University of Papua New Guinea
School of Medicine and Health Sciences
Division of Basic Medical Sciences
Discipline of Biochemistry and Molecular Biology

PBL Seminar – MBBS II

WHY THE NEED FOR OXYGEN?

- Significant role of Oxygen (O_2) in cellular and whole body metabolism cannot be overemphasized
- Daily needs for Oxygen depends on Energy expenditure of individual
- Energy expended depends on four main factors:
  - **Basal Metabolic Rate (BMR):**
    - Energy expenditure to maintain basic physiologic functions at rest
  - **Thermogenic Effect (Specific dynamic action)** of food:
    - Equivalent to 5 – 10% of total energy expenditure: related to energy for digestion and stimulation of metabolic processes
  - **Physical Activity**: Largest variable affecting energy expenditure of individuals
  - **Environmental Temperature**:
    - At low Temperatures: Shivering causes increased energy expenditure
    - At high Temperatures: Extra energy is expended in cooling (sweating causes cooling of body surface)

Energy metabolism with special emphasis on Glycolysis:

What is Glycolysis?

- **Glycolysis is**:
  - A Major metabolic pathway for Energy production via degradation of Glucose and other Monosaccharides
  - Unique pathway because it can occur either:
    - In the **absence of O_2** (**Anaerobic Glycolysis**), and in cells that do not contain mitochondria, or
    - In the **presence of O_2** (**Aerobic Glycolysis**) in cells that contain mitochondria

What is the significant of Anaerobic Glycolysis?

- Anaerobic Glycolysis is of major Biomedical significance, because:
  - It provides tissues like skeletal muscle with energy (ATP) at low O_2 tension,
  - It allows tissues with significant Glycolytic ability to survive Hypoxic episodes
- However, Cardiac muscle, which is adopted for Aerobic oxidation has relatively poor glycolytic ability and poor survival under conditions of **Ischaemia**

What are some of the consequences of prolonged Anaerobic Glycolysis?

- **Anaerobic Glycolysis** leads to production of **2 molecules of Lactic Acid** (**Lactate**) and a **Total of 4 ATP,** which ultimately gives a **Net of 2 ATP per molecule of Glucose**

    - Summary of Overall equation for Anaerobic Glycolysis:
        - (All enzymes are present in Cytosol)

Glucose + 2ADP + 2P ==========➔ 2 Lactate + 2 ATP + $2H^+$

- End product of Anaerobic Glycolysis is Lactic acid
- Prolonged Anaerobic Glycolysis can affect the blood buffer, causing Lactic Acidosis
    - Muscles become Tired and Sore
- Lungs respond by Hyperventilation, blowing out CO_2, which helps to reduce accumulation of acid in the cells and restore Acid – Base balance
- Lactic acid is removed from the body under appropriate conditions

What is significant about Aerobic Glycolysis?

- **Aerobic Glycolysis** occurs in the presence of O_2 in cells that contain Mitochondria,
- Aerobic Glycolysis leads to production of **2 molecules of Pyruvic Acid** (**Pyruvate**), a **Total of 10 ATP**, which ultimately gives a **Net of 8 ATP per molecule of Glucose**

- Under Aerobic conditions the end product of Glycolysis is **Pyruvate**
    - It occurs in cells that contain mitochondria
- Pyruvate is then converted to Acetyl-CoA in the mitochondria
- Acetyl-CoA is then oxidized by enzymes in the TCA cycle
- Reducing Equivalents ($FADH_2$ and NADH) produced in the TCA cycle are sent to the Electron Transport Chain (ETC) for production of ATP (via Oxidative Phosphorylation)
- Energy (ATP), CO_2 and H_2O are the end products
- A Net of **38 ATP** are produced per molecule of Glucose oxidized

How significant is O_2 for normal function of the Brain?

- Adequate amount of energy is required to maintain normal Brain functions
- Energy is needed for:
    - Maintenance of Blood-Brain Barrier,
    - Impulse transmission and signal Transduction,
- Oxygen and Glucose are very important for energy production in cerebral tissue (Brain)
- Cerebral tissue appears to utilize O_2 more than other tissues;
    - Example: cerebral tissue utilizes about 20 times more O_2 than muscle tissue when at rest

- Aerobic and Anaerobic Glycolysis occurs in the Brain tissue
    - Aerobic Glycolysis occurs mainly in Grey matter
    - Anaerobic Glycolysis occurs mainly in White matter

- Energy production is mainly via **Aerobic Glycolysis**
- In cerebral tissues, O_2 is also used by specific enzymes, such as, Mixed Functional Oxygenases that require molecular O_2 as substrates
- Continuous replenishment of O_2 by the circulation is essential, because O_2 stored in the cerebral tissue is extremely small compared to the rate of utilization
- If cerebral blood flow is completely interrupted (Ischaemia), consciousness is loss within minutes, or the amount of time required for consuming the O_2 contained within the brain and its blood content

How does Hypoxia affect energy metabolism?

- Major metabolic consequence of Hypoxia is reduction in the rate of Aerobic Glycolysis (Oxidative Phosphorylation) resulting in loss of energy production in cells of most tissues
- During hypoxia, as the rate of aerobic glycolysis slows down the amount of ATP in cells reduces, while the amount of AMP increases
- Increased level of AMP stimulates production of ATP via Anaerobic Glycolysis leading to production of Lactic acid
    - Lactic acid can accumulate in the blood, and in some cases results in low blood pH and low Bicarbonate level causing Lactic acidosis
- Lactate accumulates in the blood because the cells of tissues cannot effectively utilize lactate when Oxygen supply is low (Hypoxia)

How does Hypoxia affect energy metabolism in the brain?

- Effect of hypoxia on the brain is more severe than on other tissues
- Brain is one of the most metabolically active tissues in the body
- Brain depends mainly on Oxidative Phosphorylation (Aerobic respiration) to produce the amount of energy required for maintenance of its functional and structural integrity
- A major metabolic change that occurs in brain tissue during hypoxia is a drastic slowdown in the rate of Oxidative Phosphorylation
- As a result, there is an increase in Anaerobic Glycolysis, leading to an increase in cellular levels of Lactate, which consequently can, in some cases result in intracellular acidosis
- This compensatory mechanism that occurs in brain tissue during hypoxia is called **"Pasteur Effect"**
    - Pasteur Effect implies inhibition of Anaerobic Glycolysis in the presence of Oxygen
        - In other words, Anaerobic Glycolysis increases in the absence of Oxygen supply
- However, Anaerobic Glycolysis even at its maximum cannot provide sufficient energy to meet the metabolic requirements of the brain

- Hypoxia causes:
  - Increase in Glucose utilization by cerebral tissues, together with a decrease in cerebral glucose concentration
  - The total effect results in an increase of Lactic acid and to a lesser extent Pyruvic acid in the brain
  - Affect the rate of production of some Neurotransmitters (chemical compounds that transfer signals from one nerve cell to another nerve cell or to a muscle cell)
    - Synthesis and metabolism of some of these Neurotransmitters are Oxygen dependent