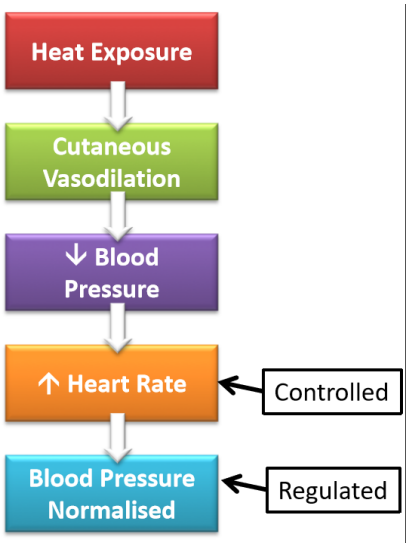
MEDI211 Lecture Notes

Lecture 1 - Homeostasis



Control vs Regulation

Physiological Control: – Modifying physiological functions to support life, e.g. heart rate

Physiological Regulation (result): – 'regulate' a variable (e.g. blood pressure) in a manner that supports life

- Control involves interpreting and responding to information –Afferent signals from receptors (receivers of error)
- System error identification –Required for response
- Means through which to react to error –Efferent signals (to effector

Types of Control

- On / Off Control: Effector is either maximally turned on, or maximally turned off –e.g. 211 Brand hot water heater thermostat
- Proportional Control: Output signal is in direct proportion to the stimulus supplied

Types of Feedback

Negative Feedback:

- Most homeostatic control mechanisms are negative feedback mechanisms
- Output stops/reduces original effect of stimulus
- Direction of change is opposite to direction of initial change

Positive Feedback:

- Output enhances original effect of stimulus
- Direction of change is the same as the direction of initial change
- Purpose: control infrequent events that do not require regulation

Feedforward:

- Neural anticipatory signal sent to prime the control mechanism
- Initiated from brain via autonomic nervous system
- e.g. starting exercise causes ANS to prepare - ^HR & ventilation

Other Considerations for Homeostasis

- Redundancy: the more critical the parameter, the more systems dedicated to its preservation
- Equilibrium: parameter is well-regulated –No energy expense
- Acclimatisation: setting a new equilibrium –e.g. changes in breathing in response to high altitude

Lecture 2 - Metabolism 1

Encompasses all chemical reactions by which the body obtains and spends energy from nutrients

Oxidation and Reduction

- Oxidation: losing electrons
- Reduction:gaining electrons
- Oxidation must be controlled in biological systems to avoid dangerous rates of heat production
- Oxidation in cellular metabolism results in ATP formation (energy $$)
- Not 100% efficient, energy wasted energy as heat

Metabolic Coupling: One metabolic reaction cannot proceed without the reactions it is linked to

1kcal= 4.2kJ

Calorimetry

Bomb Calorimetry: measures kcal in food – C and H bonds break and energy released as heat

- Direct calorimetry: heat provides a measure of food energy composition as kcalories:
- Indirect calorimetry: Measure of O2 consumption and CO2 production as an indicator of heat production and O2 consumption is directly proportional to heat production, heat comes from cellular respiration

Respiratory Quotient RQ = CO_2/O_2

Ratio of moles CO2 produced per mole O2 consumed at the tissue level

- Eg. Fat $C_{16}H_{32}O_2 + 23O_2 \rightarrow 16CO_2 + 16H_2O$ – RQ pure fat diet = 16/23 = 0.7

Energy Balance

Chemical transformations always result in a loss of free energy available to drive metabolic processes

Gibbs Free Energy: G - Free energy available to drive metabolic processes

Total internal energy: E – Wasted energy (mainly lost as heat) (T.S)

E = G + TS

Energy Expenditure: Metabolic Rate

Resting Metabolic Rate:

- Estimate of energy required while at rest
- Healthy young 70 kg human requires 2100 kcal/day to sustain metabolism
- Number of calories required can rise in response to heavy exercise, cold exposure, illness
- Measured by indirect calorimetry

Basal Metabolic Rate:

- A clinical measurement of metabolism, measured under several standardised conditions
- AM measurement after good sleep
- Fasted 12-hrs
- 1hr quiet rest
- 25OC air temp

Lecture 3 - Metabolism 2

Carbohydrates

Monosaccharides: small molecules (monomer) directly absorbed by intestine

Disaccharides: – Some are non-digestible and cannot be directly absorbed by intestine

Oligo and polysaccharide digestion: Starts with salivary amylase in mouth then pancreatic amylase in small intestine

Products of amylase digestion still too large to be absorbed thus are broken down into monosaccharides on the brush border of small intestine lumen

