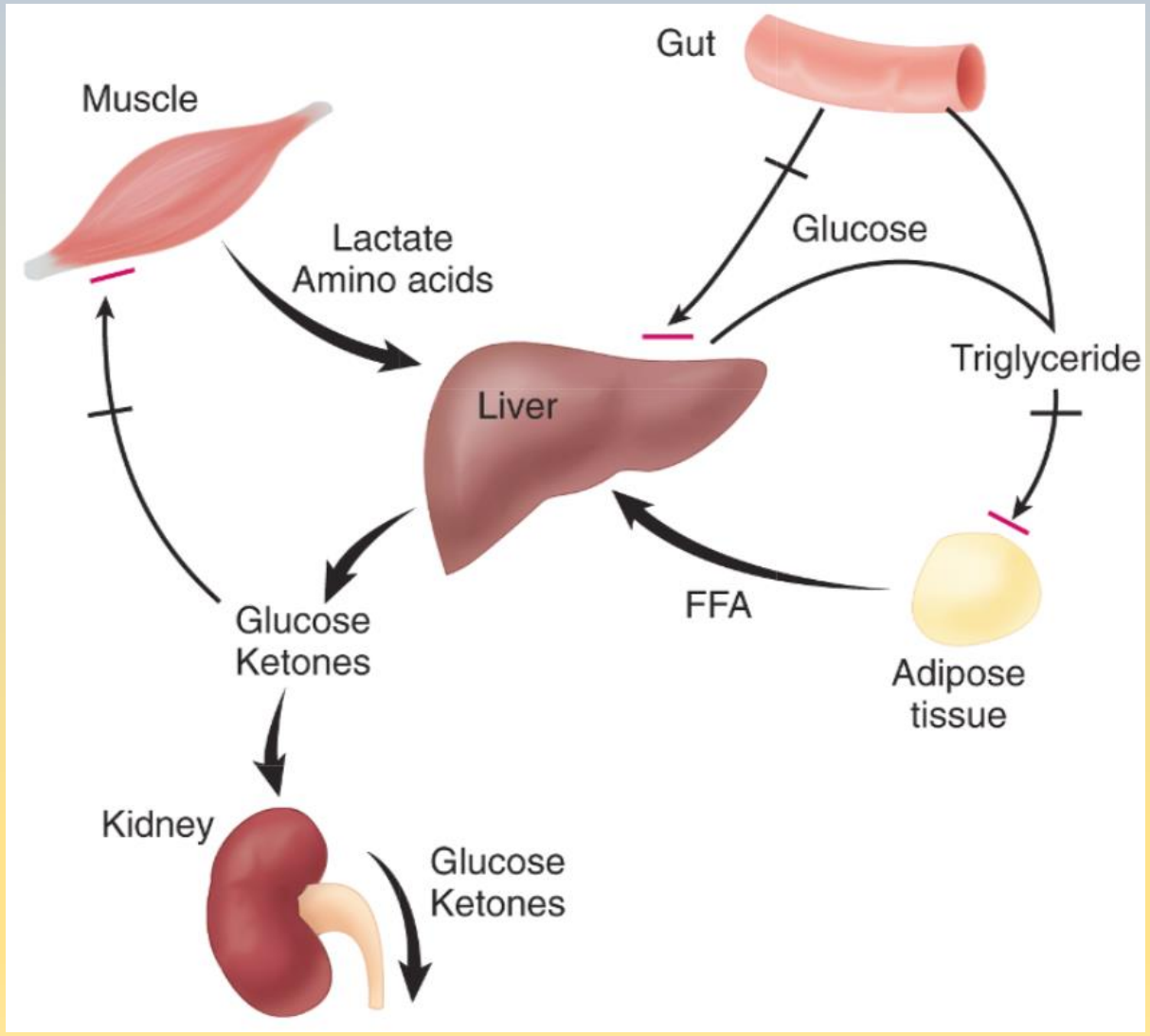
Vegetative nervous system represents an important mechanism preventing hypoglycemia.

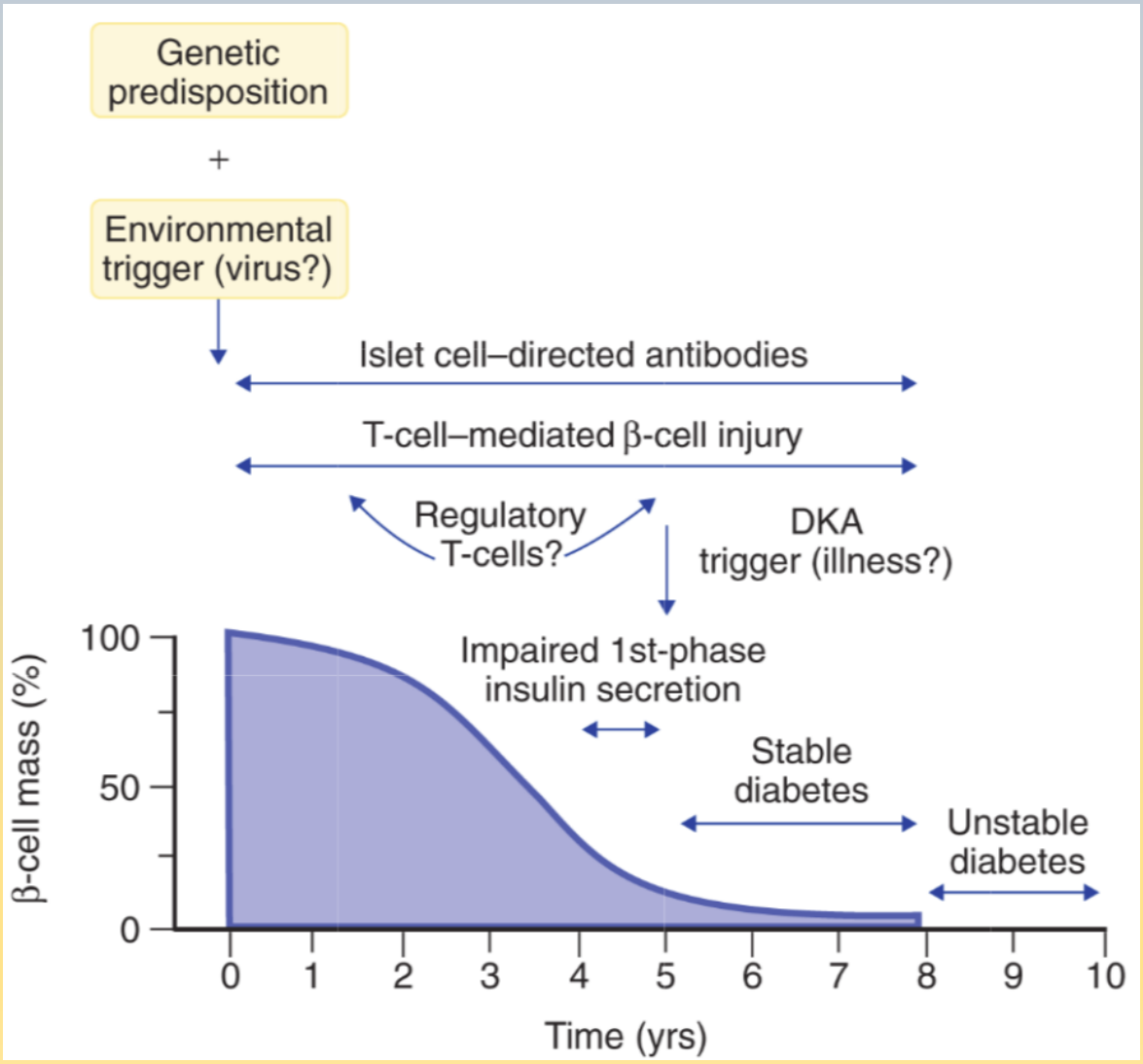
Hyperglycemic effect of adrenaline



Adrenaline prepares body to immediate performance, it mobilizes energetic substrate – glucose – as a source of energy.

