Cerebral Metabolism – An Overview

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INTRODUCTION

- Brain or Cerebral energy metabolism includes:
  - Neuronal energy metabolism
  - CNS metabolism in general;
  - Other cell types:
    - Glial and Vascular Endothelial cells not only consume energy but also play active role in the flux of energy substrates to Neurons

- **Neuron is the functional unit of the CNS;**

Why does cerebral tissue need energy?

- Neuron is an excitable cell (**Why?**)
- It is capable of generating and conducting electrical impulse by temporarily reversing its membrane potential;
- Energy is needed for major functions of neurons:
  - Excitation and Conduction, which are reflected in the unceasing electrical activity of Cerebral tissue;
  - Electrical energy is derived from chemical processes;
  - Energy consumption used for active transport of ions needed to sustain and restore membrane potentials discharged during excitation and conduction;
- **Thus, cerebral tissue requires constant supply of energy**

What substrates are used for energy production in cerebral tissue?

- Glucose is the major substrate for energy production in cerebral tissue;
- Cerebral tissue utilizes glucose directly from arterial blood;
- About **0.1% Glycogen** is stored in Cerebral tissue;
- **Insulin is not required for uptake of glucose by cerebral tissue**;
- When blood glucose is low, Glycogen stored in brain is used to maintain cerebral metabolism for a very short duration;

- Apart from Glucose, Mannose can be used to sustain normal cerebral metabolism;
- **Mannose** easily crosses the blood–brain barrier (BBB), is converted to Fructose-6-Phosphate that enters the Glycolytic pathway;
- Mannose is not normally present in the blood and cannot therefore be considered as a substrate for cerebral energy metabolism;
- Fructose, Galactose, Lactate and Pyruvate have limited permeability across the BBB, therefore cannot directly serve as substrates for cerebral energy metabolism;
- Lactate and Pyruvate when formed within the BBB are useful metabolic substrates for cerebral metabolism;

How significant is O_2 supply to brain energy metabolism?

- Brain represents 2 to 3% of total body weight of an average adult, but utilizes 20 to 25% of the total Oxygen consumed by the whole organism;
- In children up to 4 years of age, the brain utilizes about 50% of the total Oxygen consumed by the whole organism;
- Cerebral tissue utilizes Oxygen more than other tissues;
- Example, it utilizes about 20 times more Oxygen than muscle tissue at rest;

- Oxygen consumption varies throughout the brain:
- Grey matter utilizes about twice more Oxygen than White matter
- Cerebral Oxygen consumption continues unabated day and night,
- Sleep reduces cerebral Oxygen uptake by only 3%;
- Amount of Oxygen stored in the brain is extremely small compared to the rate of utilization,
- Brain requires continuous replenishment of its Oxygen via the circulation;
- Consciousness is loss when Cerebral blood flow is interrupted;

- **TAKE NOTE**:
- Reduced cerebral Oxygen uptake occurs under certain conditions that lead to depressed consciousness:
  - Insulin induced hypoglycemia,
  - Diabetic coma,
  - Cerebral tumors,
  - Uremia,
  - Gross liver damage that culminate in hepatic coma
  - Exposure to depressant drugs used during surgery

List some uses of O2 consumed by cerebral tissue?

- Energy metabolism via Oxidative Phosphorylation
- Maintenance of energy component in BBB
- Impulse transmission (Ion pumps);
- Signal transduction;
- Functioning of specific enzyme systems:
  - Mixed Functional Oxygenases used in the biosynthesis of Neurotransmitters and other biologically active compounds;

Briefly explain how carbohydrate is metabolized in cerebral tissue

- Aerobic and Anaerobic Glycolysis occurs in cerebral tissue;
- HMP shunt occurs in cerebral tissue mainly for production of NADPH, required for biosynthesis of Fatty acids and Steroids;
- Major substrate used in Blood glucose;
- Other Carbohydrates (Maltose, Fructose, Galactose, Hexose-phosphates) and Intermediate metabolites (Lactate, Pyruvate and Glyceraldehydes) are used only after their conversion to Glucose via Gluconeogenesis in the liver;
- These compounds act by raising Blood Glucose Level

- Cerebral tissue can utilize Mannose directly and rapidly from the blood to restore or maintain normal metabolic functions;
- Mannose can directly enter the Glycolytic pathway of cerebral tissues, without raising blood glucose level;
- Mannose like Glucose can easily cross the BBB and can be converted to Mannose-6-Phosphate by Hexokinase;
- **Phospho-Mannose Isomerase** is an active enzyme in cerebral tissue that converts Mannose-6-Phosphate to Fructose-6-Phosphate, which then enters the Glycolytic pathway;

- The reaction & enzymes:

1 **2**

Mannose + ATP ====> Mannose-6-P ====> Fructose-6-P

- (NB: **1** = Hexokinase; **2** = Phosphomannose Isomerase)

- {NB: Mannose is not normally present in blood in any appreciable amount and is therefore of no Physiological significance}.

Briefly comment on the amino acid content in cerebral tissue

- Cerebral tissue contains:
- Very high conc. of free amino acids compared to plasma;
- Highest amount of free Glutamate, compared to any other mammalian tissue;
- Some unusual amino acids:
  - Gamma-Aminobutyrate (GABA),
  - N-Acetyl-Aspartate and Cystathione.

