MUNI MED

# METABOLISMUS

= souhrn všech chemických (a fyzikálních) procesů zahrnutých v:

1. Produkci **energie** z vnitřních i vnějších zdrojů
2. **Syntéze** a **degradaci** strukturálních a funkčních prvků tkání
3. Odstraňování **odpadů**

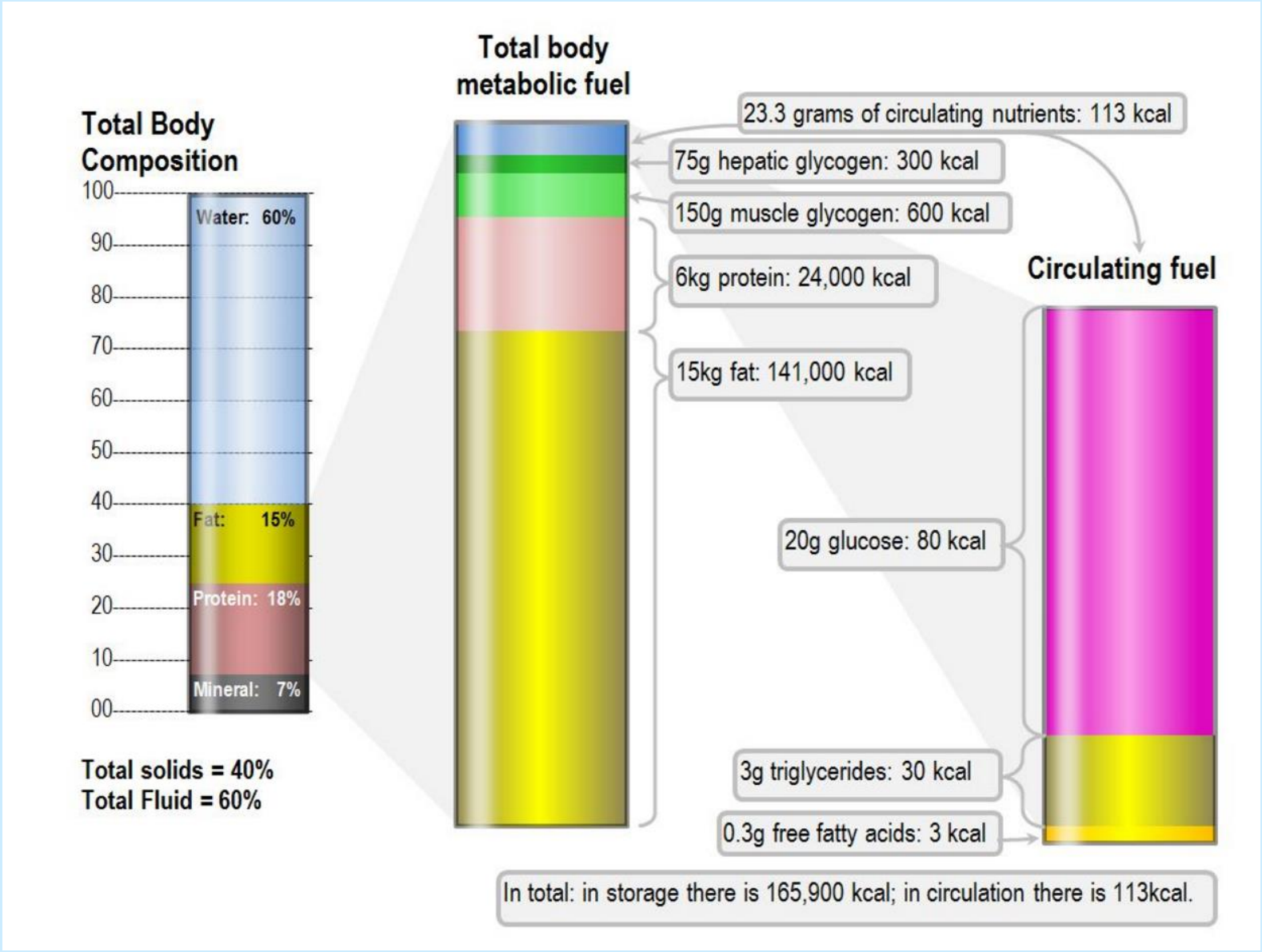
## PORUCHY METABOLISMU

1. **Vrozené** metabolické poruchy (enzymopatie)
2. **Kombinované** metabolické poruchy (DM, dna, degenerativní onemocnění kloubů a kostí)
3. Metabolické poruchy ze **zevních příčin**

METABOLISMUS

- Proteinů
- Sacharidů
- Lipidů

# Energetické zásoby lidského těla




http://www.derangedphysiology.com/main/required-reading/endocrinology-metabolism-and-nutrition/Chapter%203.1.8/physiological-adaptation-prolonged-starvation

# Tuky, cukry, bílkoviny…

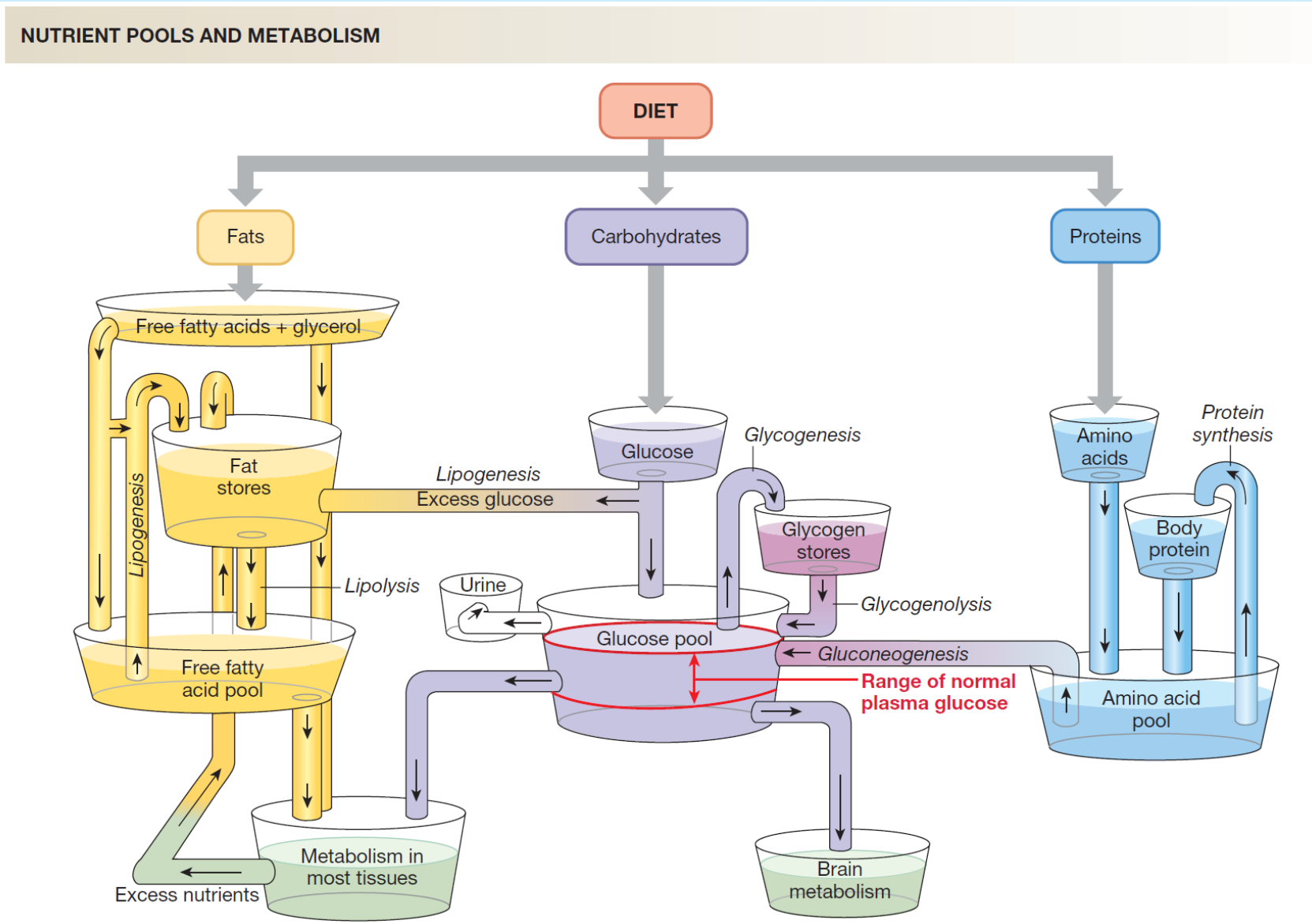
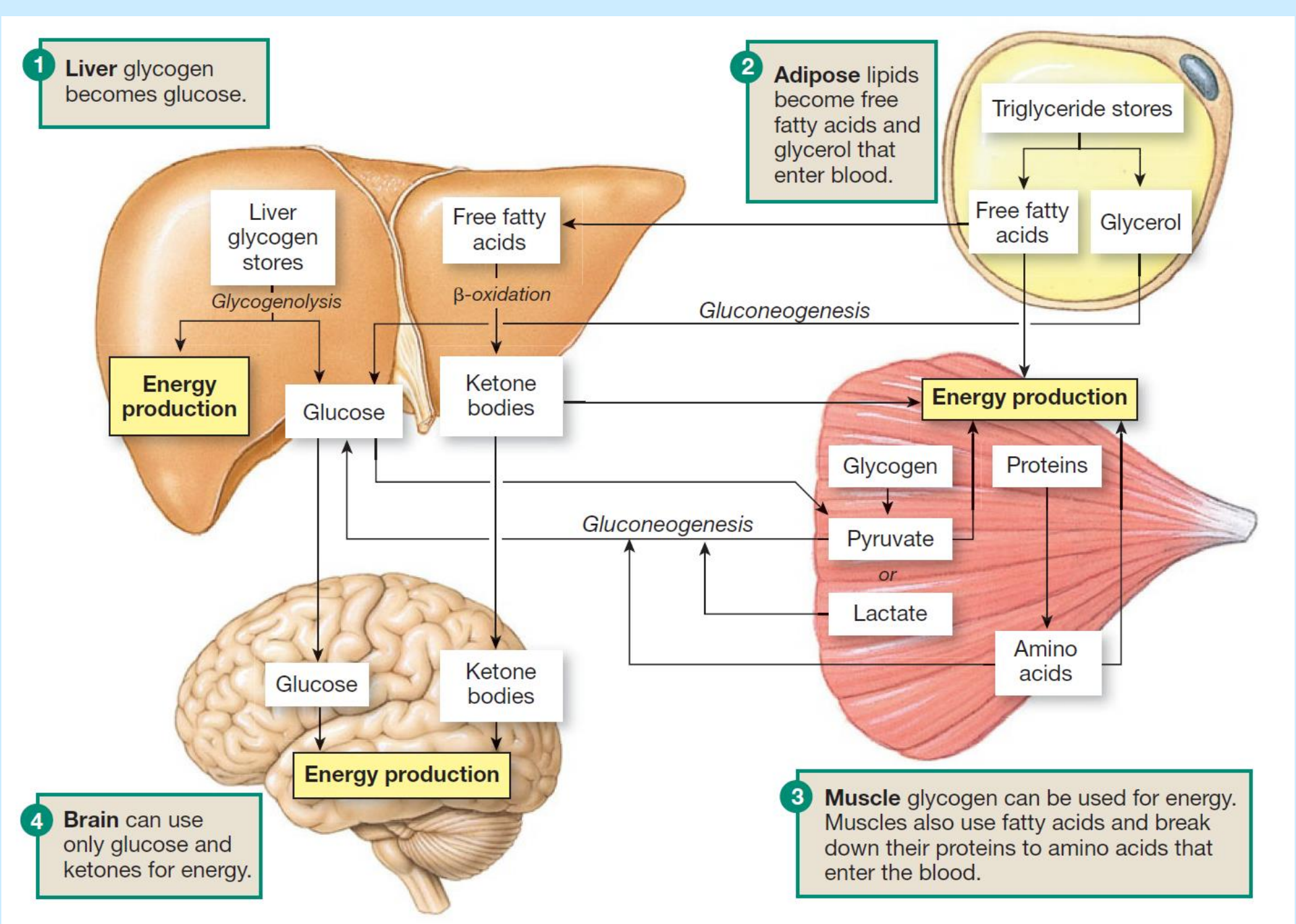
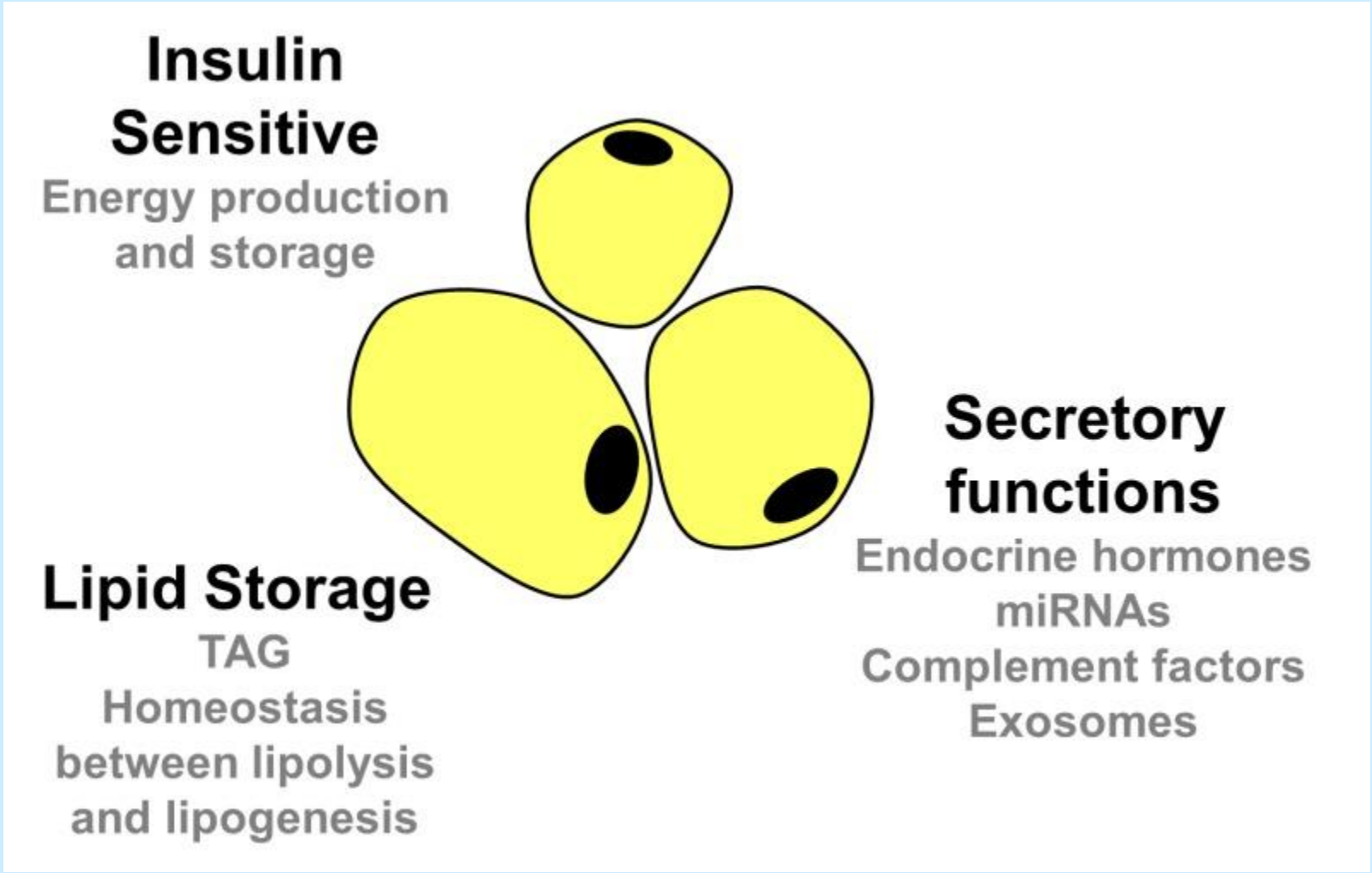