Diabetes mellitus type 1





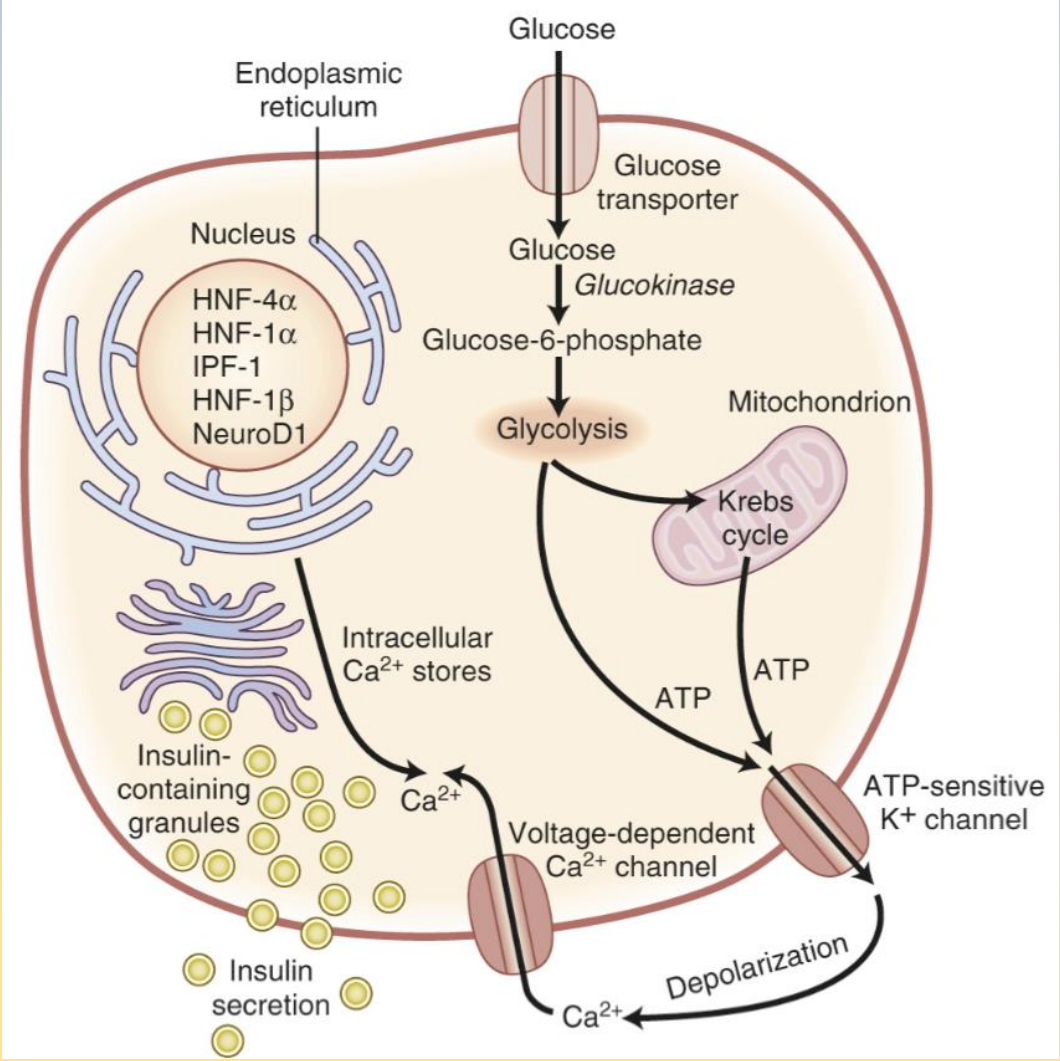
DM1 is associated with mobilization of substrates for gluconeogenesis and ketogenesis from muscle and adipose tissue, increased gluconeogenesis and ketogenesis in the liver, as well as disturbed substrate intake by peripheral tissues.

Diabetes mellitus type 2

Clinical relevance

Insulin resistance
- Mutation in IR gene

Defects in insulin secretion
- Mutation in insulin gene (proinsulin)
- Mutation in mitochondrial genes
- MODY (Maturity-onset diabetes of the young)
  - HNF-4α (MODY 1)
  - Glucokinase (MODY 2)
  - HNF-1α (MODY 3)
  - IPF1 (MODY 4)
  - HNF-1β (MODY 5)
  - NeuroD1/BETA2 (MODY 6)



DM2 is multifactorial disease connected with resistence of peripheral tissues (muscles, adipose tissue) to insulin, disturbed insulin secretion (under glycemia influence) and increased glucose production in liver.

