The Global Warming Related Epidemic Lemurian Glycolytic Syndrome

Glycolytic Renal, Cardiovascular, Pulmonary, Endocrine, Hepatic and Gastrointestinal Disease

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Global Warming Related Systemic Syndrome

Global warming leads to increase in endosymbiotic actinidic archaeal growth. Archaea are extremophiles. The actinidic archaea survive by catabolising cholesterol. The archaea and its antigens induce HIF alpha and activate the glycolytic pathway. The glycolytic pathway activation induces increased conversion of glucose to fructose by activation of the sorbitol pathway. Glucose is converted to sorbitol by the enzyme aldose reductase and sorbitol is converted to fructose by the action of sorbitol dehydrogenase. Fructose is phosphorylated by hexokinase or fructokinase to fructose phosphate. Hexokinase has a low km value for fructose and minimal amounts of fructose will be converted to fructose phosphate depleting the cellular ATP. ATP is converted to AMP and by the action of AMP deaminase is converted to uric acid. Thus there is resultant hyperuricemia and the depletion of ATP also produces membrane sodium potassium ATPase inhibition. Inhibition of membrane sodium potassium ATPase increases intracellular calcium and depletes magnesium. This produces cell death by opening up the mitochondrial PT pore, NFKB activation and immune activation, glutamate excitotoxicity and oncogene activation leading to systemic disorders. The depletion of ATP finally inhibits hexokinase as such and glucose phosphorylation stops blocking the glycolytic pathway and its coupling to the mitochondrial oxidative phosphorylation by the action of PT pore hexokinase. The cell is depleted of energy by glycolysis and the oxidative phosphorylation scheme and dies. Thus global warming via induction of glycolysis and Warburg phenotype and the increased conversion of glucose to fructose and the resultant cellular depletion of ATP can produce systemic disorders and cell dysfunction as well as death. This can produce the global warming related systemic syndrome.

Global warming leads to neanderthalisation of the human species consequent to growth of actinidic archaea. The Neanderthals were accustomed to a

ketogenic high fat, high protein diet. The ketone bodies were oxidised to generate ATP in the mitochondria. The neanderthalised humans due to actinidic archaeal growth due to consumption of a glucogenic diet leads to induction of glycolytic enzymes. The glycolytic enzymes are cytosolic. The glycolytic enzymes are antigenic in the neanderthalised humans. The glycolytic enzymes were suppressed in homo neanderthalis who ate ketogenic diet. This results in suppression of induced glycolytic enzymes by antibody formation in homo neoneanderthalis which arises due to archaeal growth consequent to global warming. The blockade of glycolysis results in blockade of cell energetics. This results in hyperglycemia and metabolic syndrome x. The glucose is converted to sorbitol by aldose reductase and sorbitol is converted to fructose by fructokinase. Fructokinase enzyme is native to Neanderthals as they consumed fruits along with fat and protein from meat. Fructose is phosphorylated to fructose phosphate which depletes the cell of ATP. This inhibits membrane sodium potassium ATPase leading onto increase in intracellular calcium and reduction in intracellular magnesium. This produces glutamate excitotoxicity and neurodegeneration, oncogene activation and malignancy, NFKB activation and autoimmune disease, release of mono amine neurotransmitters from presynaptic vesicles and schizophrenia and all systemic diseases. The increased glucose gets metabolised by archaeal glycolysis and citric acid cycle. The pyruvate generated by archaeal glycolysis enters the GABA shunt scheme generating succinyl CoA and glycine which are substrates for porphyrin synthesis. The archaeal citric acid cycle can be reductive generating carbon dioxide fixation akin to the Calvin cycle of photosynthesis or oxidative generating acetyl CoA which is used for cholesterol synthesis by the archaeal mevalonate pathway. The archaeal glycolysis also generates fructose 1,6 diphosphate which enters the pentose phosphate pathway producing D xylulose phosphate which is a substrate for DXP pathway of archaeal cholesterol synthesis. The archaea

synthesizes cholesterol by both the mevalonate pathway and DXB pathway. The archaea can use cholesterol for energetics by catabolizing it. The cholesterol ring is oxidised to pyruvate which enters the GABA shunt which provides substrates for the citric acid cycle. The pyruvate is converted to glutamate and ammonia. The archaea can oxidise ammonia for energy. The side chain of cholesterol is oxidised to butyrate and propionate which can also be further utilised for energy purposes. The archaeal energetics depends on glycolysis, citric acid cycle, ammonia oxidation and cholesterol catabolism. The antibodies against the glycolytic enzymes aldolase, enolase, GAPDH and pyruvic kinase contributes to metabolic syndrome x, schizophrenia, mood disorders, autism, multiple sclerosis, lupus, Alzheimer's disease and Parkinson's disease. The upregulation of glycolysis contributes to neoplastic state. The antibodies are produced against induced glycolytic enzymes as well as archaeal glycolytic enzymes. The blockade of glycolysis leads to a secondary mitochondrial dysfunction. The glycolytic scheme is coupled to mitochondrial oxidative phosphorylation by mitochondrial PT pore hexokinase. The antibodies against glycolysis blocks glycolysis and produce secondary mitochondrial dysfunction. The cell uses all its energetics. The depletion of ATP by phosphorylation of fructose produces membrane sodium potassium ATPase inhibition and cell hibernation as well as stem cell transformation. The human tissue systems come to a halt and form a framework for archaeal colonies to thrive. The human body becomes a zombie for archaeal colonies which are eternal. This affects the function of organ systems like the liver producing cirrhosis, the lung producing interstitial lung disease, renal fibrosis and CRF, cardiomyopathy and Alzheimer's disease. This can be called as the zombie syndrome. The depletion of ATP by phosphorylation of fructose generates ADP and AMP which by action of AMP deaminase produces uric acid and hyperuricemia. The zombie syndrome converts the human body to a framework for an archaeal colony

network. The archaea can secrete RNA and DNA viroids which can recombine with human endogenous retroviral sequences and human DNA sequences generating new RNA viruses, DNA viruses and bacteria. Thus the zombie syndrome results in the generation of new bacteria and viruses. The zombie syndrome can be treated by suppression of glycolysis. This can be done by giving a ketogenic diet derived from fibre short chain fatty acids - butyrate and acetate, polyunsaturated fatty acids and short chain fatty acids like lauric acid.

The global warming zombie syndrome results in conversion of glucose to fructose by the induction of aldose reductase consequent to dehydration. The glucose is first converted to sorbitol by aldose reductase and then by sorbitol dehydrogensase to fructose. Fructose has got a high value for ketokinase and is phosphorylated and enters the pentose phosphate pathway. Fructose is converted to glucosamine phosphate and galactosamine phosphate. There is increased synthesis of glycosaminoglycans. This produces GAG accumulation in the vessels producing mucoid angiopathy, kidney producing MEN, heart producing EMF, pancreas producing CCP and thyroid producing MNG. It can also result in fibrosis of the lung and liver producing cirrhosis and interstitial lung disease. These diseases are common in warm tropical countries, south of equator and can be called as the Lemurian syndrome. The increase km value of fructose for ketokinase results in increased phosphorylation of fructose over glucose producing hyperglycemia and metabolic syndrome. The phosphorylation of fructose depletes the cell of ATP and converts ATP to AMP and ADP which is acted upon by ATP deaminase producing uric acid. The channelling of fructose into the pentose phosphate pathway results in increased production of ribose and nucleic acid synthesis and uric acid production consequent to purine degradation. There is hyperuricemia. The tubular defect of MEN produces hypokalemia and hyponatremia. The increase in fructose

produces fructose glycation of proteins resulting in the formation of antigenic proteins and autoimmune disease. Fructose can produce inflammation and autoimmunity. This is called as fructositis. The increase in fructose which is channelled to the pentose phosphate pathway and ribose synthesis results in increased nucleic acid synthesis and cancer formation. The depletion of cellular ATP consequent to phosphorylation of fructose results in cell death and neuronal degeneration. Cell death in intestinal mucosa breaches the blood gut barrier producing leaky guts syndrome, acute phase response and metabolic syndrome x as well as autoimmunity. The phosphorylation of fructose and depletion of ATP results in membrane sodium potassium ATPase inhibition and increase in intracellular calcium and reduction in intracellular magnesium. This results in insulin resistance, glutamate excitotoxicity, oncogene activation, monoamine secretion from presynaptic vesicles and schizophrenia as well as NFKB activation and autoimmunity. The channelling of fructose to glucosamine synthesis and increased synthesis of GAG results in increased heparan sulphate synthesis which will combine with proteins forming amyloid. Amyloid formation is the basis of motor neuron disease where ribonucleoproteins form amyloid. In Parkinson's disease alpha synuclein forms amyloid. In Alzheimer's disease beta amyloid is formed. The tumour suppressor proteins forms amyloid and results in oncogenesis. The islet associated amyloid polypeptide forms the basis of defective insulin secretion in metabolic syndrome x.

Global warming leads to aldose reductase induction. Aldose reductase converts glucose to sorbitol. Sorbitol is converted to fructose by sorbitol dehydrogenase. Fructose is phosphorylated by fructokinase and ketokinases have a higher km value for fructose than glucose. This results in rapid phosphorylation of fructose and depletion of cellular ATP. The depletion of

cellular ATP has two consequences. ATP is converted to ADP and AMP. ADP and AMP are acted upon by deaminases generating uric acid. Hyperuricemia is a feature of global warming related metabolic phenomena. The depletion of ATP results in renal tubular dysfunction producing loss of electrolytes and amino acids. This results in non-specific aminoaciduria, hypokalemia and hyponatremia. There is no edema or hypertension. This produces a chronic tubulointerstitial disease called Mesoamerican nephropathy. The cellular depletion of ATP can produce cell death leading onto neuronal degeneration. The depletion of ATP produces membrane sodium potassium ATPase inhibition and increase in intracellular calcium and reduction in intracellular magnesium. This produces immune activation by NFKB induction, oncogene activation, glutamate excitotoxicity and neurodegeneration, release of monoamines into synaptic junction and schizophrenia. The depletion of ATP can also affect the gut blood barrier producing an acute phase response and leaky gut syndrome. The acute phase response can lead to metabolic syndrome x. The depletion of ATP owing to the affinity of ketokinases for fructose leads to lack of phosphorylation of glucose. This leads to hyperglycemia and metabolic syndrome x. The glucose that accumulates gets converted to fructose producing the syndrome of fructositis.

Fructose has got two metabolic fates. The fructose can get phosphorylated to fructose phosphate and enter the pentose phosphate pathway generating ribose important in nucleic acid synthesis. The purine catabolism can generate uric acid. The synthesis of nucleic acid can lead to increased cell proliferation and oncogenesis. Thus global warming related fructositis can lead to oncogenesis. The fructose that gets accumulated can also enter the pathway for glycosaminoglycan and proteoglycan synthesis. The fructose is phosphorylated and converted to fructose phosphate which can be converted to glucosamine and

galactosamine which are substrates for glycosaminoglycan synthesis. This results in accumulation of connective tissue mucopolysaccharides in the body and tissues leading onto disease states like endomyocardial fibrosis, chronic calcific pancreatitis, multinodular goitre and mucoid angiopathy which can be classified as a cardiovascular and endocrine syndrome of unknown origin related to global warming akin to MEN. The accumulation of mucopolysaccharides can occur in the liver producing cirrhosis of the liver and in the lung producing interstitial lung disease. The mucopolysaccharide, heparan sulphate can combine with prion proteins producing amyloid deposition leading onto conformational diseases. This include the prion proteins leading onto Creutzfeldt Jakob's disease, copper zinc dismutase and motor neuron disease, alpha synuclein and Parkinson's disease and tumour suppressor protein and cancer. The relation between islet associated amyloid polypeptide and diabetes mellitus is well known. Thus the conversion of fructose to GAG results in conformational disease and amyloid accumulation.

The accumulation of fructose results in fructosylation of proteins akin to glycation of proteins. Fructosylated proteins are antigenic. This results in increased frequency of autoimmune diseases like lupus and multiple sclerosis. The conversion to glucose to fructose and its phosphorylation depletes the cell of ATP and results in membrane sodium potassium ATPase inhibition. This increases the intracellular calcium which releases neurotransmitters from presynaptic vesicles. Thus there is an increase in glutamate and monoaminergic transmission leading to schizophrenia and autism. The increase in intracellular calcium can open up the mitochondrial PT pore releasing cyto C which activates the caspase cascade and cell death. This produces neuronal degeneration.

The conversion of glucose to fructose and phosphorylation of fructose results in depletion of cellular ATP. This stops the phosphorylation of glucose by

glucokinase and generation of glucose 6 phosphate stops. The glycolytic process, the TCA cycle and its coupling to mitochondrial oxidative phosphorylation is inhibited. The body depends upon fatty acids and amino acids for energetics. The body can survive only on a ketogenic diet. The accumulated glucose forms a substrate for utilisation by endosymbiotic archaea. The archaea have glycolytic pathway which can convert glucose to pyruvate. The pyruvate can then enter the GABA shunt pathway generating succinyl CoA and glycine, the substrates for porphyrin synthesis by archaea and humans. Porphyrin supramolecular arrays or porphyrions can transfer electrons synthesizing ATP. The archaea also has a partial citric acid cycle and the pyruvate generated by archaeal glycolysis can enter the partial citric acid cycle. The citrate can be used for lipid synthesis. The acetyl CoA generated from pyruvate by archaea can be used for cholesterol synthesis. The archaea can catabolize cholesterol to generate energy. The cholesterol ring is oxidised to pyruvate and the side chain oxidised to butyrate and propionate. This can be used for mitochondrial generation of ATP. The pyruvate generated by archaeal glycolysis can also undergo a reverse citric acid cycle for carbon dioxide fixation akin to the Calvin cycle. Thus the archaeal glycolysis, partial citric acid cycle, reverse citric acid cycle of carbon dioxide fixation, cholesterol synthesis by the mevalonate and DXP pathway and cholesterol catabolism dominates. The fructose generated by conversion to glucose can enter the pentose phosphate pathway generating D xylulose phosphate and can be used to synthesize cholesterol. The archaeal pyruvate generated by glycolysis can also be converted to acetyl CoA which can enter the archaeal mevalonate pathway of cholesterol synthesis. Thus the archaea has got both pathway of cholesterol synthesis - the DXP pathway and mevalonate pathway. The fructose generated by conversion from glucose due to global warming enters the DXP pathway of cholesterol synthesis, the pentose phosphate pathway and nucleic acid synthesis

and GAG synthesis. This can lead to multiple organ dysfunction with fibrosis and mucopolysaccharide accumulation which can be called as a Lemurian syndrome. The initial group of diseases EMF, CCP, MNG and mucoid angiopathy occur south of the equator in South India, South Africa and South America. The global warming related MEN is reported from Central America and South America. MEN belongs to the group of EMF, CCP, MNG and mucoid angiopathy. This can be called as the Lemurian syndrome as South Africa, South India, Australia and parts of South America were part of one single continental entity in the long past when Neanderthals exist. The global warming and resulting conversion of glucose to fructose results in depletion of ATP due to more efficient phosphorylation of fructose over glucose. This results in ineffective glucose phosphorylation and accumulation leading to archaeal growth. The accumulated fructose is converted to D xylulose phosphate and used for the DXP pathway of cholesterol synthesis by the archaea. The cholesterol is catabolized by the endosymbiotic actinidic archaea generating digoxin. The growth of actinidic archaea results in increased porphyrin synthesis and perception of low level electromagnetic fields by dipolar porphyrin mediated quantal systems. The digoxin induced membrane sodium potassium ATPase inhibition in the setting of dipolar porphyrins in the cell can produce a pumped phonon system of quantal perception. This results in atrophy of the prefrontal cortex and cerebellar dominance leading to neanderthalisation of the human brain. This results from endosymbiotic archaeal growth resulting from metabolonomics related to global warming. The same metabolonomics related to global warming results in the genesis of the Lemurian syndrome described above.

