METABOLISM
Introduction

• The fate of dietary components after digestion and absorption constitute metabolism – regulated by metabolic pathway

• 3 types:

  anabolic pathways- Synthesis of compound – e.g. synthesis protein, triacylglycerol, and glycogen

  Catabolic- breakdown of larger molecules- involve oxidative action, mainly via respiration chain

  Amphibolic pathways – link the anabolic and catabolic pathways
Introduction

• Knowledge of normal mme – important to understand abnormalities underlying disease

• Normal mme – adaptation to periods of starvation, exercise, pregnancy and lactation

• Abnormal mme- result from nutritional deficiency, enzyme def, abnormal secretion of hormones, the action of drugs and toxins – e.g- diabetes mellitus
Measuring energy changes in biochemistry

Reaction that takes place as many part of biochemical processes – hydrolysis of the compound adenosine triphosphate (ATP)
Measuring energy changes in biochemistry

- This reaction release energy - allow energy requiring reaction to proceed
- Adenosine 5’ triphosphate
- Molecular unit of currency of intracellular energy transfer
NAD+, NADH

- Nicotinamide adenine dinucleotide
- Coenzyme found in all living cells
- In mme, involved in redox reactions, carrying electrons from one reaction to another
- NAD+ - an oxidizing agent – accept e and become reduced - forming NADH
- NADH-reducing agent to donate e
Major products of digestion

• Product of digestion – glucose, f.a and glycerol, and aa

• In ruminants-cellulose is fermented by symbiotic microorganisms to short chain f.a (acetic, propionic, and butyric) – mme is adapted to use this f.a as major substrates.

• All products are metabolized to acetyl-COA – then oxidized to citric acid cycle.
Carbohydrate → Digestion and absorption → Simple sugars (mainly glucose)

Protein → Digestion and absorption → Amino acids

Fat → Digestion and absorption → Fatty acids + glycerol

Digestion and absorption → Catabolism → Acetyl-CoA

Acetyl-CoA → Citric acid cycle

Citric acid cycle → 2H → ATP → 2CO₂
DIGESTION AND ABSORPTION OF CARBOHYDRATES
Glycogen, starch, sucrose

storage

Glucose

oxidation via pentose phosphate pathway

Ribose 5-phosphate

oxidation via glycolysis

Pyruvate
Carbohydrate metabolism

• In aerobic condition- glucose is metabolized to pyruvate through glycolysis and continued to acetyl coa to enter citric acid cycle to complete oxidation to C02 and H20- linked to the formation of ATP through oxidative phosphorylation

• Glucose- major fuel of most tissues
Metabolic pathways at different levels of organization

- Amino acid and glucose – absorbed and directed to the liver via hepatic portal vein
- Liver – regulate the blood conc of most water-soluble metabolites
- Excess of glucose is converted to glycogen (glycogenesis) or fat (lipogenesis)
- Between meals, liver maintain blood glucose conc. by glycogenolysis
- Together w kidney – convert non carb metabolites (lactate, glycerol, and aa) to glucose (gluconeogenesis)
Role of liver

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• Maintainance of adequate conc of blood glucose- vital- major fuel in brain and the only fuel for erythrocytes

• Synthesize major plasma protein (e.g. albumin) and deaminates excess aa forming urea- to the kidney
Skeletal muscles

- Glucose for fuel – form lactate and CO2
- Stores glycogen as fuel – use in muscular contraction and synthesizes muscle protein fr. Plasma aa
- Muscle~ 50% of body mass- protein storage- can be used to supply aa for gluconeogenesis
Glycolysis & the oxidation of pyruvate

• Glycolysis – principal route for glucose mme and the main pathway for the mme of fructose, galactose, and other carbohydrates derived from the diet.

• Can fx aerobically or anaerobically

• Can provide ATP without 02 – allow muscle perform at very high levels when 02 supply is not sufficient – and allow tissue to survive during anoxic episode
Glycolysis

- Oxidation of glucose or glycogen to pyruvate and lactate
- Similar to the fermentation in yeast cells
Phosphorylation of glucose and conversion to two molecules of glyceraldehyde-3-phosphate: 2 ATPs are used to prime these reactions.

Conversion of glyceraldehyde-3-phosphate to pyruvate and coupled formation of four molecules of ATP.

Aerobic conditions: 2 Acetyl-CoA

Anaerobic conditions: 2 Lactate

Anaerobic glycolysis in contracting muscle

Alcoholic fermentation in yeast

Animals and plants in aerobic conditions
End Product of Glycolytic Pathway

- In the presence of O2 - Aerobic

\[
\text{Glucose} + 2\text{NAD}^+ + 2\text{ADP} + 2\text{P}_i \rightarrow 2\text{pyruvate} + 2\text{NADH} + 2\text{H}^+ + 2\text{ATP} + 2\text{H}_2\text{O}
\]

- NADH will enter the electron transfer chain and produce 3 more ATP
- \(2\text{NADH} \rightarrow 6\text{ATP}\)
- Thus total ATP produced : 8ATP
In anaerobic phase

- Without O2, NADH cannot be reoxidized in e transport chain
- At the same time, cell need NAD+ to continue glycolytic cycle
- Therefore, oxidization of NADH to produce NAD+ occur through conversion of pyruvate to lactate (without producing ATP) by lactate dehydrogenase enzyme
- Therefore, total net ATP produced, 4-2=2 ATP
Regulation of Glycolysis

1) Substrate

**Glucose** – when conc of glc increased, enzymes involved in utilization of glc are activated (glucokinase, phosphofructokinase-1 (PFK) and pyruvate kinase). enz involved for producing glc (gluconeogenesis) are inhibited
2. **Hormone**

- The secretion of insulin enhances the synthesis of the key enzyme responsible for glycolysis.
- Other hormones like epinephrin and glucagon inactivate pyruvate kinase, and thus inhibit glycolysis.