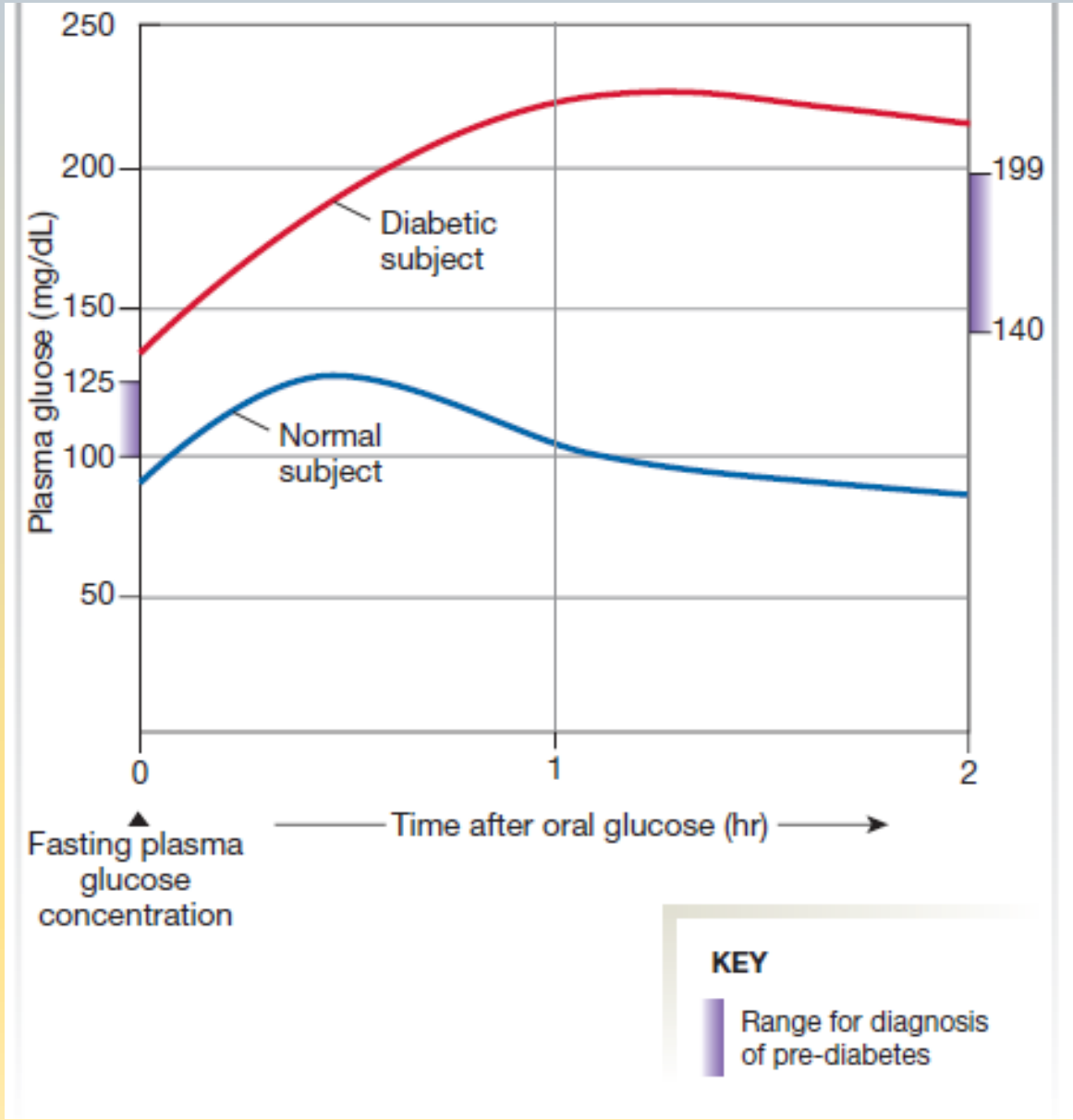
Diabetes mellitus typu 2 - consequences

Proteins
- Protein catabolism
- Negative nitrogen balance

Lipids
- Lipid catabolism with production of ketone bodies
- Decreased synthesis of FA and triglycerids
- Increased concentration of free FA
- FA catabolism, production of ketone bodies

Hyperglycemia
- Glycosuria, osmotic diuresis and **polyuria**
- Increased plasma osmolality, **polydipsia**, ADH
- Dehydratation
- Decreased blood pressure and volume of ECF
- **Polyphagy**

Ketoacidosis
- Metabolic acidosis
- Hyperventilation
- Acidification of urine
- Hyperkalemia



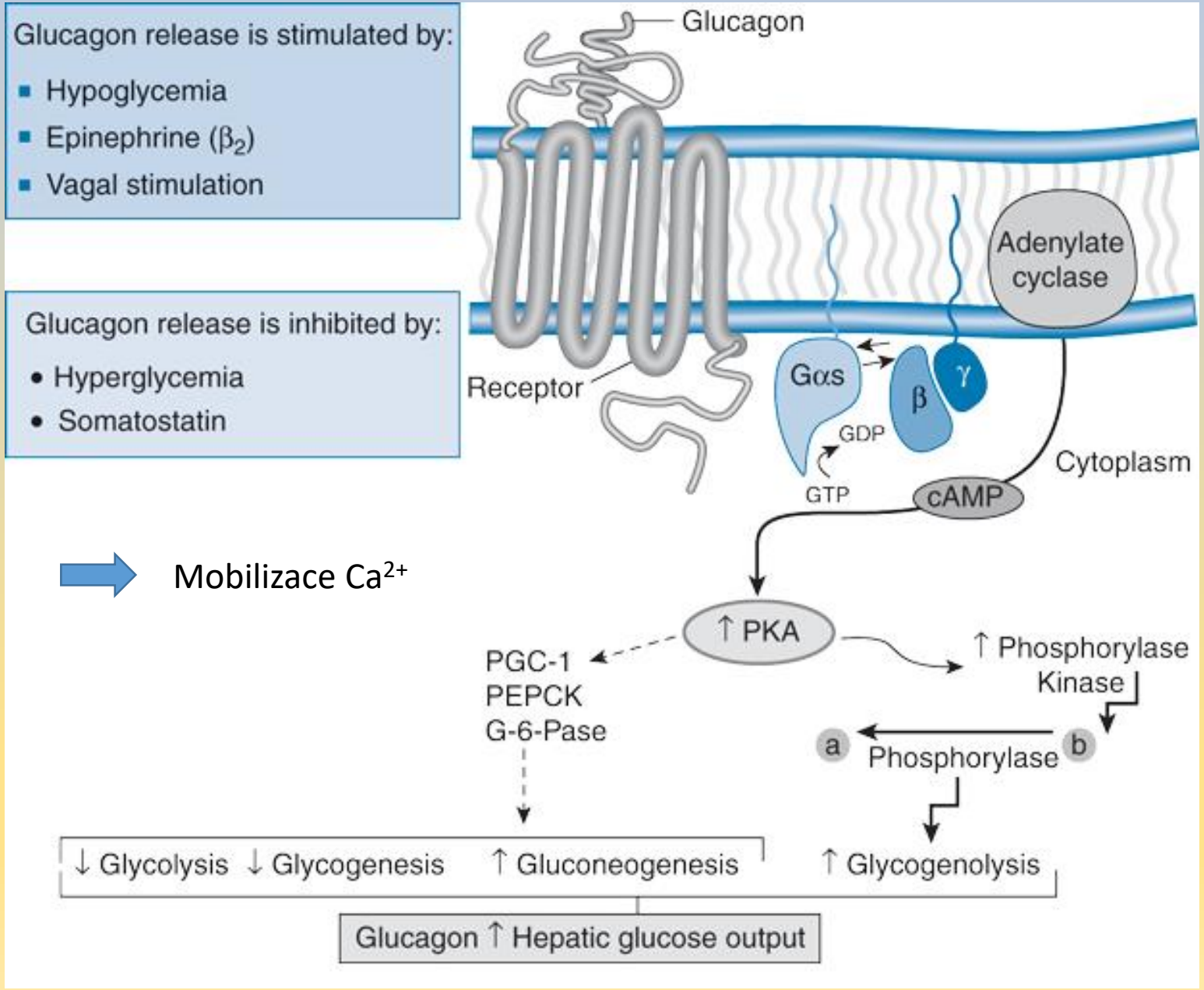
Glucagon

Characteristics
- Peptide hormone (29 AA)
- Syntesized as proglucagon
- Pancreas
- Enteroendocrine cels in GIT
- CNS
- Alternative splicing creates other peptides, most important GLP-1
- Short half-life (5 – 10 min)
- Degradation in liver

Secretion
- (+) AA
- (+) hypoglycemia

Receptors
- Liver, β cells, kidneys, heart, adipose tissue, blood vessels, CNS, stomach, adrenal glands