Lipids

- Triglycerides = 3 free fatty acid chains + glycerol
- Small congregations of lipid molecules held in water = emulsion droplets = micelle
- Glyconeogenesis: converting glucose to glycogen
- Glycogenolysis: the breakdown of glycogen to glucose
- Glycolysis: glycerol -> pyruvate

Lipoprotein Lipase (LPL)

- Exported from cells to vessel endothelium, held within plasma membrane
- Hydrolyses trigs in chylomicrons → FFA + glycerol
- Insulin promotes lipid uptake and conversion to trigs for storage

Protein Absorption

- Specialised transporter proteins allow peptides to cross the membrane from lumen into intestinal cell with the help of Co-transport: H+
- Peptidases: enzymes within cytoplasm of intestinal cell degrade peptides into AAs
- AAs exit basal membrane via AA transporter into interstitial space.

Insulin (PROMOTES GLYCOGENESIS)

Insulin secretion from the pancreatic βcell, stimulated by the presence of glucose and some AAs

- Insulin receptor (IR) is a tyrosine kinase receptor made up of:
- 4 sub-units bonded, including; 2 αchains: extracellular and 2 βchains: extracellular, membrane spanning, intracellular

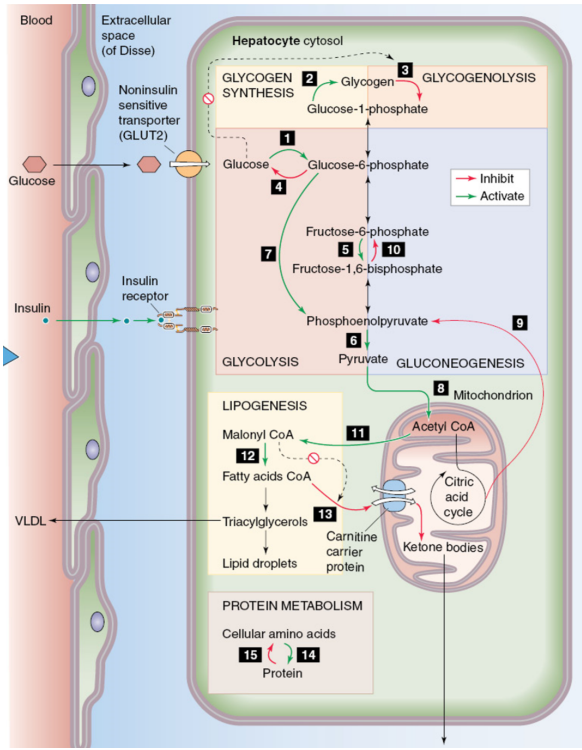
In the Liver

1. promotes glycogenesis and inhibits glycogenolysis

- Glucose can enter the liver via GLUT2 transporter (insulin insensitive)
- Insulin binds to receptor on hepatocyte →
- Activates transcription of enzymes: *Glucokinase and Glycogen synthase* which promotes glycogen synthesis
- Insulin and glucose inhibit: *Glycogen phosphorylase and Glucose-6-phosphatase* which prevents glycogen breakdown (glycogenolysis)

2. Promotes carb metabolism

- Insulin binds to receptor on hepatocyte which activates enzymes that allows pyruvate → acetyl CoA (in mitochondria) → Krebs cycle



- Excess stored as glycogen after requirements for carb metabolism are met

3. Promotes lipogenesis

- Pyruvate → Acetyl CoA → lipogenesis pathway → FFA → trigs
- Some trigs packaged into VLDL (lipoprotein) leave liver into circulation
- Others remain as storage

4. Inhibits lipolysis & ketogenesis:

- Insulin inhibits oxidation of FFAs
- Insulin prevents FFA carrier into mitochondria (no ketones)
- Explains why we can make ketones during starvation

5. Promotes protein synthesis, inhibits proteolysis

In a muscle cell

Insulin binds to IR → GLUT4 transporter incorporated in cell wall → glucose enters cell
**everything else is the same process as in the liver*

In an adipocyte

Insulin binds to IR → GLUT4 transporter incorporated in cell wall → glucose enters cell
1. Insulin promotes glycolysis
2. Insulin promotes lipogenesis: pyruvate → Acetyl CoA → fatty acids (shuttled into lipogenesis pathway) → trigs= lipid droplet
3. Insulin inhibits Hormone Sensitive Lipase (HSL initiates lipolysis)
4. Promotes synthesis of lipoprotein lipase, exported to endothelial cell to breakdown trigs in chylomicrons = free FA → into adipocyte (lipogenesis)

Lecture 4 - Metabolism 3

Glycogenolysis

The breakdown of glycogen to glucose to be used for metabolism

Skeletal Muscle:

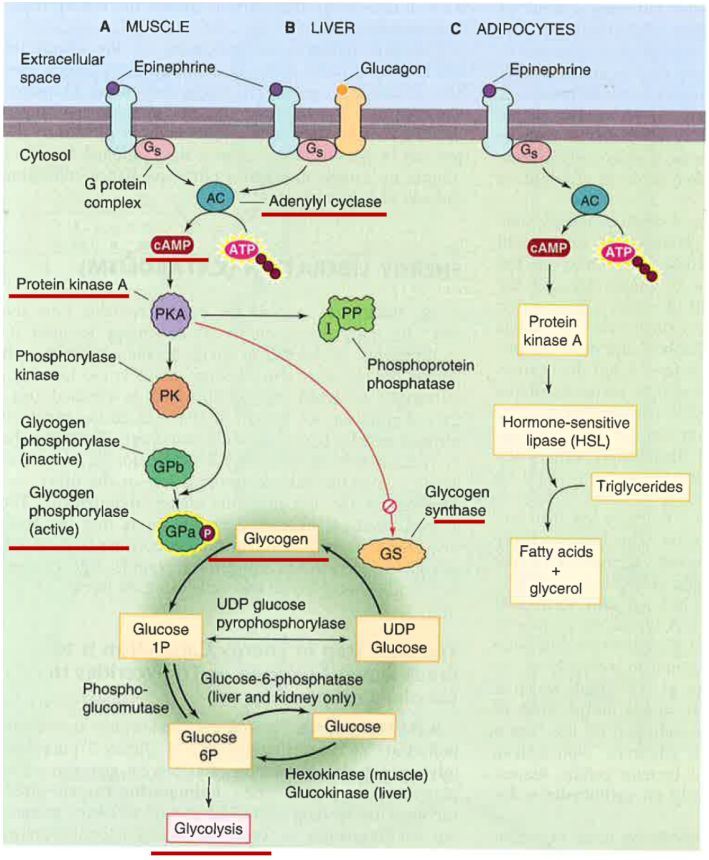
- Neurotransmitter epinephrine (adrenaline) released during low blood glucose levels (BGL)
- Binds to β-adrenergic receptors (G protein-coupled receptors (GPCRs)) on muscle cell wall
- G-protein complex stimulates adenylyl cyclase/cAMP/protein kinase (PK) pathway
- Glycogenolysis: Glycogen → glucose-1-phosphate → G-6-P → glycolysis

Liver:

- Majorly triggered by glucagon, glucagon receptor on hepatocyte cell wall
- Also, epinephrine released during low BGL (binds to β-adrenergic receptors on hepatocyte wall)
- G-protein complex stimulates adenylyl cyclase/cAMP/protein kinase (PK) pathway
- Pathway inhibits glycogen synthase enzyme (cannot create Glycogen)

Lipolysis in Adipocytes: Triglyceride Liberation

- All same as liver/muscle cells however Protein kinase activates hormone-sensitive lipase (HSL)
- Hydrolyses triglycerides → fatty acid + glycerol = lipolysis
- FFAs diffuse out of adipocytes into bloodstream and transported in the blood bound to carrier protein to site of demand.
- Activated in response to: low insulin (Insulin inhibits HSL), or epinephrine



Glucogen

Secreted from pancreatic α cells when insulin is low to increase blood glucose levels

- Primarily acts on liver: Glycogenolysis, gluconeogenesis, ketogenesis, lipolysis, proteolysis
- Some action on cardiac and skeletal muscle: glycogenolysis, adipose tissue: lipolysis
- Generally, antagonist of insulin effects

Glucose Synthesis by Liver

- Glucagon binds to glucagon receptor on hepatocyte
- Activates adenylyl cyclase/cAMP/protein kinase (PK) pathway
- Inhibits: glucokinase, glycogenesis, glycogen synthase (opposite to insulin), glycolysis
- Promotes glycogenolysis (glycogen breakdown):
- Activates glycogen phosphorylase and glucose-6-phosphatase
- Promotes gluconeogenesis: Activates enzymes for pyruvate -> glucose

Fat Oxidation in Liver

- Stimulates FA stores into mitochondria (β ox)
- Activates carnitine carrier protein
- FFAs can also enter cell from circulation → carrier
- Prevents acetyl CoA from entering lipogenesis pathway and activate enzymes that support gluconeogenesis pathway
- Promotes ketogenesis:
- Can occur if the rate of FA transport exceeds TCA capacity
- Incomplete FA oxidation → ketone bodies
- Exit hepatocyte to fuel other tissues