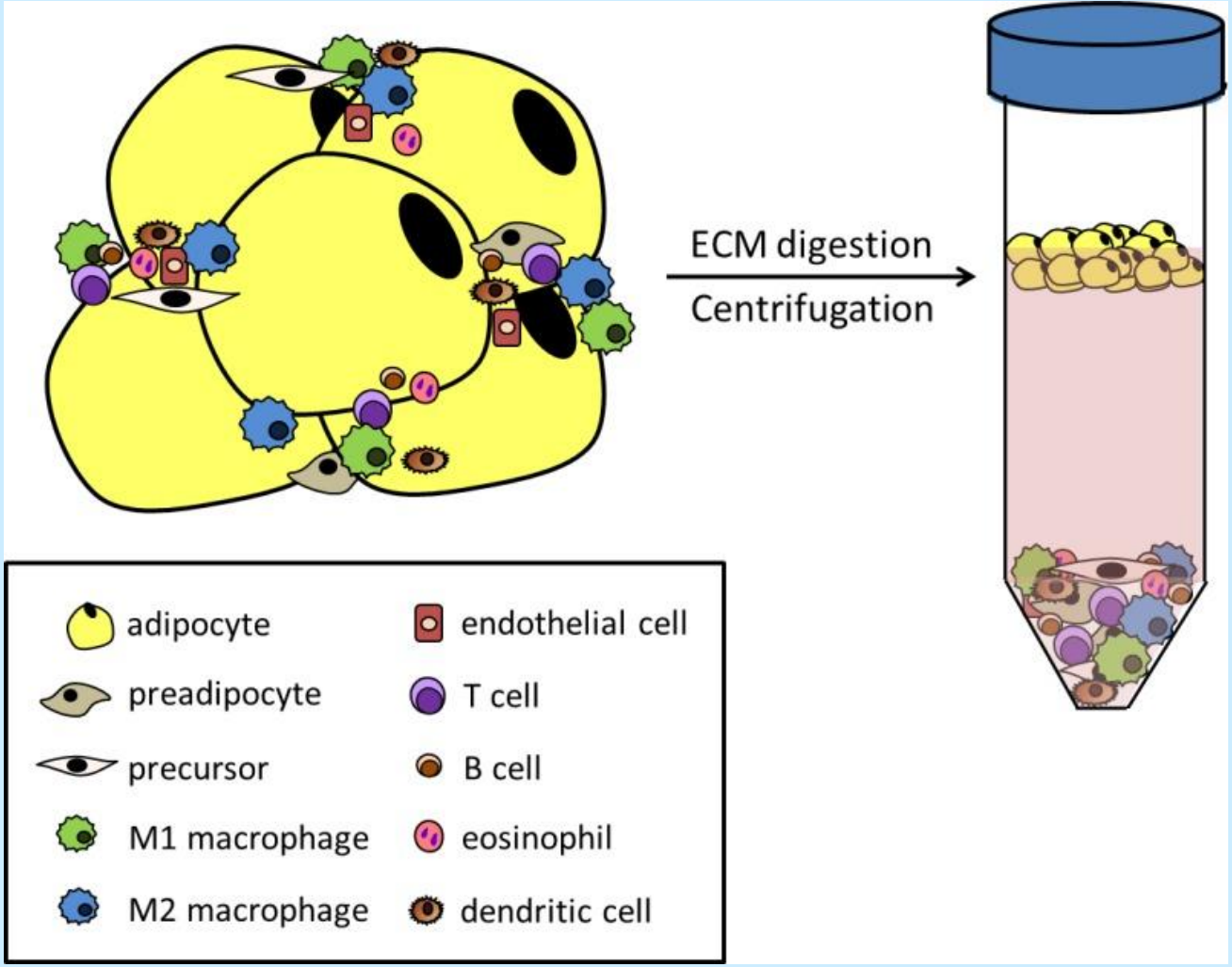

**Fig. 22.3** Adapted from L. L. Langley, *Homeostasis* (New York: Reinhold, 1965).


1 Liver glycogen becomes glucose.
2 Adipose lipids become free fatty acids and glycerol that enter blood.
Triglyceride stores
Free fatty acids
Glycerol
Liver glycogen stores
Glycogenolysis
Free fatty acids
β-oxidation
Gluconeogenesis
Energy production
Glucose
Ketone bodies
Energy production
Glycogen
Proteins
Gluconeogenesis
Pyruvate
or
Lactate
Amino acids
Glucose
Ketone bodies
Energy production
4 Brain can use only glucose and ketones for energy.
3 Muscle glycogen can be used for energy. Muscles also use fatty acids and break down their proteins to amino acids that enter the blood.

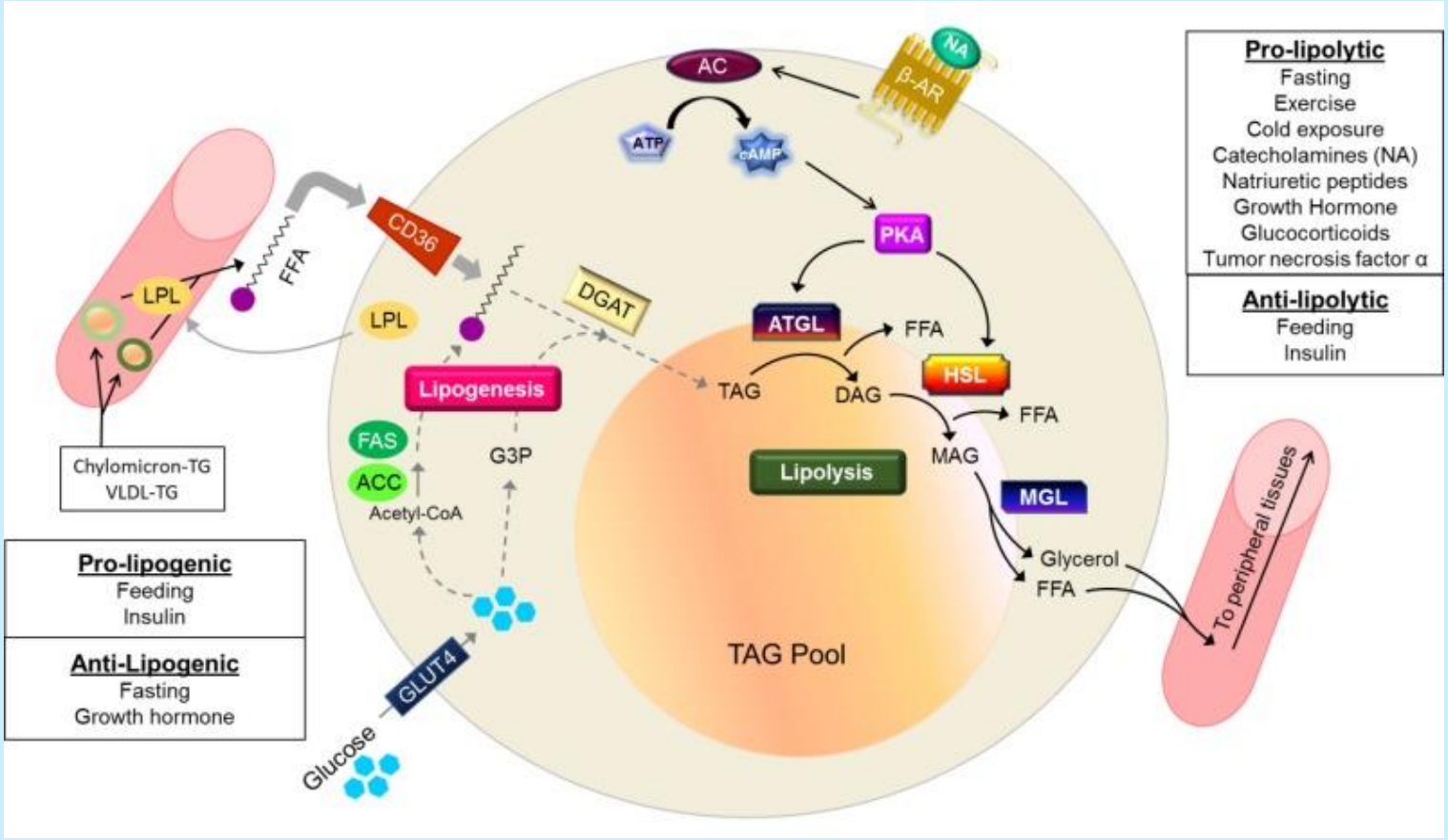
# Tuková tkáň


Insulin Sensitive
Energy production and storage
Secretory functions
Endocrine hormones
miRNAs
Complement factors
Exosomes
Lipid Storage
TAG
Homeostasis between lipolysis and lipogenesis