Functions
- Glucose homeostasis – insulin antagonism



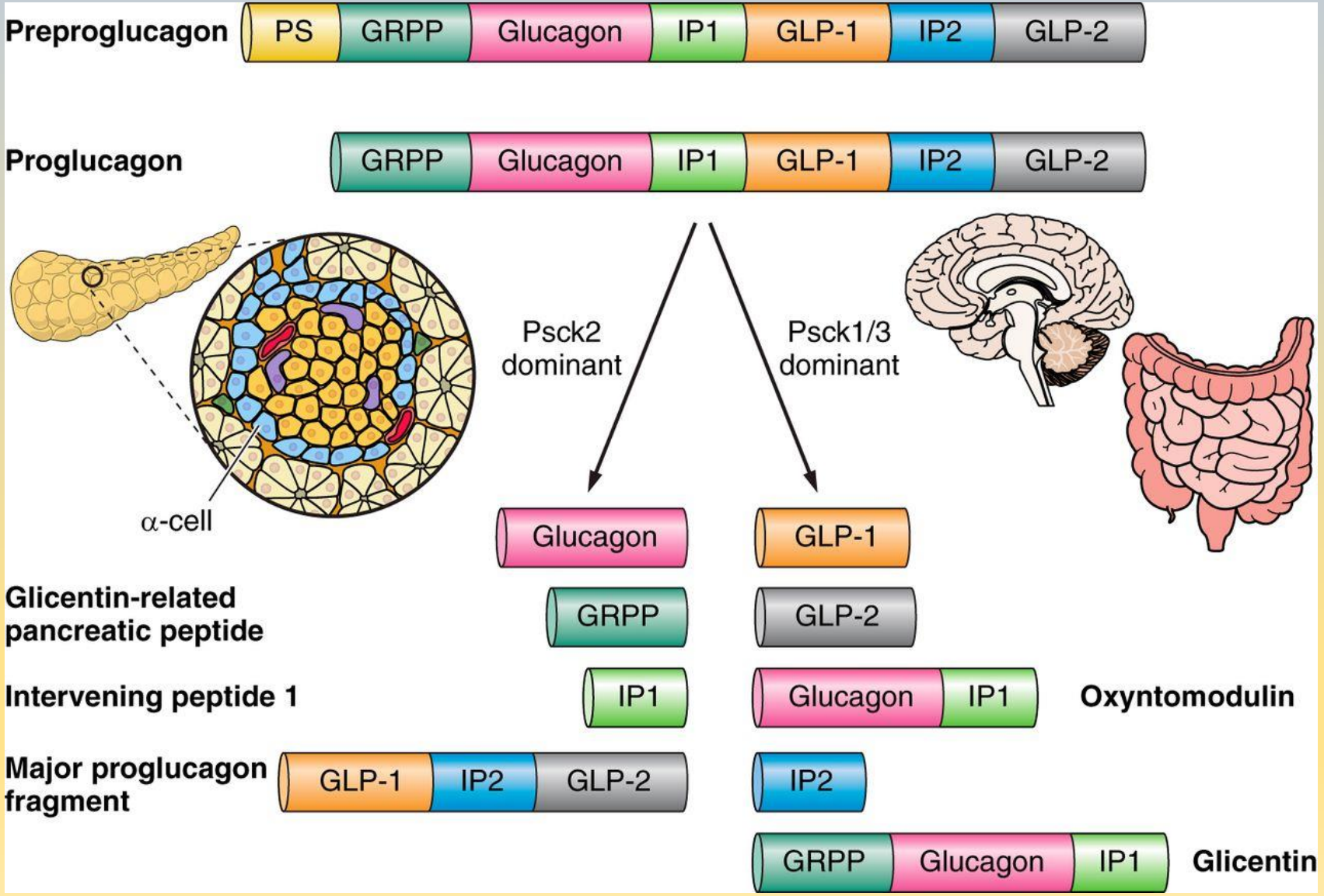
Proglucagon – alternative splicing

Glicentin – L-cells (small intestine)
- Stimulation of insulin secretion
- Inhibition of stomach secretion
- Trophic effect in intestine

Oxyntomodulin – colon (anorexigenic factor)
- Postprandial secretion
- Increased energy expandituree
- (+) glucose tolerance

GRPP
(inhibition of Glu-stimulated insulin secretion, modulator of energy metabolism)

IP-1, IP-2
L-cells
(modulation of insulin secretion?)



GLP-1 and GLP-2

Charakteristics
- Neuroendocrine L cells

Functions – GLP-1 (GLP1R)
- (+) insulin secretion
- (-) glucagon secretion
- Stimulation of neogenesis and proliferation of pancreatic isles
- Inhibition of β cell apoptosis

Functions – GLP-2 (GLP2R)
- Inhibition of antrum motility
- Inhibition of gastric juice secretion stimulated by food
- Trophic effect (small intestine, colon)
- Inhibition of enterocyte apoptosis
- Stimulation of blood flow and nutrient absorption

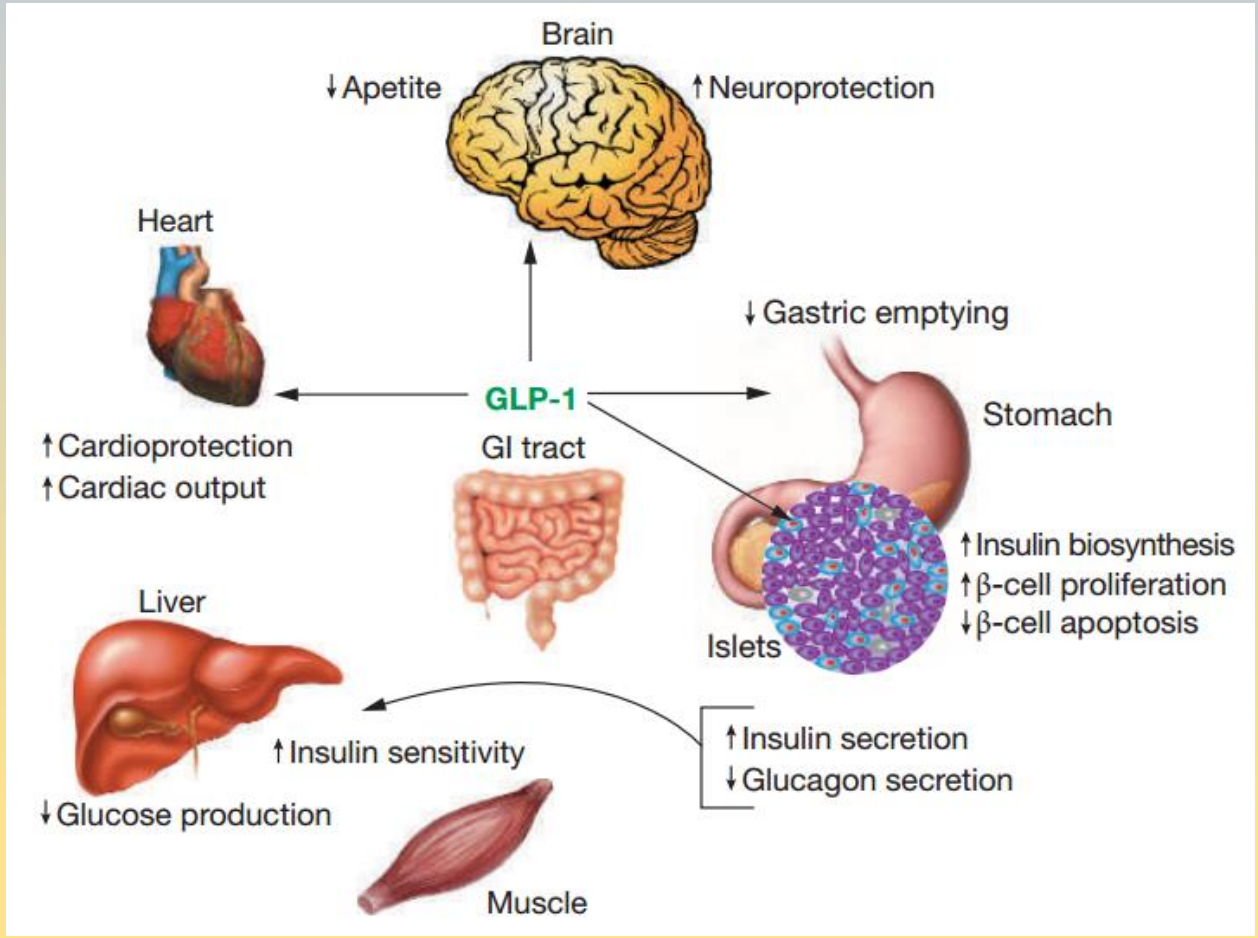
CNS
- Caudal NTS – viscerosensoric information
- Activation of POMC neurons
- Inhibition of food intake (anorexigenic factor)
- Induction of satiety