The fructose metabolic pathway is called fructolysis. Oxidative stress and osmotic stress due to global warming and actinidic archaeal growth leads to

induction of aldose reductase. This converts glucose to sorbitol and sorbitol is acted upon by sorbitol dehydrogenase produce fructose. Fructose normally undergoes fructolysis. Glycolysis is inhibited at the level of phosphofructokinase by ATP and citrate. The fructolytic pathway and fructose metabolism is confined to the liver and certain tissues and is not under this regulatory control. Fructose is converted to fructose 1-phosphate by fructokinase. Fructose 1-phosphate is acted upon by aldolase B or fructose 1-phosphate aldolase converting it into dihydroxy acetone phosphate. Dihydroxy acetone phosphate has got two fates: It is acted upon by triose phosphate isomerase to glyceraldehyde 3-phosphate. Glyceraldehyde 3-phosphate is coverted to glucose 6-phosphate and then glucose 1-phosphate. Glucose 1-phosphate is used for glycogenesis. Dihydroxy acetone phosphate is acted upon by glycerol 3-phosphate dehydrogenase to glycerol 3-phosphate. Fructose 1-phosphate can be oxidised to pyruvate. Pyruvate can be decarboxylated to acetyl CoA. Acetyl CoA is used for fatty acid and cholesterol synthesis. Thus leads to triglyceride synthesis and VLDL formation. Fructose can thus be converted to storage glycogen, triglycerides and cholesterol. Global warming and ice age are extremophilic states. The human body goes into a state of hibernation and stores nutrients as glycogen and triglycerides. Fructose can increase lypogenic enzymes pyruvate kinase, malate dehydrogenase, citrate lyase, acetyl CoA carboxylase, pyruvate dehydrogenase and fatty acid synthase. Thus the metabolism is switched to the hibernatory mode from glucose catabolism. Glucose catabolism stops. The glucose that accumulates enters the archaeal primitive glycolytic and partial citric acid cycle as well as the GABA shunt pathway. The GABA shunt pathway of the archaea generates succinyl CoA and glycine the substrates for the porphyrin synthesis. Porphyrins can self organise to form supramolecular structures which can self replicate called porphyrions. Porphyrions are the ultimate self replicators. They can have a photoinduction induced electron transport chain and ATP synthesis. The porphyrions are dipolar

and in the setting of porphyrin intercalating cell membrane producing sodium potassium ATPase inhibition can produce a pumped phonon system. This is a superconductive state at room temperature and can produce quantal perception. The porphyrins are macromolecular structures with a wave particular existence. Porphyrions are the ultimate quantal observer and mediate the conversion of the quantal foam to the particulate world. This global warming induced fructosemia and accumulated free glucose get catabolized by partial citric acid cycle and GABA shunt of archaea to porphyrins generating porphyrions which can assume the quantal foam state and inhabit a multiverse universe with an eternal existence. The porphyrions can undergo photooxidation generating redox stress. Redox stress will further induce aldose reductase and increase fructosemia. The glucose remains unphosphorylated owing to the high km value of glucose for ketokinase as compared to fructose. The free glucose is catabolized by archaeal enzymes to porphyrins and porphyrions. The human body becomes a zombie for self replicating porphyrions. The porphyrions have quantal perception of low level of EMF. This produces prefrontal cortex atrophy and cerebellar dominance leading to neanderthalisation of the human brain. The human metabolic pathways of glycolysis and oxidative phosphorylation are blocked. The synthesis of glycogen, lipids, cholesterol and glycosaminoglycans dominates. The body switches into the anabolic hibernatory mode. The fructokinase induced by osmotic stress and oxidative stress of global warming is the switch for hibernatory mode leading onto metabolic syndrome or fat storage disease. The free glucose undergoes catabolism by archaeal glycolysis and GABA shunt to porphyrions. The porphyrins can act as a template formation of RNA viroids, DNA viroids, prions and they eventually symbiosed and live together as nanoarchaea. Thus the nanoarchaea can arise from porphyrin templates. The supramolecular porphyrin arrays can have an electron transport chain and ATP synthesis, a primitive form of mitochondria. The nanoarchaea can form as well as self replicate on porphyrin

templates. The porphyrin supramolecular arrays or porphyrions can also self replicate. The human body becomes a zombie for abiogenetic porphyrions and nanoarchaea. The porphyrions can have a macroscopic quantal existence and inhabit multiverse universes. Thus the human metabolism grinds to a halt and the world of nanoarchaea and porphyrions which are eternal steps in. The human race as we know of extincts owing to the metabolonomics of global warming. It is back to the work board of evolution once more.

This syndrome can also be called as fructosemia or fructositis. Oxidative stress can induce aldose reductase and convert glucose to fructose. The endosymbiotic archaea synthesizes digoxin by cholesterol catabolism. Digoxin inhibits membrane sodium potassium ATPase and increases intracellular calcium opening up the mitochondrial PT pore. This produces mitochondrial dysfunction and oxidative stress. Oxidative stress can induce aldose reductase and convert all glucose to fructose. Fructose has got a low km value for ketokinase compared to glucose and is preferentially phosphorylated. The glucose remains unphosphorylated and the glycolytic scheme and its coupled mitochondrial oxidative phosphorylation is slowed down or inhibited. The mitochondrial ATP and citrate can inhibit the phosophofructokinase and glycolysis, but cannot inhibit fructokinase or aldose reductase. Therefore the conversion of glucose to fructose continues. The fructose generated can inhibit mitochondrial function leading to more oxidative stress and still further induction of aldose reductase. The efficient phosphorylation of fructose depletes the cell of ATP producing oxidative stress and induction of NFKB resulting in chronic inflammation. Oxidative stress due to depletion of ATP can produce still further induction of aldose reductase and generation of fructose. The depletion of ATP makes the patient fatigue. The increase in fructose inhibits satiety and the patient feeding behaviour is altered leading onto obesity. This leads to a metabolic syndrome x. Metabolic syndrome

x is a fat storage syndrome akin to hibernation. The fructose that is generated is converted to alpha glycerophosphate which is used for triglyceride synthesis. Fructose consumption can increase triglyceride synthesis and fatty liver. The depleted ATP due to fructose phosphorylation generates AMP and ADP which is converted to uric acid by deaminases. Uric acid can inhibit mitochondrial function. Uric acid can contribute to insulin resistance and metabolic syndrome x. Uric acid can also produce endothelial dysfunction contributing to coronary artery disease and stroke. Uric acid inhibits aconitase which leads to accumulation of citrate. Uric acid can induce citrate lyase and fatty acyl CoA synthase leading onto fatty acid synthesis. The accumulated citrate can block the glycolytic pathway. The accumulated glucose gets converted to fructose by aldose reductase. Uric acid decreases reduced NADPH and oxidised NAD+. This affects the redox potential and leads to oxidative stress which further induces aldose reductase. Aldose reductase can be induced by hyperosmotic stress. This includes that created by hyperglycemia consequent to blockade of glucose phosphorylation as a result of selective fructose phosphorylation because of the low km value of fructose for ketokinase. The same mechanism operates in the dehydration induced by global warming. This leads to hyperosmolarity which induces aldose reductase. These mechanisms are similar to what happens in hibernation in animals. Hibernating animals develop a metabolic syndrome put on weight, store fat, increase triglycerides, develop fatty liver and develop insulin resistance. Hibernation and metabolic syndrome x are fat storage syndromes. The Neanderthals evolved in the cold Eurasian steppes and developed a hibernation syndrome similar to metabolic syndrome with fat storage. The stress of the ice age would have induced redox stress, induce aldose reductase and converted glucose to fructose. The fructose would have been selectively phosphorylated to fructose phosphate which would have entered the pentose phosphate pathway generating ribose for nucleic acid synthesis, the glucosamine pathway for glycosaminoglycan synthesis and/or

converted to alpha glycerophosphate for fatty acid and triglyceride synthesis. Fructosamia can also affect brain function. Fructose can inhibit BDNF and inhibit cortical growth producing a cerebellar dominant brain and prefrontal cortex atrophy. This would have resulted in neanderthalisation of the brain. The conversion of fructose phosphate to ribose via the pentose phosphate pathway increases nucleic acid synthesis and cell proliferation. This leads to oncogenesis. The cell proliferation can also contribute to the bulky phenotype of the Neanderthal population. The fructokinase enzyme acts as an obesity switch. The opening of the obesity switch also contributes to the bulky phenotype Neanderthal population. The oxidative stress and osmotic stress of the ice age and global warming can induce aldose reductase mediated conversion of glucose to fructose via the enzyme sorbitol dehydrogenase. This also leads to induction of fructokinase, generation of fructose, frucotsemia and fructositis. The increased fructose can fructosylate proteins producing antigenic proteins and autoimmune disease. Thus fructosemia can contribute to oncogenesis, metabolic syndrome x, neurodegeneration, psychiatric disorders like schizophrenia and autism as well as autoimmune disease. Fructosemia can contribute to insulin resistance. The selective phosphorylation of fructose owing to the low km value of ketokinase for fructose results in nonphosphorylation of glucose and hyperglycemia. Insulin resistance leads to further induction of aldose reductase and fructokinase. Fructose can produce ATP depletion and oxidative stress. Oxidative stress can induce NFKB producing chronic inflammation and TNF alpha can produce insulin resistance acting at the level of insulin receptor. The insulin resistance activates the aldose reductase fructokinase system still further which is also further activated by the osmotic and oxidative stress of extremes of climate like global warming and ice age. This leads to the Lemurian systemic syndrome of fructosemia and fructositis. Lemurian syndrome can produce CKD of unknown

origin, pulmonary disease, cardiovascular disease, cirrhosis liver, gastro-intestinal disease and diabetes mellitus.

The Neanderthals lived in the Eurasian Steppes which was cold. They evolved hibernatory metabolism and a fat storage syndrome to protect them from the cold. The Neanderthals evolved due to endosymbiotic archaeal growth. Endosymbiotic archaea are extremophiles and grow in extremes of climate - the ice age and global warming. The global warming results in increase in endosymbiotic archaeal growth and neanderthalisation of the homo sapien species. Neanderthalisation is a symbiotic phenomena. The global warming can lead to dehydration and osmotic stress. The archaea can catabolize cholesterol generating digoxin which can induce redox stress. Osmotic stress and redox stress leads to induction of the enzyme aldose reductase which converts glucose to sorbitol. Sorbitol is acted upon by sorbitol dehydrogenase and converted to fructose. Fructose can enter three metabolic schemes. The fructose is converted to alpha glycerophosphate and triglycerides. This results in storage of glucose and fructose as fat and a fat storage syndrome. The subcutaneous fat protects against variation in climatic temperature. The fructose can inhibit mitochondrial function and mitochondrial beta oxidation of fatty acids accentuating storage of fat. Fat can further fuel insulin resistance by fatty acids acting upon the insulin receptor. Insulin resistance leads to still further aldose reductase induction. The fructose can also enter the glucosamine pathway resulting in GAG synthesis and accumulation of mucopolysaccharides and proteoglycans. This can lead onto systemic connective tissue accumulation in visceral organs like liver producing cirrhosis, lung producing interstitial lung disease, kidney producing the MEN syndrome, the pancreas producing pancreatic fibrosis and CCP, the heart producing cardiomyopathy and EMF and the vascular tree producing mucoid angiopathy. The fructose has got a low km value for ketokinases as compared to

glucose and gets selectively phosphorylated. This results in cellular depletion of ATP and membrane sodium potassium ATPase inhibition resulting in increase of intracellular calcium. The calcium produces mitochondrial PT pore dysfunction and redox stress. Redox stress can induce aldose reductase. The depletion of ATP results in further inhibition of phosphorylation of glucose. This results in hyperglycemia. The archaea has got the glycolytic pathway, a partial citric acid cycle and a reverse citric acid cycle for carbon dioxide fixation. The archaea can induce the Warburg phenotype in the human tissues with increase glycolysis, inhibition of pyruvate dehydrogenase and mitochondrial oxidative phosphorylation inhibition. This results in accumulation of pyruvate which enters the GABA shunt scheme generating succinyl CoA and glycine for porphyrin synthesis. The accumulated glucose due to blockade of glucose phosphorylation is metabolized by archaea generating pyruvate. The pyruvate can enter the TCA cycle via pyruvate dehydrogenase generating acetyl CoA for fatty acid and cholesterol synthesis. The archaea can catabolize cholesterol and generate energy. The archaea can convert pyruvate via GABA shunt as said before to porphyrins. Thus there is increased porphyrin synthesis, cholesterol synthesis and catabolism, triglyceride synthesis, nucleic acid synthesis and GAG synthesis. The metabolic patterns changes. The blockade of glucose phosphorylation by fructose results in hyperglycemia which can block or inhibit porphyrin accumulation. The porphyrins have a wave particle existence in the macroscopic state and contributes to quantal perception or extrasensory perception in homo neanderthalis. The cellular depletion of ATP consequent to fructose phosphorylation results in generation of ADP and AMP which are acted upon by deaminases producing uric acid. Uric acid can block mitochondrial function generating redox stress and further induction of aldose reductase. Uric acid can inhibit the TCA cycle due to aconitase inhibition. This results in accumulation

of citrate which blocks glycolysis still further. The citrate is acted upon by the induced citrate lyase and fatty acid synthase producing fatty acids. This can lead to triglyceride synthesis and accumulation and a fat storage syndrome. Fatty acids can block glucose metabolism and the glycolytic pathway. The mitochondrial function is blocked by uric acid, fructose and digoxin. The porphyrin arrays can function as a supramolecular organism called porphyrions and transfer electrons and photons. This functions as a primitive form of mitochondria generating ATP. The inhibition of membrane sodium potassium ATPase due to ATP depletion results in membrane sodium potassium ATPase mediated ATP synthesis. The porphyrin array and membrane sodium potassium ATPase mediated ATP synthesis can provide for body energetics. The fructosemia can lead to increased ribose synthesis via the pentose phosphate pathway inducing nucleic acid synthesis and cell proliferation. This can lead to oncogenesis. The fructosemia can lead to fructosylation of proteins producing antigenic proteins. The depletion of ATP consequent to fructose phosphorylation can produce redox stress, NFKB activation and immune activation. This leads to autoimmune disease. Fructose can inhibit brain derived neurotrophic growth factor and lead to genesis of schizophrenia and autism. The cellular depletion of ATP due to fructose phosphorylation can lead to cell death and neurodegeneration. The low km value of fructose for ketokinase can lead to selective phosphorylation of fructose at a rapid rate depleting the cell of ATP stores. This inhibits glucose phosphorylation producing inhibition of glucose metabolism resulting in hyperglycemia and metabolic syndrome. The uric acid generated by this pathway can result in endothelial dysfunction, coronary artery disease and strokes. Thus the global warming related actinidic archaeal growth can lead onto fructositis, fructosemia and a Lemurian syndrome affecting multiple organ systems.

