Endocrine control of energy metabolism

Challenges:

• Periodic (phasic) food uptake - continuous energy expenditure
• Mismatch between the fuel (energy) uptake/consumption
• Cell- and organ specific uptake/metabolism/storage of energy substrates

Coping strategies:

Utilisation of basic energy substrates (distribution among different organs)
[(glucose (Glu), free fatty acid (FFA), amino acids (AA), keton bodies (KB)]
Energy reserves (fat, glycogen, structure proteins)
Endogenous synthesis of energy substrates:
(FFA→acetoacetyl acid; glucose→lactate; gluconeogenesis)
Regulatory mechanisms: hormonal (endocrine) and neural (food uptake)
**Liver:**
- Glycogen synthesis/breakdown
- Gluconeogenesis (AA, lactate, glycerate)
- FFA synthesis/breakdown
- Ketogenesis (acetyl-CoA > ketons)
- Synthesis of lipoproteins (VLDL)
- Protein synthesis/breakdown

**Muscle:**
- Protein
- Glycogen synthesis/breakdown
- Lactate production

**Adipocytes:**
- Triglycerids
- Synthesis/breakdown
- FFA synthesis

**GI tract:**
- Absorption of nutrients

**Brain:**
- Glucose dependency!
- (ketonbodies)

**Red blood cells:**
- Glucose dependency!
- Lactate production

**Phases of energy metabolism**

Absorptive phase (2-2.5 hours after meal; post-prandial)

Interdigestive (post-absorptive) phase

Special conditions: increased physical workload, fasting, diseases etc.

**Regulatory factors**

Endocrine control:
- Direct effects: insulin, glucagon, adrenalin,
  growth hormone, glucocorticoids, thyroid hormones (T3/T4)

Neural control:
- Autonomic nervous syst. (Sy/Psy)
- Motor nerves
- Hypothalamus (hunger/satiety)
The endocrine pancreas

J. v. Mering, O. Minkowsky (1890) - extirpation of pancreas - experimental diabetes mellitus

Endocrine cells: islets of Langerhans (Paul Langerhans; 1869)
~1-2 million islets, 2% of the total weight of pancreas

Cell types:
- A (α) cells: glucagon (10%, islet periphery)
- B (β) cells: insulin (80% central) + amylin
- D (δ) cells: somatostatin (5-10%)
- PP (F) cells: pancreatic polypeptide

Intercellular communication:
- paracrine communication, gap junctions (electric coupling)
- GABA – glutamate decarboxylase (GAD)

Blood supply: arteries: system circulation - venous outflow: v. Portae (Liver!)

Innervation: sympathetic and parasympathetic (n. X.) nerves

Islets of Langerhans - microscopic structure
Unique Arrangement of $\alpha$- and $\beta$-Cells in Human Islets of Langerhans (Bosco et al. Diabetes, 2010.)

Charles Best, Frederic Banting and the dog… Toronto, 1920s
Insulin: polypeptide (protein) hormone (51 AA) – insulin/IGF family
(Banting, Macleod NP 1923; shared with Best and Collip) – Sanger, NP 1958.
Synthesis/secretion: pre-pro-insulin (-signal sequence) → pro-insulin (C-peptide) ⇒ insulin; stored in cytoplasmic granules (Zn\(^{2+}\))
calcium-dependent secretion - exocytosis

Significance of the C-peptide: verification of endogenous insulin secretion; estimation the amount of the secreted insulin (no first pass effect)
Mechanism of insulin secretion

Insulin - glucagon (functional antagonism)
Net effect: maintenance of a constant (physiological) glucose level;
insulin prevents the (alimentary) hypoglycemia; glucagon prevents the hypoglycemia.

Regulation of the insulin secretion

Key regulator: plasma glucose!
Other metabolites: arginin, alanin, lysin, leucin, fructose, FFA, ketonbodies

Paracrine factors:
- glucagon - increases
- somatostatin - inhibits

Incretin effect: If glucose is administered orally, it produces stronger increase in the insulin secretion compared to the effect of i.v. administration
the role of GIT hormones
Gastric Inhibitory Peptide (GIP)= Glucose-dependent Insulinotrop Peptide
Glucagon-Like Peptide (GLP-1), Cholecystokinin

Neural factors:
- Acetylcholin – increases (Psy nerves, n. X.);
- Noradrenalin: direct inhibition (α2 receptors);
  indirect effect (A-cells; β rec.)