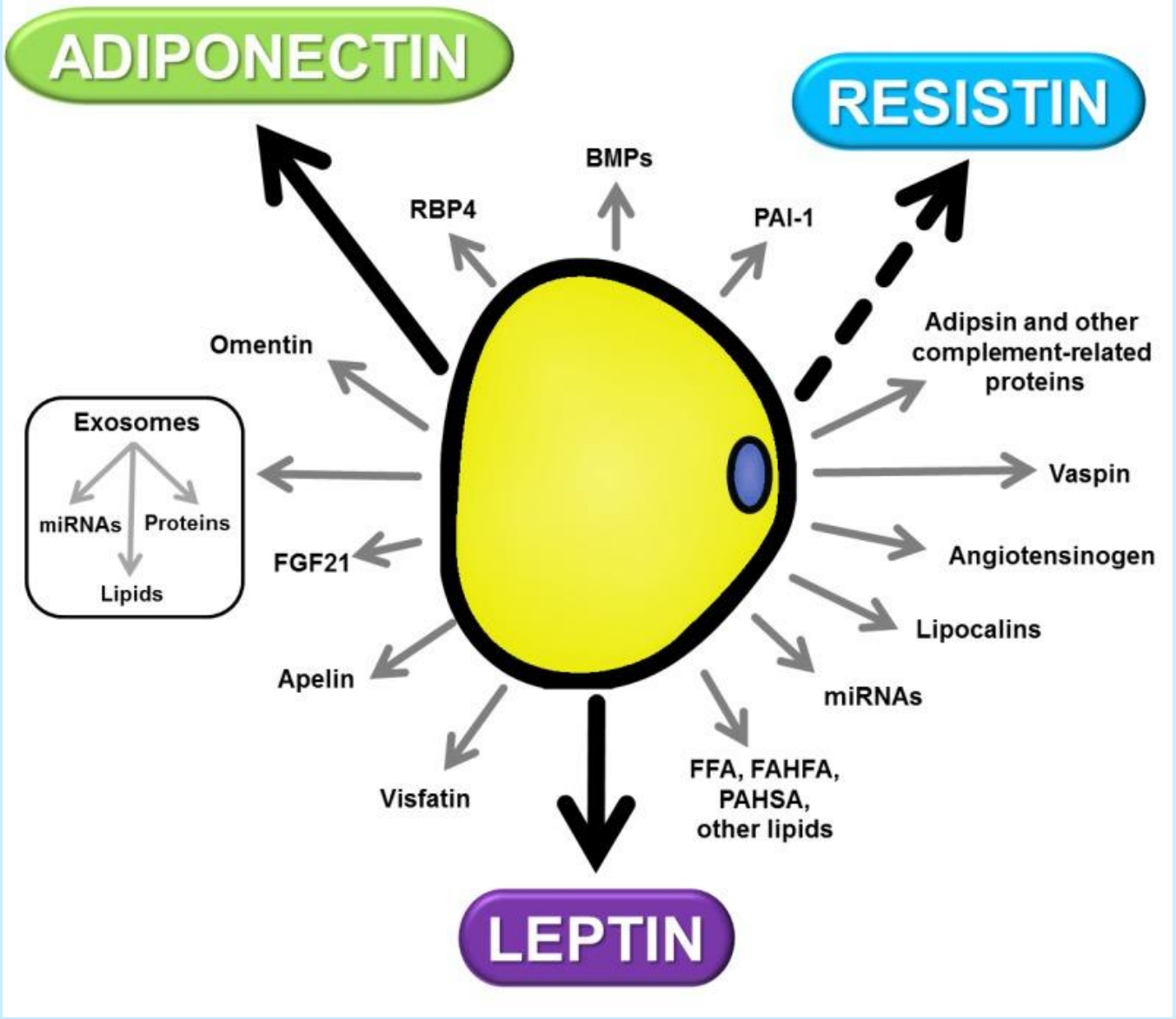
# Bílá, béžová a hnědá TT

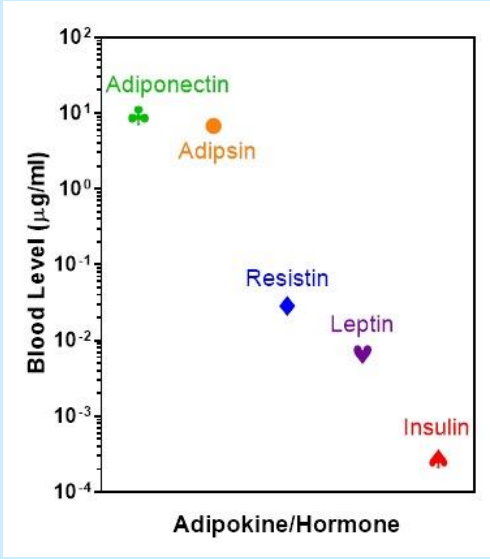



Constituents of adipose tissue (AT). Left: Along with mature, functional adipocytes and precursor cells, many cell types related to vasculature and immune function reside within AT. They perform both physiological and pathophysiological functions by communicating with the adipocytes via secreted factors and scavenging lipid from dying fat cells. The number and diversity of these cell types increases with developing obesity and metabolic dysfunction. Right: The non-adipocyte cells are collectively referred to as the stromal vascular fraction (SVF), and the SVF can be separated from lipid-containing adipocytes by digesting the extracellular matrix (ECM) and centrifuging the cellular mixture. The SVF will form a pellet at the bottom of the tube, while the adipocytes will float and form a visible lipid layer at the top of the aqueous medium. This separation technique is critical to studying the cellular composition of adipose tissue and gaining insight regarding the individual functions of these diverse and distinct cell types under physiological and pathophysiological conditions.




A critical balance between lipogenesis and lipolysis within adipocytes must be established to maintain whole body insulin sensitivity and energy homeostasis. Lipogenesis is shown on the left (gray arrows mark the pathway), whereas lipolysis is shown on the right and is marked by black arrows. Nutritional and hormonal cues regulate both processes. Lipid droplet associated proteins, such as perilipin and comparative gene identification-58 (CGI-58) are not shown but play important roles in lipolysis. CD36 (cluster of differentiation 36) is a fatty acid transporter that facilitates entry of free fatty acids (FFAs) into the cell. Insulin stimulates glucose uptake into fat cells by increasing the localization of the insulin responsive glucose transporter, GLUT4, within the plasma membrane. Other abbreviations: VLDL-TG – triglyceride-containing very low density lipoprotein; LPL – lipoprotein lipase; ACC - acetyl-CoA carboxylase 1; FAS – fatty acid synthase; G3P – glycerol 3 phosphate; DGAT - diacylglycerol acyltransferase; β-AR – β-adrenergic receptor; NA – noradrenaline; AC – adenylyl cyclase; PKA – protein kinase A; ATGL - adipocyte triglyceride lipase; HSL - hormone sensitive lipase; MGL - monoacylglycerol lipase; TAG – triacylglycerol; DAG – diacylglycerol; MAG – monoacylglycerol.

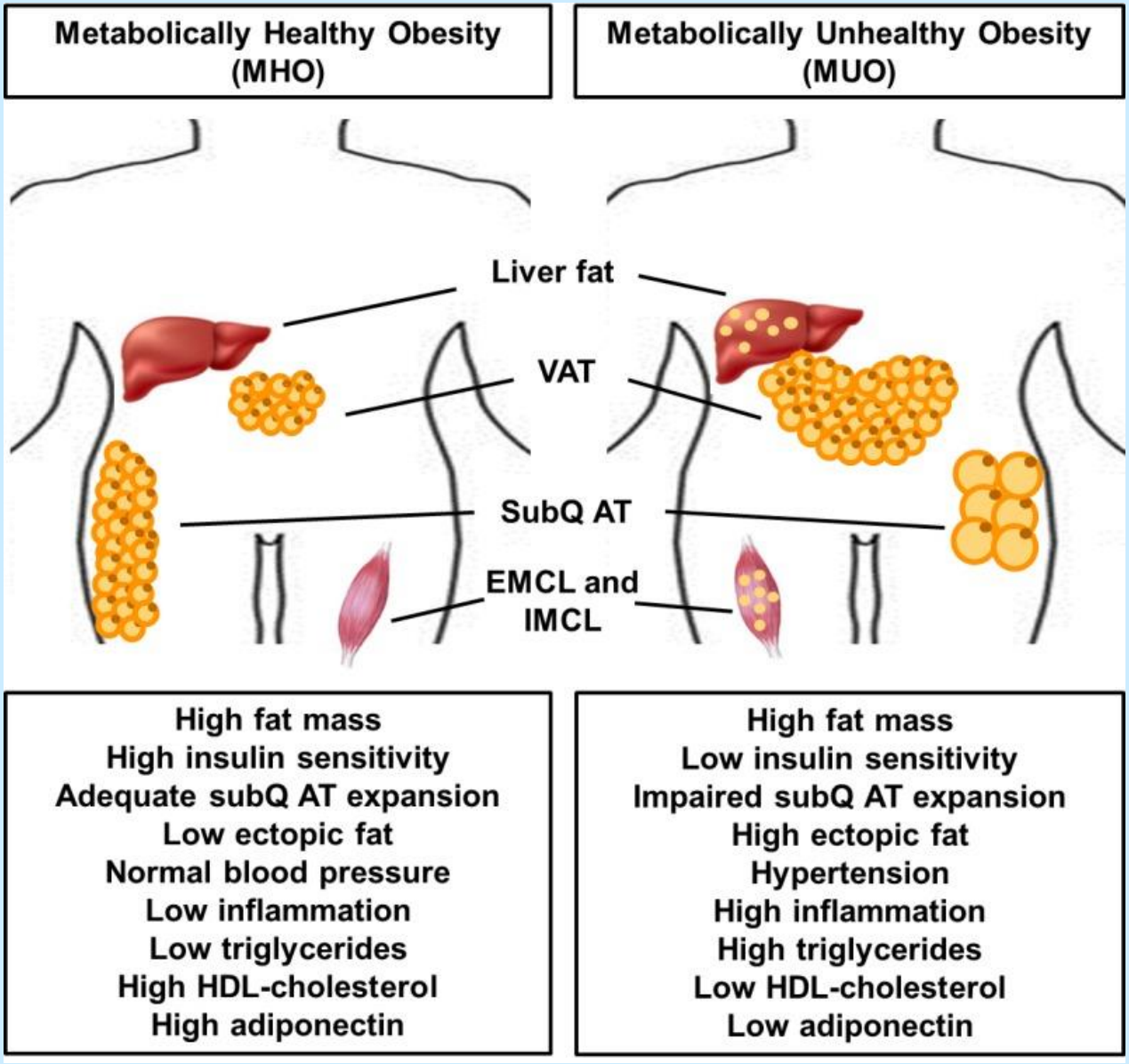



Abbreviations are RBP4 – retinol binding protein 4, BMPs – bone morphogenetic proteins, PAI-1 – plasminogen activator inhibitor 1, miRNA – microRNA, FFA – free fatty acid, FAHFA - fatty acid esters of hydroxyl fatty acids, PAHSA – palmitic-acid-hydroxy-steric-acid, FGF21 – fibroblast growth factor 21

| | LEPTIN | | ADIPONECTIN | RESISTIN |
|---|---|---|---|---|
| Expression in Obesity | ↑ | | ↓ | ↑ |
| Receptor(s) | Leptin Receptor (LR) (multiple isoforms) | | T-cadherin, AdipoR1, & AdipoR2 | TLR4 & CAP1 |
| Target Tissues | Brain & CNS | Hepatocytes & β-cells | Liver, Skeletal Muscle, AT, Bone, Cartilage, Heart | AT, Liver, Endothelium, & Heart |
| Main Metabolic Actions | ↓ Food Intake<br>↑ Energy Expenditure | Glucose & Lipid Metabolism | ↓ Gluconeogenesis, glucose output, lipogenesis & TAG accumulation in liver<br>↑ Insulin Sensitivity, FAO, & EE in muscle | ↑ Insulin Resistance<br>↓ Adipogenesis & ↑ Proinflammatory response in AT<br>↓ Glucose uptake & ↑ gluconeogenesis in liver |
| Other Functions | Reproduction<br>Angiogenesis<br>Bone homeostasis<br>Wound healing<br>Immune Responses<br>Cancer | | ↓ Liver fibrosis & inflammation<br>↑ Cell survival<br>↑ Cardioprotection<br>Reproduction | ↑ Vascular Dysfunction<br>↑ Cell Adhesion<br>↓ Contractility<br>↑ Heart Failure |

Summary of adipocyte-specific adipokines, and their actions on other tissues. Abbreviations: TLR4 - Toll-like receptor 4; CAP1 - adenylyl cyclase-associated protein 1; AdipoR1 & R2 - Adiponectin receptors 1 and 2; CNS - Central nervous system; FAO – fatty acid oxidation; EE – energy expenditure.




Clinical and biological factors thought to distinguish metabolically healthy obesity (MHO) from metabolically unhealthy obesity (MUO). Abbreviations: VAT – Visceral AT, SubQ AT – Subcutaneous AT, EMCL - extramyocellular lipid; IMCL – intramyocellular lipid; HDL – high density lipoprotein.