2

A Cholesterol and Actinide Dependent Shadow Biosphere of Archaea and Viroids in Chronic Renal Failure

Introduction

Endomyocardial fibrosis (EMF) along with the root wilt disease of coconut is endemic to Kerala with its radioactive actinide beach sands. Actinides like rutile producing intracellular magnesium deficiency due to rutile-magnesium exchange sites in the cell membrane have been implicated in the etiology of EMF.[1] Endogenous digoxin, a steroidal glycoside which functions as a membrane sodium-potassium ATPase inhibitor has also been related to its etiology due to the intracellular magnesium deficiency it produces.[2] Organisms like phytoplasmas and viroids have also been demonstrated to play a role in the etiology of these diseases.[3, 4] Endogenous digoxin has been related to the pathogenesis of chronic renal failure - chronic glomerulonephritis.[2] The possibility of endogenous digoxin synthesis by actinide based primitive organism like archaea with a mevalonate pathway and cholesterol catabolism was considered.[5-7] Davies has put forward the concept of a shadow biosphere of organisms with alternate biochemistry present in earth itself.[8] An actinide dependent shadow biosphere of archaea and viroids in the above mentioned disease states is described.[6]

Actinidic archaea has been related to global warming and human diseases. The growth of endosymbiotic actinidic archaea in relation to climate change and global warming leads to neanderthalisation of the humans. Neanderthal metabolonomics include the Warburg phenotype and cholesterol catabolism resulting in hyperdigoxinemia. Digoxin produced by archaeal cholesterol catabolism produces neanderthalisation. The neanderthalisation of the human brain due to endosymbiotic archaeal overgrowth results in prefrontal cortical atrophy and cerebellar hyperplasia. This leads on to dysautonomia with

sympathetic hyperactivity and parasympathetic neuropathy in these disorders. This can lead onto a chronic renal failure of unknown origin. Global warming can lead to osmotic stress consequent to dehydration. The increase in actinidic archaeal growth leads to cholesterol catabolism and digoxin synthesis. Digoxin produces membrane sodium potassium ATPase inhibition and increase in intracellular calcium producing mitochondrial dysfunction. This results in oxidative stress. The oxidative stress and osmotic stress can induce the enzyme aldose reductase which converts glucose to fructose. Fructose has got a low km value for ketokinase as compared to glucose. Therefore fructose gets phosphorylated more to fructose phosphate and the cell is depleted of ATP. The cell depletion of ATP leads to oxidative stress and chronic inflammation consequent to induction of NFKB. Oxidative stress can open the mitochondrial PT pore producing release of cyto C and activation of the caspase cascade of cell death. The fructose phosphate can enter the pentose phosphate pathway synthesizing ribose and nucleic acid. The depletion of cellular ATP results in generation of AMP and ADP which are acted upon by deaminases causing hyperuricemia. Uric acid can produce endothelial dysfunction and vascular disease. Uric acid can also produce mitochondrial dysfunction. The fructose phosphate can enter the glucosamine pathway synthesizing GAG and producing mucopolysaccharide accumulation. Fructose can fructosylate proteins making them antigenic and producing an autoimmune response. This is exemplified by MEN - the Mesoamerican nephropathy syndrome. The patient develops a chronic renal failure of unknown origin. There is tubular dysfunction and tubular atrophy with fibrosis. There is secondary glomurulosclerosis and mild proteinuria. There is hypokalemia and hyponatraemia. There is also hyperuricemia. Hypertension and edema is absent. MEN syndrome has been attributed to global warming related osmotic stress and induction of the enzyme aldose reductase and fructokinase. Fructose can produce renal injury. CKD of

unknown origin in the absence of diabetes and hypertension has been described in the Kerala population. This could be the basis of global warming related kidney disease.

Materials and Methods

Informed consent of the subjects and the approval of the ethics committee were obtained for the study. The following groups were included in the study: - chronic renal failure - chronic glomerulonephritis. There were 10 patients in each group and each patient had an age and sex matched healthy control selected randomly from the general population. The blood samples were drawn in the fasting state before treatment was initiated. Plasma from fasting heparinised blood was used and the experimental protocol was as follows (I) Plasma+phosphate buffered saline, (II) same as I+cholesterol substrate, (III) same as II+rutile 0.1 mg/ml, (IV) same as II+ciprofloxacine and doxycycline each in a concentration of 1 mg/ml. Cholesterol substrate was prepared as described by Richmond.[9] Aliquots were withdrawn at zero time immediately after mixing and after incubation at 37 ℃ for 1 hour. The following estimations were carried out: - Cytochrome F420, free RNA, free DNA, muramic acid, polycyclic aromatic hydrocarbon, hydrogen peroxide, serotonin, pyruvate, ammonia, glutamate, cytochrome C, hexokinase, ATP synthase, HMG CoA reductase, digoxin and bile acids.[10-13] Cytochrome F420 was estimated flourimetrically (excitation wavelength 420 nm and emission wavelength 520 nm). Polycyclic aromatic hydrocarbon was estimated by measuring hydrogen peroxide liberated by using glucose reagent. The statistical analysis was done by ANOVA.

Results

The parameters checked as indicated above were: - cytochrome F420, free RNA, free DNA, muramic acid, polycyclic aromatic hydrocarbon, hydrogen peroxide, serotonin, pyruvate, ammonia, glutamate, cytochrome C, hexokinase, ATP synthase, HMG CoA reductase, digoxin and bile acids. Plasma of control subjects showed increased levels of the above mentioned parameters with after incubation for 1 hour and addition of cholesterol substrate resulted in still further significant increase in these parameters. The plasma of patients showed similar results but the extent of increase was more. The addition of antibiotics to the control plasma caused a decrease in all the parameters while addition of rutile increased their levels. The addition of antibiotics to the patient's plasma caused a decrease in all the parameters while addition of rutile increased their levels but the extent of change was more in patient's sera as compared to controls. The results are expressed in tables 1-7 as percentage change in the parameters after 1 hour incubation as compared to the values at zero time.

Table 1. *Effect of rutile and antibiotics on muramic acid and serotonin.*

Group	Muramic acid % change (Increase with Rutile)		Muramic acid % change (Decrease with Doxy+Cipro)		5 HT % (Increase without Doxy)		5 HT % (Decrease with Doxy)	
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
Normal	4.41	0.15	18.63	0.12	4.34	0.15	18.24	0.37
CRF	23.41	1.55	66.36	4.31	23.49	1.19	64.63	6.58
F value	403.394		680.284		348.867		364.999	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 2. *Effect of rutile and antibiotics on free DNA and RNA.*

Group	DNA % change (Increase with Rutile)		DNA % change (Decrease with Doxy)		RNA % change (Increase with Rutile)		RNA % change (Decrease with Doxy)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Normal	4.37	0.15	18.39	0.38	4.37	0.13	18.38	0.48
CRF	22.52	2.06	66.09	5.73	23.34	1.58	65.76	3.91
F value	337.577		356.621		427.828		654.453	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 3. *Effect of rutile and antibiotics on HMG CoA reductase and PAH.*

Group	HMG CoA R % change (Increase with Rutile)		HMG CoA R % change (Decrease with Doxy)		PAH % change (Increase with Rutile)		PAH % change (Decrease with Doxy)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Normal	4.30	0.20	18.35	0.35	4.45	0.14	18.25	0.72
CRF	23.88	1.68	63.69	7.06	23.69	1.57	66.86	3.61
F value	319.332		199.553		391.318		257.996	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 4. *Effect of rutile and antibiotics on digoxin and bile acids.*

Group	Digoxin (ng/ml) (Increase with Rutile)		Digoxin (ng/ml) (Decrease with Doxy+Cipro)		Bile acids % change (Increase with Rutile)		Bile acids % change (Decrease with Doxy)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Normal	0.11	0.00	0.054	0.003	4.29	0.18	18.15	0.58
CRF	0.51	0.06	0.192	0.035	23.29	1.41	62.44	7.64
F value	135.116		71.706		290.441		203.651	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 5. *Effect of rutile and antibiotics on pyruvate and hexokinase.*

Group	Pyruvate % change (Increase with Rutile)		Pyruvate % change (Decrease with Doxy)		Hexokinase % change (Increase with Rutile)		Hexokinase % change (Decrease with Doxy)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Normal	4.34	0.21	18.43	0.82	4.21	0.16	18.56	0.76
CRF	21.00	2.02	61.03	7.33	22.95	1.49	65.72	4.58
F value	321.255		115.242		292.065		317.966	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 6. *Effect of rutile and antibiotics on hydrogen peroxide and delta amino levulinic acid.*

Group	H_2O_2 % (Increase with Rutile)		H_2O_2 % (Decrease with Doxy)		ALA % (Increase with Rutile)		ALA % (Decrease with Doxy)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Normal	4.43	0.19	18.13	0.63	4.40	0.10	18.48	0.39
CRF	22.63	2.02	58.08	6.30	24.00	1.64	66.04	4.36
F value	380.721		171.228		372.716		556.411	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 7. *Effect of rutile and antibiotics on ATP synthase and cytochrome F420.*

Group	ATP synthase % (Increase with Rutile)		ATP synthase % (Decrease with Doxy)		CYT F420 % (Increase with Rutile)		CYT F420 % (Decrease with Doxy)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Normal	4.40	0.11	18.78	0.11	4.48	0.15	18.24	0.66
CRF	23.22	1.35	66.42	4.21	22.46	1.75	63.22	8.22
F value	449.503		673.081		306.749		130.054	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Abbreviation

CRF: Chronic renal failure

Discussion

There was increase in cytochrome F420 indicating archaeal growth in chronic renal failure - chronic glomerulonephritis. The archaea can synthesize and use cholesterol as a carbon and energy source.[14, 15] The archaeal origin of the enzyme activities was indicated by antibiotic induced suppression. The study indicates the presence of actinide based archaea with an alternate actinide based enzymes or metalloenzymes in the system as indicated by rutile induced increase in enzyme activities.[16] There was also an increase in archaeal HMG CoA reductase activity indicating increased cholesterol synthesis by the archaeal mevalonate pathway. The archaeal beta hydroxyl steroid dehydrogenase activity indicating digoxin synthesis and archaeal cholesterol hydroxylase activity indicating bile acid synthesis were increased.[7] The archaeal cholesterol oxidase activity was increased resulting in generation of pyruvate and hydrogen peroxide.[15] The pyruvate gets converted to glutamate and ammonia by the GABA shunt pathway. The archaeal aromatization of cholesterol generating PAH, serotonin and dopamine was also detected.[17] The archaeal glycolytic hexokinase activity and archaeal extracellular ATP synthase activity were increased. The archaea can undergo magnetite and calcium carbonate mineralization and can exist as calcified nanoforms.[18] There was an increase in free RNA indicating self replicating RNA viroids and free DNA indicating generation of viroid complementary DNA strands by archaeal reverse transcriptase activity. The actinides modulate RNA folding and catalyse its ribozymal action. Digoxin can cut and paste the viroidal strands by modulating

RNA splicing generating RNA viroidal diversity. The viroids are evolutionarily escaped archaeal group I introns which have retrotransposition and self splicing qualities.[19] Archaeal pyruvate can produce histone deacetylase inhibition resulting in endogenous retroviral (HERV) reverse transcriptase and integrase expression. This can integrate the RNA viroidal complementary DNA into the noncoding region of eukaryotic non coding DNA using HERV integrase as has been described for borna and ebola viruses.[20] The noncoding DNA is lengthened by integrating RNA viroidal complementary DNA with the integration going on as a continuing event. The archaea genome can also get integrated into human genome using integrase as has been described for trypanosomes.[21] The integrated viroids and archaea can undergo vertical transmission and can exist as genomic parasites.[20, 21] This increases the length and alters the grammar of the noncoding region producing memes or memory of acquired characters.[22] The viroidal complementary DNA can function as jumping genes producing a dynamic genome important in HLA gene expression. This modulation of HLA gene expression by viroidal complementary DNA can result in immune activation. The RNA viroids can regulate mRNA function by RNA interference.[19] The phenomena of RNA interference can modulate T cell and B cell function and euchromatin/heterochromatin expression. RNA viroidal mRNA interference plays a role in the pathogenesis of chronic renal failure - chronic glomerulonephritis due to immune activation.

The presence of muramic acid, HMG CoA reductase and cholesterol oxidase activity inhibited by antibiotics indicates the presence of bacteria with mevalonate pathway. The bacterial with mevalonate pathway include streptococcus, staphylococcus, actinomycetes, listeria, coxiella and borrelia.[23] The bacteria and archaea with mevalonate pathway and cholesterol catabolism had a evolutionarily advantage and constitutes the isoprenoidal clade organism

with the archaea evolving into mevalonate pathway gram positive and gram negative organism through horizontal gene transfer of viroidal and virus genes.[24] The isoprenoidal clade prokaryotes develop into other groups of prokaryotes via viroidal/virus as well as eukaryotic horizontal gene transfer producing bacterial speciation.[25] The RNA viroids and its complementary DNA developed into cholesterol enveloped RNA and DNA viruses like herpes, retrovirus, influenza virus, borna virus, cytomegalo virus and Ebstein Barr virus by recombining with eukaryotic and human genes resulting in viral speciation. Bacterial and viral species are ill defined and fuzzy with all of them forming one common genetic pool with frequent horizontal gene transfer and recombination. Thus the multi and unicellular eukaryote with its genes serves the purpose of prokaryotic and viral speciation. The multicellular eukaryote developed so that their endosymbiotic archaeal colonies could survive and forage better. The multicellular eukaryotes are like bacterial biofilms. The archaea and bacteria with a mevalonate pathway uses the extracellular RNA viroids and DNA viroids for quorum sensing and in the generation of symbiotic biofilm like structures which develop into multicellular eukaryotes.[26, 27] The endosymbiotic archaea and bacteria with mevalonate pathway still uses the RNA viroids and DNA viroids for the regulation of muticellular eukaryote. Pollution is induced by the primitive nanoarchaea and mevalonate pathway bacteria synthesised PAH and methane leading on to redox stress. Redox stress leads to sodium potassium ATPase inhibition, inward movement of plasma membrane cholesterol, defective SREBP sensing, increased cholesterol synthesis and nanoarchaeal/mevalonate pathway bacterial growth.[28] Redox stress leads on to viroidal and archaeal multiplication. Redox stress can also lead to HERV reverse transcriptase and integrase expression. The noncoding DNA is formed of integrating RNA viroidal complementary DNA and archaea with the integration going on as a continuing event. The archaeal pox like

dsDNA virus forms evolutionarily the nucleus. The integrated viroidal, archaeal and mevalonate pathway bacterial sequences can undergo vertical transmission and can exist as genomic parasites. The genomic integrated archaea, mevalonate pathway bacteria and viroids form a genomic reserve of bacteria and viruses which can recombine with human and eukaryotic genes producing bacterial and viral speciation. Bacteria and viruses have been related to the pathogenesis of chronic renal failure- chronic glomerulonephritis.[29, 30] The change in the length and grammar of the noncoding region produces eukaryotic speciation and individuality.[31] Changes in the length of noncoding region especially human endogenous retroviruses can lead onto immune activation and autoimmune diseases.[32] The integration of nanoarchaea, mevalonate pathway prokaryotes and viroids in to the eukaryotic and human genome produces a chimera which can multiply producing biofilm like multicellular structures having a mixed archaeal, viroidal, prokaryotic and eukaryotic characters which is a regression from the multicellular eukaryotic tissue This results in a new neuronal, metabolic, immune and tissue phenotype or microchimeras leading to human diseases like chronic renal failure - chronic glomerulonephritis. The microchimeras formed can lead to autoantigens and immune activation resulting in chronic renal failure- chronic glomerulonephritis.

Archaea and RNA viroid can bind the TLR receptor induce NFKB producing immune activation and cytokine TNF alpha secretion. The archaeal DXP and mevalonate pathway metabolites can bind γδ TCR and digoxin induced calcium signalling can activate NFKB producing chronic immune activation.[2, 33] The archaeal cholesterol aromatase generated PAH can produce immune activation. The archaea and viroid induced chronic immune activation and generation of superantigens can lead on to immune activation and autoimmune disease.