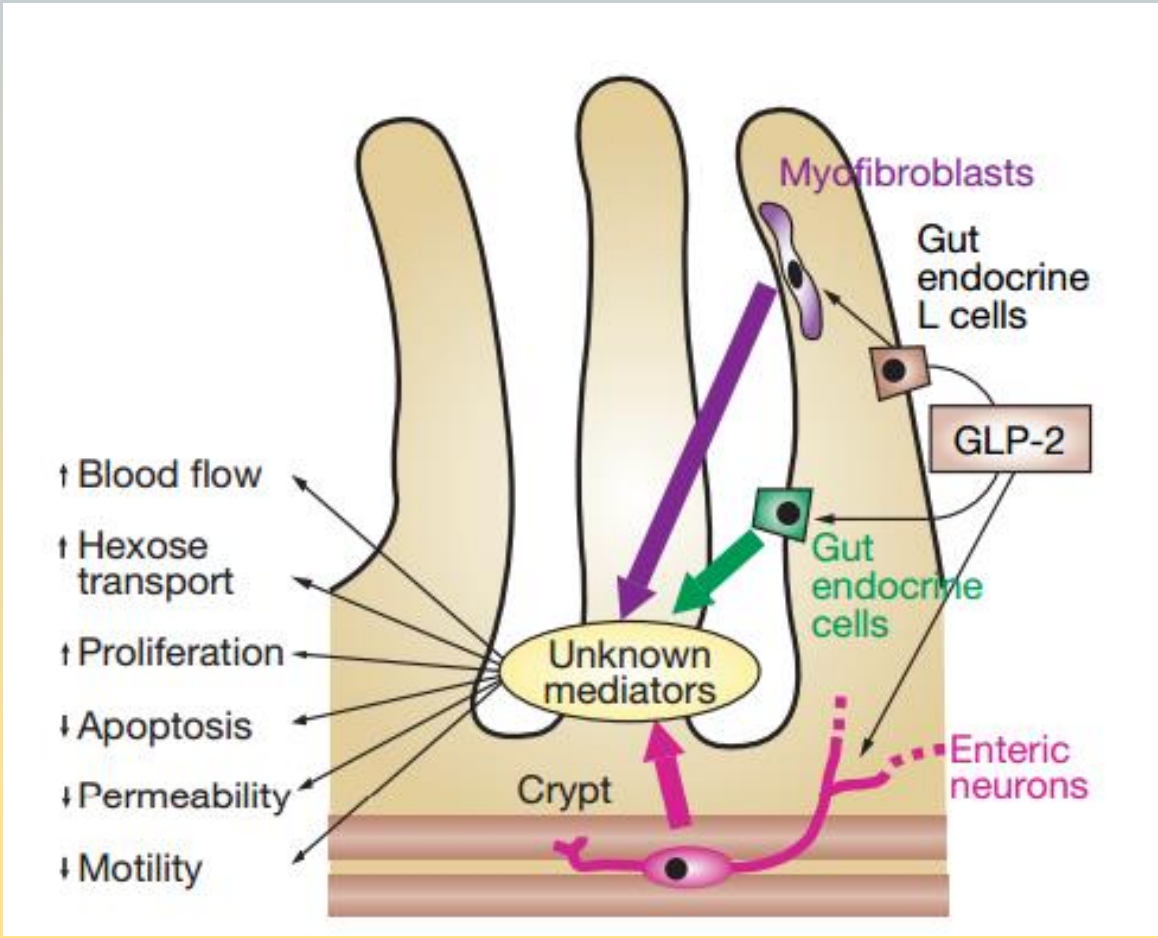
= quick modification of food intake based on metabolic substrates (glucose), hormones (leptin) and neuropeptides.

Clinical relevance
- Agonists of GLP1R – treatment of DM2
  - Exenatid, lixisenatid
  - Liraglutid
  - Albiglutid, dulaglutid
- Inhibitors of dipeptidyl peptidase 4 (DPP4)
  - sitagliptin, vildagliptin, saxagliptin, alogliptin, linagliptin
  - DM2

GLP-1 and GLP-2 show incretin effect preparing insulin secretion in dependence on glucose presence in GIT lumen.