# Hnědá TT

Specifická lokalizace

Sympatická inervace jak cév, tak lipocytů

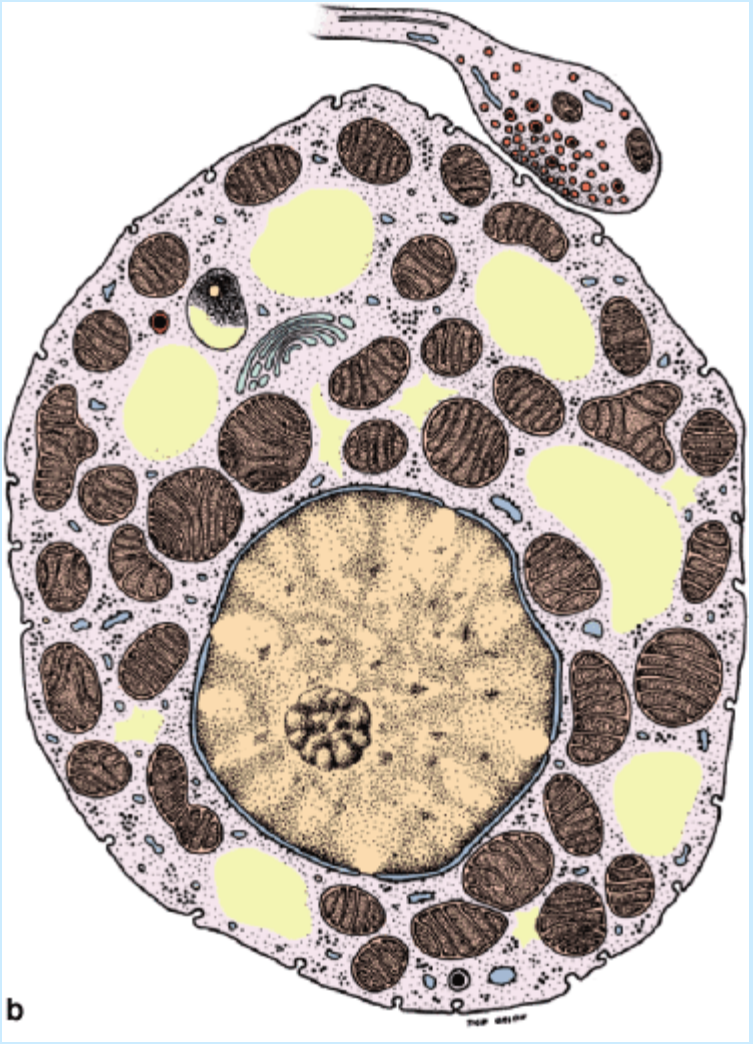
Několik kapének tuku v lipocytu

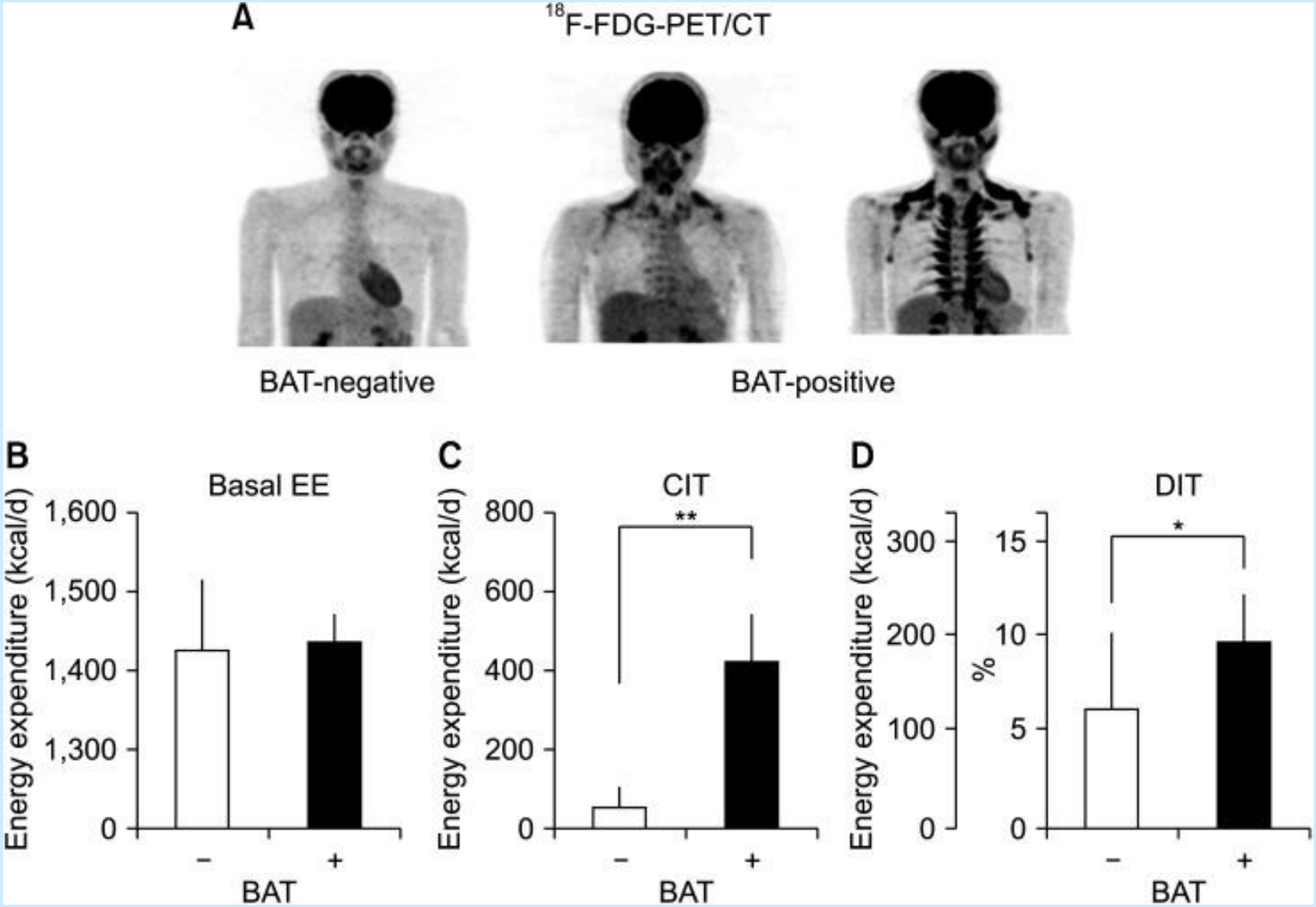
Více mitochondrií

Produkce tepla

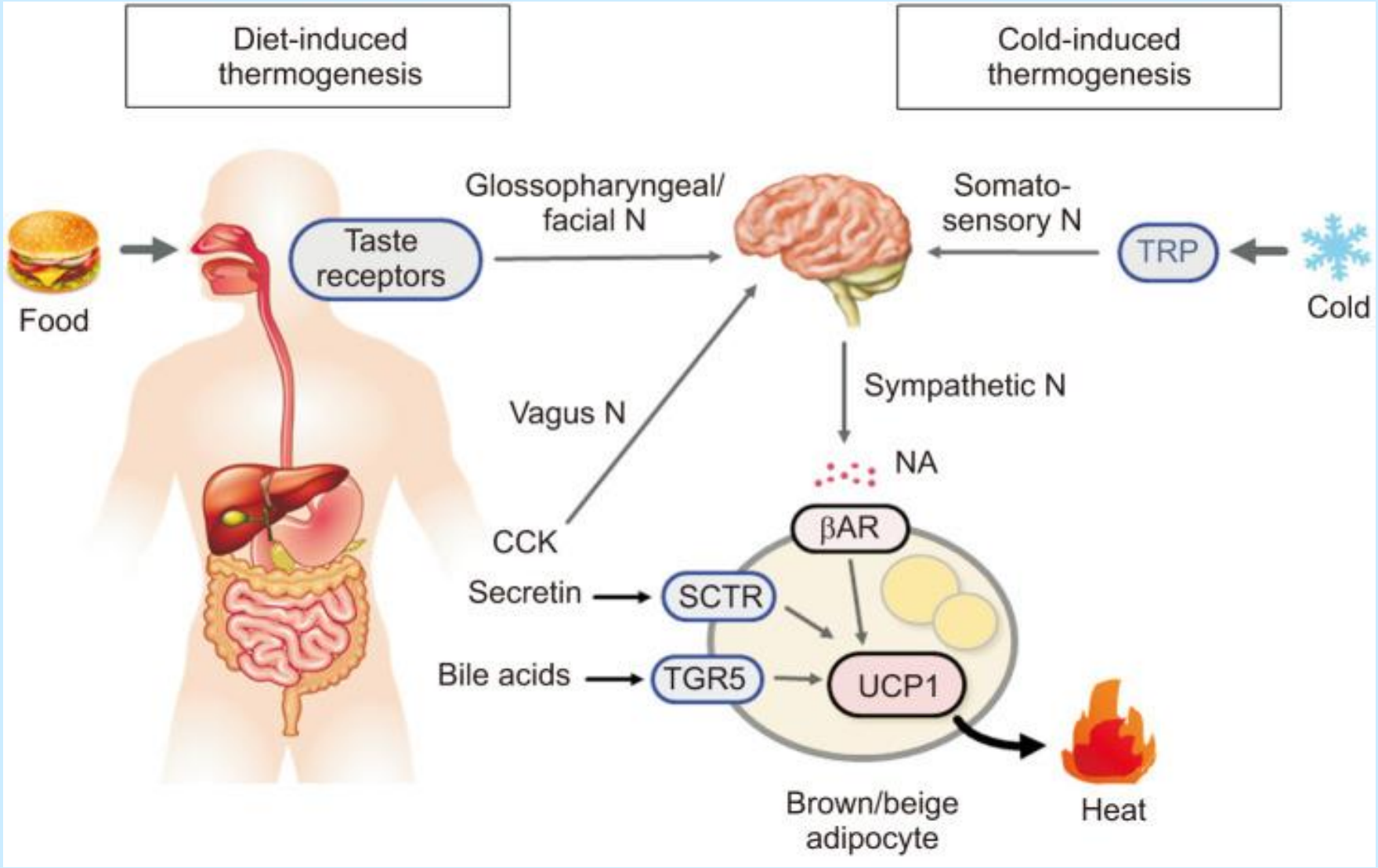
Adaptace na chlad

Po příjmu potravy zvýšení produkce tepla

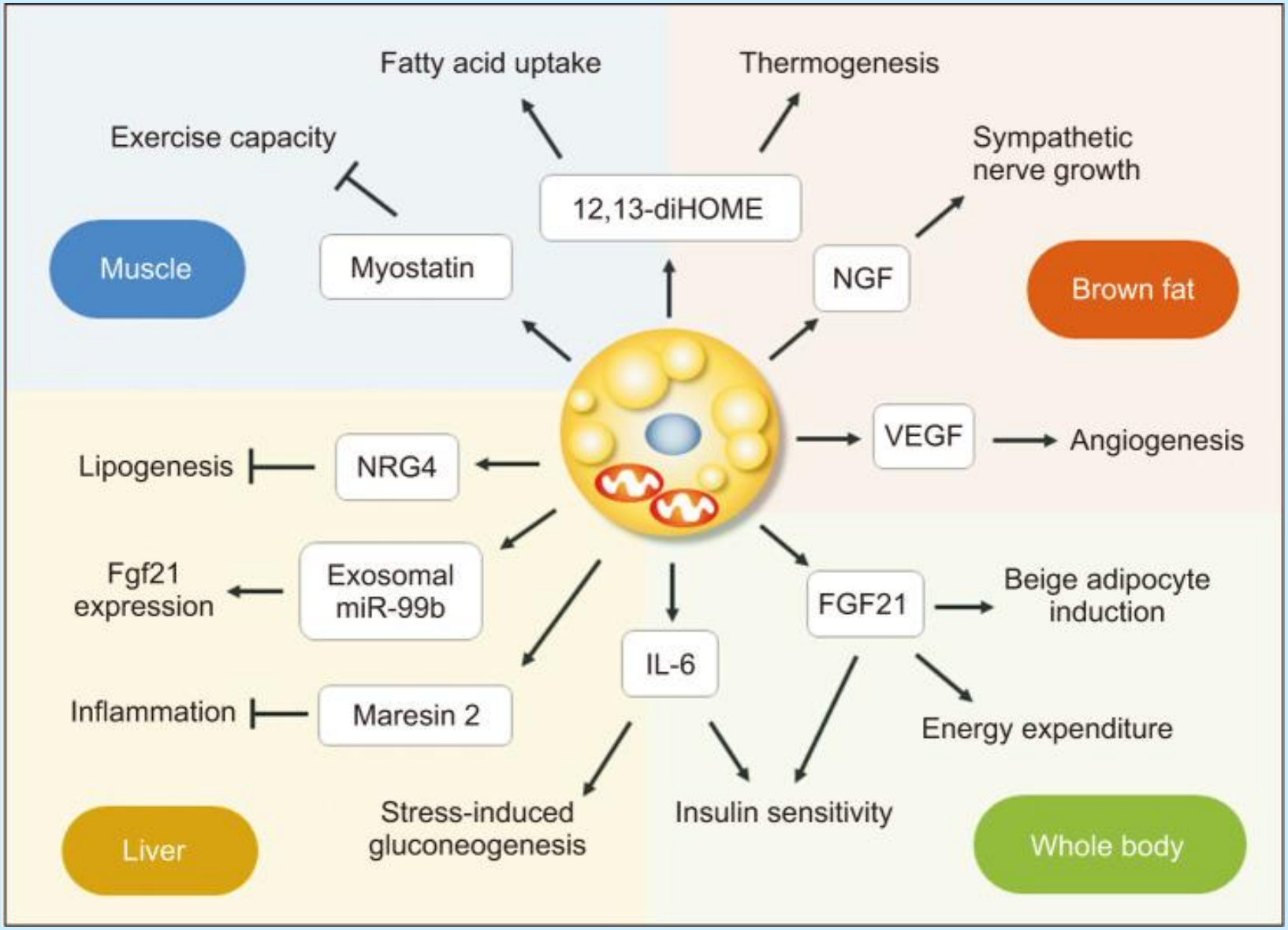




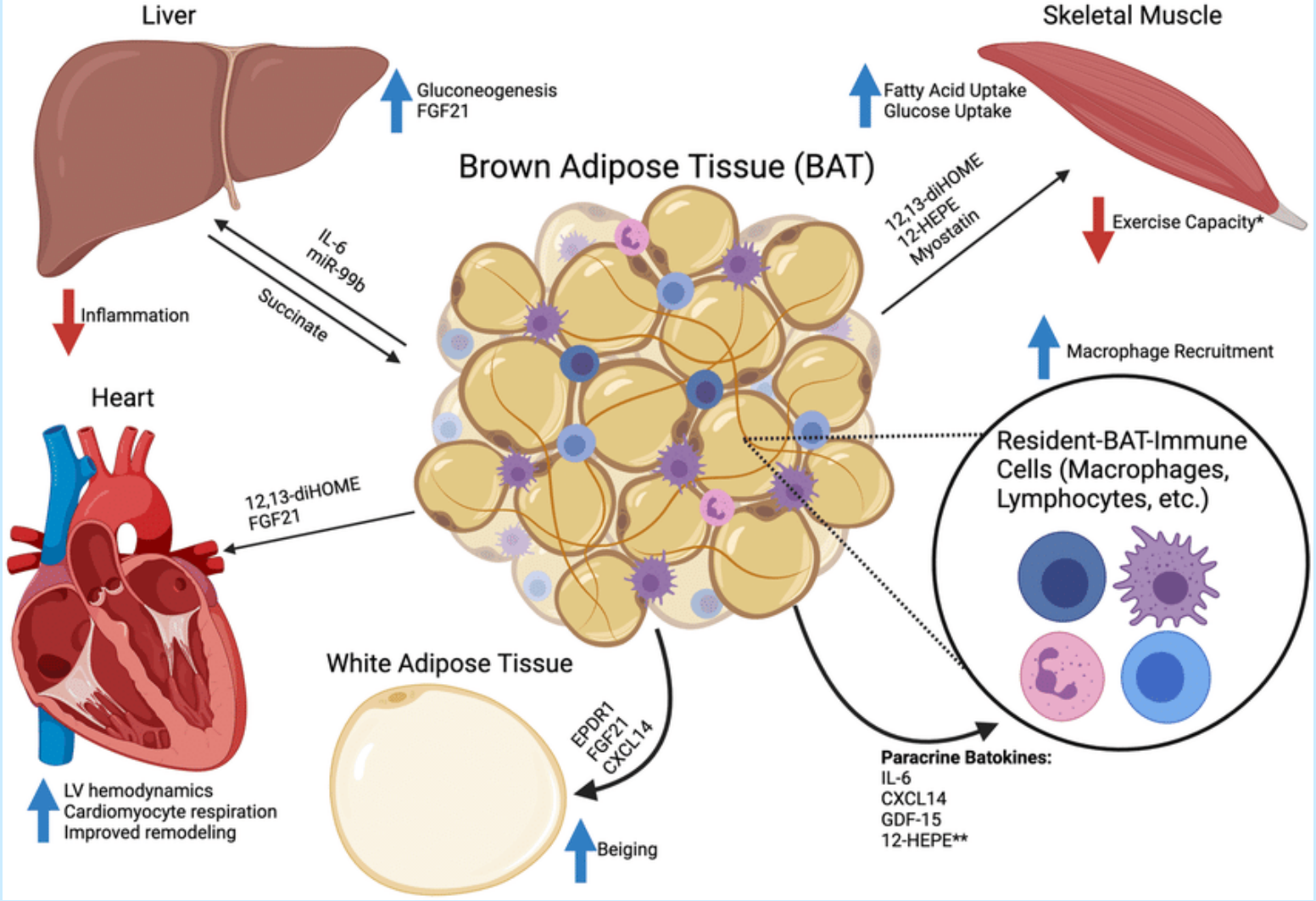

Brown adipose tissue (BAT), energy expenditure (EE), and non-shivering thermogenesis. (A) BAT detected by 18F-FDG-PET/CT after acute cold exposure. (B) Basal EE under a warm condition. (C) Cold-induced thermogenesis (CIT) after acute cold exposure. (D) Diet-induced thermogenesis (DIT) after meal intake. *p<0.05, **p<0.01. Adapted from Yoneshiro