Immune activation has been related to the pathogenesis of chronic renal failure-chronic glomerulonephritis.[29, 30]

The archaea and viroids can regulate the nervous system including the NMDA synaptic transmission.[2] NMDA can be activated by digoxin induced calcium oscillations, PAH and viroid induced RNA interference.[2] The cholesterol ring oxidase generated pyruvate can be converted by the GABA shunt pathway to glutamate. The archaeal cholesterol aromatase can generate serotonin.[17] Glutamatergic and serotoninergic transmission can lead to immune activation. Immune activation mediated by neurotransmitters can contribute to chronic renal failure - chronic glomerulonephritis. The higher degree of integration of the archaea into the genome produces increased digoxin synthesis producing right hemispheric dominance and lesser degree producing left hemispheric dominance.[2] Right hemispheric dominance can lead to chronic renal failure - chronic glomerulonephritis.[2]

Archaea, viroids and digoxin can induce the host AKT PI3K, AMPK, HIF alpha and NFKB producing the Warburg metabolic phenotype.[34] The increased glycolytic hexokinase activity, decrease in blood ATP, leakage of cytochrome C, increase in serum pyruvate and decrease in acetyl CoA indicates the generation of the Warburg phenotype. There is induction of glycolysis, inhibition of PDH activity and mitochondrial dysfunction resulting in inefficient energetics. The lymphocytes depend on glycolysis for their energy needs. The increased glycolysis induced by the Warburg phenotype leads to immune activation. Lactic acid generated by increased glycolysis leads to immune stimulation. Immune activation consequent to the generation of the Warburg phenotype can lead to chronic renal failure - chronic glomerulonephritis. Cholesterol oxidase activity, increased glycolysis related NADPH oxidase activity, bacterial porphyrin induced redox stress and mitochondrial dysfunction generates free

radicals important in the pathogenesis of chronic renal failure - chronic glomerulonephritis. The accumulated pyruvate enters the GABA shunt pathway and is converted to citrate which is acted upon by citrate lyase and converted to acetyl CoA, used for cholesterol synthesis.[34] The pyruvate can be converted to glutamate and ammonia which is oxidised by archaea for energy needs. The increased cholesterol substrate leads to increased archaeal growth and digoxin synthesis leading to metabolic channelling to the mevalonate pathway. Hyperdigoxinemia is important in the pathogenesis of chronic renal failure - chronic glomerulonephritis.[2] Digoxin can increase lymphocytic intracellular calcium which leads on to induction of NFKB and immune activation.[2] The archaeal cholesterol catabolism can deplete the lymphocytic cell membranes of cholesterol resulting in alteration of lymphocytic cell membrane microdomains related receptors producing immune activation. Digoxin and membrane cholesterol depletion induced immune activation can contribute to chronic renal failure - chronic glomerulonephritis. The archaeal bile acids can bind GPCR and modulate D2 regulating the conversion of T4 to T3. T3 activates uncoupling proteins reducing redox stress. Bile acids can also activate NRF ½ inducing NQO1, GST, HOI reducing redox stress. Bile acids can bind PXR inducing the bile acid shunt pathway of cholesterol detoxification. Bile acids can bind macrophage GPCR and VDR producing immunosuppression and inhibiting NFKB. This helps to modulate the archaea and viroid induced chronic immune activation. Bile acids are thus protective compounds and put a break on the archaea and viroid induced changes.[35] Thus the actinide, viroid and mevalonate pathway bacteria induced metabolic, genetic, immune and neuronal transmission changes can lead onto chronic renal failure - chronic glomerulonephritis.

Global warming can lead to osmotic stress consequent to dehydration. The increase in actinidic archaeal growth leads to cholesterol catabolism and digoxin synthesis. Digoxin produces membrane sodium potassium ATPase inhibition and increase in intracellular calcium producing mitochondrial dysfunction. This results in oxidative stress. The oxidative stress and osmotic stress can induce the enzyme aldose reductase which converts glucose to fructose. Fructose has got a low km value for ketokinase as compared to glucose. Therefore fructose gets phosphorylated more to fructose phosphate and the cell is depleted of ATP. The cell depletion of ATP leads to oxidative stress and chronic inflammation consequent to induction of NFKB. Oxidative stress can open the mitochondrial PT pore producing release of cyto C and activation of the caspase cascade of cell death. The fructose phosphate can enter the pentose phosphate pathway synthesizing ribose and nucleic acid. The depletion of cellular ATP results in generation of AMP and ADP which are acted upon by deaminases causing hyperuricemia. Uric acid can produce endothelial dysfunction and vascular disease. Uric acid can also produce mitochondrial dysfunction. The fructose phosphate can enter the glucosamine pathway synthesizing GAG and producing mucopolysaccharide accumulation. Fructose can fructosylate proteins making them antigenic and producing an autoimmune response. This can lead to global warming related kidney disease.

References

[1] Valiathan M. S., Somers, K., Kartha, C. C. (1993). *Endomyocardial Fibrosis.* Delhi: Oxford University Press.

[2] Kurup R., Kurup, P. A. (2009). *Hypothalamic digoxin, cerebral dominance and brain function in health and diseases*. New York: Nova Science Publishers.

[3] Hanold D., Randies, J. W. (1991). Coconut cadang-cadang disease and its viroid agent, *Plant Disease,* 75, 330-335.

[4] Edwin B. T., Mohankumaran, C. (2007). Kerala wilt disease phytoplasma: Phylogenetic analysis and identification of a vector, *Proutista moesta*, *Physiological and Molecular Plant Pathology*, 71(1-3), 41-47.

[5] Eckburg P. B., Lepp, P. W., Relman, D. A. (2003). Archaea and their potential role in human disease, *Infect Immun*, 71, 591-596.

[6] Adam Z. (2007). Actinides and Life's Origins, *Astrobiology*, 7, 6-10.

[7] Schoner W. (2002). Endogenous cardiac glycosides, a new class of steroid hormones, *Eur J Biochem*, 269, 2440-2448.

[8] Davies P. C. W., Benner, S. A., Cleland, C. E., Lineweaver, C. H., McKay, C. P., Wolfe-Simon, F. (2009). Signatures of a Shadow Biosphere, *Astrobiology*, 10, 241-249.

[9] Richmond W. (1973). Preparation and properties of a cholesterol oxidase from nocardia species and its application to the enzymatic assay of total cholesterol in serum, *Clin Chem*, 19, 1350-1356.

[10] Snell E. D., Snell, C. T. (1961). *Colorimetric Methods of Analysis.* Vol 3A. New York: Van Nostrand.

[11] Glick D. (1971). *Methods of Biochemical Analysis.* Vol 5. New York: Interscience Publishers.

[12] Colowick, Kaplan, N. O. (1955). *Methods in Enzymology.* Vol 2. New York: Academic Press.

[13] Maarten A. H., Marie-Jose, M., Cornelia, G., van Helden-Meewsen, Fritz, E., Marten, P. H. (1995). Detection of muramic acid in human spleen, *Infection and Immunity*, 63(5), 1652-1657.

[14] Smit A., Mushegian, A. (2000). Biosynthesis of isoprenoids via mevalonate in Archaea: the lost pathway, *Genome Res*, 10(10), 1468-84.

[15] Van der Geize R., Yam, K., Heuser, T., Wilbrink, M. H., Hara, H., Anderton, M. C. (2007). A gene cluster encoding cholesterol catabolism in a soil actinomycete provides insight into Mycobacterium tuberculosis survival in macrophages, *Proc Natl Acad Sci USA*, 104(6), 1947-52.

[16] Francis A. J. (1998). Biotransformation of uranium and other actinides in radioactive wastes, *Journal of Alloys and Compounds*, 271(273), 78-84.

[17] Probian C., Wülfing, A., Harder, J. (2003). Anaerobic mineralization of quaternary carbon atoms: Isolation of denitrifying bacteria on pivalic acid (2,2-Dimethylpropionic acid), *Applied and Environmental Microbiology*, 69(3), 1866-1870.

[18] Vainshtein M., Suzina, N., Kudryashova, E., Ariskina, E. (2002). New Magnet-Sensitive Structures in Bacterial and Archaeal Cells, *Biol Cell*, 94(1), 29-35.

[19] Tsagris E. M., de Alba, A. E., Gozmanova, M., Kalantidis, K. (2008). Viroids, *Cell Microbiol*, 10, 2168.

[20] Horie M., Honda, T., Suzuki, Y., Kobayashi, Y., Daito, T., Oshida, T. (2010). Endogenous non-retroviral RNA virus elements in mammalian genomes, *Nature*, 463, 84-87.

[21] Hecht M., Nitz, N., Araujo, P., Sousa, A., Rosa, A., Gomes, D. (2010). Genes from Chagas parasite can transfer to humans and be passed on to children. Inheritance of DNA Transferred from American Trypanosomes to Human Hosts, *PLoS ONE*, 5, 2-10.

[22] Flam F. (1994). Hints of a language in junk DNA, *Science*, 266, 1320.

[23] Horbach S., Sahm, H., Welle, R. (1993). Isoprenoid biosynthesis in bacteria: two different pathways? *FEMS Microbiol Lett*, 111, 135-140.

[24] Gupta R. S. (1998). Protein phylogenetics and signature sequences: a reappraisal of evolutionary relationship among archaebacteria, eubacteria, and eukaryotes, *Microbiol Mol Biol Rev*, 62, 1435-1491.

[25] Hanage W., Fraser, C., Spratt, B. (2005). Fuzzy species among recombinogenic bacteria, *BMC Biology*, 3, 6-10.

[26] Webb J. S., Givskov, M., Kjelleberg, S. (2003). Bacterial biofilms: prokaryotic adventures in multicellularity, *Curr Opin Microbiol*, 6(6), 578-85.

[27] Whitchurch C. B., Tolker-Nielsen, T., Ragas, P. C., Mattick, J. S. (2002). Extracellular DNA Required for Bacterial Biofilm Formation. *Science*, 295(5559), 1487.

[28] Chen Y., Cai, T., Wang, H., Li, Z., Loreaux, E., Lingrel, J. B. (2009). Regulation of intracellular cholesterol distribution by Na/K-ATPase, *J Biol Chem*, 284(22), 14881-90.

[29] Fauci A. S. (2009). *Harrison's Principles of Internal Medicine*. New York: McGraw-Hill.

[30] Brenner B. M. (2000). *The Kidney*, 5th edn. Philadelphia: Saunders.

[31] Poole A. M. (2006). Did group II intron proliferation in an endosymbiont-bearing archaeon create eukaryotes? *Biol Direct*, 1, 36-40.

[32] Villarreal L. P. (2006). How viruses shape the tree of life, *Future Virology*, 1(5), 587-595.

[33] Eberl M., Hintz, M., Reichenberg, A., Kollas, A., Wiesner, J., Jomaa, H. (2010). Microbial isoprenoid biosynthesis and human γδ T cell activation, *FEBS Letters*, 544(1), 4-10.

[34] Wallace D. C. (2005). Mitochondria and Cancer: Warburg Addressed, *Cold Spring Harbor Symposia on Quantitative Biology*, 70, 363-374.

[35] Lefebvre P., Cariou, B., Lien, F., Kuipers, F., Staels, B. (2009). Role of Bile Acids and Bile Acid Receptors in Metabolic Regulation, *Physiol Rev*, 89(1), 147-191.

3

A Cholesterol and Actinide Dependent Shadow Biosphere of Archaea and Viroids in Cardiovascular Disease

Introduction

The human body synthesises an endogenous sodium potassium ATPase inhibitor digoxin which plays a role in neuro-immuno-endocrine integration as well as in cardiovascular / metabolic disorders. Endomyocardial fibrosis (EMF) along with the root wilt disease of coconut is endemic to Kerala with its radioactive actinide beach sands. Actinides like rutile producing intracellular magnesium deficiency due to rutile-magnesium exchange sites in the cell membrane has been implicated in the etiology of EMF.[1] Endogenous digoxin, a steroidal glycoside which functions as a membrane sodium-potassium ATPase inhibitor has also been related to its etiology due to the intracellular magnesium deficiency it produces.[2] Organisms like phytoplasmas and viroids have also been demonstrated to play a role in the etiology of these diseases.[3, 4] Endogenous digoxin has been related to the pathogenesis of type 2 diabetes mellitus, coronary artery disease and cerebrovascular disease.[2] The possibility of endogenous digoxin synthesis by actinide based primitive organism like archaea with a mevalonate pathway and cholesterol catabolism was considered.[5-7] Davies has put forward the concept of a shadow biosphere of organisms with alternate biochemistry present in earth itself.[8] An actinide dependent shadow biosphere of archaea and viroids in the above mentioned disease states is described.[6] The intracellular endosymbionts archaea and their intron derived viroids constitute the third element regulating the human body.

Actinidic archaea has been related to global warming and human diseases. The growth of endosymbiotic actinidic archaea in relation to climate change and global warming leads to neanderthalisation of the humans. Neanderthal metabolonomics include the Warburg phenotype and cholesterol catabolism

resulting in hyperdigoxinemia. Digoxin produced by archaeal cholesterol catabolism produces neanderthalisation. The neanderthalisation of the human brain due to endosymbiotic archaeal overgrowth results in prefrontal cortical atrophy and cerebellar hyperplasia. This leads on to dysautonomia with sympathetic hyperactivity and parasympathetic neuropathy in these disorders.

Global warming can lead to osmotic stress consequent to dehydration. The increase in actinidic archaeal growth leads to cholesterol catabolism and digoxin synthesis. Digoxin produces membrane sodium potassium ATPase inhibition and increase in intracellular calcium producing mitochondrial dysfunction. This results in oxidative stress. The oxidative stress and osmotic stress can induce the enzyme aldose reductase which converts glucose to fructose. Fructose has got a low km value for ketokinase as compared to glucose. Therefore fructose gets phosphorylated more to fructose phosphate and the cell is depleted of ATP. The cell depletion of ATP leads to oxidative stress and chronic inflammation consequent to induction of NFKB. Oxidative stress can open the mitochondrial PT pore producing release of cyto C and activation of the caspase cascade of cell death. The fructose phosphate can enter the pentose phosphate pathway synthesizing ribose and nucleic acid. The depletion of cellular ATP results in generation of AMP and ADP which are acted upon by deaminases causing hyperuricemia. Uric acid can produce endothelial dysfunction and vascular disease. Uric acid can also produce mitochondrial dysfunction. The fructose phosphate can enter the glucosamine pathway synthesizing GAG and producing mucopolysaccharide accumulation. Fructose can fructosylate proteins making them antigenic and producing an autoimmune response. This can lead to global warming related cardiac and vascular disease.

Materials and Methods

Informed consent of the subjects and the approval of the ethics committee were obtained for the study. The following groups were included in the study: - type 2 diabetes mellitus, coronary artery disease - acute coronary syndrome and acute cerebrovascular thrombotic stroke. The coronary artery disease and cerebrovascular disease patients chosen for the study did not have type 2 diabetes mellitus as a risk factor. There were 10 patients in each group and each patient had an age and sex matched healthy control selected randomly from the general population. The blood samples were drawn in the fasting state before treatment was initiated. Plasma from fasting heparinised blood was used and the experimental protocol was as follows (I) Plasma+phosphate buffered saline, (II) same as I+cholesterol substrate, (III) same as II+rutile 0.1 mg/ml, (IV) same as II+ciprofloxacine and doxycycline each in a concentration of 1 mg/ml. Cholesterol substrate was prepared as described by Richmond.[9] Aliquots were withdrawn at zero time immediately after mixing and after incubation at 37 ℃ for 1 hour. The following estimations were carried out: - Cytochrome F420, free RNA, free DNA, muramic acid, polycyclic aromatic hydrocarbon, hydrogen peroxide, serotonin, pyruvate, ammonia, glutamate, cytochrome C, hexokinase, ATP synthase, HMG CoA reductase, digoxin and bile acids.[10-13] Cytochrome F420 was estimated flourimetrically (excitation wavelength 420 nm and emission wavelength 520 nm). Polycyclic aromatic hydrocarbon was estimated by measuring hydrogen peroxide liberated by using glucose reagent. The statistical analysis was done by ANOVA.

Results

The parameters checked as indicated above were: - cytochrome F420, free RNA, free DNA, muramic acid, polycyclic aromatic hydrocarbon, hydrogen peroxide, serotonin, pyruvate, ammonia, glutamate, cytochrome C, hexokinase, ATP synthase, HMG CoA reductase, digoxin and bile acids. Plasma of control subjects showed increased levels of the above mentioned parameters with after incubation for 1 hour and addition of cholesterol substrate resulted in still further significant increase in these parameters. The plasma of patients showed similar results but the extent of increase was more. The addition of antibiotics to the control plasma caused a decrease in all the parameters while addition of rutile increased their levels. The addition of antibiotics to the patient's plasma caused a decrease in all the parameters while addition of rutile increased their levels but the extent of change was more in patient's sera as compared to controls. The results are expressed in tables 1-7 as percentage change in the parameters after 1 hour incubation as compared to the values at zero time.

