Chapter 2

Climate Change Related Fructosemia, Lipid Storage and Connective Tissue Mucopolysaccharidosis

Climate change and global warming leads to endosymbiotic actinidic archaeal growth in the human body. This leads to metabolonomic changes contributing to human disease. The archaea induces the glycolytic pathway and glycolytic enzymes especially the ketokinases. The archaea and bacteria can also induce enzyme aldose reductase. This results in the archaea induced aldose reductase converting glucose to sorbitol which gets acted upon by sorbitol dehydrogenase generating fructose. Thus the human glucose gets converted to fructose by archaea induced metabolonomic changes. Ketokinases have a lower KM value for fructose than glucose. The ketokinases especially fructokinase therefore selectively phosphorylates fructose at a higher rate than glucose. This results in generation of fructose 1-phosphate. The phosphorylation of fructose depletes the cell of ATP inhibiting sodium potassium ATPases. The working of membrane sodium potassium pump needs 80% of the energy produced by the body. The inhibition of membrane sodium potassium ATPase consequent to ATP depletion as a result of fructose phosphorylation results in conserving of ATP and cell hibernation. The inhibited sodium potassium ATPase can synthesize ATP by its ATP synthesis action. The depletion of ATP consequent to fructose phosphorylation generates ADP and AMP which are acted upon by deaminases generating uric acid. Therefore there will be resultant hyperuricemic syndrome. Uric acid can produce membrane dysfunction contributing to coronary artery disease and stroke.

The selectively phosphorylated fructose undergoes fructolysis. The fructose 1-phosphate is converted to dihydroxy acetone phosphate (DHAP) and glyceraldehydes. The glyceraldehyde and DHAP gets acted upon by triose phosphate isomerase generating glyceraldehyde phosphate which is converted to glucose 1-phosphate and glycogen which is stored. The glyceraldehyde 3-phosphate can continue in the fructolytic pathway generating pyruvate which enters the citric acid cycle producing citrate. Citrate gets acted upon by

lipogenic enzymes citrate lyase, malate dehydrogenase, fatty acid synthase and acetyl CoA carboxylase synthesizing fatty acids. The DHAP and glyceraldehyde gets reduced to form the glycerol. This is done by the enzyme glycerol dehydrogenase. Glycerol and fatty acids are substrates for triglyceride synthesis. Thus there is lipid storage and glycogen storage akin to cell hibernation. This produces a hibernatory syndrome. The human body does not depend upon glycolysis and mitochondrial oxidative phosphorylation for energy needs. Energetics is obtained by oxidation of ketone bodies obtained from fat and proteins. The pyruvate generated by fructolysis can enter the GABA shunt scheme generating succinyl CoA and glycine which are used for porphyrin synthesis. Porphyrin molecules can self organize to form supramolecular self replicating structures called porphyrions which can generate ATP by photon or electron transport. The pyruvate generated by fructolysis can get converted to glutamate which is acted upon by glutamate dehydrogenase generating ammonia. The actinidic archaea are ammonia oxidizing and can use ammonia as energy substrate.

The fructolytic pathway generates fructose 1,6-diphosphate due to the action of phosphofructokinase and fructose 1,6-diphosphate enters the pentose phosphate pathway generating pentose sugars like ribose, digitoxose and rhamnose. Ribose is required for nucleic acid synthesis contributing to cell proliferation. The actinidic archaea are capable of cholesterol catabolism generating the endogenous membrane sodium potassium ATPase inhibitor digoxin. Digoxin has got a cyclopentano perhydro phenanthrene ring system and sugar moites like rhamnose and digitoxose are added to it forming a glycosidic structure. Digoxin can produce membrane sodium potassium ATPase inhibition decreasing the need for ATP utilization contributing to cell hibernation.

The fructose 1,6-diphosphate can enter the pentose phosphate pathway generating sugars like glucosamine and glucuronic acid contributing to glycosaminoglycan synthesis. This leads onto a connective tissue mucopolysaccharidotic syndrome. This leads to fibrosis and dysfunction of multiple organ systems the liver, lung, gut, cardiac, vascular tree, bones and joints and brain constituting a mucopolysaccharidotic syndrome. This is exemplified by the increasing incidence of cirrhosis, chronic renal failure due to unknown cause, mucoid angiopathic strokes and coronary artery disease, interstitial lung disease, osteoarthritis, degenerative spine disease and Alzheimer's disease where the accumulation of connective tissue mucopolysaccharides plays a pivotal pathogenetic role.