et al (Obeisty [Silver Spring] 2011;19:13-6) [12] and constructed from Hibi et al (Int J Obes [Lond] 2016;40:1655-61)




Neuro-endocrine mechanisms of cold- and diet-induced brown fat thermogenesis.βAR: β-adrenergic receptor, CCK: cholecystokinin, SCTR: secretin receptor, N: nerve, NA: noradrenaline, TGR5: G-protein-coupled bile acid-activated receptor, TRP: transient receptor potential channel, UCP1: uncoupling protein 1.

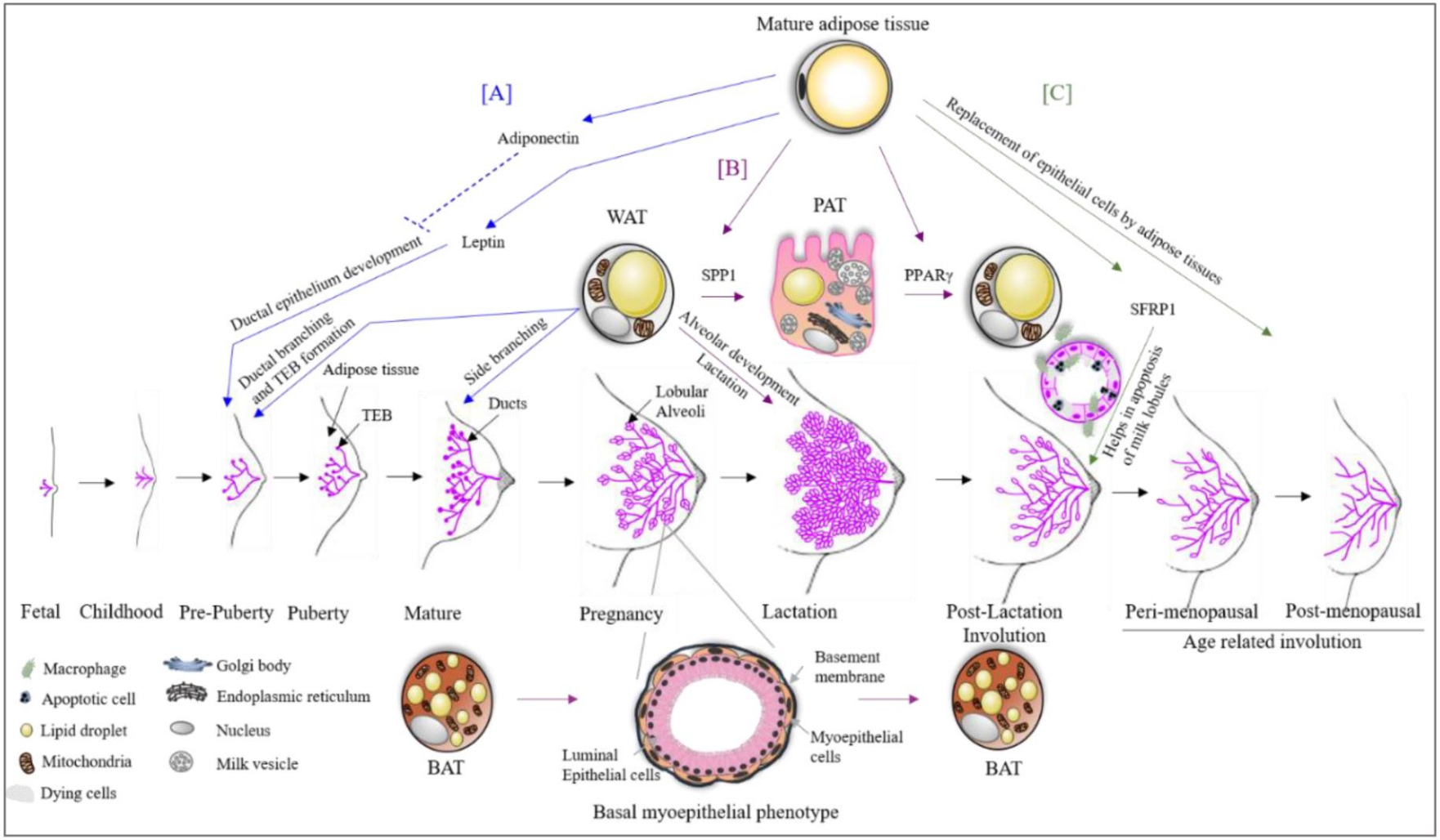



Endocrine actions of brown fat-derived factors, BATkines: 12,13-diHOME,12,13-dihydroxyoctadecaenoic acid, FA: fatty acid, FGF21: fibroblast growth factor 21, IL-6: interleukin-6, miR: microRNA, NGF: nerve growth factor, NRG: neuregulin 4, VEGF: vascular endothelial growth factor.