Table 1. *Effect of rutile and antibiotics on muramic acid and cytochrome F420.*

Group	Muramic acid % (Increase with Rutile)		Muramic acid % (Decrease with Doxy)		CYT F420 % (Increase with rutile)		CYT F420 % (Decrease with Doxy)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Normal	4.41	0.15	18.63	0.12	4.48	0.15	18.24	0.66
DM	24.10	1.61	65.78	4.43	22.59	1.86	57.05	8.45
CAD	23.34	1.75	66.80	3.43	22.76	2.26	60.49	6.86
CVA	22.94	1.99	68.30	2.52	21.01	2.29	62.37	8.01
F value	403.394		680.284		306.749		130.054	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 2. *Effect of rutile and antibiotics on free DNA and RNA.*

Group	DNA % change (Increase with Rutile)		DNA % change (Decrease with Doxy)		RNA % change (Increase with Rutile)		RNA % change (Decrease with Doxy)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Normal	4.37	0.15	18.39	0.38	4.37	0.13	18.38	0.48
DM	23.01	1.67	65.35	3.56	23.33	1.86	66.46	3.65
CAD	23.12	1.71	65.12	5.58	24.01	1.17	66.66	3.84
CVA	22.51	1.85	63.56	5.29	22.95	1.90	66.39	3.83
F value	337.577		356.621		427.828		654.453	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 3. *Effect of rutile and antibiotics on HMG CoA reductase and PAH.*

Group	HMG CoA R % change (Increase with Rutile)		HMG CoA R % change (Decrease with Doxy)		PAH % change (Increase with Rutile)		PAH % change (Decrease with Doxy)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Normal	4.30	0.20	18.35	0.35	4.45	0.14	18.25	0.72
DM	23.06	1.65	62.25	6.24	23.40	1.55	65.77	5.27
CAD	23.63	1.58	61.19	7.03	22.22	2.33	61.73	6.33
CVA	22.51	2.47	60.77	5.89	23.87	1.64	66.01	5.78
F value	319.332		199.553		391.318		257.996	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 4. *Effect of rutile and antibiotics on digoxin and bile acids.*

Group	Digoxin (ng/ml) (Increase with Rutile)		Digoxin (ng/ml) (Decrease with Doxy+Cipro)		Bile acids % change (Increase with Rutile)		Bile acids % change (Decrease with Doxy)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Normal	0.11	0.00	0.054	0.003	4.29	0.18	18.15	0.58
DM	0.47	0.04	0.202	0.025	22.87	2.58	64.51	5.93
CAD	0.49	0.07	0.202	0.021	22.22	2.44	63.47	6.98
CVA	0.51	0.07	0.195	0.023	22.33	2.18	62.20	6.33
F value	135.116		71.706		290.441		203.651	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 5. *Effect of rutile and antibiotics on pyruvate and hexokinase.*

Group	Pyruvate % change (Increase with Rutile)		Pyruvate % change (Decrease with Doxy)		Hexokinase % change (Increase with Rutile)		Hexokinase % change (Decrease with Doxy)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Normal	4.34	0.21	18.43	0.82	4.21	0.16	18.56	0.76
DM	20.67	1.38	58.75	8.12	23.23	1.88	65.11	5.14
CAD	20.16	1.07	57.08	9.83	21.88	2.11	65.02	4.40
CVA	20.60	1.81	58.97	7.03	21.98	2.12	65.78	6.08
F value	321.255		115.242		292.065		317.966	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 6. *Effect of rutile and antibiotics on ATP synthase and hydrogen peroxide.*

Group	ATP synthase % (Increase with Rutile)		ATP synthase % (Decrease with Doxy)		H_2O_2 % (Increase with Rutile)		H_2O_2 % (Decrease with Doxy)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Normal	4.40	0.11	18.78	0.11	4.43	0.19	18.13	0.63
DM	23.72	1.73	66.25	3.69	23.27	1.53	58.91	6.09
CAD	23.78	1.20	66.90	4.10	23.24	1.85	57.08	7.42
CVA	23.47	1.60	66.27	3.88	23.32	1.60	61.45	7.01
F value	449.503		673.081		380.721		171.228	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 7. *Effect of rutile and antibiotics on serotonin and delta amino levulinic acid.*

Group	5 HT % (Increase with Rutile)		5 HT % (Decrease with Doxy)		PORPHYRIN % (Increase with Rutile)		PORPHYRIN % (Decrease with Doxy)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Normal	4.34	0.15	18.24	0.37	4.40	0.10	18.48	0.39
DM	22.73	2.46	65.87	4.35	22.87	1.84	66.31	3.68
CAD	22.42	1.99	61.14	3.47	23.81	1.90	66.95	3.67
CVA	23.35	1.83	63.73	6.52	23.73	1.70	66.44	3.92
F value	348.867		364.999		372.716		556.411	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Abbreviations

DM: Type 2 diabetes mellitus

CAD: Coronary artery disease

CVA: Cerebrovascular thrombosis

Discussion

There was increase in cytochrome F420 indicating archaeal growth in type 2 diabetes mellitus, coronary artery disease and cerebrovascular disease. The archaea can synthesise and use cholesterol as a carbon and energy source.[14, 15] The archaeal origin of the enzyme activities was indicated by antibiotic induced suppression. The study indicates the presence of actinide based archaea with an alternate actinide based enzymes or metalloenzymes in the system as indicated by rutile induced increase in enzyme activities.[16] There was also an increase in archaeal HMG CoA reductase activity indicating increased cholesterol synthesis by the archaeal mevalonate pathway. The archaeal beta hydroxyl steroid dehydrogenase activity indicating digoxin synthesis and archaeal cholesterol hydroxylase activity indicating bile acid synthesis were increased.[7] The archaeal cholesterol oxidase activity was increased resulting in generation of pyruvate and hydrogen peroxide.[15] The pyruvate gets converted to glutamate and ammonia by the GABA shunt pathway. The archaeal aromatization of cholesterol generating PAH, serotonin and dopamine was also detected.[17] The archaeal glycolytic hexokinase activity and archaeal extracellular ATP synthase activity were increased. The archaea can undergo magnetite and calcium carbonate mineralization and can exist as calcified nanoforms.[18] There was an increase in free RNA indicating self replicating RNA viroids and free DNA

indicating generation of viroid complementary DNA strands by archaeal reverse transcriptase activity. The actinides modulate RNA folding and catalyse its ribozymal action. Digoxin can cut and paste the viroidal strands by modulating RNA splicing generating RNA viroidal diversity. The viroids are probably escaped archaeal group I introns which have retrotransposition and self splicing qualities.[19] The decrease in free self replicating RNA and DNA with the addition of antibiotics indicates that the RNA viroids are derived from archaeal introns. Archaeal pyruvate can produce histone deacetylase inhibition resulting in endogenous retroviral (HERV) reverse transcriptase and integrase expression. This can integrate the RNA viroidal complementary DNA into the noncoding region of eukaryotic noncoding DNA using HERV integrase as has been described for borna and ebola viruses.[20] The noncoding DNA is lengthened by integrating RNA viroidal complementary DNA with the integration going on as a continuing event. The archaea genome can also get integrated into human genome using integrase as has been described for trypanosomes.[21] The integrated viroids and archaea can undergo vertical transmission and can exist as genomic parasites.[20, 21] This increases the length and alters the grammar of the noncoding region producing memes or memory of acquired characters.[22] The viroidal complementary DNA can function as jumping genes producing a dynamic genome and changing DNA sequences. The type 2 diabetes mellitus has been related to altered genomic sequences mediated by HERV jumping genes. HERV particles have been related to the etiology of type 1 diabetes mellitus an autoimmune disease. The RNA viroids can regulate mRNA function by RNA interference.[19] The phenomena of RNA interference can modulate euchromatin / heterochromatin expression. RNA viroidal mRNA interference plays a role in the pathogenesis of type 2 diabetes mellitus, coronary artery disease and cerebrovascular disease. Viroidal RNA mediated mRNA interference can modulate lipid metabolism triggering of dyslipidemias

important in atherogenesis. The viroidal RNA modulation of T cell and B cell function by mRNA interference can lead to immune activation. Monocytic infiltration of the vascular wall is important in atherogenesis. Insulin resistance due to TNF alpha modulation of the insulin receptor can contribute to type 2 diabetes mellitus. The viroidal RNA mediated mRNA interference can also modulate insulin signalling and secretion leading onto type 2 diabetes mellitus.

The presence of muramic acid, HMG CoA reductase and cholesterol oxidase activity inhibited by antibiotics indicates the presence of bacteria with mevalonate pathway. The bacterial with mevalonate pathway include streptococcus, staphylococcus, actinomycetes, listeria, coxiella and borrelia.[23] The bacteria and archaea with mevalonate pathway and cholesterol catabolism had a evolutionarily advantage and constitutes the isoprenoidal clade organism with the archaea evolving into mevalonate pathway gram positive and gram negative organism through horizontal gene transfer of viroidal and virus genes.[24] The isoprenoidal clade prokaryotes develop into other groups of prokaryotes via viroidal/virus as well as eukaryotic horizontal gene transfer producing bacterial speciation.[25] The RNA viroids and its complementary DNA developed into cholesterol enveloped RNA and DNA viruses like herpes, retrovirus, influenza virus, borna virus, cytomegalo virus and Ebstein Barr virus by recombining with eukaryotic and human genes resulting in viral speciation. Bacterial and viral species are ill defined and fuzzy with all of them forming one common genetic pool with frequent horizontal gene transfer and recombination. Thus the multi and unicellular eukaryote with its genes serves the purpose of prokaryotic and viral speciation. The multicellular eukaryote developed so that their endosymbiotic archaeal colonies could survive and forage better. The multicellular eukaryotes are like bacterial biofilms. The archaea and bacteria with a mevalonate pathway uses the extracellular RNA

viroids and DNA viroids for quorum sensing and in the generation of symbiotic biofilm like structures which develop into multicellular eukaryotes.[26, 27] The endosymbiotic archaea and bacteria with mevalonate pathway still uses the RNA viroids and DNA viroids for the regulation of muticellular eukaryote. Pollution is induced by the primitive nanoarchaea and mevalonate pathway bacteria synthesised PAH and methane leading on to redox stress. Redox stress leads to sodium potassium ATPase inhibition, inward movement of plasma membrane cholesterol, defective SREBP sensing, increased cholesterol synthesis and nanoarchaeal/mevalonate pathway bacterial growth.[28] Redox stress leads on to viroidal and archaeal multiplication. Redox stress can also lead to HERV reverse transcriptase and integrase expression. The noncoding DNA is formed of integrating RNA viroidal complementary DNA and archaea with the integration going on as a continuing event. The archaeal pox like dsDNA virus forms evolutionarily the nucleus. The integrated viroidal, archaeal and mevalonate pathway bacterial sequences can undergo vertical transmission and can exist as genomic parasites. The genomic integrated archaea, mevalonate pathway bacteria and viroids form a genomic reserve of bacteria and viruses which can recombine with human and eukaryotic genes producing bacterial and viral speciation. Bacteria and viruses have been related to the pathogenesis of atherogenesis and type 2 diabetes mellitus. Archaea, chlamydia, rickettsia, mycoplasma, cytomegalovirus and herpes virus has been related to the etiology of atherosclerosis.[29] Type 2 diabetes mellitus is related to an acute phase response and TNF alpha mediated insulin resistance. Persistent bacterial and viroid symbiosis can lead to immune activation and TNF alpha mediated insulin resistance.[30] The change in the length and grammar of the noncoding region produces eukaryotic speciation and individuality.[31] Changes in the length of noncoding region especially human endogenous retroviruses can lead onto type 2 diabetes mellitus, coronary artery disease and cerebrovascular disease.[32]

HERV sequences functioning as jumping genes can produce alteration in DNA sequences contributing to type 2 diabetes mellitus.[32] The viroid complementary DNA integrated into the genome can also function as jumping genes producing new genomic sequences leading onto type 2 diabetes mellitus. The integration of nanoarchaea, mevalonate pathway prokaryotes and viroids in to the eukaryotic and human genome produces a chimera which can multiply producing biofilm like multicellular structures having a mixed archaeal, viroidal, prokaryotic and eukaryotic characters which is a regression from the multicellular eukaryotic tissue. This results in a new metabolic and immune phenotype leading to human diseases like type 2 diabetes mellitus, coronary artery disease and cerebrovascular disease. The microchimeras formed can lead to atherogenesis and type 2 diabetes mellitus.

Archaea and RNA viroid can bind the TLR receptor induce NFKB producing immune activation and cytokine TNF alpha secretion. The archaeal DXP and mevalonate pathway metabolites can bind γδ TCR and digoxin induced calcium signalling can activate NFKB producing chronic immune activation.[2, 33] The archaea and viroid induced chronic immune activation and generation of superantigens. Immune activation results in induction of NADPH oxidase which generates hydrogen peroxide. Cholesterol oxidase activity also generates hydrogen peroxide. Hydrogen peroxide can increase protein tyrosine kinase activity and suppress protein phosphatase activity increasing insulin receptor function. Immune activated NOX and bacterial cholesterol oxidase can thus regulate insulin receptor function. Immune activation can also produce insulin resistance. TNF alpha produced by chronic immune activation can modulate the insulin receptor producing insulin resistance.[30] Chronic immune activation and cholesterol oxidase generated hydrogen peroxide can induce neutral sphingomyelinase generating ceramide producing insulin resistance.[34] Immune

activation and NFKB induction can suppress the nuclear receptors LXR, PXR and FXR. LXR suppression by NFKB stimulates HMG CoA reductase activity and suppresses cholesterol 7 alpha hydroxylase activity.[35] This stimulates cholesterol synthesis and inhibits its degradation via the bile acid pathway. PXR suppression by NFKB prevents cholesterol detoxification via the bile acid shunt pathway.[36] Thus LXR and PXR suppression by NFKB produces acute cholesterol toxicity. This NFKB induced suppression of LXR and PXR can contribute to increased lipid and cholesterol synthesis contributing to obesity. FXR suppression can also lead to insulin resistance, dyslipidemias and increased connective tissue MPS deposition in vessel wall and atherogenesis. The cholesterol toxicity can lead to lipoprotein and cholesterol uptake by monocytes in the vessel wall producing atherogenesis. The archaea and viroid induced chronic immune activation can lead to monocyte infiltration of the vessel wall. This sets the stage for the atherogenetic process.[29] The increased cholesterol synthesis is important in stimulating archaeal growth which uses cholesterol as a carbon and energy source. Archaea, viroids and digoxin can induce the host AKT PI3K, AMPK, HIF alpha and NFKB producing the Warburg metabolic phenotype.[37] The increased glycolytic hexokinase activity, decrease in blood ATP, leakage of cytochrome C, increase in serum pyruvate and decrease in acetyl CoA indicates the generation of the Warburg phenotype. There is induction of glycolysis, inhibition of PDH activity and mitochondrial dysfunction resulting in inefficient energetics. Inefficient energetics owing to the Warburg's phenotype can contribute to metabolic syndrome x. The accumulated pyruvate enters the GABA shunt pathway and is converted to citrate which is acted upon by citrate lyase and converted to acetyl CoA, used for cholesterol synthesis.[37] The pyruvate can be converted to glutamate and ammonia which is oxidised by archaea for energy needs. Ammonia can stimulate membrane sodium-potassium ATPase increasing ATP utilisation,

