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

GENERAL REVIEW OF NEUROCHEMISTRY – MBBS III

CEREBRAL METABOLISM:

What are some major uses of energy in nervous system?

- Neuron is an excitable cell: capable of changing membrane potential
- Excitation and Conduction are two major functions of nervous tissues
  - Reflected in unceasing electrical activity of cerebral tissue
  - Electrical activity requires energy derived from metabolic processes
  - Energy required for Active Transport of ions needed to Sustain and Restore Membrane Potentials discharged during Excitation and Conduction
- Energy required for maintenance of blood-brain barrier
- Energy required for biosynthesis of neurotransmitters and other components
- Oxygen and Glucose are major substrates for energy production in cerebral tissue

How significant is O_2 supply for normal brain function?

- Brain represents 2 to 3% of total body weight of an average adult, yet it utilizes about **20 to 25% of total O_2 consumed by the whole organism**
- Brain tissue utilizes O_2 more than other tissues: e.g., it utilizes about 20 times more O_2 than muscle tissue when at rest
- O_2 consumption throughout the whole brain is not constant
  - Gray Matter utilizes about twice more O_2 than White Matter
    - Grey matter: energy is via Aerobic Glycolysis
    - White matter: energy is via Anaerobic Glycolysis

- Cerebral tissue contains mixed functional Oxygenases (Oxidases and Hydroxylases) that require molecular O_2 as substrates for biosynthesis of biologically active compounds
- Brain requires continuous supply of O_2 via circulation because O_2 stored in the brain is extremely small compared to its rate of utilization
- If cerebral blood flow is completely interrupted (Ischaemia), consciousness is loss within a few seconds, or the amount of time required for consuming the O_2 contained within the brain and its blood content
- Reduced cerebral O_2 uptake has been shown to occur under certain conditions that lead to depressed consciousness: Examples include:
  - Insulin Hypoglycemia, Diabetic Coma, Cerebral Tumors, Uremia, Gross Liver damage leading to hepatic coma, Anesthetic used during surgery

What are the sources of Glucose for cerebral metabolism?

- Cerebral tissue utilizes glucose directly from arterial blood
- Insulin does not mediate the uptake of blood Glucose by cerebral tissue
  - Uptake of blood Glucose by cerebral tissue is via an High Affinity, High Capacity uptake system
- In conditions of low blood glucose, Cerebral tissue can utilize the small store of Glycogen (about 0.1%) to maintain cerebral metabolism for a very short time
- **During Hypoglycemia few Carbohydrates, such as Mannose, can act as substrates for cerebral energy metabolism**

- Not that compounds such as Maltose, Fructose, Galactose, Hexosephosphates, Lactate, Pyruvate and Glyceraldehyde cannot directly act as substrates for cerebral energy metabolism
    - They can act as substrate only after their conversion to glucose via Gluconeogenesis in the liver
        - Thus, these compounds act by raising blood glucose level

- **In the absence of glucose the brain can utilize Mannose directly and rapidly to restore or maintain normal metabolic function**
- **Mannose can enter directly into the Glycolytic pathway of brain tissues, without raising blood glucose level**
- **Mannose like glucose can easily cross the blood-brain-barrier and can be converted to Mannose-6-phosphate by Hexokinase**
- **Phosphomannose Isomerase, which** is an active enzyme in brain tissue then converts Mannose-6-phosphate to Fructose-6-phosphate, which then enters the Glycolytic pathway

How is ammonia metabolized in cerebral tissue?

- Urea cycle is not the major pathway for removal of Ammonia in Cerebral tissue
- Activity of Carbamoyl-phosphate synthetase, which is the first enzyme in Urea cycle, is extremely low or absent in Cerebral tissue
- **Removal of Ammonia from Cerebral tissue involves two reactions:**
    - **First is: Glutamate Dehydrogenase (GDH) reaction**

$$\textbf{Alpha-oxoglutarate} + \textbf{NH}_3 + \textbf{NADH} + \textbf{H}^+ \xleftarrow{\text{GDH}} \textbf{Glutamate} + \textbf{NAD}$$

- **Second is: Glutamine Synthetase reaction**

$$\textbf{Glutamate} + \textbf{NH}_3 + \textbf{ATP} \xrightarrow{\text{Glutamine Synthetase}} \textbf{Glutamine} + \textbf{ADP} + \textbf{P}_i$$

- **Alpha-Oxoglutarate is taken form the TCA cycle, thus provided there is an adequate supply of Alpha-oxoglutarate the concentration of Ammonia in Cerebral tissue will be kept low**