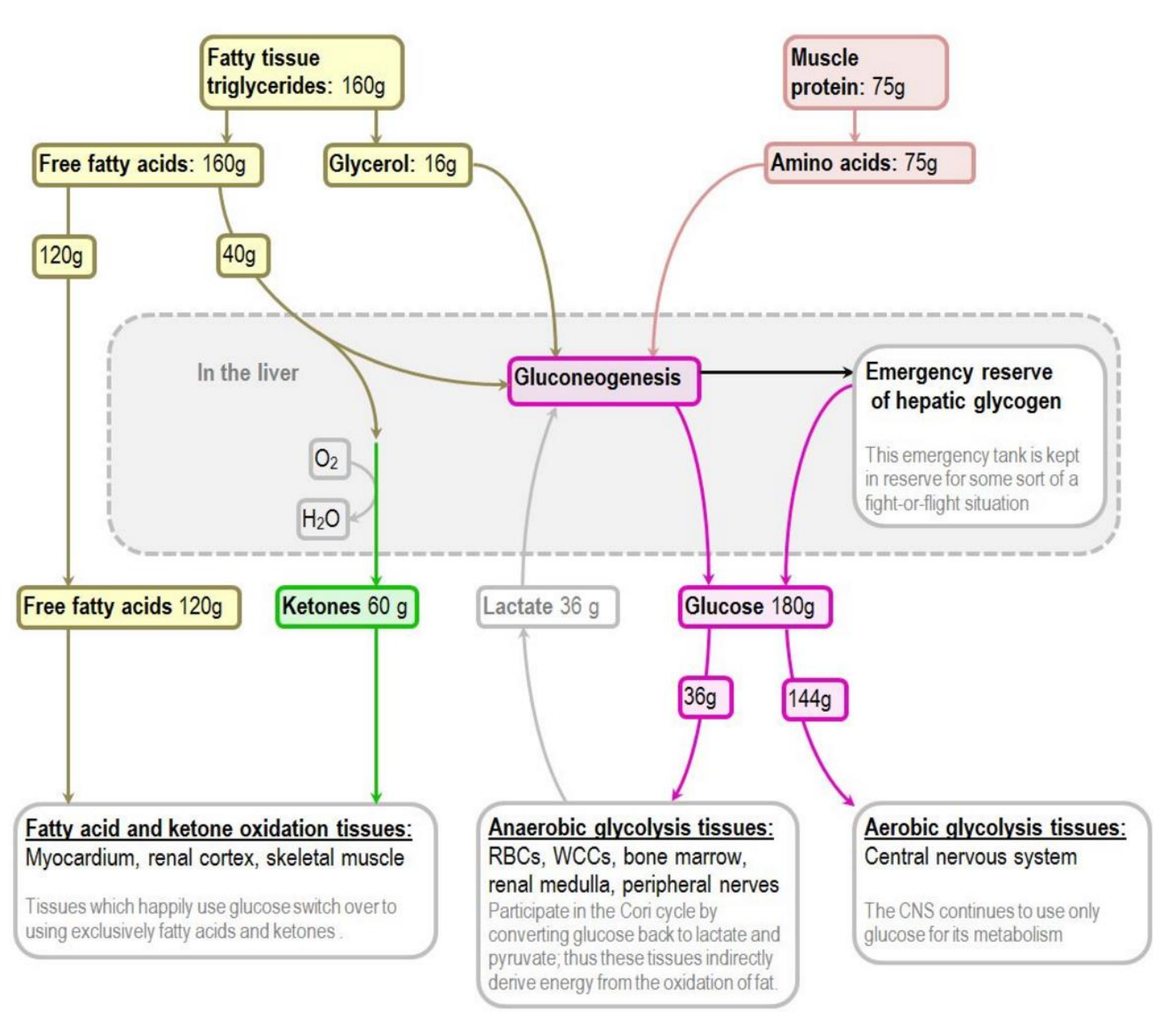


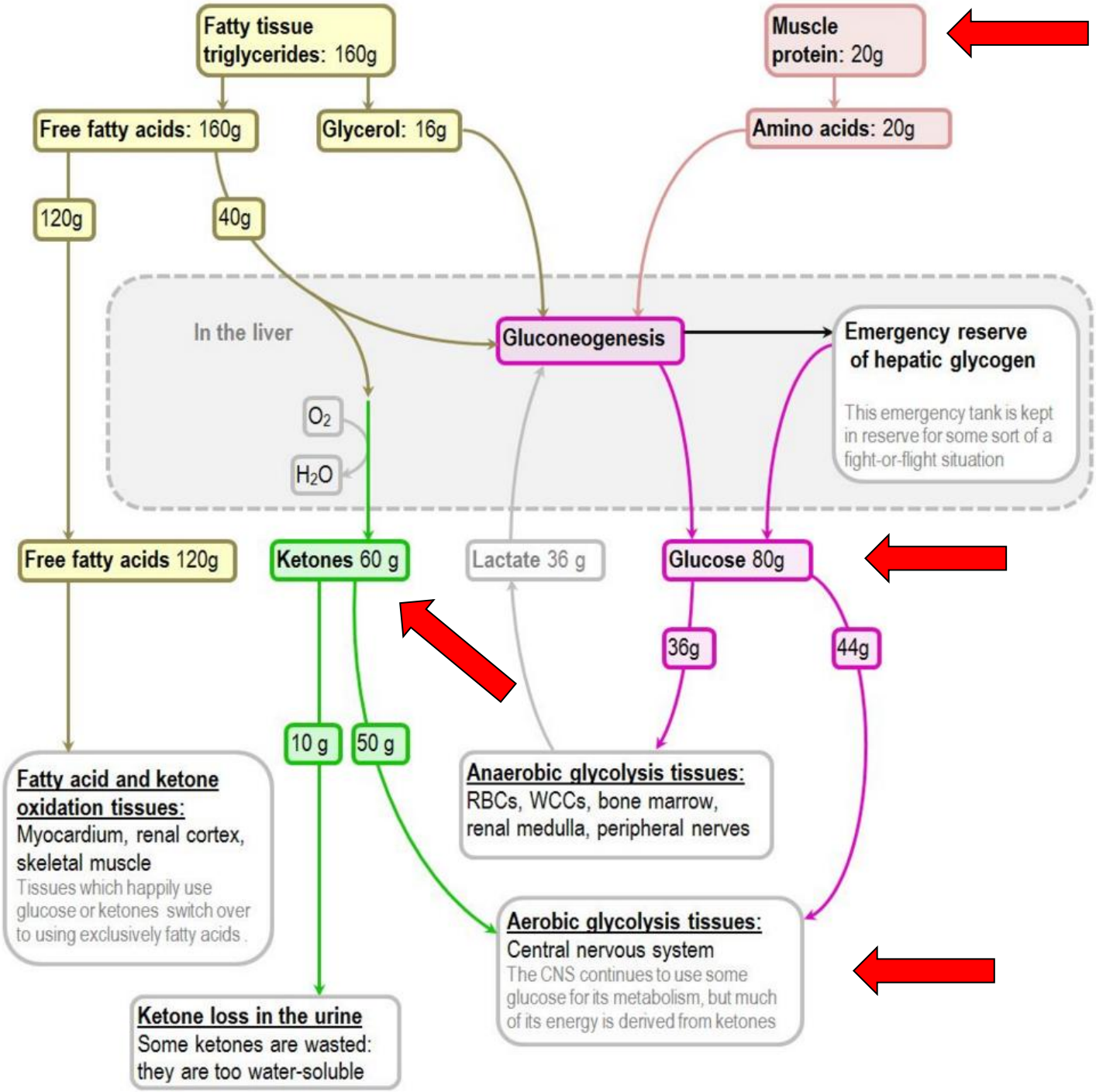

Brown adipose tissue inter-tissue and inter-cellular communication. Mechanisms of brown adipose tissue (BAT) bi-directional tissue and cellular communication. Batokines (secreted factors from BAT) target organs such as the white adipose tissue, liver, skeletal muscle, and heart. Additionally, many paracrine batokines target immune cells with the most well-studied effects on macrophages. *The reduction in exercise capacity is due to secretion of myostatin from BAT at thermoneutral conditions. **No study has specifically shown an effect of 12-HEPE on resident-BAT immune cells; the effects of BAT-derived lipokines on local immune cells is still unknown.

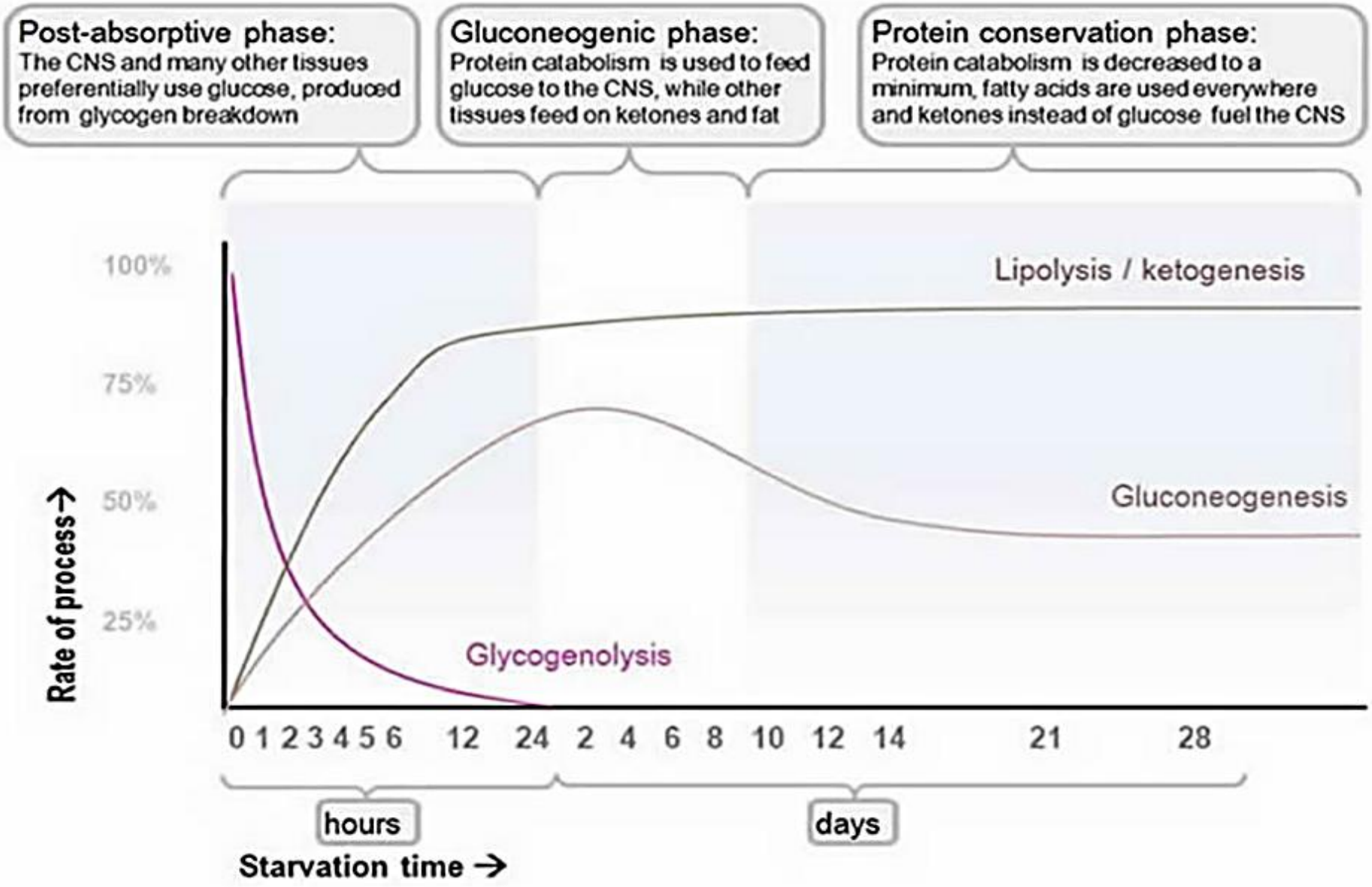
# Růžová tuková tkáň a její funkce

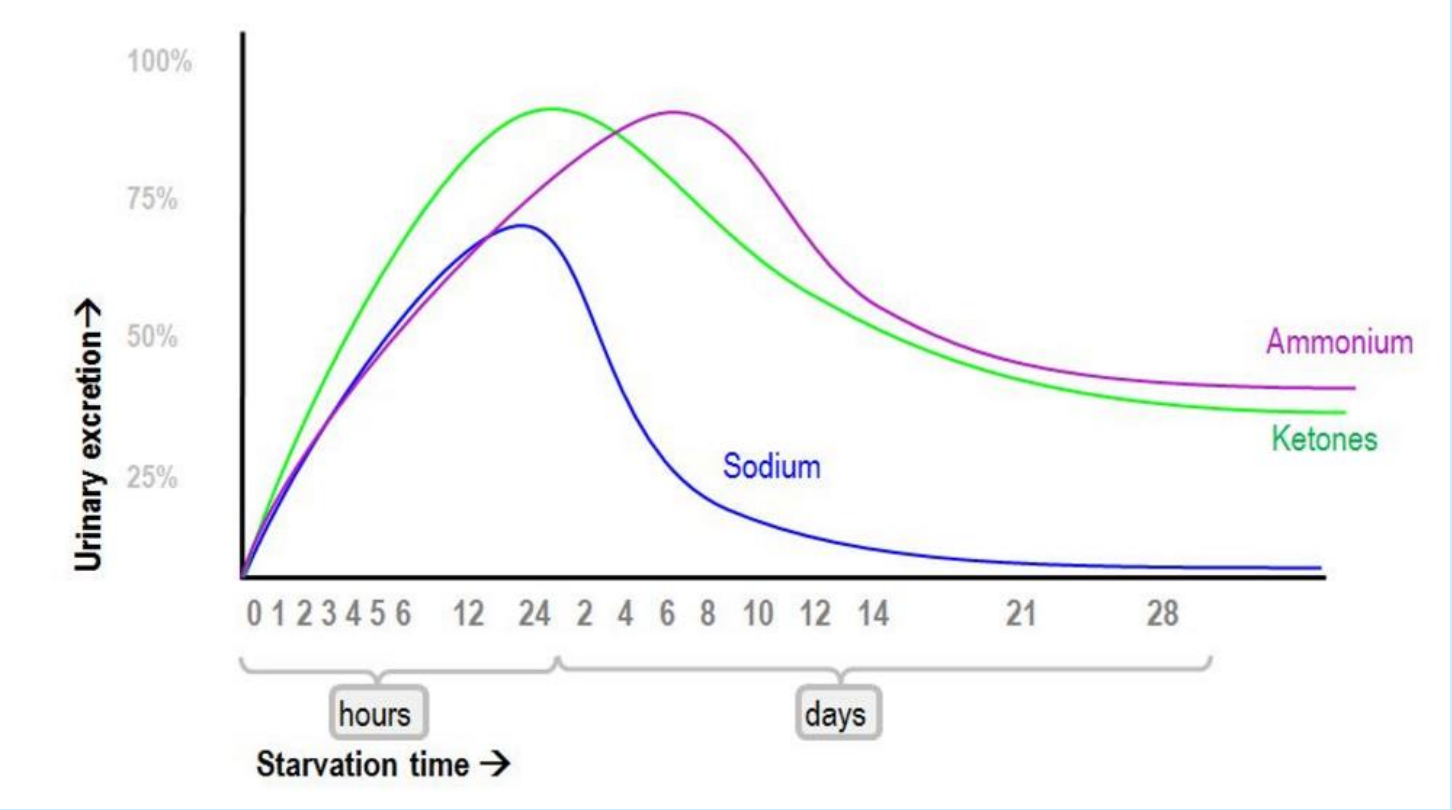


# Co se děje při hladovění?




Fatty tissue triglycerides: 160g
Muscle protein: 20g
Free fatty acids: 160g
Glycerol: 16g
Amino acids: 20g
120g
40g
In the liver
Gluconeogenesis
Emergency reserve of hepatic glycogen
This emergency tank is kept in reserve for some sort of a fight-or-flight situation
$O_2$
$H_2O$
Free fatty acids 120g
Ketones 60 g
Lactate 36 g
Glucose 80g
36g
44g
10 g
50 g
Fatty acid and ketone oxidation tissues:
Myocardium, renal cortex, skeletal muscle
Tissues which happily use glucose or ketones switch over to using exclusively fatty acids.
Anaerobic glycolysis tissues:
RBCs, WCCs, bone marrow, renal medulla, peripheral nerves
Aerobic glycolysis tissues:
Central nervous system
The CNS continues to use some glucose for its metabolism, but much of its energy is derived from ketones
Ketone loss in the urine
Some ketones are wasted: they are too water-soluble