produce mitochondrial transmembrane potential changes and produce mitochondrial dysfunction important in type 2 diabetes mellitus. The increased cholesterol substrate also leads to increased archaeal growth and digoxin synthesis due to metabolic channeling to the mevalonate pathway. Digoxin can produce sodium-potassium ATPase inhibition and inward movement of plasma membrane cholesterol. This produces defective SREBP sensing, increased HMG CoA reductase activity and cholesterol synthesis.[28] The digoxin induced inward movement of plasma membrane cholesterol can alter membrane cholesterol/sphingomyelin ratio producing modified lipid microdomains.[38] The digoxin induced lipid microdomain modulation can regulate the GPCR couple adrenaline, noradrenaline, glucagon and neuropeptide receptors as well as protein tyrosine kinase linked insulin receptor. The digoxin mediated inhibition of nuclear membrane sodium-potassium ATPase can modulate nuclear membrane lipid microdomains and steroidal/thyroxine DNA receptor function. Thus endogenous digoxin can modulate all the endocrine receptors by regulating lipid microdomains. Hyperdigoxinemia is important in the pathogenesis of atherogenesis and metabolic syndrome X. Digoxin induced sodium-potassium ATPase inhibition results in an ATP sparing effect.[39] Eighty percent of the ATP generated is used to run the sodium-potassium ATPase pump. The digoxin inhibition of the sodium-potassium ATPase spares this ATP which is then used for lipid synthesis. Thus endogenous digoxin and the shadow biosphere generated Warburg phenotype can produce increased lipid synthesis and obesity important in metabolic syndrome X. Fat fuels insulin resistance by binding to the toll receptor and producing immune activation and immune infiltration of the adipose tissue. Digoxin can also increase lymphocytic intracellular calcium which leads on to induction of NFKB and immune activation.[2] The archaeal cholesterol catabolism can deplete the lymphocytic cell membranes of cholesterol resulting in alteration of lymphocytic cell

membrane microdomains related receptors producing immune activation. The archaeal bile acids are steroidal hormones.[40] The archaeal bile acids can bind GPCR and modulate D2 regulating the conversion of T4 to T3. T3 activates uncoupling proteins reducing redox stress. Bile acids can also activate NRF ½ inducing NQO1, GST, HOI reducing redox stress. Bile acids can bind FXR regulating insulin receptor sensitivity and bind PXR inducing the bile acid shunt pathway of cholesterol detoxification. Bile acids can bind macrophage GPCR and VDR producing immunosuppression and inhibiting NFKB. This helps to modulate the archaea and viroid induced chronic immune activation. Thus the archaeal bile acids have a role opposite to digoxin and help to increase insulin sensitivity. The archaea and viroids can regulate the nervous system including the NMDA synaptic transmission.[2] NMDA can be activated by digoxin induced calcium oscillations, PAH and viroid induced RNA interference.[2] The cholesterol ring oxidase generated pyruvate can be converted by the GABA shunt pathway to glutamate. Glutamatergic transmission can lead to immune activation, atherogenesis and increased insulin signalling/release. The archaeal cholesterol aromatase can generate PAH.[17] The PAH can also lead to insulin resistance and atherogenesis. Particulate pollution has been related to metabolic syndrome X, type 2 diabetes mellitus and vascular thrombosis. The aromatase generated serotonin and dopamine can lead onto mood disorders common in type 2 diabetes mellitus. The increased cholesterol catabolism generated glutamate can lead onto NMDA excitotoxicity and archaea/viroids can lead onto reactive amyloid deposition important in the pathogenesis of alzheimer's disease common in type 2 diabetes mellitus. The Warburg phenotype can lead onto oncogenesis common in type 2 diabetes mellitus. The higher degree of integration of the archaea into the genome produces increased digoxin synthesis producing right hemispheric dominance and lesser degree producing left hemispheric dominance.[2] Right hemispheric dominance can lead to type 2

diabetes mellitus and vascular thrombosis. Thus the actinide, viroid and mevalonate pathway bacteria induced metabolic, genetic, immune and neuronal transmission changes can lead onto metabolic syndrome X and atherogenesis.

Global warming can lead to osmotic stress consequent to dehydration. The increase in actinidic archaeal growth leads to cholesterol catabolism and digoxin synthesis. Digoxin produces membrane sodium potassium ATPase inhibition and increase in intracellular calcium producing mitochondrial dysfunction. This results in oxidative stress. The oxidative stress and osmotic stress can induce the enzyme aldose reductase which converts glucose to fructose. Fructose has got a low km value for ketokinase as compared to glucose. Therefore fructose gets phosphorylated more to fructose phosphate and the cell is depleted of ATP. The cell depletion of ATP leads to oxidative stress and chronic inflammation consequent to induction of NFKB. Oxidative stress can open the mitochondrial PT pore producing release of cyto C and activation of the caspase cascade of cell death. The fructose phosphate can enter the pentose phosphate pathway synthesizing ribose and nucleic acid. The depletion of cellular ATP results in generation of AMP and ADP which are acted upon by deaminases causing hyperuricemia. Uric acid can produce endothelial dysfunction and vascular disease. Uric acid can also produce mitochondrial dysfunction. The fructose phosphate can enter the glucosamine pathway synthesizing GAG and producing mucopolysaccharide accumulation. Fructose can fructosylate proteins making them antigenic and producing an autoimmune response. This can lead to global warming related cardiovascular disease and metabolic syndrome x.

An actinide dependent shadow biosphere of archaea and viroids is described in type 2 diabetes mellitus, coronary artery disease - acute coronary syndrome and acute cerebrovascular thrombosis contributing to their pathogenesis. The

archaea secreted digoxin serves as a messenger regulating metabolic and endocrine systems.

References

[1] Valiathan M. S., Somers, K., Kartha, C. C. (1993). *Endomyocardial Fibrosis.* Delhi: Oxford University Press.

[2] Kurup R., Kurup, P. A. (2009). *Hypothalamic digoxin, cerebral dominance and brain function in health and diseases*. New York: Nova Science Publishers.

[3] Hanold D., Randies, J. W. (1991). Coconut cadang-cadang disease and its viroid agent, *Plant Disease,* 75, 330-335.

[4] Edwin B. T., Mohankumaran, C. (2007). Kerala wilt disease phytoplasma: Phylogenetic analysis and identification of a vector, *Proutista moesta*, *Physiological and Molecular Plant Pathology*, 71(1-3), 41-47.

[5] Eckburg P. B., Lepp, P. W., Relman, D. A. (2003). Archaea and their potential role in human disease, *Infect Immun*, 71, 591-596.

[6] Adam Z. (2007). Actinides and Life's Origins, *Astrobiology*, 7, 6-10.

[7] Schoner W. (2002). Endogenous cardiac glycosides, a new class of steroid hormones, *Eur J Biochem*, 269, 2440-2448.

[8] Davies P. C. W., Benner, S. A., Cleland, C. E., Lineweaver, C. H., McKay, C. P., Wolfe-Simon, F. (2009). Signatures of a Shadow Biosphere, *Astrobiology*, 10, 241-249.

[9] Richmond W. (1973). Preparation and properties of a cholesterol oxidase from nocardia species and its application to the enzymatic assay of total cholesterol in serum, *Clin Chem*, 19, 1350-1356.

[10] Snell E. D., Snell, C. T. (1961). *Colorimetric Methods of Analysis.* Vol 3A. New York: Van Nostrand.

[11] Glick D. (1971). *Methods of Biochemical Analysis.* Vol 5. New York: Interscience Publishers.

[12] Colowick, Kaplan, N. O. (1955). *Methods in Enzymology*. Vol 2. New York: Academic Press.

[13] Maarten A. H., Marie-Jose, M., Cornelia, G., van Helden-Meewsen, Fritz, E., Marten, P. H. (1995). Detection of muramic acid in human spleen, *Infection and Immunity*, 63(5), 1652-1657.

[14] Smit A., Mushegian, A. (2000). Biosynthesis of isoprenoids via mevalonate in Archaea: the lost pathway, *Genome Res*, 10(10), 1468-84.

[15] Van der Geize R., Yam, K., Heuser, T., Wilbrink, M. H., Hara, H., Anderton, M. C. (2007). A gene cluster encoding cholesterol catabolism in a soil actinomycete provides insight into Mycobacterium tuberculosis survival in macrophages, *Proc Natl Acad Sci USA*, 104(6), 1947-52.

[16] Francis A. J. (1998). Biotransformation of uranium and other actinides in radioactive wastes, *Journal of Alloys and Compounds*, 271(273), 78-84.

[17] Probian C., Wülfing, A., Harder, J. (2003). Anaerobic mineralization of quaternary carbon atoms: Isolation of denitrifying bacteria on pivalic acid (2,2-Dimethylpropionic acid), *Applied and Environmental Microbiology*, 69(3), 1866-1870.

[18] Vainshtein M., Suzina, N., Kudryashova, E., Ariskina, E. (2002). New Magnet-Sensitive Structures in Bacterial and Archaeal Cells, *Biol Cell*, 94(1), 29-35.

[19] Tsagris E. M., de Alba, A. E., Gozmanova, M., Kalantidis, K. (2008). Viroids, *Cell Microbiol*, 10, 2168.

[20] Horie M., Honda, T., Suzuki, Y., Kobayashi, Y., Daito, T., Oshida, T. (2010). Endogenous non-retroviral RNA virus elements in mammalian genomes, *Nature*, 463, 84-87.

[21] Hecht M., Nitz, N., Araujo, P., Sousa, A., Rosa, A., Gomes, D. (2010). Genes from Chagas parasite can transfer to humans and be passed on to children. Inheritance of DNA Transferred from American Trypanosomes to Human Hosts, *PLoS ONE*, 5, 2-10.

[22] Flam F. (1994). Hints of a language in junk DNA, *Science*, 266, 1320.

[23] Horbach S., Sahm, H., Welle, R. (1993). Isoprenoid biosynthesis in bacteria: two different pathways? *FEMS Microbiol Lett,* 111, 135-140.

[24] Gupta R. S. (1998). Protein phylogenetics and signature sequences: a reappraisal of evolutionary relationship among archaebacteria, eubacteria, and eukaryotes, *Microbiol Mol Biol Rev,* 62, 1435-1491.

[25] Hanage W., Fraser, C., Spratt, B. (2005). Fuzzy species among recombinogenic bacteria, *BMC Biology,* 3, 6-10.

[26] Webb J. S., Givskov, M., Kjelleberg, S. (2003). Bacterial biofilms: prokaryotic adventures in multicellularity, *Curr Opin Microbiol,* 6(6), 578-85.

[27] Whitchurch C. B., Tolker-Nielsen, T., Ragas, P. C., Mattick, J. S. (2002). Extracellular DNA Required for Bacterial Biofilm Formation. *Science,* 295(5559), 1487.

[28] Chen Y., Cai, T., Wang, H., Li, Z., Loreaux, E., Lingrel, J. B. (2009). Regulation of intracellular cholesterol distribution by Na/K-ATPase, *J Biol Chem,* 284(22), 14881-90.

[29] Khovidhunkit W., Kim, M. S., Memon, R. A., Shigenaga, J. K., Moser, A. H., Feingold, K. R. (2004). Thematic review series: The Pathogenesis of Atherosclerosis. Effects of infection and inflammation on lipid and lipoprotein metabolism mechanisms and consequences to the host. *J Lip Res,* 45(7), 1169-1196.

[30] Cani P. D., Amar, J., Iglesias, M. A., Poggi, M., Knauf, C., Bastelica, D. (2007). Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes,* 56, 1761-1772.

[31] Poole A. M. (2006). Did group II intron proliferation in an endosymbiont-bearing archaeon create eukaryotes? *Biol Direct,* 1, 36-40.

[32] Villarreal L. P. (2006). How viruses shape the tree of life, *Future Virology,* 1(5), 587-595.

[33] Eberl M., Hintz, M., Reichenberg, A., Kollas, A., Wiesner, J., Jomaa, H. (2010). Microbial isoprenoid biosynthesis and human γδ T cell activation, *FEBS Letters,* 544(1), 4-10.

[34] Memon R. A., Holleran, W. M., Moser, A. H., Seki, T., Uchida, Y., Fuller, J. (1998). Endotoxin and Cytokines Increase Hepatic Sphingolipid Biosynthesis and Produce Lipoproteins Enriched in Ceramides and Sphingomyelin. *Arterioscler Thromb Vasc Biol*, 18(8), 1257-1265.

[35] Carayol N., Chen, J., Yang, F., Jin, T., Jin, L., States, D. (2006). A dominant function of IKK/NF-kB signaling in global LPS-induced gene expression. *J Biol Chem*, 10, 1074.

[36] Kliewer S. A. (2005). Cholesterol detoxification by the nuclear pregnane X receptor. *Proc Natl Acad Sci USA*, 102(8), 2675-6.

[37] Wallace D. C. (2005). Mitochondria and Cancer: Warburg Addressed, *Cold Spring Harbor Symposia on Quantitative Biology*, 70, 363-374.

[38] Paila Y. D., Tiwari, S., Chattopadhyay, A. (2009). Are specific nonannular cholesterol binding sites present in G-protein coupled receptors? *Biochim Biophys Acta*, 1788(2), 295-302.

[39] Ebensperger G., Ebensperger, R., Herrera, E. A., Riquelme, R. A., Sanhueza, E. M., Lesage, F. (2005). Fetal brain hypometabolism during prolonged hypoxaemia in the llama. *J Physiol*, 567(3), 963-975.

[40] Lefebvre P., Cariou, B., Lien, F., Kuipers, F., Staels, B. (2009). Role of Bile Acids and Bile Acid Receptors in Metabolic Regulation, *Physiol Rev*, 89(1), 147-191.

4

Actinidic Archaea and Viroids Related Hepato-Gastro-Intestinal Syndrome

Introduction

Endomyocardial fibrosis (EMF) along with the root wilt disease of coconut is endemic to Kerala with its radioactive actinide beach sands. Actinides like cerium producing intracellular magnesium deficiency due to cerium-magnesium exchange sites in the cell membrane has been implicated in the etiology of EMF.[1] Endogenous digoxin, a steroidal glycoside which functions as a membrane sodium-potassium ATPase inhibitor has also been related to its etiology due to the intracellular magnesium deficiency it produces.[2] Organisms like phytoplasmas and viroids have also been demonstrated to play a role in the etiology of these diseases.[3, 4] Endogenous digoxin has been related to the pathogenesis of cirrhosis liver, ulcerative colitis, irritable bowel syndrome and peptic ulcer disease.[2] The possibility of endogenous digoxin synthesis by actinide based primitive organism like archaea with a mevalonate pathway and cholesterol catabolism was considered.[5-7] Davies has put forward the concept of a shadow biosphere of organisms with alternate biochemistry present in earth itself.[8] An actinide dependent shadow biosphere of archaea and viroids in the above mentioned disease states is described.[6]

Actinidic archaea has been related to global warming and human diseases. The growth of endosymbiotic actinidic archaea in relation to climate change and global warming leads to neanderthalisation of the humans. Neanderthal metabolonomics include the Warburg phenotype and cholesterol catabolism resulting in hyperdigoxinemia. Digoxin produced by archaeal cholesterol catabolism produces neanderthalisation. The neanderthalisation of the human brain due to endosymbiotic archaeal overgrowth results in prefrontal cortical

atrophy and cerebellar hyperplasia. This leads on to dysautonomia with sympathetic hyperactivity and parasympathetic neuropathy in these disorders.

Global warming can lead to osmotic stress consequent to dehydration. The increase in actinidic archaeal growth leads to cholesterol catabolism and digoxin synthesis. Digoxin produces membrane sodium potassium ATPase inhibition and increase in intracellular calcium producing mitochondrial dysfunction. This results in oxidative stress. The oxidative stress and osmotic stress can induce the enzyme aldose reductase which converts glucose to fructose. Fructose has got a low km value for ketokinase as compared to glucose. Therefore fructose gets phosphorylated more to fructose phosphate and the cell is depleted of ATP. The cell depletion of ATP leads to oxidative stress and chronic inflammation consequent to induction of NFKB. Oxidative stress can open the mitochondrial PT pore producing release of cyto C and activation of the caspase cascade of cell death. The fructose phosphate can enter the pentose phosphate pathway synthesizing ribose and nucleic acid. The depletion of cellular ATP results in generation of AMP and ADP which are acted upon by deaminases causing hyperuricemia. Uric acid can produce endothelial dysfunction and vascular disease. Uric acid can also produce mitochondrial dysfunction. The fructose phosphate can enter the glucosamine pathway synthesizing GAG and producing mucopolysaccharide accumulation. Fructose can fructosylate proteins making them antigenic and producing an autoimmune response. This can lead to global warming related hepatic and gastro-intestinal disease.

