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REVIEW ARTICLE

Enzyme Inhibitors Involving Various Diseases

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ABSTRACT

Enzymes are protein molecules which work as catalyst. Enzymes speed up chemical reaction in the bodyall biochemical reaction in living thing need enzymes. The human body contain approximately 750000 are exist in the human body. It divided into three types; Metabolic enzymes that run our body and Digestive enzyme digestion our food. Food enzymes raw foods that start our food digestion. Enzyme inhibitors is a molecule that binds to an enzyme and decrease it's activity. Since blocking the enzyme activity kill the pathogen. There are three types of inhibitors. They are, Competitive inhibitors.(Raises Km only), Noncompetitive/ Mixed inhibitors.(Lowers Vmax & Km), Uncompetitive inhibitors. (Lowers Vmax only) Competitive inhibitors mean compete with substrate to bind to the enzyme at the same site. The inhibitor has an affinity for the active site of enzyme e.g pencillin inhibit the bacterial cell wall synthesis, Noncompetitive inhibitors e.g are combine cyanide or potassium cyanide with combine dehydrogenase with the cytochrome enzyme response for transfer of hydrogen atom during cellular respiration, antibiotic enzyme inhibitors are noncompetitive inhibitor can combine with either free enzyme because it binding site of enzyme distinct from the active site. Reversible inhibitor means the binding of an inhibitor can stop substrate from entering enzymes active site. Either reversible or irreversible inhibitor usually react with the enzyme and change it chemically via chemical bond formation. Irreversible inhibitor, inhibitors bind at or near the active site of the enzyme. It occupy or destroy the active sites of enzyme permanently and decrease the reaction rate. It combines with the functional group of aminoacid in the active site inhibitors. Irreversible inhibitor similarly are clinically used include drugs such as aspirin, Omeprazole and monooxidase enzyme inhibitor.

Keywords: DHFR inhibitors, Enzymes, Enzyme inhibitors, Monoamine oxidase inhibitors, PCSK9 inhibitors, Xanthine oxidation enzyme inhibitors.

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1. Introduction

Mono Amine Oxidase Inhibitors:

It is a natural enzyme that break down serotonin, epinephrine and dopamine and these are neuro transmitter removing from the brain. MAO inhibitors inhibit the activity of MAO-A and MAO-B. Both are present in the mitochondrial outer membrane of the cell.MAO important role in the catabolism of not adrenaline in sympathetic nerves. Which includes cheese reaction that is stimulation of CVS and sympathetic nervous system.

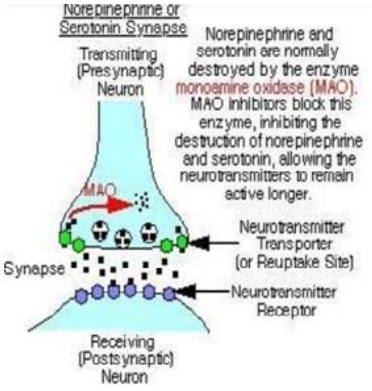

Figure 1

a) Monoamine oxidase enzyme inhibitor-A:

Human is encoded by the MAO A gene it is one of the gene family. A mutation of this gene results in Brunner Syndrome. In this associated with variety of other psychiatric disorders including anti-social behaviour.MAO gene was evaluated by Southern blot analysis using genomic DNA.MAO-A and MAO level of activity in humans.

b) Mono amine oxidase enzyme inhibitor-B:

MAO-B is a mitochondrial outer membrane of flavo enzyme it is well target for antidepressant and neuro protective drugs. MAO-B is known to be increased in a Alzheimer's disease in brain platelets. MAO activity was selectively inhibited low concentrations of the MAO B inhibitors. MAO-B activity increased up to three fold exclusively in temporal and parietal frontal cortices of Alzheimer's disease. MAO-B inhibitors currently under clinical evaluation for the treatment of parkinsonism and Alzheimer's disease. MAO-B enriched in all cortical region. These enzyme bind to the membrane through a terminal transmembrane helix and apolar loops located at various position in the sequence.

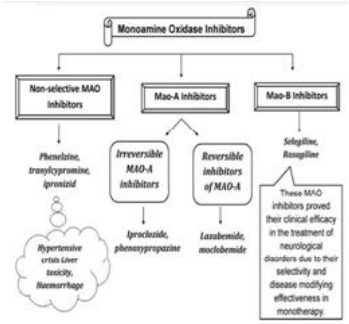

Figure 2

MAO enzyme inhibitor drugs:

SSRIs are more prescribe anti-depressant available include celena, lexapro, luvon and Zoloft this drug are affected serotonin receptors to relieve major depression.

- Rasagiline
- Phenelzine
- Selegiline
- Tranyl cypromine
- Isocarboxazid

MAOIs and diet: It is necessary to restrict tyramine eg.cheese.

