Review of Neurochemistry

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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 major functions of nervous tissues
  - Reflected in unceasing electrical activity of cerebral tissue
  - Electrical activity requires energy derived from metabolism
  - 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 for normal cerebral function?

- Brain is about 2 to 3% of total body weight of an adult, yet it utilizes 20 to 25% of total O_2 consumed by whole organism;
- Brain utilizes O_2 more than other tissues: e.g., it utilizes about 20 times more O_2 than muscle tissue at rest;
- O_2 consumption by 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 because O_2 stored in brain is limited compared to rate of utilization;
- During Ischemia, consciousness is loss within a few seconds, or time required for consuming O_2 contained within brain and its blood content ;
- Reduced cerebral O_2 uptake occurs under certain conditions that lead to depressed consciousness, eg:
  - 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 blood;
- Insulin does not mediate uptake of Glucose by brain;
  - **Uptake of 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;

- 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;
- These compounds act by raising blood glucose level;
- In absence of glucose brain can utilize **Mannose** directly and rapidly to restore or maintain normal metabolism;

- Mannose can enter directly into the Glycolytic pathway of brain tissues, without raising blood glucose level;
- Mannose like glucose can easily cross the BBB and be converted to **Mannose-6-phosphate** by Hexokinase;
- **Phosphomannose Isomerase**, an active enzyme in brain tissue, 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}.

How is ammonia metabolized in cerebral tissue?

- Urea cycle is not the major pathway for removal of Ammonia in Cerebral tissue;
- Mitochondrial N-Acetyl-Glutamate activated Carbamoyl-Phosphate Synthetase that catalyzes the first reaction in Urea cycle, is low or absent in Cerebral tissue;
- **Removal of Ammonia from Cerebral tissue involves two reactions:**

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

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

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

Glutamine Synthetase

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

- The **α-KG** is taken from TCA cycle,
  - If supply of **α-KG** is adequate, then concentration of Ammonia in Cerebral tissue will be kept low;
- Extensive utilization of **α-KG** from TCA cycle in Cerebral Tissue, would deplete intermediates in TCA cycle and thus affect energy supply to Brain,
  - Anaplerotic or Filling up reactions are switched on to replenish the depleting intermediates;
- Anaplerotic reactions are for increasing the TCA cycle intermediates,

Give examples of the Anaplerotic reactions:

- 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 Phosphorylation,
  - Resulting in increased Anaerobic Glycolysis and relative increase in conversion of Pyruvate to Lactate, which consequently leads to intracellular acidosis;
- **Pasteur Effect**: Inhibition of rate of Glycolysis in the presence of oxygen;
- Hypoxia causes:
  - Increase Glucose utilization from Cerebral blood,
  - Decrease in Cerebral Glucose concentration;

- Major effects of hypoxia on nervous system:
  - Reduction in Rate of Conversion of Pyruvate to Acetyl-CoA with a resultant decrease in both biosynthesis of Acetylcholine and Activity of TCA cycle;

- In situations 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 Ischemia affect Cerebral Metabolism?

- Ischemia: Glucose and Oxygen supply to Cerebral tissue are deficient;

During Ischemia:

- Glucose and O_2 supply are deficient;
- Cerebral Glucose level and Glycogen store are depleted;
- Coma can occur 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;
- 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 blood during starvation, thus they are able to cross the BBB 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 2 modes of impulse transmission?

Electrical mode of transmission:

- Impulse transmission along axon – Membrane transmission:
  - Involves propagation of Action Potential along axonal membrane;

Chemical mode of transmission:

- Impulse transmission across synapse – Synaptic transmission,
- Impulse transmission from neuron to muscle – Neuromuscular transmission,
  - Involves chemical process by group of compounds called Chemical Neurotransmitters;

Give brief description of neurotransmitter Acetylcholine

- Acetylcholine (Ach) is excitatory neurotransmitter
- Neurons that synthesize and release ACh are termed Cholinergic neurons;
- ACh is synthesized from Choline and Acetyl-CoA;
- Reaction catalyzed by Acetylcholine Transferase (Choline Acetyl-transferase);
- Removal of ACh from receptors at 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,**
  - **Nicotinic receptors;**
- Nicotinic receptors are divided into those at:
  - Neuromuscular junctions,
  - Neuronal synapses;

Give brief description of Catecholamine Neurotransmitters

- Catecholamines: Norepinephrine, Epinephrine and Dopamine;
- Precursor for their biosynthesis are Phenylalanine or Tyrosine;
- Catecholamines are neurotransmitters for the sympathetic nervous system effect;
- 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 remove from receptors on post-synaptic membrane by “Active Reuptake”;
- Catecholamines are degraded by sequential actions of the enzymes:
  - Catecholamine-O-Methyl-Transferase (COMT),
  - Monoamine Oxidase (MAO),
  - Aldehyde Dehydrogenase;

Briefly comment on neurotransmitter Gamma Amino Butyric Acid (GABA)

- Gamma-Amino-Butyrate, (4-Aminobutyrate or GABA) is an inhibitor neurotransmitter;
- Biosynthesis of GABA occurs via Decarboxylation of Glutamate catalyzed by Glutamate Decarboxylase (GAD);
- Neurons that secrete GABA are called GABAergic neurons;
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- GABA exerts action by binding to 2 distinct receptors
  - GABA-A,
  - 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;

State some 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;
- Link between neurotransmitter and Intracellular signaling is by association with one of the following:
  - G-proteins,
  - Protein Kinase,
  - Receptor itself in the form of a Ligand-gated ion channel (e.g, Acetylcholine receptor)

- Vast majority of neurotransmitter receptors are S**erpentine receptors**, because they exhibits a characteristic transmembrane structure that spans the cell membrane seven times;
- Neurotransmitter receptors are subjected to **ligand-Induced Desensitization**:
  - they can become unresponsive upon prolonged exposure to their neurotransmitter;

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

- Some Neurotransmitters (e.g. **Acetylcholine, Glycine, Glutamate, GABA)** have "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 (e.g. **Norepinephrine, Dopamine** and **Serotonin)** have no direct activity but act indirectly via Second Messenger systems to bring about Post-synaptic response;

- 2^{nd} Messengers (e.g. cAMP, cGMP, ITP, PGs, Epoxides and Ca^{2+} ions) act in the Cytosol to activate target proteins, including protein kinases, which in turn act on Gated Ion Channels, to produce neurotransmission effect;

- Excitatory neurotransmitters bind to receptors to cause depolarization of Post-synaptic membrane;

- Inhibitory neurotransmitters cause Hyper-polarization by increasing Chloride ion conductance of Post-synaptic membrane, thus making it more difficult for the cell to become depolarized;

Some 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 in Cholinergic neurons;

- Muscle ACh receptor is blocked by the South American arrow poison, Curare;
- Plant drug, 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 excitatory effect;