Materials and Methods

Informed consent of the subjects and the approval of the ethics committee were obtained for the study. The following groups were included in the study: -

cirrhosis liver, ulcerative colitis, irritable bowel syndrome and peptic ulcer disease. There were 10 patients in each group and each patient had an age and sex matched healthy control selected randomly from the general population. The blood samples were drawn in the fasting state before treatment was initiated. Plasma from fasting heparinised blood was used and the experimental protocol was as follows (I) Plasma+phosphate buffered saline, (II) same as I+cholesterol substrate, (III) same as II+cerium 0.1 mg/ml, (IV) same as II+ciprofloxacin and doxycycline each in a concentration of 1 mg/ml. Cholesterol substrate was prepared as described by Richmond.[9] Aliquots were withdrawn at zero time immediately after mixing and after incubation at 37 ℃ for 1 hour. The following estimations were carried out: - Cytochrome F420, free RNA, free DNA, muramic acid, polycyclic aromatic hydrocarbon, hydrogen peroxide, serotonin, pyruvate, ammonia, glutamate, cytochrome C, hexokinase, ATP synthase, HMG CoA reductase, digoxin and bile acids.[10-13] Cytochrome F420 was estimated flourimetrically (excitation wavelength 420 nm and emission wavelength 520 nm). Polycyclic aromatic hydrocarbon was estimated by measuring hydrogen peroxide liberated by using glucose reagent. The statistical analysis was done by ANOVA.

Results

The parameters checked as indicated above were: - cytochrome F420, free RNA, free DNA, muramic acid, polycyclic aromatic hydrocarbon, hydrogen peroxide, serotonin, pyruvate, ammonia, glutamate, cytochrome C, hexokinase, ATP synthase, HMG CoA reductase, digoxin and bile acids. Plasma of control subjects showed increased levels of the above mentioned parameters with after incubation for 1 hour and addition of cholesterol substrate resulted in still further significant increase in these parameters. The plasma of patients showed

similar results but the extent of increase was more. The addition of antibiotics to the control plasma caused a decrease in all the parameters while addition of cerium increased their levels. The addition of antibiotics to the patient's plasma caused a decrease in all the parameters while addition of cerium increased their levels but the extent of change was more in patient's sera as compared to controls. The results are expressed in tables 1-7 as percentage change in the parameters after 1 hour incubation as compared to the values at zero time.

Table 1. *Effect of cerium and antibiotics on muramic acid and serotonin.*

Group	Muramic acid % change (Increase with Cerium)		Muramic acid % change (Decrease with Doxy+Cipro)		5 HT % (Increase without Doxy)		5 HT % (Decrease with Doxy)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Normal	4.41	0.15	18.63	0.12	4.34	0.15	18.24	0.37
Cirrhosis	23.11	1.82	66.96	3.79	23.13	1.78	64.88	4.96
PUD	23.43	1.59	65.71	4.01	22.92	1.71	65.58	4.74
UC	23.81	1.45	66.85	3.72	22.83	1.96	63.42	5.10
IBS	23.28	1.95	66.02	3.90	22.79	1.79	62.70	5.05
F value	403.394		680.284		348.867		364.999	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 2. *Effect of cerium and antibiotics on free DNA and RNA.*

Group	DNA % change (Increase with Cerium)		DNA % change (Decrease with Doxy)		RNA % change (Increase with Cerium)		RNA % change (Decrease with Doxy)	
Normal	4.37	0.15	18.39	0.38	4.37	0.13	18.38	0.48
Cirrhosis	22.78	1.94	63.06	6.20	22.91	1.69	66.23	3.44
PUD	23.07	1.50	62.99	5.27	23.32	1.92	66.07	4.11
UC	23.28	1.93	61.81	2.75	22.89	1.85	66.33	3.73
IBS	23.61	1.53	67.77	3.23	22.94	1.88	65.84	4.20
F value	337.577		356.621		427.828		654.453	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 3. *Effect of cerium and antibiotics on HMG CoA reductase and PAH.*

Group	HMG CoA R % change (Increase with Cerium)		HMG CoA R % change (Decrease with Doxy)		PAH % change (Increase with Cerium)		PAH % change (Decrease with Doxy)	
Normal	4.30	0.20	18.35	0.35	4.45	0.14	18.25	0.72
Cirrhosis	23.29	1.67	59.19	7.18	23.39	1.63	65.88	5.01
PUD	23.56	1.83	63.61	6.60	23.06	1.56	64.49	4.64
UC	23.24	1.79	63.55	8.01	23.49	1.48	64.96	5.02
IBS	23.66	1.47	66.11	6.52	23.32	1.46	62.95	7.18
F value	319.332		199.553		391.318		257.996	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 4. *Effect of cerium and antibiotics on digoxin and bile acids.*

Group	Digoxin (ng/ml) (Increase with Cerium)		Digoxin (ng/ml) (Decrease with Doxy+Cipro)		Bile acids % change (Increase with Cerium)		Bile acids % change (Decrease with Doxy)	
Normal	0.11	0.00	0.054	0.003	4.29	0.18	18.15	0.58
Cirrhosis	0.50	0.06	0.206	0.034	22.08	1.76	64.20	5.16
PUD	0.50	0.05	0.223	0.025	22.72	1.76	61.84	7.63
UC	0.49	0.06	0.230	0.034	22.30	1.76	62.76	7.49
IBS	0.51	0.06	0.221	0.030	22.62	1.89	63.41	8.47
F value	135.116		71.706		290.441		203.651	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 5. *Effect of cerium and antibiotics on pyruvate and hexokinase.*

Group	Pyruvate % change (Increase with Cerium)		Pyruvate % change (Decrease with Doxy)		Hexokinase % change (Increase with Cerium)		Hexokinase % change (Decrease with Doxy)	
Normal	4.34	0.21	18.43	0.82	4.21	0.16	18.56	0.76
Cirrhosis	21.52	2.26	60.42	7.65	21.70	1.90	65.26	5.62
PUD	21.29	2.38	57.56	8.70	22.80	2.33	64.43	5.74
UC	21.34	2.24	60.25	8.94	22.29	2.22	65.14	5.66
IBS	20.74	1.47	61.98	6.44	22.36	2.40	63.46	5.69
F value	321.255		115.242		292.065		317.966	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 6. *Effect of cerium and antibiotics on hydrogen peroxide and delta amino levulinic acid.*

Group	H_2O_2 % (Increase with Cerium)		H_2O_2 % (Decrease with Doxy)		ALA % (Increase with Cerium)		ALA % (Decrease with Doxy)	
Normal	4.43	0.19	18.13	0.63	4.40	0.10	18.48	0.39
Cirrhosis	23.46	1.61	61.77	6.79	23.98	1.72	66.76	4.01
PUD	22.38	1.65	64.59	7.12	23.52	1.74	67.75	3.43
UC	23.65	1.11	59.37	6.93	23.13	1.96	65.86	3.83
IBS	23.22	1.76	59.12	5.14	23.32	1.95	66.69	3.91
F value	380.721		171.228		372.716		556.411	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 7. *Effect of cerium and antibiotics on ATP synthase and cytochrome F420.*

Group	ATP synthase % (Increase with Cerium)		ATP synthase % (Decrease with Doxy)		CYT F420 % (Increase with Cerium)		CYT F420 % (Decrease with Doxy)	
Normal	4.40	0.11	18.78	0.11	4.48	0.15	18.24	0.66
Cirrhosis	23.27	1.56	66.43	3.77	22.46	2.39	61.42	7.26
PUD	23.09	1.43	66.43	4.07	22.41	2.02	60.47	8.32
UC	23.14	1.80	66.40	3.64	22.95	1.53	58.86	6.97
IBS	23.16	1.31	67.28	3.54	22.52	1.33	61.43	11.16
F value	449.503		673.081		306.749		130.054	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Abbreviations

PUD: Peptic ulcer disease

UC: Ulcerative colitis

IBS: Irritable bowel syndrome

Discussion

There was increase in cytochrome F420 indicating archaeal growth in cirrhosis liver, ulcerative colitis, irritable bowel syndrome and peptic ulcer disease. The archaea can synthesize and use cholesterol as a carbon and energy source.[14, 15] The archaeal origin of the enzyme activities was indicated by antibiotic induced suppression. The study indicates the presence of actinide based archaea with an alternate actinide based enzymes or metalloenzymes in the system as indicated by cerium induced increase in enzyme activities.[16] There was also an increase in archaeal HMG CoA reductase activity indicating increased cholesterol synthesis by the archaeal mevalonate pathway. The archaeal beta hydroxyl steroid dehydrogenase activity indicating digoxin synthesis and archaeal cholesterol hydroxylase activity indicating bile acid synthesis were increased.[7] The archaeal cholesterol oxidase activity was increased resulting in generation of pyruvate and hydrogen peroxide.[15] The pyruvate gets converted to glutamate and ammonia by the GABA shunt pathway. The archaeal aromatization of cholesterol generating PAH, serotonin and dopamine was also detected.[17] The archaeal glycolytic hexokinase activity and archaeal extracellular ATP synthase activity were increased. The archaea can undergo magnetite and calcium carbonate mineralization and can exist as calcified nanoforms.[18] There was an increase in free RNA indicating self replicating RNA viroids and free DNA indicating generation of viroid complementary DNA strands by archaeal reverse transcriptase activity. The actinides modulate RNA folding and catalyse its ribozymal action. Digoxin can cut and paste the viroidal strands by modulating RNA splicing generating RNA viroidal diversity. The viroids are evolutionarily escaped archaeal group I introns which have retrotransposition and self splicing qualities.[19] Archaeal pyruvate can produce histone deacetylase inhibition resulting in endogenous retroviral (HERV) reverse transcriptase and integrase expression.

This can integrate the RNA viroidal complementary DNA into the noncoding region of eukaryotic noncoding DNA using HERV integrase as has been described for borna and ebola viruses.[20] The noncoding DNA is lengthened by integrating RNA viroidal complementary DNA with the integration going on as a continuing event. The archaea genome can also get integrated into human genome using integrase as has been described for trypanosomes.[21] The integrated viroids and archaea can undergo vertical transmission and can exist as genomic parasites.[20, 21] This increases the length and alters the grammar of the noncoding region producing memes or memory of acquired characters.[22] The viroidal complementary DNA can function as jumping genes producing a dynamic genome important in HLA gene expression. This modulation of HLA gene expression by viroidal complementary DNA can result in immune activation. The RNA viroids can regulate mRNA function by RNA interference.[19] The phenomena of RNA interference can modulate T cell and B cell function and euchromatin / heterochromatin expression. RNA viroidal mRNA interference related immune activation plays a role in the pathogenesis of cirrhosis liver, ulcerative colitis, irritable bowel syndrome and peptic ulcer disease.

The presence of muramic acid, HMG CoA reductase and cholesterol oxidase activity inhibited by antibiotics indicates the presence of bacteria with mevalonate pathway. The bacterial with mevalonate pathway include streptococcus, staphylococcus, actinomycetes, listeria, coxiella and borrelia.[23] The bacteria and archaea with mevalonate pathway and cholesterol catabolism had a evolutionarily advantage and constitutes the isoprenoidal clade organism with the archaea evolving into mevalonate pathway gram positive and gram negative organism through horizontal gene transfer of viroidal and virus genes.[24] The isoprenoidal clade prokaryotes develop into other groups of prokaryotes via viroidal/virus as well as eukaryotic horizontal gene transfer

producing bacterial speciation.[25] The RNA viroids and its complementary DNA developed into cholesterol enveloped RNA and DNA viruses like herpes, retrovirus, influenza virus, borna virus, cytomegalo virus and Ebstein Barr virus by recombining with eukaryotic and human genes resulting in viral speciation. Bacterial and viral species are ill defined and fuzzy with all of them forming one common genetic pool with frequent horizontal gene transfer and recombination. Thus the multi and unicellular eukaryote with its genes serves the purpose of prokaryotic and viral speciation. The multicellular eukaryote developed so that their endosymbiotic archaeal colonies could survive and forage better. The multicellular eukaryotes are like bacterial biofilms. The archaea and bacteria with a mevalonate pathway uses the extracellular RNA viroids and DNA viroids for quorum sensing and in the generation of symbiotic biofilm like structures which develop into multicellular eukaryotes.[26, 27] The endosymbiotic archaea and bacteria with mevalonate pathway still uses the RNA viroids and DNA viroids for the regulation of muticellular eukaryote. Pollution is induced by the primitive nanoarchaea and mevalonate pathway bacteria synthesised PAH and methane leading on to redox stress. Redox stress leads to sodium potassium ATPase inhibition, inward movement of plasma membrane cholesterol, defective SREBP sensing, increased cholesterol synthesis and nanoarchaeal/mevalonate pathway bacterial growth.[28] Redox stress leads on to viroidal and archaeal multiplication. Redox stress can also lead to HERV reverse transcriptase and integrase expression. The noncoding DNA is formed of integrating RNA viroidal complementary DNA and archaea with the integration going on as a continuing event. The archaeal pox like dsDNA virus forms evolutionarily the nucleus. The integrated viroidal, archaeal and mevalonate pathway bacterial sequences can undergo vertical transmission and can exist as genomic parasites. The genomic integrated archaea, mevalonate pathway bacteria and viroids form a genomic reserve of bacteria and viruses

which can recombine with human and eukaryotic genes producing bacterial and viral speciation. Bacteria and viruses have been related to the pathogenesis of cirrhosis liver, ulcerative colitis, irritable bowel syndrome and peptic ulcer disease.[29, 30] *Helicobacter pylori* has been related to the pathogenesis of peptic ulcer disease.[29] Mollicutes, atypical mycobacteria and enterobacteria has been implicated in inflammatory bowel disease.[29, 30] Gut bacteria and endotoxinemia contributes to the pathogenesis of cirrhosis liver.[29] Gut bacteria also plays a role in irritable bowel syndrome.[29] The change in the length and grammar of the noncoding region produces eukaryotic speciation and individuality.[31] Changes in the length of noncoding region especially human endogenous retroviruses can lead onto autoimmune diseases.[32] The integration of nanoarchaea, mevalonate pathway prokaryotes and viroids in to the eukaryotic and human genome produces a chimera which can multiply producing biofilm like multicellular structures having a mixed archaeal, viroidal, prokaryotic and eukaryotic characters which is a regression from the multicellular eukaryotic tissue This results in a new neuronal, metabolic, immune and tissue phenotype or microchimeras leading to human diseases like cirrhosis liver, ulcerative colitis, irritable bowel syndrome and peptic ulcer disease. The microchimeras formed can lead to autoantigens, immune activation and autoimmune pathology. Autoimmunity has been described in inflammatory bowel disease.[29]

Archaea and RNA viroid can bind the TLR receptor induce NFKB producing immune activation and cytokine TNF alpha secretion. The archaeal DXP and mevalonate pathway metabolites can bind γδ TCR and digoxin induced calcium signalling can activate NFKB producing chronic immune activation.[2, 33] The archaeal cholesterol aromatase generated PAH can produce immune activation. The archaea and viroid induced chronic immune activation and generation of superantigens can lead on to autoimmune disease and immune activation.

