

UNIVERSITY OF PAPUA NEW GUINEA
SCHOOL OF MEDICINE AND HEALTH SCIENCES
DIVISION OF BASIC MEDICAL SCIENCES
DISCIPLINE OF BIOCHEMISTRY AND MOLECULAR BIOLOGY
PBL SEMINAR
ANAEROBIC METABOLISM - An Overview

How is Glucose metabolized in mammalian tissues?

- Glycolysis is the major pathway for Glucose metabolism
- Glycolysis can occur either in the:
 - Presence of Oxygen (**Aerobic Glycolysis**) and Mitochondria
 - Absence of Oxygen (**Anaerobic Glycolysis**)
- Anaerobic Glycolysis is of major significance, because:
 - It provides Skeletal Muscle with ATP at low oxygen tension,
 - It allows tissues with significant Glycolytic ability to survive Anoxic episodes
- Cardiac Muscle, has relatively Poor Glycolytic Ability and poor survival under conditions of **Ischaemia**
- Extent and end products of Glycolysis of Glucose are different under Anaerobic and Aerobic conditions
- **Aerobic Glycolysis of Glucose:**
 - End product of Glycolysis is Pyruvate
 - Pyruvate is converted to Acetyl-CoA,
 - Acetyl-CoA is oxidized to CO₂ and H₂O within the mitochondria
 - TCA cycle and Electron Transport Chain are involved (Oxidative Phosphorylation)
 - Complete oxidation of one molecule of Glucose to CO₂ and H₂O under Aerobic Condition produces 36 to 38 molecules of ATP

What is the significance of ANAEROBIC GLYCOLYSIS?

- Under Anaerobic conditions the principal end product of Glycolysis is Lactic acid
- NADH formed by *Glyceraldehyde 3-phosphate Dehydrogenase* during Glycolysis (in the formation of 1,3-bisphosphoglycerate) must be converted to NAD⁺ if **Glycolysis** is to continue
- **Under Aerobic** condition NADH is converted to NAD⁺ in Electron Transport Chain
- **Under Anaerobic** condition, as in muscle during vigorous contraction, NADH is converted to NAD⁺ in the **Lactate Dehydrogenase (LDH)** reaction:



- Lactic acid then accumulates in the cell under Anaerobic condition
- When O₂ becomes available LDH reaction reverses to generate Pyruvate, which is converted by Pyruvate Dehydrogenase to Acetyl-CoA, which then enters the TCA cycle
- **LDH reaction in mammalian cells is a mechanism for conversion of NADH to NAD⁺ so as to allow Glycolysis to continue, and ATP to be produced, under Anaerobic conditions**

- **Example:**
 - Skeletal muscle during vigorous exercise: (**Cori Cycle**):
 - Lactate produced is transported in Blood to the Liver to be converted back to Glucose via Gluconeogenesis
 - Glucose formed is then returned once again via the blood to Skeletal Muscle to be metabolized to yield energy.

TAKE NOTE:

- During Anaerobic Glycolysis a **Total of 4 ATP** and **Net of 2 ATP** are produced per molecule of Glucose
- Consequently, to provide a given amount of ATP, much more glucose must undergo Glycolysis under Anaerobic conditions as compared with Aerobic conditions
- Phenomenon is known as **Pasteur effect**: – **that is, Rate of Glycolysis is Indirectly suppressed in the presence of Oxygen**
- **Fig 1** shows the different ways in which Glucose is metabolized within cells of different tissues of the body

What is the relationship between Intracellular pH and ANAEROBIC GLYCOLYSIS?

- Understanding the Glycolytic reaction catalyzed by **6-Phosphofructo-1-Kinase** (also called **Phosphofructokinase-1**) is needed to answer this question



- **Phosphofructokinase-1:**
 - Rate-limiting Enzyme and important Regulatory Site of Glycolysis
 - Reaction is Irreversible under Intracellular Conditions
- Most important **Negative Allosteric Effectors** are:
 - Hydrogen ions (Low pH), Citrate, ATP,
- Most important **Positive Allosteric Effectors** are:
 - AMP, Fructose 2,6-bisphosphate, and P_i
- Under Anaerobic conditions:
 - End product of Glycolysis is Lactic acid
 - Cells must dispose of Lactic Acid so as to prevent its accumulation
 - Excessive Glycolysis in tissues can lower blood pH causing Lactic acidosis
- Plasma membrane in a cell contains a Symport mechanism for transportation of Lactate and H^+ ions out of the cell into the blood
 - It is a regulatory mechanism that prevents accumulation of Lactate and H^+ ions in the cell, thereby preventing the lowering of pH in cells
 - Inhibition of Phosphofructokinase-1 by H^+ ions is also part of this mechanism
- In effect H^+ ions are able to shut off Glycolysis, the process that is responsible for decreasing pH in cells
- Removal of Lactic acid requires that blood is available to carry it away