- Extensive utilization of Alpha-oxoglutarate produced in TCA cycle within Cerebral Tissue, would deplete intermediates in the TCA cycle and thus affect energy supply to the Brain, unless a mechanism (Anaplerotic or Filling up reaction) of replenishing the intermediates is available

    - Anaplerotic reactions increase concentrations of TCA cycle intermediates, allowing increased formation Acetyl-CoA for maintenance of TCA cycle

Anaplerotic reactions include:

- Pyruvate Carboxylase reaction: catalyzes formation of Pyruvate from Oxaloacetate using ATP and Biotin
- Transamination reactions: forms Alpha-oxoglutarate, a TCA cycle intermediate
- Glutamate Dehydrogenase reaction: forms Alpha-oxoglutarate
- Succinyl-CoA formation from Isoleucine, Valine, Methionine, and Threonine

SOME FACTORS THAT CAN AFFECT CEREBRAL METABOLISM:

How does Hypoxia affect Cerebral Metabolism?

- Hypoxia causes drastic slowdown in rate of Oxidative metabolism
  - Resulting in increased Anaerobic Glycolytic activity and relative increase in conversion of Pyruvate to Lactate, which consequently leads to intracellular acidosis, in most cases
    - **Pasteur Effect**: That is, **Inhibition of rate of Glycolysis in the presence of oxygen**
- **Hypoxia brings about Increase Glucose utilization from Cerebral blood stream, together with a Decrease in Cerebral glucose concentration**
- **Major effects of hypoxia on nervous system include:**
  - **Reduction in Rate of Conversion of Pyruvate to Acetyl-CoA with a resultant decrease in both biosynthesis of Acetylcholine and Activity of the TCA cycle**
- In situation of low Acetyl-CoA availability the Cerebral tissue may use the available acetyl-CoA for energy production so as to maintain membrane potentials in preference to its use in the biosynthesis of compounds

How does Ischaemia affect Cerebral Metabolism?

- Ischaemia: Glucose and Oxygen supply to Cerebral tissue are deficient
  - Causes rapid depletion of small store of Glycogen in Cerebral tissue
  - If condition persists then coma ensures leading to cerebral tissue damage

How does hypoglycemia affect cerebral metabolism?

- Hypoglycemia severely affect cerebral energy metabolism because, the brain uses glucose almost exclusively as substrate for energy metabolism
  - Unlike other tissues such as muscle, nervous system does not depend on Insulin for uptake of Glucose from blood
- During starvation Cerebral Tissue can use Ketone bodies (Beta-hydroxybutyrate, and Acetone) as substrate for energy metabolism
- Ketone Bodies are usually very high in the blood during starvation, thus they are able to cross the blood-brain barrier without much restriction

NEUROTRANSMISSION:

- Neuron is an excitable cell: it is capable of generating and conducting electrical impulse by temporarily reversing its membrane potential
- Synapse: contact between two neurons
- Neuromuscular Junction: contact between neuron and muscle fiber

What are the two ways of impulse transmission by neurons?

- **Impulse transmission along Axon:**
  - **Membrane Transmission**:
    - Mode of Transmission is Electrical
    - Propagation of Action Potential along membrane of Axon
- **Impulse transmission Across Synapse:**
  - **Synaptic Transmission (and also impulse transmission from Neuron to Muscle i.e., across the Neuromuscular Junction):**
    - Mode of Transmission is Chemical
    - Process carried out Chemical Compounds (Neurotransmitters)

Give a brief outline of the neurotransmitter Acetylcholine:

- Acetylcholine (ACh) is a simple molecule synthesized from Choline and Acetyl-CoA through the action of Acetylcholine Transferase (also called Choline Acetyltransferase)
- Neurons that synthesize and release ACh are termed Cholinergic neurons
- Acetylcholine is an excitatory neurotransmitter
- Removal of ACh from receptors at the Postsynaptic membrane is by hydrolysis catalyzed by True Acetyl-Cholinesterase located at nerve endings
- ACh receptors are Ligand-Gated Cation channels composed of four different polypeptide subunits arranged in the form [(α2)(β)(γ)(δ)]
- Two main classes of ACh receptors **Muscarinic receptors and Nicotinic receptors**
- Nicotinic receptors are further divided into those found at neuromuscular junctions and those found at neuronal synapses

Catecholamines:

- Major Catecholamines are **Norepinephrine, Epinephrine and Dopamine**
- Catecholamines are the neurotransmitters for the sympathetic nervous system effect
- Phenylalanine or Tyrosine can serve a precursor for their biosynthesis
- **Catecholamines bind to two different classes of receptors termed α- and β-Adrenergic receptors, which are** classical serpentine receptors that couple to intracellular G-proteins
- **Catecholamines are also known as Adrenergic neurotransmitters**
- Catecholamines are degraded to inactive compounds through sequential actions of the enzymes: Catecholamine-O-Methyl-Transferase (COMT), Monoamine Oxidase (MAO) and Aldehyde Dehydrogenase

Briefly comment on Gamma Amino Butyric Acid (GABA):

- Several amino acids have distinct excitatory or inhibitory effects on the Nervous System
- Gamma-Amino-Butyrate, also called 4-Aminobutyrate, (GABA) is an inhibitor of Presynaptic Transmission in CNS, and Retina
- Biosynthesis of GABA occurs via Decarboxylation of Glutamate catalyzed by Glutamate Decarboxylase (GAD), which is found in many nerve endings in brain and in beta cells of the Pancreas
- Neurons that secrete GABA are called GABAergic neurons
- GABA exerts its effects by binding to two distinct receptors: GABA-A and GABA-B
- GABA-A receptors form Chloride ion channel:
    - Binding of GABA to GABA-A receptors increases Chloride ion conductance of Presynaptic neurons
- GABA-B receptors are coupled to Intracellular G-protein and act by increasing conductance of associated K^+ channel

What are some of the characteristics of Neurotransmitter Receptors?

- Neurotransmitter receptors are located on the surface of Postsynaptic neurons and also on some Presynaptic neurons
- Receptors on Presynaptic neurons act to inhibit further release of neurotransmitter
- Vast majority of neurotransmitter receptors belong to a class of proteins known as S**erpentine receptors**, because they exhibits a characteristic transmembrane structure that spans the cell membrane seven times
- **Link between neurotransmitters and Intracellular signaling is carried out by association either with G-proteins (small GTP-binding and hydrolyzing proteins) or with Protein Kinase, or by the Receptor itself in the form of a Ligand-gated ion channel (for example, the Acetylcholine receptor)**

- Neurotransmitter receptors are subjected to **ligand-Induced Desensitization**: That is, they can become unresponsive upon prolonged exposure to their neurotransmitter

What are the effects of Neurotransmitters on Post-synaptic receptors?

- Effects of neurotransmitters on Post-synaptic receptors varies:
- Some Neurotransmitters (such as, **Acetylcholine, Glycine, Glutamate, GABA)** have an "Inherent" biological activity.
    - Act directly to cause increase in conductance to certain ions by binding to "Ligand-Activated" ion channels at the post-synaptic membrane

- Other Neurotransmitters (such as, **Norepinephrine, Dopamine** and **Serotonin)** have no direct activity but act indirectly via Second Messenger systems to bring about Post-synaptic response
- Second Messenger systems involve compound (such as, cAMP, cGMP, ITP, PGs, Epoxides and Ca^{2+} ions) that act in the cytosol to activate target proteins, including protein kinases, which in turn act on substances such as, ion channels, to produce the neurotransmission effect
- Excitatory neurotransmitters bind to the receptors to cause depolarization of the membrane of the Post-synaptic cell
- Inhibitory neurotransmitters cause Hyper-polarization by increasing the Chloride ion conductance of the Post-synaptic membrane, thus making it more difficult for the cell to become depolarized

Toxins & Diseases That Affect Neuromuscular Junction & Synaptic Transmission:

- ACh release in the NMJ is inhibited by Botulinum Toxin causing flaccid paralysis
- Glycine release in the CNS is inhibited by Tetanus Toxin causing spastic paralysis
- Black widow spider toxin, Alpha-Latrotoxin, stimulates fusion and depletion of neurotransmitter vesicles
- Plant poison, Physostigmine, Nerve Gases and Organo-phosphorus pesticides inhibit Acetyl-cholinesterase, the enzyme that degrades ACh into Acetate and Choline
- Muscle ACh receptor is blocked by the South American arrow poison, Curare
- Atropine, inhibits ACh receptors of the Autonomic nervous system (but not the NMJ)
- Strychnine binds to Glycine receptor protein and inhibits IPSPs in the spinal cord
- Cocaine blocks recycling of Dopamine and Norepinephrine neurotransmitters in the brain causing an excitatory effect