Effect of GLP-1 and GLP-2 - overview



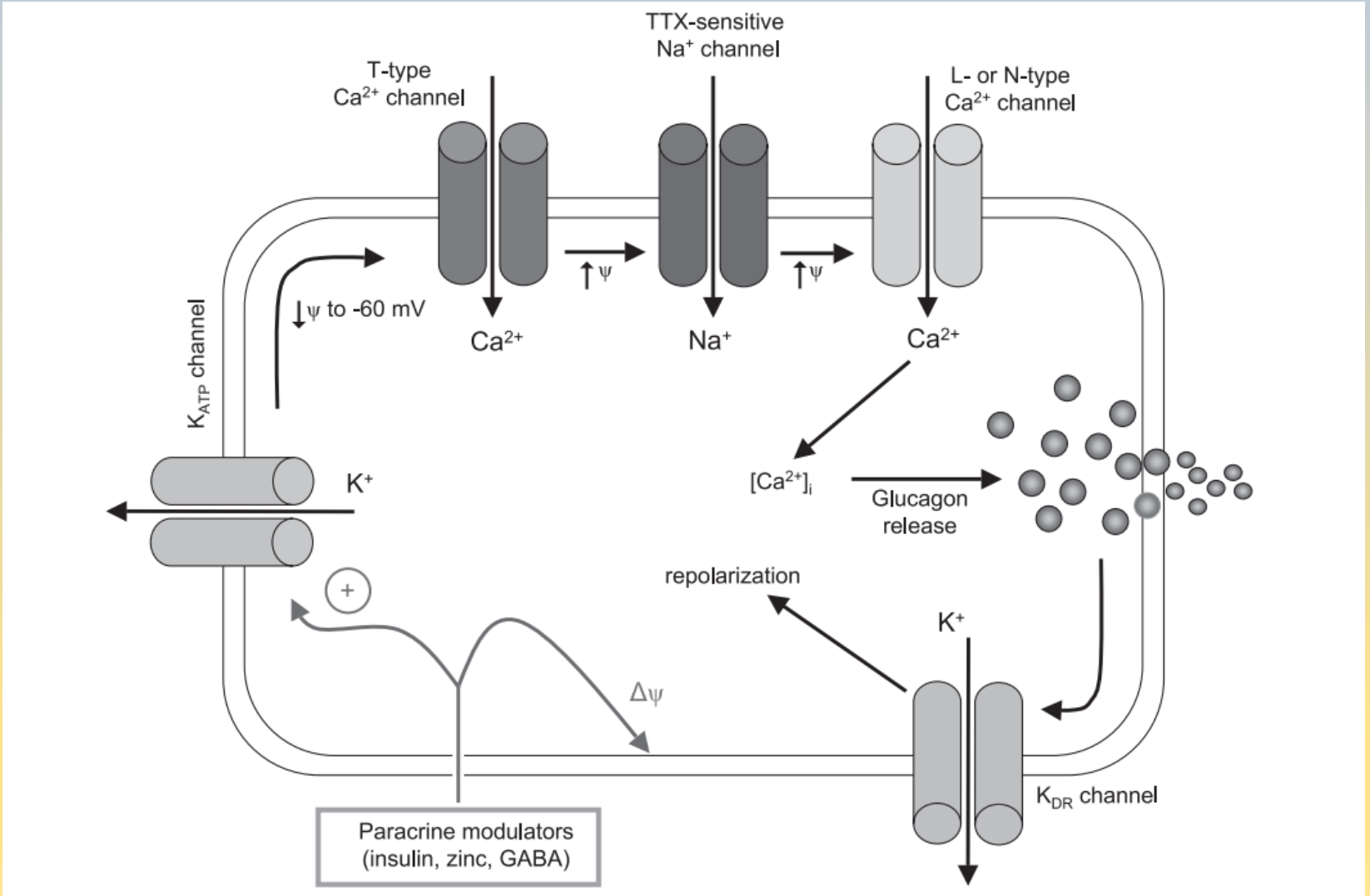


GLP-1

GLP-2

Glucagon – secretion and its regulation

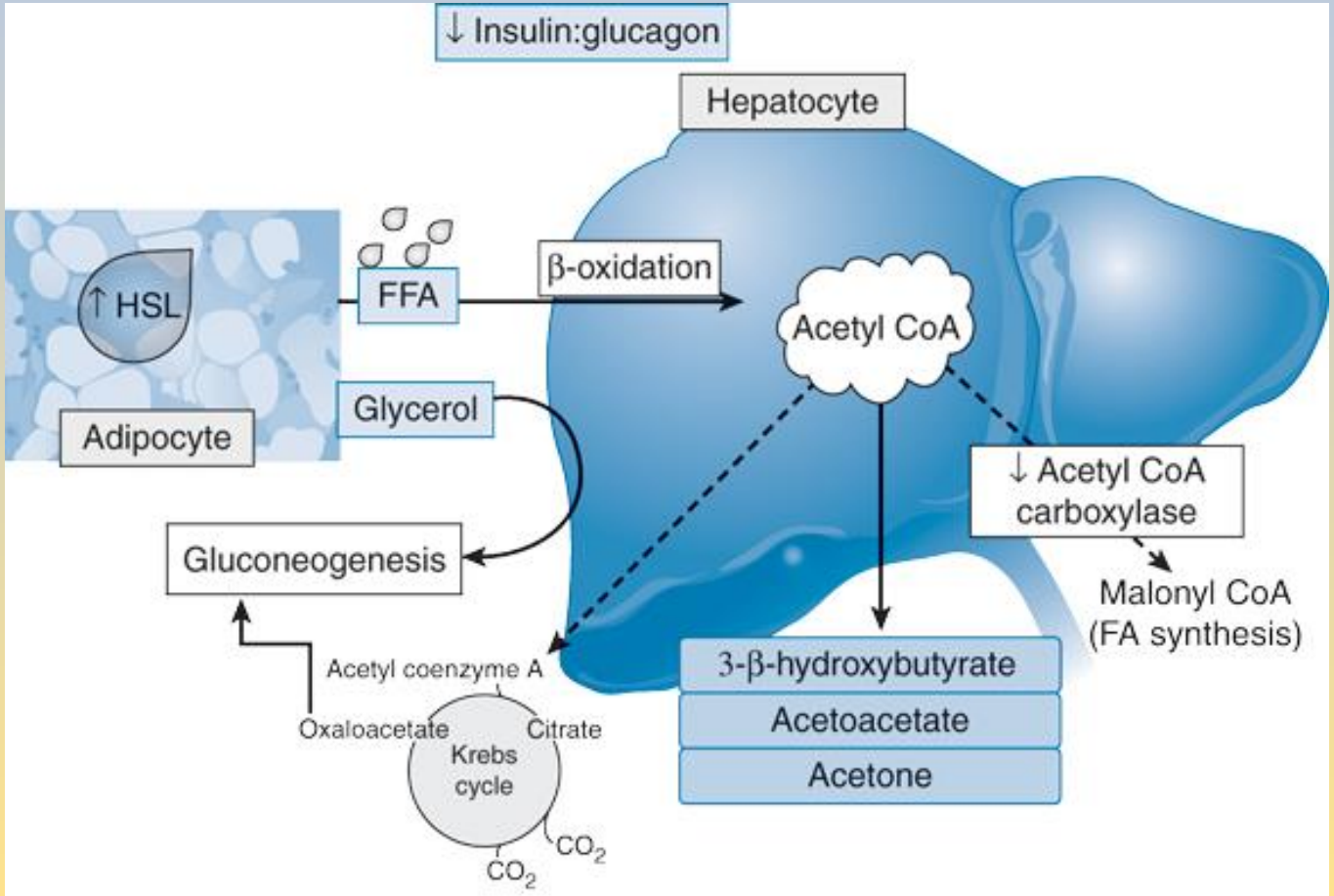
1. T-type Ca^{2+} IC
2. TTX-sensitive Na^{+} IC
3. Activation of L-/N-type of Ca^{2+} IC
4. Influx Ca^{2+}
5. Secretion of glucagon – exocytosis
6. Repolarization – K_{DR} IC
7. K_{ATP} IC – dependence on Glu!
    1. Low concentration Glu – open
    2. High concentration Glu – change ATP/ADP - closed



Glucagon secretion requires depolarizing cascade which ends with Ca^{2+} influx and glucagon secretion.