- **GABA** is an inhibitory neurotransmitter that acts by increasing the passage of Chloride ions through the Post-synaptic membrane of Neurons;
- **Glutamate** is involved in several metabolic processes: Biosynthesis of GABA, Detoxification of Ammonia and as Neurotransmitter;

How is Ammonia formed in cerebral tissue?

Adenylate Deaminase reaction:

Adenylate Deaminase

AMP ==========> IMP + NH_4^+

Glutamate Dehydrogenase (GDH) reaction:

- High conc. of Glutamate in blood causes Ammonia toxicity;
- GDH catalyzes formation of Ammonia from Glutamate;

GDH

Glutamate + NAD + H_2O ⇐====⇒ α-KG+ NH_3 + NADH + H^+

{α-KG = α-Ketoglutarate (α-Oxoglutarate)}

How is Ammonia removed from Cerebral tissue?

- Rate of urea formation in Cerebral tissue is too low to account for removal of Ammonia via Urea Cycle, **Why?**
  - Mitochondrial N-Acetyl-Glutamate activated Carbamoyl-Phosphate Synthetase that catalyzes the first reaction in Urea cycle, is low or absent in Cerebral tissue;
- Two reactions are involved in removal of Ammonia from Cerebral tissue:

First is formation of Glutamate from Alpha-Oxoglutarate and Ammonia, by Glutamate Dehydrogenase (GDH) reaction:

GDH

α-KG+ NH_3 + NADH + H^+ ⟵===⟶Glutamate + NAD + H_2O

Second is formation of Glutamine from Glutamate and Ammonia, by Glutamine Synthetase reaction:

Glutamine Synthetase

Glutamate + NH_3 + ATP ======> Glutamine + ADP + P_i

- Concentration of Ammonia in Cerebral tissue is kept low when there is adequate supply of Alpha-Oxoglutarate;
- Extensive utilization of Alpha-Oxoglutarate in Cerebral tissue, can deplete TCA cycle Intermediates and affects energy supply to the Brain, unless mechanisms to replenishing the intermediates are available;
- Major mechanism is Anaplerotic (Filling-up) reaction;
- It involves formation of TCA cycle intermediates in cerebral tissue
- Anaplerotic reactions increase the concentrations of TCA cycle intermediates, allowing increased rate of oxidation of Acetyl-CoA

Give examples of Anaplerotic reactions

- Pyruvate Carboxylase reaction: formation of Pyruvate from Oxaloacetate using ATP and Biotin;
- Some Transamination reactions;
- Glutamate Dehydrogenase reaction to form Alpha-Oxoglutarate;
- Succinyl-CoA formation from Isoleucine, Valine, Methionine, and Threonine;

SOME FACTORS THAT CAN AFFECT CELEBRAL METABOLISM

- Oxygen and Glucose:
  - Two major substrates required for normal energy metabolism

- Hypoxia and Ischaemia;

How does hypoxia affect cerebral metabolism?

- After a brief period of hypoxia:
- There is drastic slowdown in Oxidative Phosphorylation ;
- Rate of Glycolysis is increased;
- Lactic acid production is increased, which can consequently lead to intracellular acidosis;
- These changes are due to the **Pasteur effect;**
- **Inhibition of Glycolysis in the presence of oxygen;**
- Pasteur effect reflects the increased energy yield obtained via Aerobic metabolism of glucose as compared to Anaerobic metabolism;

- Hypoxia causes an increase in Glucose utilization from cerebral blood stream, followed by a decrease in cerebral glucose concentration;
- Resulting is an increase in Lactic acid production in cerebral tissue;
- Gradual increase in Spinal fluid Lactate level occurs during hypoxia;

IMPORTANT TO NOTE:

- The earliest detectable Neuro-chemical change in brain caused by Hypoxia is not elevation of cerebral lactate concentration, but a reduction in synthesis of Acetylcholine;
- Major effect of Hypoxia on the Nervous system is reduction in the rate of conversion of Pyruvate to Acetyl-CoA with a resultant decrease in both biosynthesis of Acetylcholine and the activity of the TCA cycle;
- In situation of low Acetyl-CoA availability the brain may use the available Acetyl-CoA for energy production so as to maintain membrane potentials in preference to its use in the biosynthesis of any compound;

How does Ischemia affect cerebral metabolism?

- During Ischaemia:
- Glucose and O_2 supply are deficient;
- Cerebral Glucose level and Glycogen store are depleted;
- Coma can occur leading to cerebral tissue damage;
- Hypoglycemia can severely affect cerebral energy metabolism because glucose is almost exclusively used by the brain as the substrate for energy metabolism;

IMPORTANT TO NOTE

- During starvation cerebral tissue can use Ketone bodies (Beta-hydroxybutyrate, Acetone) as substrate for energy metabolism;
- Concentration of Ketone bodies are usually very high in blood during starvation, thus they can cross the BBB;
- Vitamin deficiency can lead to abnormality in cerebral metabolism and function;
- Effect of vitamin deficiency can be either direct or indirect, because of the role of vitamins on biochemical processes;

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