Regulation

Regulation at the level of the cellular

Compartmentalization: some enzymatic reactions are separated in different compartments; characteristic of eukaryotes; transporters which control the entry to the compartment regulate indirectly the enzymes there

Benefits:

1. it ensures different milieu
2. the enzyme do not need to share the substrate in the cytosol
3. individual enzyme regulatory options
4. membrane – associated processes (terminal oxidation, citP450)
5. cascading system: eg. formation of proteins: nucleus – transcription
   RER – translation
   Golgi - amendment

Regulation at the level of the cellular

Multi enzyme systems: considered as *a* compartment (*compartmentalization)*

- intermediates are transported directly from active site of an enzyme to the next, resulting in increased efficiency and less possibility of error
- high local concentration can be achieved with a substantially lower relative cell concentration
- thereby coordinated regulation of more enzymes can be achieved
- examples: fatty acid synthase complex, pyruvate dehydrogenase

Regulation at the level of the tissue

- there is a permanent material, information, energy flow between the cell and the distal tissue (and with the cell itself also): integrated neuroendocrine regulation

- the cell picks up, integrates and summarizes the information by its receptors

it regulates its own operation and works unit with the organism

Regulation at the level of the tissue

Forms:

1. **on intracellular receptors:**

- long-term effects (days): possibility for accommodation
- steroid hormones, T3/T4
- hormone-responsive elements in nuclear DNA

2. **on cell membrane receptors:**

- short-term effects, instantaneous regulation
- receptor: seven-transmembrane proteins (metabotropic)
  one transmembrane proteins - Tyr kinase
- signaltransduction: G proteins
  PIP_2 system
  ras proteins
  Tyr kinases

Regulation at the level of the organism

Requirements:

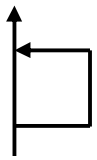
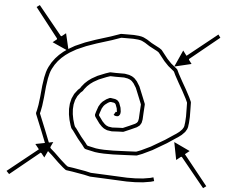
- opened system
- organised – low entropy level
- conservative
- adaptation is provided for long term – at the level of individuals as well

Levels of regulation:

- nuclear
- chemical:
  - enzymatic: K_M-type (phophorylation) and V_{max}-type (new enzyme synthesis)
  - substrate level – first order reaction
  - non-enzymatic – pathological (glycation, free radical formation)

Regulation at the level of the organism

Biochemical regulation: signs of organisation:

- consecutive: A → B → C → D
- divergency (anabolism): A → B, A → C
- convergency (catabolism): A → C, B → C
- shunts: 
- cycles: 

Regulation at the level of the organism

Adaptation during starvation:

- afferent events: stomach wall streching, gastrointestinal hormones, low blood glucose level
- center: hypotalamus
- efferent events:
  - hypotalamo-hypophyseal system:
    ACTH-adrenal cortex: glucocorticoids
    TSH: T_3/T_4
  - pancreas: glucagon: (blood glucose)
    insulin (blood glucose, acetyl-choline)
  - adrenal medulla: adrenaline, noradrenaline

Regulation at the level of the organism

- tissue metabolism during starvation:

LIVER: until 24 h glycogen in the liver + gluconeogenesis + formation of ketone bodies

glycogenolysis: glycogen phosphorylase

gluconeogenesis: phosphofructokinase II

inhibited glycolysis: phosphofructokinase II

fatty acid oxidation (free fatty acids from adipose tissue)

formation of ketone bodies from acetyl-CoA precursor comes from fatty acid oxidation

ADIPOCYTE: degradation of triacylglycerols: hormon sensitive lipase

MUSCLE: glycogenolysis: phosphorylase

glycolysis: usage of glucose-6-phosphate

protein degradation: Ala-cycle supply glucoplastic AA for the liver

- energy supply during starvation:

BRAIN: glucose, ketone bodies (fatty acids cannot pass the blood-brain-barrier)

HEART MUSCLE: fatty acid oxidation , ketone bodies , glucose

SKELETAL MUSCLE: glycogenolysis, protein degradation

Regulation at the level of the organism

Adaptation at enhanced food intake:

- regulation: insulin

  LIVER: active glycogenesis
  inhibited gluconeogenesis
  active glycolysis
  active fatty acid synthesis
  inhibited ketone body formation
  active synthetic pathways
  cholesterol synthesis
  biotransformation

  ADIPOCYTE: synthesis of triacylglycerols

  MUSCLE: active glycogenesis
  active glycolysis
  synthesis of proteins

Regulation at the level of the organism

Adaptation at stress situation:

- Canon-type fight or fly stress reaction + theory of Selye János
- regulation
  - adrenaline from adrenal medulla, noradrenaline from CNS
    gluconeogenesis + glycogenolysis
    heart: positive crono-, dromo-, batmo-, inotrop - tachycardia
    dilatation of bronchus – tachypnoe
    inhibited gastrointestinal tract
    dilatation of pupillae
    enhanced blood supply of muscle, but more vazospazm later
  - hypotalamo-hypophyseal system : ACTH-adrenal cortex-glucocorticoids
    enhanced effect of adrenaline, noradrenaline
    gluconeogenesis
    enzyme induction
    decreased inflammatory processes

Regulation at the level of the organism

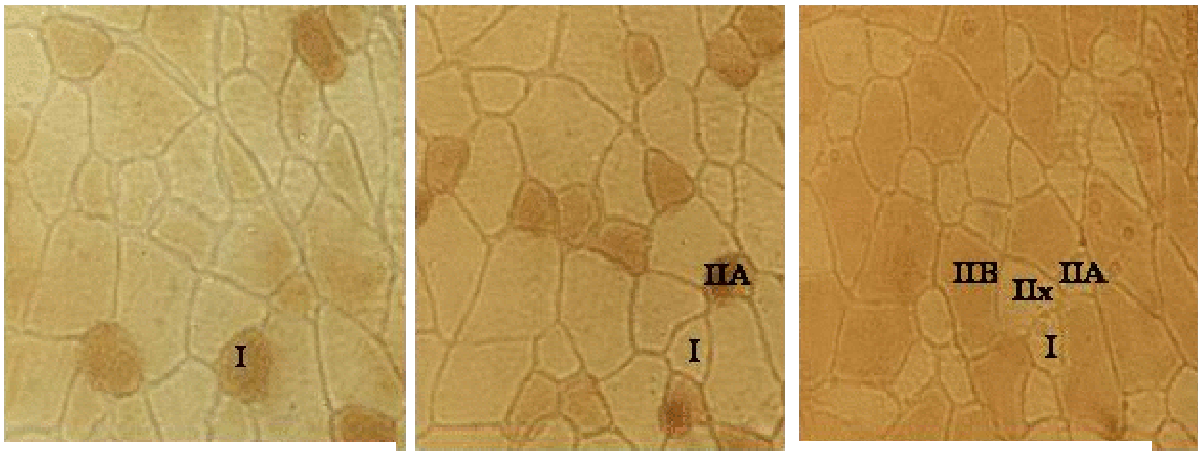
Adaptation during physical activity:

SKELETAL MUSCLE:

red muscle (oxidative fibres): good blood supply (vessels β_2 receptors), high level of mioglobin, glycogenolysis – aerob pathway

white fibres (glycolytic fibers): glycolysis – anaerob pathway

types of muscle fibers



slow-oxidative fast - oxidative fast - glycolytic

Regulation at the level of the organism

Adaptation during pregnancy:

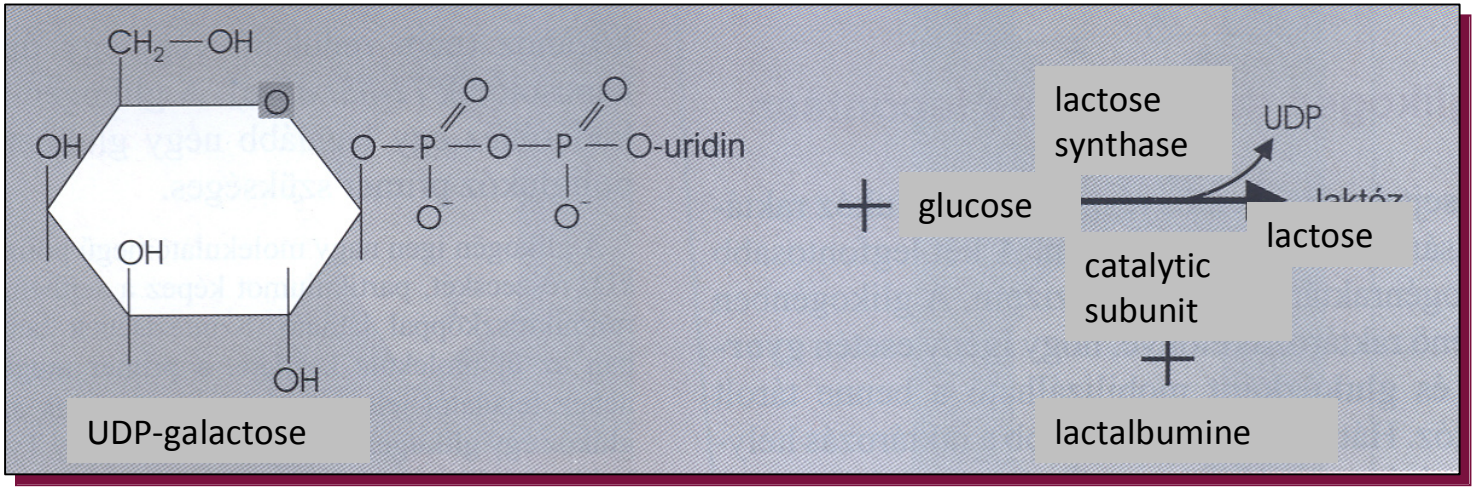
1. trimester:
   corpus luteum gestationis: progesterone: support of uterus mucosa
   development of breast milk ducts
   estrogene
   low level of FSH: no formation of new follicles
   LH increases: for milk production (lactation): breast milk ducts formation
2. trimester:
   formation of placenta: atrophy of corpus luteum
   production of estrogens and progesterone
   + Human Placentar Lactogene: GH effect (diabetes during pregnancy)
3. trimester:
   low level of progesterone at delivery
   prostaglandins-induction of delivery (uterus contractions)
   oxitocine: uterus contractions

Regulation at the level of the organism

Adaptation during lactation:

High level of LH: inhibited follicle maturation

breast milk production: lactose synthase: synthesis of α-lactalbumine, glucose is the substrate of lactose synthase (lack of α-lactalbumine: substrate is the N-acetil glucoseamine- glucoprotein synthesis)



Oxitocine: ejection of milk from milk ducts during nursing/feeding

Regulation at the level of the organism

Limits of adaptation:

adaptation depends on the amplitude and frequency of alteration rate and
power of adaptation is important
set to the setpoint (minimalisation of overreactions)
very slow alterations moves the evoluation due to the selection
decreased adaptation ability:

infancy:	lack of blood-brain-barrier
	immatured conjugation capacity of the liver not fully expressed enzymes
senior:	higher fluctuation around the setpoint
	parasympatic tone sensitvity increased
	organ capacity decreased (liver, heart)
	accumulation of toxic metabolic intermediers
	water/fat ration decreased
	blood supply decreased

Supraindividual regulation:

Above individuals – in commune

for ex.: communication among state forming ants

Very severe change in environment (hit of meteor) in this case the most developed creatures could not survive , while the less-developed can

in case of nuclear disaster arthropods are in better situation than mammals

Supraindividual regulation:

Biochemical interpretation of health and disease:

health:

- enzymes of the organism work in perfect coordination
- regulation is coordinated – in balance
- organism protects aganist high entropy
- adaptation according to endogen and exogen changes

disease:

- adaptation problem of the inbalaned organism
- death: exergon, increase of entropy

  give up of endergon processes

  this a process, not one time point