Neuropeptides: Gastrin-releasing peptide (GRP), Galanin, CGRP(?)

Physiological range: 3.5 – 5.6 mM
Cellular mechanism of the insulin secretion

Glucose uptake into the B-cells: GLUT-2 transporter (facilitated diffusion)
ATP sensitive K⁺ channel (K⁺ATP, Kir6.2): connection between the intra- (extra-) cellular glucose level and insulin secretion
Plasma glucose↑ → Intracellular Glucose↑ → ATP synthesis↑ → K⁺ATP closure↑ → B cell depolarisation
voltage sensitive Ca²⁺ channels: Ic Ca²⁺↑ - exocytosis (insulin release)
K⁺ATP antagonists: sulphonyl-ureas (secretagogue) - oral antidiabetic drugs

K⁺ATP channel is a functional octamer of four Kir6 subunits, and each subunit is associated with one SUR1 subunit
(SUR1: sulfonylurea receptor type 1)
FIGURE 2. Simplified model outlining potential cellular mechanisms of β-cell adaptation to insulin resistance. Mechanisms linking obesity to insulin resistance and type 2 diabetes

Phases of insulin secretion during food uptake:

• Cephalic phase: neural control (n. X.): anticipation

• Intestinal phase: incretin effect (GIT hormones - GIP etc.)

• Pancreatic phase: direct effect of increased plasma glucose and other metabolites

First two phases protect us from the development of severe postprandial (after meal) hyperglycaemia! (late dumping Sy. – gastrectomy)
Insulin receptor signaling

Hetero-tetramer transmembrane receptor (2α-2β subunits) tyrosine-kinase activity – autophosphorylation upon insulin binding - downstream elements

Effects of insulin

acute effects: increased glucose permeability of plasma membrane
activation or inhibition of insulin-sensitive enzymes
late effects: protein synthesis (genomic effects, control of transcription)

Facilitation of glucose uptake: translocation of glucose transporters from the cytoplasm into the cell membrane; insulin sensitive transporter: GLUT-4

GLUT family:

- GLUT-1: brain, retina, testis, RBC
- GLUT-2: pancreas B-cells, hepatocytes, RBCs
- GLUT-3: neuron, placenta (chorion), enterocyte (basolateral)
- GLUT-4: skeletal muscle, myocardium, adipocytes
- GLUT-5: enterocyte (apical), brain, spermium

Insulin independent glucose uptake:
neurons, RBCs, hepatocytes, pancreas β-cells, tubular epithel (kidney)
Insulin-induced translocation of the GLUT-4 glucose transporter

Effects of insulin: regulation of enzymatic activity

liver:
- synthesis of glycogen (glucokinase, glycogen synthase)
  - to avoid postprandial hyperglycemia
- synthesis of triglycerids (FFA/glycerin → triglycerid, VLDL)
- protein synthesis (plasma proteins)
- suppression of gluconeogenesis, ketogenesis

adipocytes:
- glucose uptake↑ (phospho-glycerate; FFA synthesis)
- lipoprotein-lipase↑
- inhibition of triglycerid breakdown (hormone-sensitive lipase↓)
- anti-ketogenic effect

muscle:
- glucose uptake- utilisation/glycogen synthesis
- increased uptake of amino acids, inhibition of proteolysis

decrease of IC cAMP level - activation of phosphodiesterases (hormons antagonising the effects of insulin act via the increase of cAMP)
Long term effects:

• Enhanced glucose utilisation (glycolysis, glycogen synthesis, FFA production)
• Increased fat utilisation/elimination: lipoprotein-lipase activity (CM, VLDL - FFA); anti-ketogenic effect

Other functions:

• Growth - synergism with GH and IGFs
• Inhibition of glucagon secretion
• Suppresses hunger, promotes satiety - hypothalamus
• Influence on the Ic/Ec K⁺ distribution (insulin administration will shift the balance between transmembrane K⁺ leakage and uptake in many cell types – risk of hypokalemia!!)