Xanthine Oxidase Enzyme Inhibitors:

Xanthine oxidation enzyme response for uric acid synthesis. Allopurinol is the xanthine oxidase enzyme inhibitor it is a noncompetitive inhibitor primary responsible for uric acid synthesis. Decrease plasma concentration of uric acid and increased hypoxanthine and xanthine. In place of uric acid alone all three 3 oxy purines are excreted in urine. Xanthine and hypoxanthine are more soluble. Alternative to increased uric acid excretion in the treatment of gout is to reduce it synthesis by inhibiting xanthine oxidase with allopurinol. Uric acid is a pure anti-oxidant xanthine oxidase inhibitors to also block oxidants generated during the production of uric acid from xanthine. Uric acid causes cardiovascular disease appears due to the intracellular effect of uric acid so treatment that block the uric acid synthesis such as allopurinol. Genome wide association studies have to found several polymorphism in urate transport that predict hyperuricemia and gout.The polymorphism alter the transport of uric acid in and out of cells. Allopurinol commonly used for the treatment of hyperuricemia and gout. hyperuricaemia is a marker of impaired oxidative metabolism. Hyperuricaemia via XO inhibit might benefit heart failure and decreased blood pressure. Recently extended to the treatment of leishmaniasis and trypanosoma cruzi infection. Xanthine oxidase enzyme present in heart. Xanthine oxidase enzyme inhibitor has potential to play a therapeutic role in patients with acute and chronic post myocardial infraction and left ventricular dysfunction causes non ischemic cause. Long term allopurinol treatment initiated established chronic heart failure. Allopurinol therapy improves endothelial dysfunction.

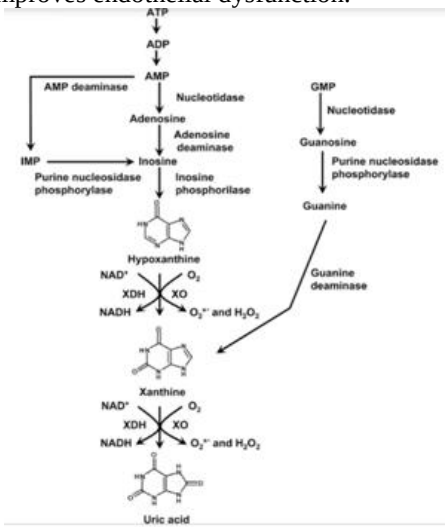

Figure 3

Proprotein Convertase Subtilisin\Kexin 9 (Pcsk9) Enzyme Inhibitors: PCSK9 synthesized as soluble zymogen that undergoes auto catalytic intramolecular processing in the endoplasmic reticulum.The protein may function as proprotein convertase. Seidah and colleagues discovered PCSK9 is a secreted glycoprotein, that regulates degradation of the LDL receptor. PCSK9 inhibitors are monoclonal antibodies (MABs), a type of biological drug .It bind to the in activate enzyme in the liver called PCSK9 because of the liver cell surface that transport LDL into the liver for the metabolism. Hepatic protease that attaches and internalizes LDL receptors into lysosomes hence promoting their destruction .By prevent LDL receptor destruction. Lower LDL is better than the heart and can protect against heart disease and stroke.

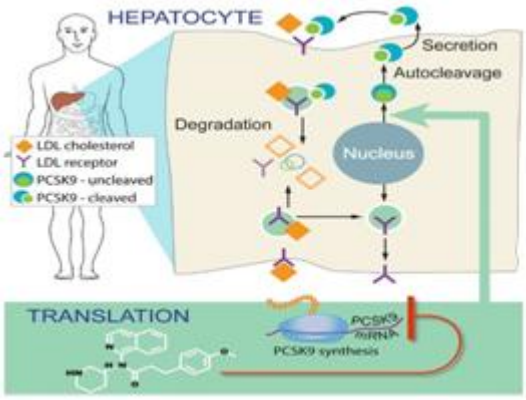

Figure 4

FDA approved two novel medications for LDL – cholesterol reduction evolocumab and allirocumab. These agents target and inactivate PCSK9LDL – C can be achieved by decreased above that 50-60% achieved by statin therapy alone. Statins are known as HMG-COA reductase inhibitors. Statins are the corner stone of treatment to help regulate cholesterol production. Statin work are inhibit the enzyme involved in the number of low density lipoprotein receptors to help clear the body of LDL (bad cholesterol). PCSK9 inhibitors used in the treatment of hyperlipoproteinemia (hypercholesterolemia) loss of function of mutation in the gene result in lower level of LDL and protective against cardia vascular disease. In human PCSK9 was initially discovered as a protein expressed in the brain however expressed in the liver, intestine, kidney and CNS. PCSK9 also plays important role in intestinal triglyceride – rich apo B lipo protein production in small intestine and post prandial lipemia. The plasma PCSK9 concentrations higher in women compared to men.