Physiologic effects of glucagon

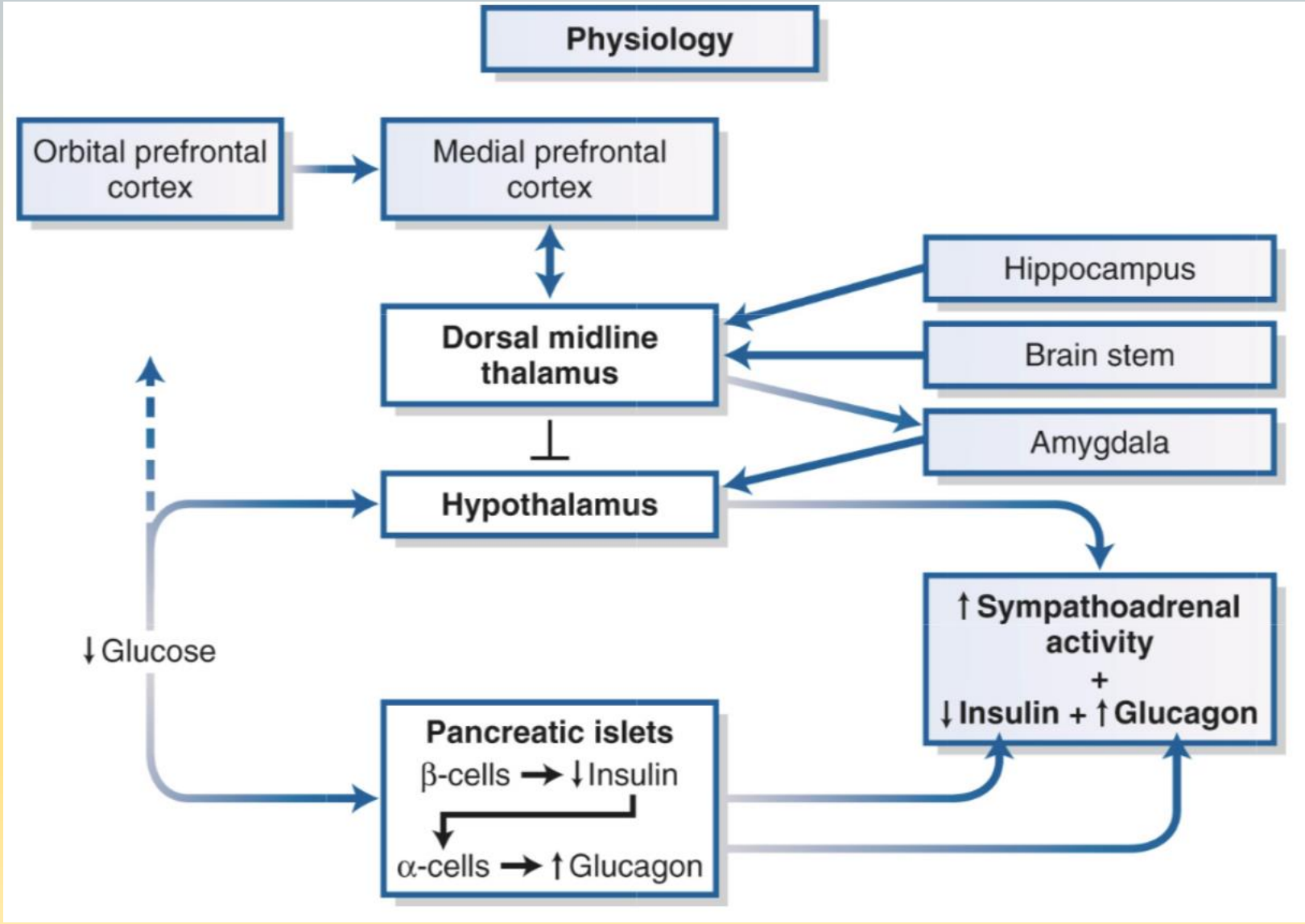
Target enzyme	Metabolic response
(+) Glu-6-phosphatase expression	Glu entering circulation
(-) glucokinases	Lower rate of Glu entering glycolytic cascade
(+) phosphorylation (activation) of glycogen phosphorylase	Stimulation of glycogenolysis
Inhibition of glycogen synthase	Inhibition of glycogen synthesis
Inactivation of phosphofructokinase 2, activation of fructose-6-phosphatase	Inhibition of glycolysis, stimulation of gluconeogenesis
Inhibition of pyruvate kinase	Inhibition of glycolysis



Other effects
- Stimulation of phosphorylation (activation) of hormone-sensitive lipase and lipolysis – substrates for gluconeogenesis and antibody production
- FFA as a source of energy mainly for skeletal muscles

Target organ for glucagon effect is liver, where it stimulates gluconeogenesis and glycogenolysis, thus increasing glycemia.