Clinical testing of the secretion capacity of β cells and insulin sensitivity of the target organs

OGTT: Oral Glucose Tolerance Test
Impaired glucose tolerance
Manifest diabetes mellitus: Type 1 (former insulin dependent)
Type 2 (former insulin non-dependent)

Glucose: 75 g per os
Evaluation of the fasting glucose level (FBG) and the results of the Oral Glucose Tolerance Test (OGTT) - recommendations of the American Diabetes Association

- fasting glucose level (FBG) – after 12 hours fasting
  normal < \textbf{5.6 mM} < impaired FG < \textbf{6.9 mM} < diabetes

- OGTT with 75 g per os - 120 min:
  normal < \textbf{7.8 mM} < impaired GT < \textbf{11.1 mM} < diabetes

Assessment of the insulin sensitivity of the peripheral organs: glucose clamp technique

Euglycemic-hyperinsulinemic clamp: constant suprabasal insulin level
Adjustable rate of glucose infusion – frequent sampling glucose test
Steady state - Index of Sensitivity: \( (Si) = \frac{G_{inf}}{i} \)

Corrections of the failure of glucose homeostasis:
1. Increasing of the glucose sensitivity (e.g. metformin; PPAR\(\gamma\) activators)
2. Increasing the insulin level/secretion (pl. sulfonylurea)

Euglycaemic – Hyperinsulinaemic Glucose Clamp recording

https://www.profil.com/services/hyperinsulinemic-euglycemic-clamp

Insulin substitution therapy

The basal-bolus principle

Theoretical representations of insulin profiles
CLINICAL SYMPTOMS OF HYPERGLYCEMIA AND HYPOGLYCEMIA

- **Hyperglycemia (BG>~10 mM):** Early manifestations include weakness, polyuria, polydipsia, altered vision, weight loss (dehydration), xerostomy (dry mouth).

  For prolonged or severe hyperglycemia, manifestations include dry and red skin, Kussmaul hyperventilation (deep, rapid breathing > metabolic acidosis, ketacidosis), stupor, coma, hypotension, and cardiac arrhythmias.

- **Hypoglycemia (BG<~3 mM):** Early manifestations include palpitations, tachycardia (sympathetic activation!), pale and wet skin (diaphoresis), anxiety, hyperventilation, shakiness, weakness, hunger and nausea.

  For prolonged or severe hypoglycemia, manifestations include confusion, unusual behavior, hallucinations, seizures, hypothermia, focal neurologic deficits and coma.

**Continuous Glucose Monitoring System + Insulin pump**

*Sense and Sensibility of Insulin Pumps*

*Sci Transl Med* 16 October 2013:
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Glucagon

Product of the α-cells: single chain polypeptide
(29 AA; member of the secretin family)
Glucagon receptor: 7 transmembrane domain receptor - G-protein coupled - cAMP↑

function: prevention of hypoglycemia (interdigestive phase, fasting)

Functional antagonist of insulin

Regulation of glucagon secretion:

Increase of secretion:  
- Low plasma glucose
- Increased levels of amino acids (Arg, Ala, Glu)
- Sympathetic activity (noradrenalin)
- Growth hormone, glucocorticoids (permissive action)

inhibition of secretion:  
- high plasma glucose
- somatostatin
- insulin

How does the composition of the food influence the secreted insulin/glucagon ratio?

Carbohydrate rich nutrition: 
- high insulin – low glucagon secretion (prevents from hyperglycaemia)

Carbohydrate poor nutrition: 
- lower insulin – higher glucagon
  (lack of glucose induced suppression, role of amino acids)
Actions of glucagon:

Liver: (primary target)
- glycogenolysis ↑ (phosphorilase activity↑)
- gluconeogenesis↑ (amino acid, glycerate uptake↑)
- glucose release into the circulation↑ (glucose-6-phosphate - phosphatase↑)
- ketogenesis↑

adipocyte: breakdown of triglycerids↑ (hormone-sensitive lipase)

muscle: proteolysis↑ (AA release - liver)

Pancreas: slight increase in the insulin secretion
Somatostatin

Product of the D-cells
Tonic paracrine inhibition of insulin and glucagon secretion
Prevention of overshoots in hormone secretion
GIT effects – reduced nutrient absorption

Metabolic pathways – absorptive phase

Insulin – hormon of abundance

Numbers represent the estimated utilisation rate of glucose (g/hour)
Metabolic pathways – post-absorptive (interdigestive) phase

Numbers represent the estimated utilisation rate of glucose (g/hour)