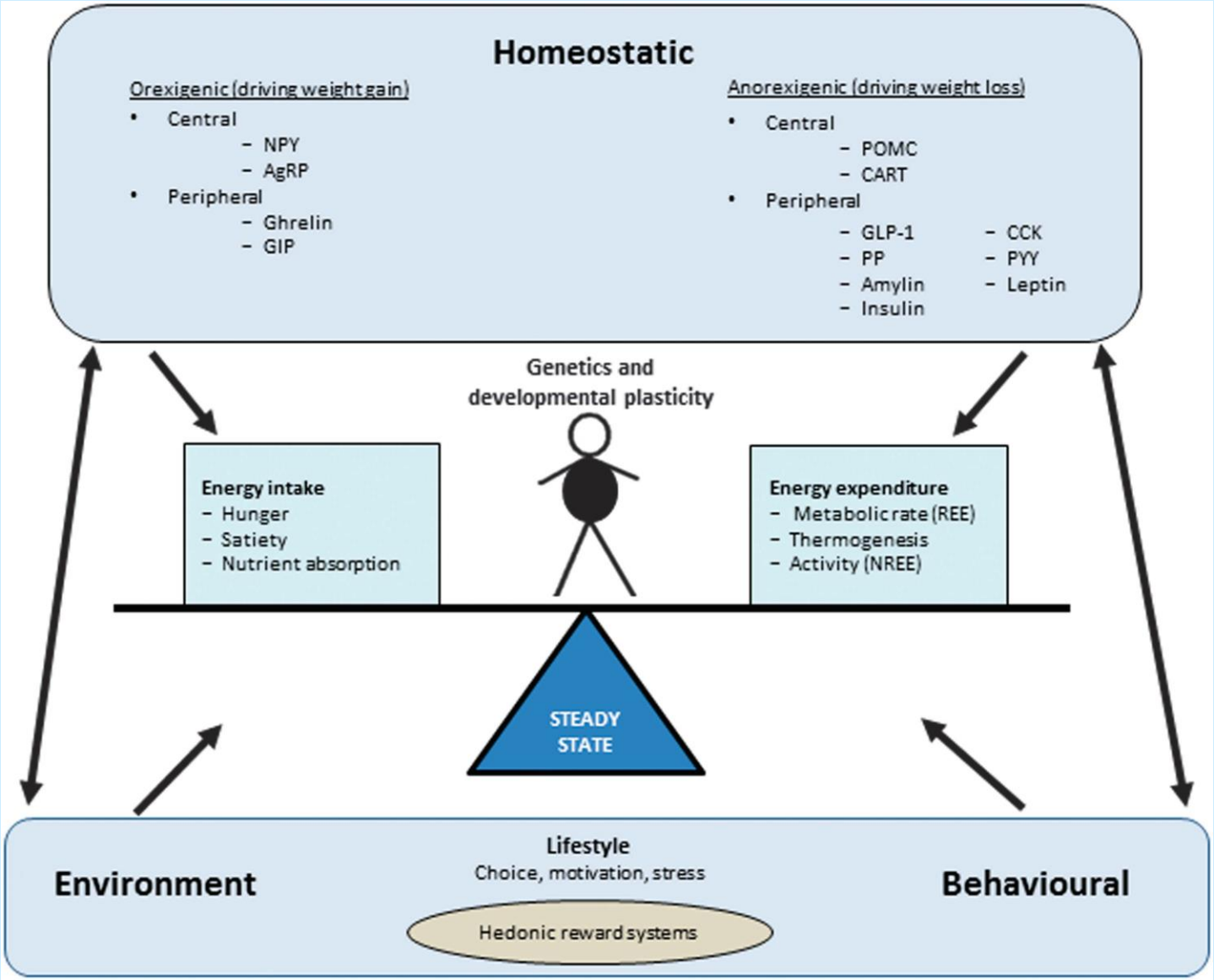

Post-absorptive phase:
The CNS and many other tissues preferentially use glucose, produced from glycogen breakdown
Gluconeogenic phase:
Protein catabolism is used to feed glucose to the CNS, while other tissues feed on ketones and fat
Protein conservation phase:
Protein catabolism is decreased to a minimum, fatty acids are used everywhere and ketones instead of glucose fuel the CNS
100%
75%
50%
25%
Rate of process →
Lipolysis / ketogenesis
Gluconeogenesis
Glycogenolysis
0 1 2 3 4 5 6 12 24 2 4 6 8 10 12 14 21 28
hours
days
Starvation time →


100%
75%
50%
25%
Urinary excretion→
Ammonium
Ketones
Sodium
0 1 2 3 4 5 6 12 24 2 4 6 8 10 12 14 21 28
hours
days
Starvation time →

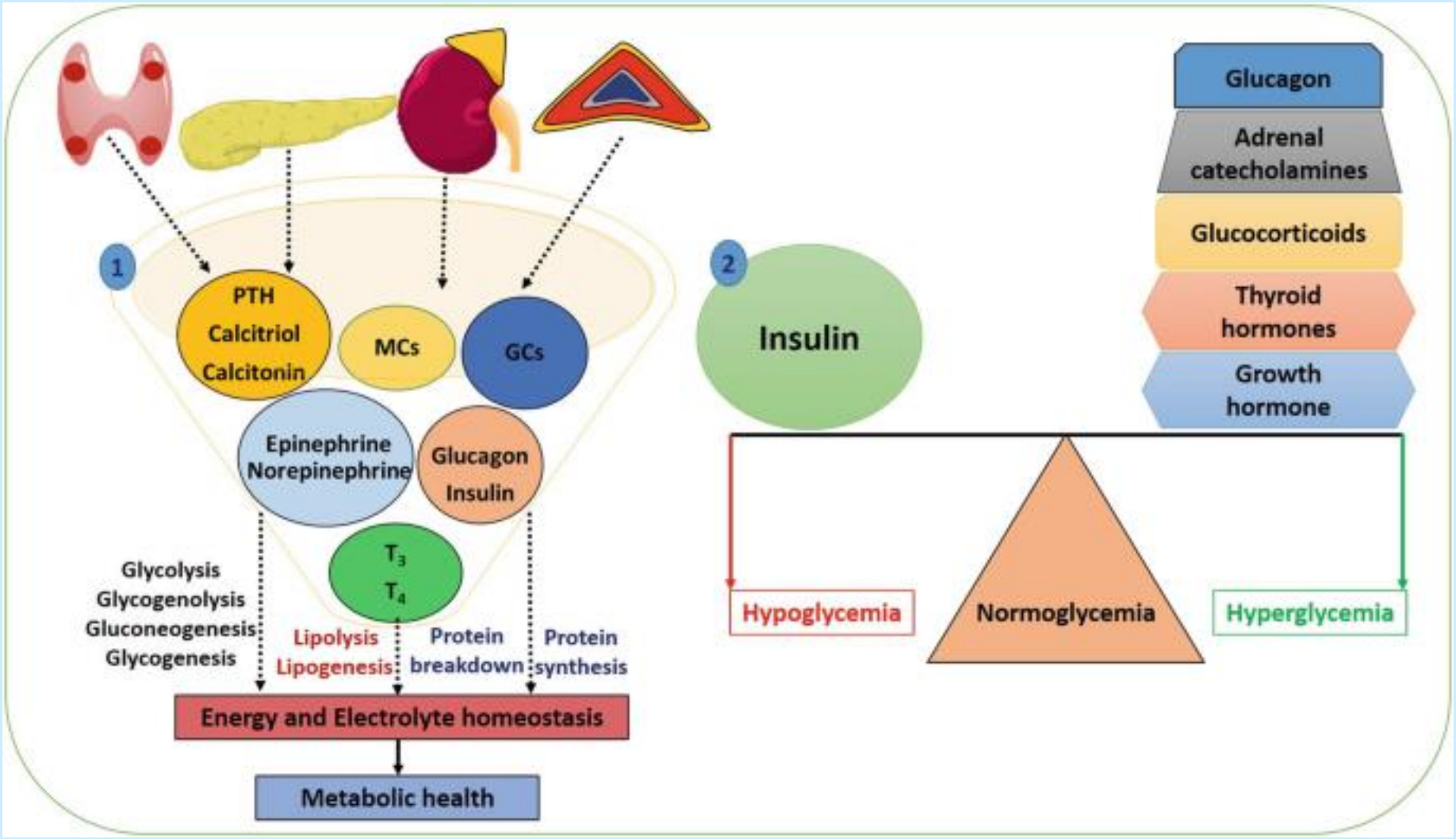
**Další změny v důsledku hladovění:**

- Ztráty $K^+$ v počáteční fázi, stabilní koncentrace 3 mmol/L
- $Mg^{2+}$ - beze změny nebo jen mírná hypokalémie
- $Ca^{2+}$ - beze změny
- Fosfáty – beze změny
- Kyselina močová – vzestup (katabolismus proteinů)
- Dále:
  - ❑ Pokles srdeční frekvence (35 t/min, od 4. týdne mírný vzestup)
  - ❑ Pokles TK
  - ❑ Změny EKG – oploštění T vlny, snížení amplitudy QRS intervalu
  - ❑ Při extrémním hladovění – prodloužení QT intervalu, inverze T vlny, deprese ST úseku
  - ❑ Proč?
    - o Pokles syntézy proteinů – myofibrily, myofilamenta
    - o Změny složení ECT/ICT
    - o Ztráty stopových prvků (Cu – ischémie)
    - o Sympatikus (katecholaminy) - arytmie

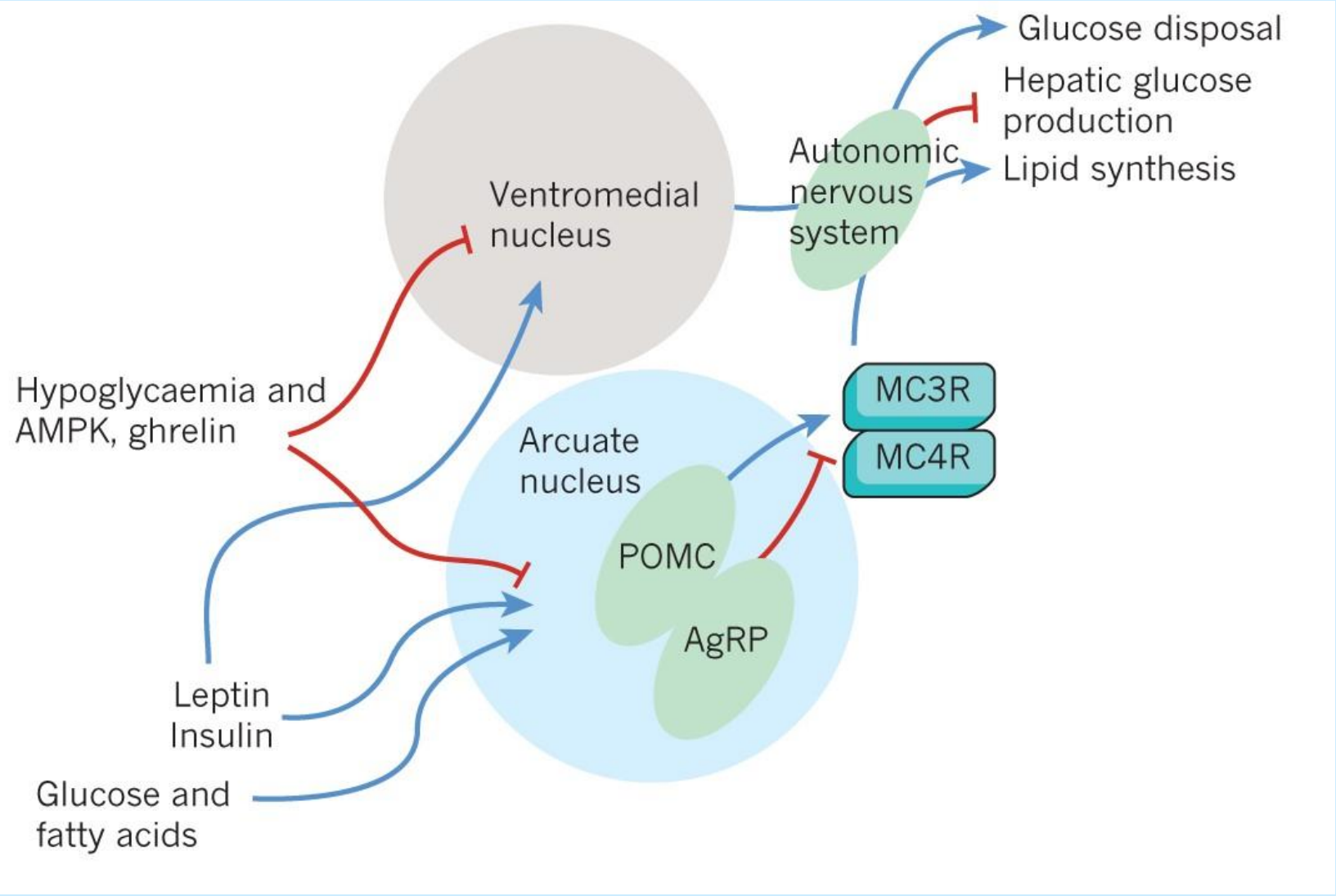
# Jaké faktory ovlivňují EM?