3. **End products**

- PFK are inhibited by citrate and ATP, but activated by AMP.
- AMP acts as the energy indicator of energy status of cells.
- ATP is used in energy requiring processes – increasing AMP concentration.
- Normally the concentration of ATP is 50 times higher than AMP. Small decrease in ATP, lead to several fold increase in concentration of AMP. Thus activated PFK to allow more glycolysis to occur.
LIST CHEMICAL THAT INHIBIT PARTICULAR ENZYME IN GLYCOLYSIS AND THEIR MECHANISM OF INHIBITION
• **Rapoport-Luebering Shunt or Cycle**

• Part of glycolytic pathway in RBC in which 2,3 Biphosphoglycerate is formed as an intermediate between 1,3-BPG and 3-BPG.

Glycolytic pathway in RBC differ with the other tissues...
1. Role in Hb
   • In adult Hb- 2,3-BPG will reduce affinity of HB to O2 – excellent O2 carrier
   • In fetal HB – Conc of BPG is low, affinity to O2 is more

2. Role in hypoxia
   • Tissue hypoxia – lead to increase conc of BPG in RBC, thus enhancing unloading of O2 from RB to tissue
Fates of pyruvic acid (PYRUVATE) formed from glucose

1. With O2, oxidatively decarboxylated to acetylCoA – ready to enter kreb cycle (by pyruvate dehydrogenase)

2. Absence of O2, converted to lactic acid
   - occurs in the skeletal muscle during working conditions
   - pyruvate store H+ from NADH to form NAD+ needed in the glycolysis
   - pyruvate is thus reduced to lactic acid
Anaplerotic reactions

• Sudden influx of acetyl coa- deplete the source of OAA required for the citrate synthase reaction
• Anaplerotic – filling up reactions
• 2 reactions: PA is converted to OAA by pyruvate carboxylase
• Through malic acid formation
Energetics

• 1 molecule of glc produce 2 PA in glycolysis
• By oxidative decarboxilation, 2PA will produce 2 acetyl coa and 2NADH
• 2NADH will be oxidized to 2 molecule of 2NAD+ producing 6 ATP molecules in respiratory chain
Biomedical importance of glycolysis

- Provide energy
- Importance in skeletal muscle - can survive anoxic episode
- Heart muscle - adapted for aerobic condition only, thus has poor survival under ischaemic condition
- Fast growing cancer cells - rate of glycolysis very high, produces more PA than TCA cycle can handle. >>>> of PA lead to >>> lactic acid production - local acidosis - interfere with the cancer therapy
- Hexokinase deficiency and pyruvate kinase deficiency can cause haemolytic anemia
Utilization of glucose in the body

• After absorption of monosaccharides into the portal blood, it passes through the ‘liver filter’ – before ‘presented’ to other tissues for their energy

• In liver:
  Withdrawal of carb from blood
  Release of gluc by liver into the blood
  These processes – finely regulated in the liver cells
  Hepatic cells – freely permeable to glucose
  Other cell – active transport
  Insulin increases uptake of glucose by many extra-hepatic tissues as skeletal muscle, heart muscle, diaphragm, adipose tissue, lactating mammary gland, etc.
Citric acid cycle

- TCA (tricarboxylic acid cycle), krebs cycle
- Final common pathway for breakdown of carb, prot and fats
- Acetylcoa derived from glc, f.a and aa
- Aerobic process, anoxia or hypoxia cause total or partial inhibition of the cycle
- H atoms produced will be transferred to electron transport system to produce ATP molecules
TCA cycle is amphibolic in nature. Why?

TCA has dual role:

• Catabolic – 2 acetyl coa produced are oxidized in this cycle to produce CO2, H2O, energy as ATP

• Anabolic and synthetic role - Intermediates of TCA cycle are utilized for synthesis of various compounds
Anabolic and synthetic role

1. Synthesis of non essential aa
2. Formation of glucose
3. Fatty acid synthesis
4. Synthesis of cholesterol and steroids
5. Heme synthesis
6. Formation of aceto acetyl coa
TASK

Calculate total ATP produced from glycolysis and TCA cycle per one glucose
Gluconeogenesis

- Glucose is major fuel for some tissues – brain, rbc, testes, renal medulla and embryonic tissues
- Supply of glucose can come from diet, glycogen storage. But glycogen storage are limited – need supply from another sources
- Gluconeogenesis – converts pyruvate and related 3-4C compounds to glucose
- Generally a reverse process of glycolysis
- Mainly in liver, and in renal cortex
Substrate for gluconeogenesis

1. Glucogenic amino acids
2. Lactates and pyruvates
3. Glycerol
4. Propionic acid – important in ruminant
METABOLISM OF GLYCOGEN

- Glycogen – storage of glucose
- Stored in animal body esp in liver and muscles
- Mobilized as glucose whenever the body tissues require
Why store glycogen?

• Insoluble – so will not disturb intracellular fluid content and does not diffuse from its storage site
• Has a higher energy level than glucose
• Readily broken down under influence of enzyme
Glycogenesis

• Formation of glycogen from glucose
• Usually occur in liver and skeletal muscle – can occur in every tissue for some extent
• Liver may contain 4-6% of glycogen per weight of the organ when analysed shortly after a meal high in carbohydrate
• After 12-18 hours of fasting- liver almost depleted of glycogen

- **Glycogen synthase** is the key enzyme
Glycogenolysis

• Breakdown of glycogen to glucose
• Involve phosphorylase enzyme
TASK

• LIST THE GLYCOGEN STORAGE DISEASE IN ANIMALS AND EXPLAIN THE MECHANISMS OF THE DISEASE