- When blood flow is inadequate, (e.g., Heavy Exercise of Skeletal Muscle or Attack of Angina Pectoris in case of the Heart) the H^+ ions cannot escape from the cell fast enough
 - **Yet the need for ATP within such cells, because of lack of Oxygen, may partially over-ride the Allosteric Inhibition of Phosphofructokinase-1 by H^+ ions**
 - Anaerobic Glycolysis will proceed leading to accumulation of H^+ ions and Lactate in the cells, resulting in pain sensation (**Fig. 2**)
- **Examples:**
 - **Skeletal muscle:** Pain sensation can be removed by terminating the exercise, thus allowing for removal of excess Lactic acid from the muscle cells (**Cori cycle**)
 - **Heart:** Rest or Pharmacological agents that increase blood flow or decrease the need for ATP within cells may be effective

What is Lactic Acidosis and what causes it?

- **Lactic acidosis**, the most common form of metabolic acidosis, is characterized by elevation of Lactic Acid, decrease pH and low Bicarbonate concentration in Blood
- Lactic Acidosis: Overproduction or Underutilization of Lactate, or both
- Under Hypoxic condition, tissues respond with Increase in Anaerobic Glycolysis resulting in production of Lactate
 - Decrease O_2 availability therefore increases Lactate production and decreases Lactate utilization
 - Decrease in Lactate utilization can be due to liver diseases, ethanol, and a number of drugs
- Tissue Hypoxia occurs, during Shock, Convulsions, and in diseases involving circulatory and pulmonary failure
- Important to eliminate the cause of overproduction and/or underutilization of Lactic acid
- May involve restoration of circulation of oxygenated blood to affected tissues

What is ANGINA PECTORIS AND how is it related to MYOCARDIAL INFARCTION?

- Chest pain associated with reversible Myocardial Ischaemia is termed Angina Pectoris (literally, strangling pain in the chest)
- Pain is the result of an Imbalance between Demand for and Supply of blood flow to Cardiac Muscles and is most commonly caused by narrowing of Coronary Arteries
- Attacks usually occur during exertion, last about 1 to 15 minutes, and are relieved by rest
- Coronary Arteries involved are usually obstructed by Atherosclerosis (i.e., Cholesterol-rich arterial thickenings - Atheromas) or less commonly narrowed by spasm
- Myocardial Infarction occurs if the Ischaemia persists long enough to cause severe damage (necrosis) to the cardiac muscle
- Commonly, a blood clot forms at the site of narrowing and obstructs the vessel
- In Myocardial Infarction, tissue death occurs and the characteristic pain is longer lasting, and often more severe
- Nitroglycerin can relieve the pain cause by Myocardial Ischaemia of Angina Pectoris
- Nitroglycerin causes dilation of Coronary Arteries, improving O_2 delivery to the Heart and washing out accumulated Lactic acid in cardiac tissues
- Breakdown of Nitroglycerin produces Nitric Oxide (NO), a compound that relaxes smooth muscle, causing Veno-dilation throughout the body

- ❑ Reducing Arterial Pressure and allows blood to accumulate in the veins
- ❑ Resulting is decreased return of blood to the heart, and a reduced volume of blood the heart has to pump, which reduces the energy requirement of the heart
- ❑ In addition the heart empties itself against less pressure, which also spares energy
- ❑ Overall effect is a lowering of the O₂ requirement of the heart, bringing it in line with the O₂ supply via the diseased coronary arteries

What is Angina?

- ❑ Angina is Chest Pain or discomfort that occurs when blood flow to Cardiac Muscle is reduced
- ❑ Angina may feel like Pressure or a Squeezing Pain in the Chest, or Shoulders, Arms, Neck, Jaw, or Back, or a combination of any of these
- ❑ Angina may also feel like Indigestion
- ❑ Angina is a Symptom of Coronary Artery Disease (CAD)
- ❑ CAD occurs when Plaque builds up in the Coronary Arteries (Atherosclerosis),
- ❑ Coronary Arteries become narrow and stiff reducing blood flow and Oxygen supply to Cardiac Muscle

What are the different types of Angina?