The fructose 1,6-diphosphate can further travel along with fructolytic pathway. This generates glyceraldehydes 3-phosphate and pyruvate which combine to form 1-deoxy D xylulose phosphate (DOXP) which is further converted to 2-C methyl erythritol phosphate. These are substrates for the archaeal DXP pathway of cholesterol synthesis. Thus cholesterol that is synthesized can be used for archaeal energetics. The cycloperhydro phenanthrane ring system can be acted upon by ring oxidase generating pyruvate which can enter the GABA shunt scheme. The pyruvate is converted to glutamate and then GABA. The other substrates generated are succinyl CoA and glycine. Succinyl CoA and glycine are substrates for porphyrin synthesis. Thus the upregulated fructolytic pathway generates cholesterol by the DXP pathway and the cholesterol is catabolized by cholesterol oxidases of archaea generating energy. The side chain is oxidized to short chain fatty acids butyrate and propionate which can be oxidized by SCFA oxidation in the mitochondria generating energy. The cholesterol nucleus and side chain can get acted upon by 7-alpha hydroxylase generating bile acids which are important in the regulation of carbohydrate lipid metabolism. Bile acids can bind to FXR, LXR and PXR

receptor regulating lipid metabolism. Bile acids can act upon olfactory receptors in the limbic lobe producing a sense of group identity which gets defective in disorders like autism. Bile acid deficiency can lead to metabolic syndrome X and hyperlipidemia. The bile acids especially lithocholic acid can bind to VDR receptor producing immune activation behaving like vitamin D. Bile acids can also uncouple oxidative phosphorylation by acting upon UCP proteins producing cell hibernation. Bile acids are important regulatory molecules of metabolism. The cholesterol ring can be acted upon by archaeal aromatases generating the phenyl nucleus which can be the substrate for tyrosine, tryptophan and phenyl alanine. Thus archaeal ring oxidases, side chain oxidases, 7-alpha hydroxylase and aromatases can catabolize cholesterol.

The fructolytic scheme generates phosphoenol pyruvate which combines with erythrose 4-phosphate generating DAHP 3-deoxy D arabino heptulosonate 7-phosphate which is further converted to dehydroquinate and dehydrated to 3-dehydro shikimic acid. Shikimic acid which further generated from this pathway. The shikimic acid pathway can generate phenyl alanine, tyrosine and tryptophan. Shikimic acid 3-phosphate gets combined with phosphoenol pyruvate generating chorismate. The chorismate gets converted to prephenic acid which gets converted to parahydroxy phenyl pyruvate. This contributes to tyrosine and phenyl alanine synthesis along with contribution from the substrate glutamate. This contributes to synthesis of neurotransmitters adrenaline, noradrenalin, serotonin and dopamine as well as neuroactive alkaloids like strychnine, morphine and nicotine. All of these can regulate brain function.

The fructose that is generated by aldose reductase can fructosylate protein producing FRUAGE molecules binding to RAGE receptors producing immune activation. Therefore the fructose accumulation produces fructolysis and immune activation. The fructosylated proteins are antigenic and contribute to autoimmune disease.

Thus the global warming related endosymbiotic actinidic archaeal growth can lead to fructosemia and fructositis, an autoinflammatory state and autoimmunity against fructosylated proteins. It can also lead to a hibernatory syndrome with conversion of glucose to fructose and lipids and glycogen for storage. This can also produce the systemic connective tissue syndrome with mucopolysaccharidosis. The human cell due to membrane sodium potassium ATPase inhibition and conservation of ATP stores becomes a zombie for the endosymbiotic actinidic archaea to flourish. The actinidic archaea obtains its energy by cholesterol oxidation and ammonia oxidation. The fructolytic pathway is directed towards the DXP pathway of cholesterol synthesis and the GABA shunt/glutamate pathway generating ammonia and porphyrins. The porphyrion arrays can generate energy for the archaea by electron transport and ATP synthesis. This leads onto an epidemic of metabolic syndrome X, diabetes mellitus, mucoid angiopathic strokes, mucoid angiopathic CAD, chronic renal failure due to renal fibrosis, cirrhosis of the liver, cardiomyopathy, Alzheimer's disease and interstitial lung disease.