Integrated effect of glucagon - insulin

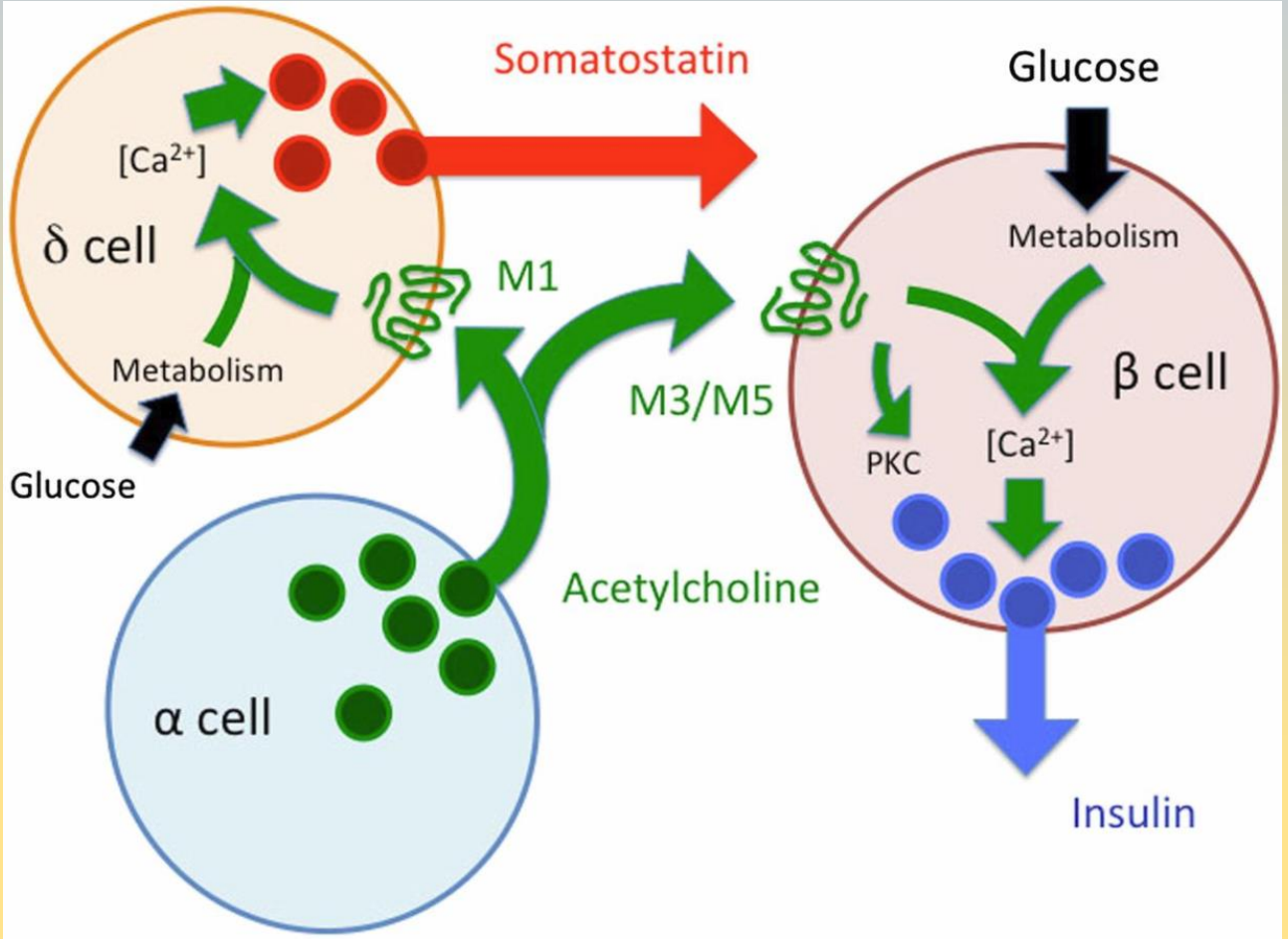


Somatostatin

Characteristics
- Peptide hormone (14 AA)
- Secretion stimulated by:
  - food rich in lipids (FFA)
  - food rich in saccharides (Glu)
  - food rich in proteins (AA – Leu, Arg)

Functions
- Paracrine effect – (-) insulin, glucagon, PP
- Inhibition of practically all exocrine and endocrine GIT functions
- Inhibition of motility

Clinical relevance
- Somatostatin analogues and insulin/glucagon-producing tumors

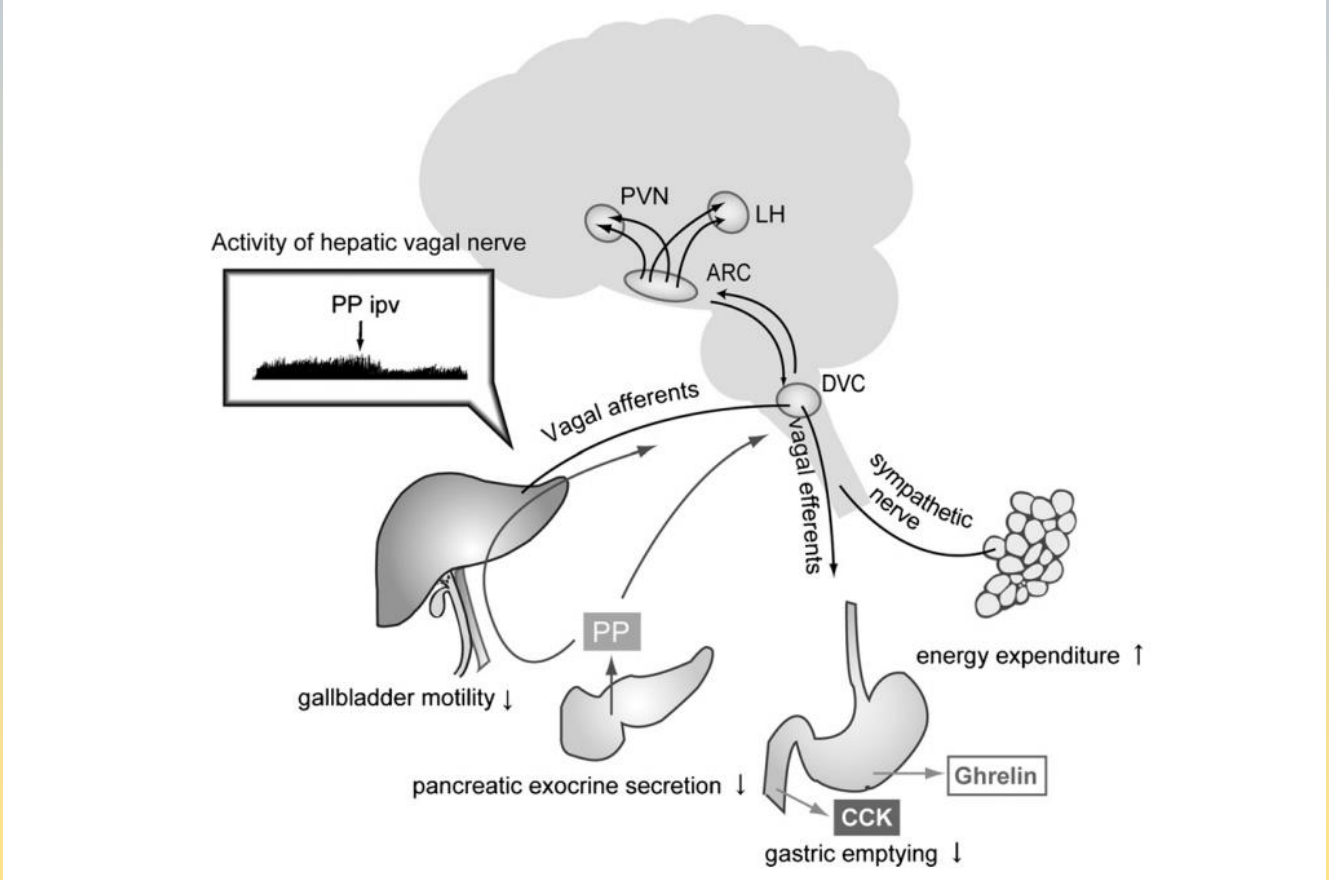


Role of paracrine cholinergic signaling in somatostatin secretion – paracrine effect of acetylcholine stimulates insulin secretion, but also secretion of somatostatin.

Pancreatic polypeptide - PP

Characteristics
- Peptide hormone (36 AA)
- Secretion stimulated by:
  - Food (proteins), distention of stomach
  - Exercise
  - Direct vagal stimulation
  - Insulin-induced hypoglycemia
- Secretion inhibited by:
  - Hyperglycemia
  - Bombesin, somatostatin
- Receptors:
  - Stomach, small intestine, colon, pankreas, prostate, enteric NS, CNS

Functions
- Inhibition of pancreatic exocrine secretion
- Inhibition of gallbladder contraction
- Modulation of stomach secretion
- Modulation of stomach motility
- Regulation of food intake?



Pancreatic polypeptide stimulates energy consumption through sympathetic stimulation of brown adipose tissue. It also modulates secretion of CCK and inhibits ghrelin secretion.

Amylin

Characteristics
- Peptide hormone (37 AA)
- β cells, stomach, proximal small intestine
- Posttranslational modification (amidation)
- Secretion together with insulin and C-peptide
- Increase after application of:
  - p.o. and p.e. glucose

Function
- Slowing of emptying of stomach on vagal basis
- Inhibition of glucagon secretion (postprandial)
- Muscles
  - Inhibition of glycogen synthesis
  - Stimulation of glycogenolysis, glycolysis and lactate production

Clinical relevance
- Increased plasmatic concentration during obesity, gastric diabetes and DM2
- Analogue of amylin DM1 and DM2 therapy (pramlintid) – amylin-deficient states