- ❑ Three Types of Angina:
 - **Stable, Unstable, Variant**
- ❑ **Stable Angina:**
 - Stable Angina is the most common type
 - It occurs when the heart is working harder than usual
 - There is usually a regular pattern to stable angina
 - After several episodes, an individual can easily recognize the pattern and can predict when it will occur
 - Chest Pain usually goes away in a few minutes after resting or after consuming appropriate medication
 - Stable Angina is not a heart attack but makes it more likely that the patient may have a heart attack in the future
- ❑ **Unstable Angina:**
 - Unstable Angina is a very dangerous condition and should be considered as a Medical Emergency
 - Unstable Angina is a sign that a heart attack could occur soon
 - Unstable Angina does not follow any pattern
 - It can occur without Physical Exertion and is not relieved by Rest or Medication
- ❑ **Variant Angina**
 - Variant angina is rare
 - It usually occurs at rest
 - Chest Pain can be severe and usually occurs between Midnight and Early Morning
 - It is relieved by appropriate medication

Fig 1: Glucose metabolism in various tissues:

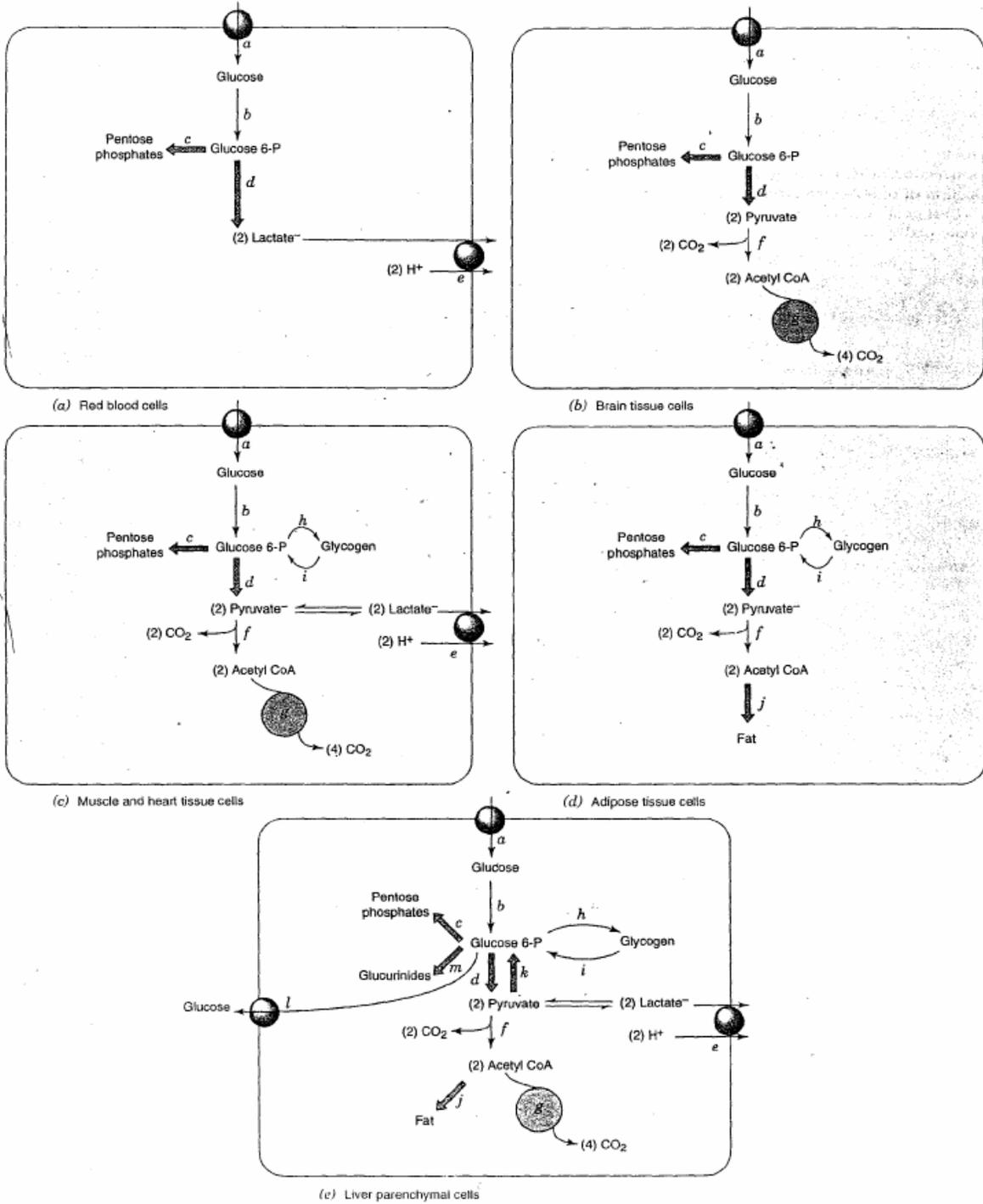


Fig 2: Regulation of anaerobic Glycolysis

FIGURE 7.17
Unless lactate formed by glycolysis is transported out of the cell, the intracellular pH will be decreased by the accumulation of intracellular lactic acid.
 The low pH decreases 6-phosphofructo-1-kinase activity so that further lactic acid production by glycolysis is shut off. (a) Glucose transport into the cell. (b) All work performances that convert ATP back to ADP and P_i . (c) Lactate–hydrogen ion symport (actual stoichiometry of one lactate⁻ and one H^+ transported by the symport).