PCSK9 levels directly correlated with plasma sortilin levels(SORT-1) is a protein that in human is encoded by the SORT- 1 gene on chromosome. It is a type- 1membrane glycoprotein family of sortling receptor.pcsk9 binds to the LDLR and it is highly expressed in arterial wall such as endothelium, smooth muscle cells, macrophages with a local effect that can regulate atherosclerosis. Current state of clinically available inhibitors of PCSK9.A new class of drug may change the face of lowering LDL cholesterol. These drugs are known as the PCSK9 inhibitors.

Dihydrofolate Reductase Enzyme Inhibitors:

DHFR inhibitors have progressed as antibiotics and it is a anti-bacterial agent .In human the DHFR enzyme is encoded by the DHFR gene. Folate analogue depend reaction in the body are inhibited by folate analogues or antagonists (eg: methotrexate). DHFR is competitively inhibited by methotrexate. DHFR is need for synthesis of DNA precursors. A deficiency causes most harm to those cells which synthesis DNA rapidly certain type of cancer (eg: leukaemias) exhibit high rate of cell division and particularly susceptible to folate antagonists.

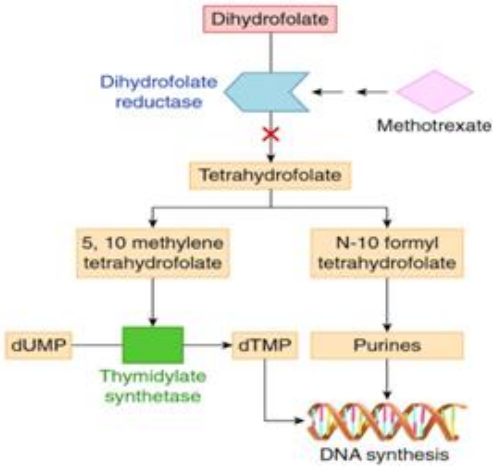

Figure 5

DHFR is a crucial enzyme for the synthesisof purines, pyrimidines and some amino acids. Folate is rapidly needed by dividing cells to make thymine (eg: methotrexate is used as cancer chemotherapy because it can prevent neoplastic cells from dividing). Methotrexate is an antimetabolite of the anti folate type it is thought to affect cancer and rheumatoid arthritis by two different pathway for cancer. Methotraxate is a competitive inhibitor. DHFR include di amino quinazoline, diamino pyrrolo quinazoline,diamino pyrimidine, diamino pterdine and diamino triazines most of above specified inhibitors are structural analogues of the substrate DHF bind to the active site of the enzyme. Allosteric site binders can inhibit the enzyme either uncompetitively or non competitively. Human DHFR calculated by comparing the energy of each minimize system with methotrexate bound and unbound in the active site. The inhibition of DHFR by a variety of inhibitors is the basis for its popularity as a target for cancer chemotherapy, malaria treatment, antibiotics and anti-helminthics.

Para amino benzoic acid is used by bacteria in the synthesis of folic acid (pteroyl glutamic acid) which function as a coenzyme in one carbon transfer reaction that are important in the amino acid metabolism. In the synthesis of RNA and DNA cell growth and division sulfonamides inhibit the bacterial enzyme it leads to bacteriostatic occur. Bacteria also need to DHFR to grow and multiple and DHFR found application as anti-bacterial agents. Purification and

characterization of this enzyme from one insect Drosophila melanogaste.

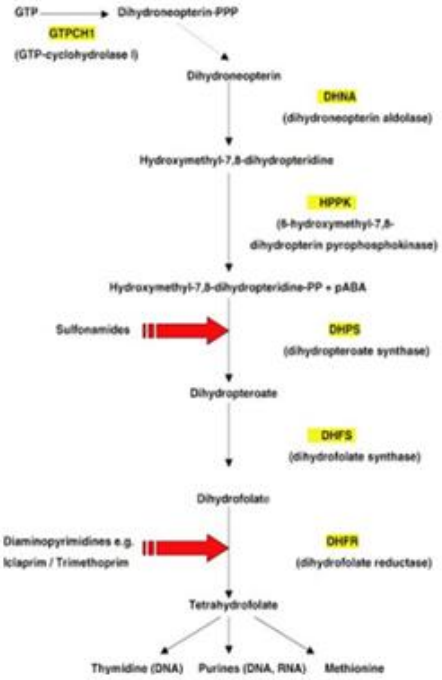

Figure 6

2. Conclusion

The present review concluded that it gives the complete information about various types of enzyme inhibitors.The inhibitor has an affinity for the active site of enzyme e.g penicillin inhibit the bacterial cell wall synthesis, Noncompetitive inhibitors e.g are combine cyanide or potassium cyanide with combine dehydrogenase with the cytochrome enzyme response for transfer of hydrogen atom during cellular respiration, antibiotic enzyme inhibitors are noncompetitive inhibitor can combine with either free enzyme because it binding site of enzyme distinct from the active site.

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