# Endokrinní regulace metabolismu



# CNS a energetický metabolismus



# Jak měříme metabolismus?

# RESPIRAČNÍ KVOCIENT

$$RQ = V_{CO2} : V_{O2}$$

**(za jednotku času, za ustáleného stavu, obvykle vztažený k 1 l kyslíku)**

**Cukry: RQ = 1**
**Tuky: RQ = 0,7**
**Proteiny: RQ = 0,8**

**R – poměr respirační výměny (není ustálený stav!, v kterémkoliv časovém úseku)**

- Sacharidy (glukoza)

$$C_6H_{12}O_6 + 6O_2 = 6CO_2 + 6H_20$$
$$RQ = 6/6 = 1,00$$

- Tuky (tripalmitin)

$$2\ C_{51}H_{96}O_6 + 145\ O_2 = 102\ CO_2 + 98\ H_2O$$
$$RQ = 102/145 = 0,703\ (obecně\ 0,70)$$

- Při hyperventilaci RQ stoupá (vydechován více $CO_2$).
- Při intenzivní zátěži RQ až 2,00 (vydechován více $CO_2$ a kyselina mléčná se mění na $CO_2$).
- Po skončení zátěže klesá RQ až na 0,50.
- Při metabolické acidóze RQ stoupá.
- Při metabolické alkalóze RQ klesá.

**Table 1** — Summary of methods to assess energy intake.

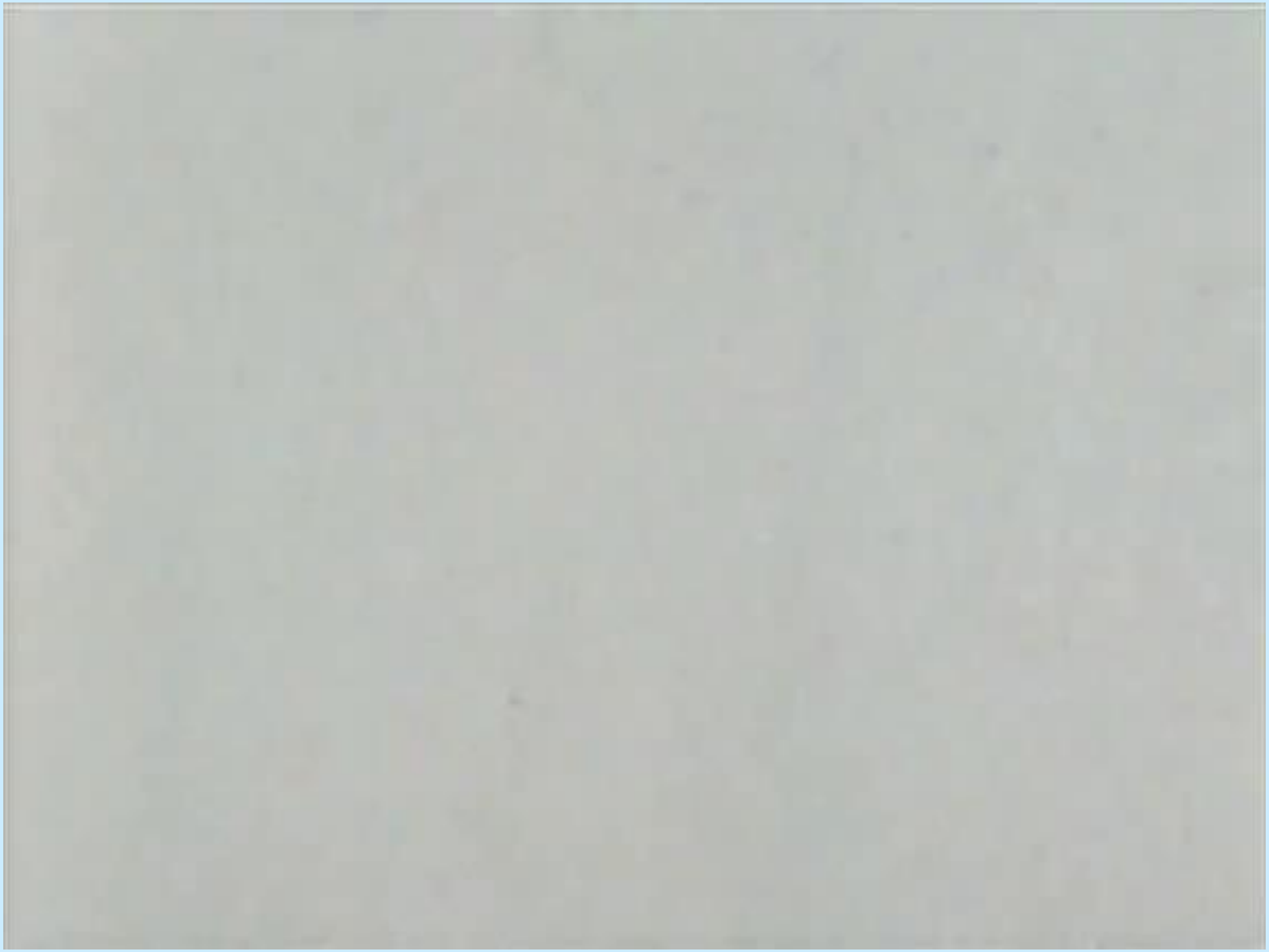
| Method | Duration of use | Accuracy & precision | Cost | Advantages | Limitations |
|---|---|---|---|---|---|
| Food recall | 1 day | Interviewer-dependent[a] | Low | Easy to administer, suitable for assessing short-term dietary interventions | Low representability, labor-intensive analysis[a] |
| Food diary | 3–7 days | Low due to under-reporting and mis-quantifying food intake[a] | Low | Easy to administer, suitable for assessing short-term dietary interventions | Participant burden, labor-intensive analysis[a] |
| Food frequency questionnaire | 3–12 months | Low due to "non-memory-based" response | Low (develop in-house) to moderate (use commercially available questionnaire) | Easy to administer, suitable for epidemiological studies and ranking individuals, can be tailored for specific populations, nutrients or food groups | Less accurate for absolute intake estimation |
| Observed intake | Flexible | High with food weighing | Low | Tightly controlled environmental factors | Creates less realistic eating behavior, repetitive testing alters "real" intake |
| Biomarkers | Hours to days for nutrient/ metabolite turnover, months for biomarker abundance in tissues | High | High | Objective and unbiased, high specificity | Limited well-validated markers, often requires invasive sampling (e.g. blood draw), confounded by respondent characteristics |
| Mathematical modeling and intake-balance method | Flexible | Limited due to multiple assumptions in modeling | Low (based on demographics and anthropometry) to high (based on precise body composition and energy expenditure measurements) | Objective and unbiased, ongoing tracking allows real-time assessment of intake | Labor-intensive for body composition and energy expenditure measurements, no consumption data on specific nutrients |

[a] Possible improvements with computer-, internet- or image-assisted technology.

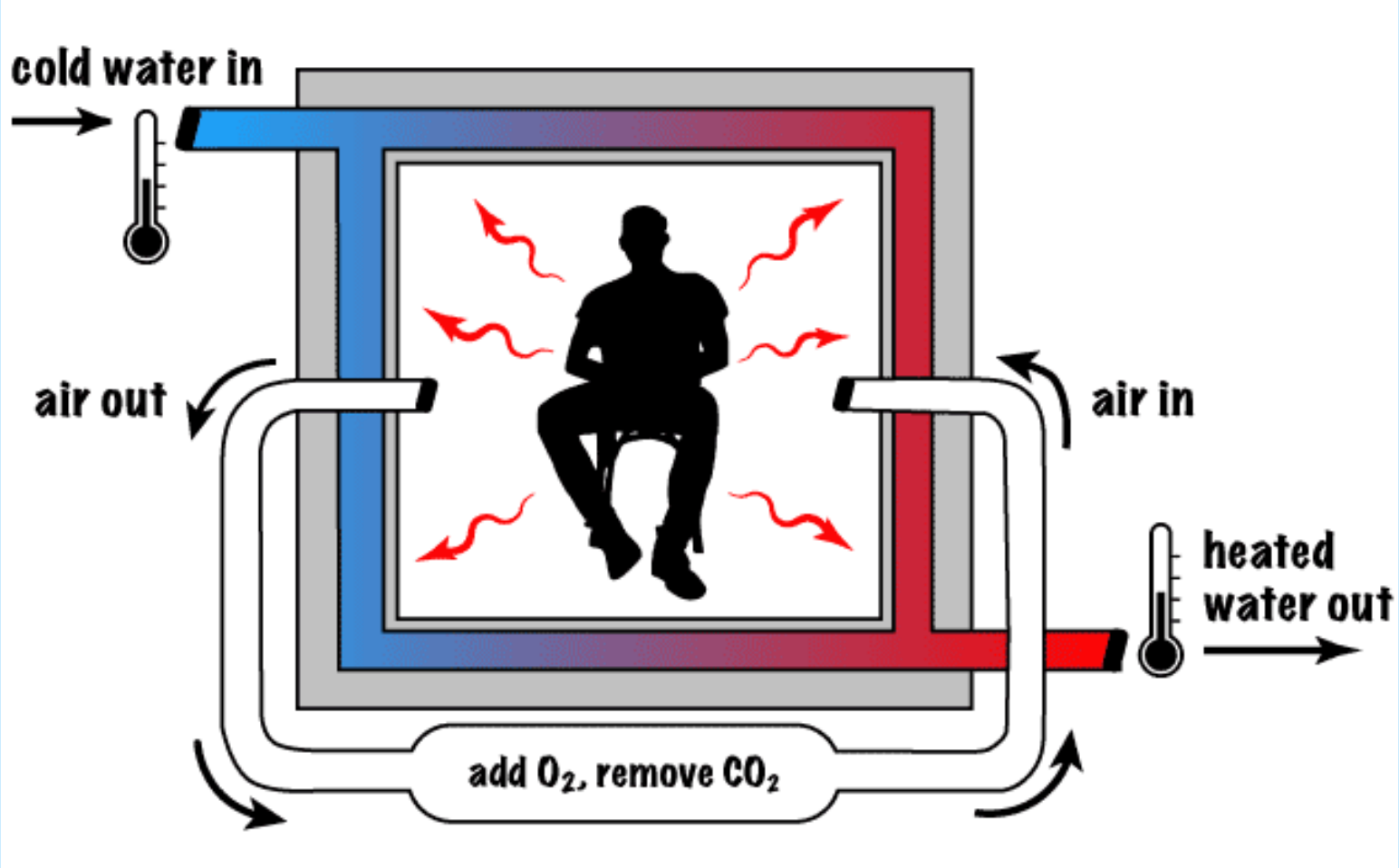
**Table 2** — Summary of methods to measure energy expenditure (EE).

| Method | Duration of use | Accuracy & precision | Cost | Advantages | Limitations |
|---|---|---|---|---|---|
| Direct calorimetry | Hours to several days | High except with intense physical activity or temperature outside the thermoneutal zone | High due to equipment set up and maintenance | Direct measure of heat production, complete control of environmental factors | Technically demanding, unable to detect acute changes, respondent restricted to confined space |
| Whole-room respiratory chamber | Hours to several days | High | High due to equipment set up and maintenance | Real-time minute-by-minute data, allow measurement of components of EE and substrate utilization | Technically demanding, respondent restricted to confined space |
| Metabolic cart | Hours | High for resting metabolic rate, moderate when estimating total daily EE | Moderate | Quick response time, easy to operate, feasible in clinical setting | Restricted respondent mobility |
| Doubly labeled water | 4—21 days | High | High due to isotope cost | Gold standard in free-living conditions, applicable to wide range of protocols | No time-course data, unable to differentiate components of EE |
| Physical activity log | 3—7 days | Low due to significant errors in extrapolating activity data to EE estimation | Low | Easy to administer | Participant burden may compromise data quality |
| Kinematic measurements | Flexible | Low due to significant errors in extrapolating movement data to EE estimation | Low to moderate | Easy to administer, objective and unbiased | Pedometers provide no data on patterns and intensity of physical activity |
| Heart rate monitoring | Flexible | Moderate at a group level, low at individual estimations | Low to moderate | Easy to administer, objective and unbiased | Requires individualized calibration, significant loss of data points |
| Ventilation monitoring | Hours | Low to moderate | Low to moderate | Less sensitive to physical and mental confounders | Low applicability in free-living conditions |

# Přímá kalorimetrie?



# Přímá kalorimetrie!



# Nepřímá kalorimetrie