Immune activation has been related to the pathogenesis of cirrhosis liver, ulcerative colitis, irritable bowel syndrome and peptic ulcer disease.[29, 30]

The archaea and viroids can regulate the nervous system including the NMDA synaptic transmission.[2] NMDA can be activated by digoxin induced calcium oscillations, PAH and viroid induced RNA interference.[2] The cholesterol ring oxidase generated pyruvate can be converted by the GABA shunt pathway to glutamate. The archaeal cholesterol aromatase can generate serotonin.[17] Glutamatergic and serotoninergic transmission can lead to immune activation which is important in the pathogenesis of cirrhosis liver, ulcerative colitis, irritable bowel syndrome and peptic ulcer disease. Monoamine neurotransmitters and glutamate have been implicated in abnormal gut motility of irritable bowel syndrome. The higher degree of integration of the archaea into the genome produces increased digoxin synthesis producing right hemispheric dominance and lesser degree producing left hemispheric dominance.[2] Right hemispheric dominance can lead to cirrhosis liver, ulcerative colitis, irritable bowel syndrome and peptic ulcer disease.[2]

Archaea, viroids and digoxin can induce the host AKT PI3K, AMPK, HIF alpha and NFKB producing the Warburg metabolic phenotype.[34] The increased glycolytic hexokinase activity, decrease in blood ATP, leakage of cytochrome C, increase in serum pyruvate and decrease in acetyl CoA indicates the generation of the Warburg phenotype. There is induction of glycolysis, inhibition of PDH activity and mitochondrial dysfunction resulting in inefficient energetics. The lymphocytes depend on glycolysis for their energy needs. The increased glycolysis induced by the Warburg phenotype leads to immune activation. Lactic acid generated by increased glycolysis leads to immune stimulation. Immune activation as noted before is important in the pathogenesis of cirrhosis liver, ulcerative colitis, irritable bowel syndrome and peptic ulcer disease.

Cholesterol oxidase activity, increased glycolysis related NADPH oxidase activity, bacterial porphyrin induced redox stress and mitochondrial dysfunction generates free radicals important in the pathogenesis of cirrhosis liver, ulcerative colitis, irritable bowel syndrome and peptic ulcer disease. The accumulated pyruvate enters the GABA shunt pathway and is converted to citrate which is acted upon by citrate lyase and converted to acetyl CoA, used for cholesterol synthesis.[34] The pyruvate can be converted to glutamate and ammonia which is oxidised by archaea for energy needs. The increased cholesterol substrate leads to increased archaeal growth and digoxin synthesis leading to metabolic channelling to the mevalonate pathway. The archaeal cholesterol catabolism can deplete the lymphocytic cell membranes of cholesterol resulting in alteration of lymphocytic cell membrane microdomains related receptors producing immune activation. Hyperdigoxinemia is important in the pathogenesis of cirrhosis liver, ulcerative colitis, irritable bowel syndrome and peptic ulcer disease.[2] Digoxin can increase lymphocytic intracellular calcium which leads on to induction of NFKB and immune activation.[2] The archaeal bile acids can bind GPCR and modulate D2 regulating the conversion of T4 to T3. T3 activates uncoupling proteins reducing redox stress. Bile acids can also activate NRF ½ inducing NQO1, GST, HOI reducing redox stress. Bile acids can bind PXR inducing the bile acid shunt pathway of cholesterol detoxification. Bile acids can bind macrophage GPCR and VDR producing immunosuppression and inhibiting NFKB. This helps to modulate the archaea and viroid induced chronic immune activation. Bile acids are thus protective compounds and put a break on the archaea and viroid induced changes.[35] Thus the actinide, viroid and mevalonate pathway bacteria induced metabolic, genetic, immune and neuronal transmission changes can lead onto cirrhosis liver, ulcerative colitis, irritable bowel syndrome and peptic ulcer disease.

Global warming can lead to osmotic stress consequent to dehydration. The increase in actinidic archaeal growth leads to cholesterol catabolism and digoxin synthesis. Digoxin produces membrane sodium potassium ATPase inhibition and increase in intracellular calcium producing mitochondrial dysfunction. This results in oxidative stress. The oxidative stress and osmotic stress can induce the enzyme aldose reductase which converts glucose to fructose. Fructose has got a low km value for ketokinase as compared to glucose. Therefore fructose gets phosphorylated more to fructose phosphate and the cell is depleted of ATP. The cell depletion of ATP leads to oxidative stress and chronic inflammation consequent to induction of NFKB. Oxidative stress can open the mitochondrial PT pore producing release of cyto C and activation of the caspase cascade of cell death. The fructose phosphate can enter the pentose phosphate pathway synthesizing ribose and nucleic acid. The depletion of cellular ATP results in generation of AMP and ADP which are acted upon by deaminases causing hyperuricemia. Uric acid can produce endothelial dysfunction and vascular disease. Uric acid can also produce mitochondrial dysfunction. The fructose phosphate can enter the glucosamine pathway synthesizing GAG and producing mucopolysaccharide accumulation. Fructose can fructosylate proteins making them antigenic and producing an autoimmune response. This can lead to global warming related gastro-intestinal and liver disease.

References

[1] Valiathan M. S., Somers, K., Kartha, C. C. (1993). *Endomyocardial Fibrosis.* Delhi: Oxford University Press.

[2] Kurup R., Kurup, P. A. (2009). *Hypothalamic digoxin, cerebral dominance and brain function in health and diseases*. New York: Nova Science Publishers.

[3] Hanold D., Randies, J. W. (1991). Coconut cadang-cadang disease and its viroid agent, *Plant Disease,* 75, 330-335.

[4] Edwin B. T., Mohankumaran, C. (2007). Kerala wilt disease phytoplasma: Phylogenetic analysis and identification of a vector, *Proutista moesta*, *Physiological and Molecular Plant Pathology*, 71(1-3), 41-47.

[5] Eckburg P. B., Lepp, P. W., Relman, D. A. (2003). Archaea and their potential role in human disease, *Infect Immun*, 71, 591-596.

[6] Adam Z. (2007). Actinides and Life's Origins, *Astrobiology*, 7, 6-10.

[7] Schoner W. (2002). Endogenous cardiac glycosides, a new class of steroid hormones, *Eur J Biochem*, 269, 2440-2448.

[8] Davies P. C. W., Benner, S. A., Cleland, C. E., Lineweaver, C. H., McKay, C. P., Wolfe-Simon, F. (2009). Signatures of a Shadow Biosphere, *Astrobiology*, 10, 241-249.

[9] Richmond W. (1973). Preparation and properties of a cholesterol oxidase from nocardia species and its application to the enzymatic assay of total cholesterol in serum, *Clin Chem*, 19, 1350-1356.

[10] Snell E. D., Snell, C. T. (1961). *Colorimetric Methods of Analysis.* Vol 3A. New York: Van Nostrand.

[11] Glick D. (1971). *Methods of Biochemical Analysis.* Vol 5. New York: Interscience Publishers.

[12] Colowick, Kaplan, N. O. (1955). *Methods in Enzymology.* Vol 2. New York: Academic Press.

[13] Maarten A. H., Marie-Jose, M., Cornelia, G., van Helden-Meewsen, Fritz, E., Marten, P. H. (1995). Detection of muramic acid in human spleen, *Infection and Immunity*, 63(5), 1652-1657.

[14] Smit A., Mushegian, A. (2000). Biosynthesis of isoprenoids via mevalonate in Archaea: the lost pathway, *Genome Res*, 10(10), 1468-84.

[15] Van der Geize R., Yam, K., Heuser, T., Wilbrink, M. H., Hara, H., Anderton, M. C. (2007). A gene cluster encoding cholesterol catabolism in a soil actinomycete provides insight into Mycobacterium tuberculosis survival in macrophages, *Proc Natl Acad Sci USA*, 104(6), 1947-52.

[16] Francis A. J. (1998). Biotransformation of uranium and other actinides in radioactive wastes, *Journal of Alloys and Compounds*, 271(273), 78-84.

[17] Probian C., Wülfing, A., Harder, J. (2003). Anaerobic mineralization of quaternary carbon atoms: Isolation of denitrifying bacteria on pivalic acid (2,2-Dimethylpropionic acid), *Applied and Environmental Microbiology*, 69(3), 1866-1870.

[18] Vainshtein M., Suzina, N., Kudryashova, E., Ariskina, E. (2002). New Magnet-Sensitive Structures in Bacterial and Archaeal Cells, *Biol Cell*, 94(1), 29-35.

[19] Tsagris E. M., de Alba, A. E., Gozmanova, M., Kalantidis, K. (2008). Viroids, *Cell Microbiol*, 10, 2168.

[20] Horie M., Honda, T., Suzuki, Y., Kobayashi, Y., Daito, T., Oshida, T. (2010). Endogenous non-retroviral RNA virus elements in mammalian genomes, *Nature*, 463, 84-87.

[21] Hecht M., Nitz, N., Araujo, P., Sousa, A., Rosa, A., Gomes, D. (2010). Genes from Chagas parasite can transfer to humans and be passed on to children. Inheritance of DNA Transferred from American Trypanosomes to Human Hosts, *PLoS ONE*, 5, 2-10.

[22] Flam F. (1994). Hints of a language in junk DNA, *Science*, 266, 1320.

[23] Horbach S., Sahm, H., Welle, R. (1993). Isoprenoid biosynthesis in bacteria: two different pathways? *FEMS Microbiol Lett*, 111, 135-140.

[24] Gupta R. S. (1998). Protein phylogenetics and signature sequences: a reappraisal of evolutionary relationship among archaebacteria, eubacteria, and eukaryotes, *Microbiol Mol Biol Rev*, 62, 1435-1491.

[25] Hanage W., Fraser, C., Spratt, B. (2005). Fuzzy species among recombinogenic bacteria, *BMC Biology*, 3, 6-10.

[26] Webb J. S., Givskov, M., Kjelleberg, S. (2003). Bacterial biofilms: prokaryotic adventures in multicellularity, *Curr Opin Microbiol*, 6(6), 578-85.

[27] Whitchurch C. B., Tolker-Nielsen, T., Ragas, P. C., Mattick, J. S. (2002). Extracellular DNA Required for Bacterial Biofilm Formation. *Science*, 295(5559), 1487.

[28] Chen Y., Cai, T., Wang, H., Li, Z., Loreaux, E., Lingrel, J. B. (2009). Regulation of intracellular cholesterol distribution by Na/K-ATPase, *J Biol Chem*, 284(22), 14881-90.

[29] Fauci A. S. (2009). Harrison's Principles of Internal Medicine. New York: McGraw-Hill.

[30] Wirostko E., Johnson, L., Wirostko, B. (1990). Ulcerative colitis associated chronic uveitis. Parasitization of intraocular leucocytes by mollicute-like organisms, *J Submicrosc Cytol Pathol*, 22(2), 231-9.

[31] Poole A. M. (2006). Did group II intron proliferation in an endosymbiont-bearing archaeon create eukaryotes? *Biol Direct*, 1, 36-40.

[32] Villarreal L. P. (2006). How viruses shape the tree of life, *Future Virology*, 1(5), 587-595.

[33] Eberl M., Hintz, M., Reichenberg, A., Kollas, A., Wiesner, J., Jomaa, H. (2010). Microbial isoprenoid biosynthesis and human γδ T cell activation, *FEBS Letters*, 544(1), 4-10.

[34] Wallace D. C. (2005). Mitochondria and Cancer: Warburg Addressed, *Cold Spring Harbor Symposia on Quantitative Biology*, 70, 363-374.

[35] Lefebvre P., Cariou, B., Lien, F., Kuipers, F., Staels, B. (2009). Role of Bile Acids and Bile Acid Receptors in Metabolic Regulation, *Physiol Rev*, 89(1), 147-191.

5

A Cholesterol and Actinide Dependent Shadow Biosphere of Archaea and Viroids in Pulmonary Diseases

Introduction

Endomyocardial fibrosis (EMF) along with the root wilt disease of coconut is endemic to Kerala with its radioactive actinide beach sands. Actinides like rutile producing intracellular magnesium deficiency due to rutile-magnesium exchange sites in the cell membrane has been implicated in the etiology of EMF.[1] Endogenous digoxin, a steroidal glycoside which functions as a membrane sodium-potassium ATPase inhibitor has also been related to its etiology due to the intracellular magnesium deficiency it produces.[2] Organisms like phytoplasmas and viroids have also been demonstrated to play a role in the etiology of these diseases.[3, 4] Endogenous digoxin has been related to the pathogenesis of interstitial lung disease, chronic bronchitis emphysema and bronchial asthma.[2] The possibility of endogenous digoxin synthesis by actinide based primitive organism like archaea with a mevalonate pathway and cholesterol catabolism was considered.[5, 6, 7] Davies has put forward the concept of a shadow biosphere of organisms with alternate biochemistry present in earth itself.[8] An actinide dependent shadow biosphere of archaea and viroids in the above mentioned disease states is described.[6]

Actinidic archaea has been related to global warming and human diseases. The growth of endosymbiotic actinidic archaea in relation to climate change and global warming leads to neanderthalisation of the humans. Neanderthal metabolonomics include the Warburg phenotype and cholesterol catabolism resulting in hyperdigoxinemia. Digoxin produced by archaeal cholesterol catabolism produces neanderthalisation. The neanderthalisation of the human brain due to endosymbiotic archaeal overgrowth results in prefrontal cortical

atrophy and cerebellar hyperplasia. This leads on to dysautonomia with sympathetic hyperactivity and parasympathetic neuropathy in these disorders.

Global warming can lead to osmotic stress consequent to dehydration. The increase in actinidic archaeal growth leads to cholesterol catabolism and digoxin synthesis. Digoxin produces membrane sodium potassium ATPase inhibition and increase in intracellular calcium producing mitochondrial dysfunction. This results in oxidative stress. The oxidative stress and osmotic stress can induce the enzyme aldose reductase which converts glucose to fructose. Fructose has got a low km value for ketokinase as compared to glucose. Therefore fructose gets phosphorylated more to fructose phosphate and the cell is depleted of ATP. The cell depletion of ATP leads to oxidative stress and chronic inflammation consequent to induction of NFKB. Oxidative stress can open the mitochondrial PT pore producing release of cyto C and activation of the caspase cascade of cell death. The fructose phosphate can enter the pentose phosphate pathway synthesizing ribose and nucleic acid. The depletion of cellular ATP results in generation of AMP and ADP which are acted upon by deaminases causing hyperuricemia. Uric acid can produce endothelial dysfunction and vascular disease. Uric acid can also produce mitochondrial dysfunction. The fructose phosphate can enter the glucosamine pathway synthesizing GAG and producing mucopolysaccharide accumulation. Fructose can fructosylate proteins making them antigenic and producing an autoimmune response. This can lead to global warming related pulmonary disease.

Methods

Informed consent of the subjects and the approval of the ethics committee were obtained for the study. The following groups were included in the study: -

interstitial lung disease, chronic bronchitis emphysema and bronchial asthma. There were 10 patients in each group and each patient had an age and sex matched healthy control selected randomly from the general population. The blood samples were drawn in the fasting state before treatment was initiated. Plasma from fasting heparinised blood was used and the experimental protocol was as follows (I) Plasma+phosphate buffered saline, (II) same as I+cholesterol substrate, (III) same as II+rutile 0.1 mg/ml, (IV) same as II+ciprofloxacine and doxycycline each in a concentration of 1 mg/ml. Cholesterol substrate was prepared as described by Richmond.[9] Aliquots were withdrawn at zero time immediately after mixing and after incubation at 37 ℃ for 1 hour. The following estimations were carried out: - Cytochrome F420, free RNA, free DNA, muramic acid, polycyclic aromatic hydrocarbon, hydrogen peroxide, serotonin, pyruvate, ammonia, glutamate, cytochrome C, hexokinase, ATP synthase, HMG CoA reductase, digoxin and bile acids.[10-13] Cytochrome F420 was estimated flourimetrically (excitation wavelength 420 nm and emission wavelength 520 nm). Polycyclic aromatic hydrocarbon was estimated by measuring hydrogen peroxide liberated by using glucose reagent. The statistical analysis was done by ANOVA.

Results

The parameters checked as indicated above were: - cytochrome F420, free RNA, free DNA, muramic acid, polycyclic aromatic hydrocarbon, hydrogen peroxide, serotonin, pyruvate, ammonia, glutamate, cytochrome C, hexokinase, ATP synthase, HMG CoA reductase, digoxin and bile acids. Plasma of control subjects showed increased levels of the above mentioned parameters with after incubation for 1 hour and addition of cholesterol substrate resulted in still further significant increase in these parameters. The plasma of patients showed

similar results but the extent of increase was more. The addition of antibiotics to the control plasma caused a decrease in all the parameters while addition of rutile increased their levels. The addition of antibiotics to the patient's plasma caused a decrease in all the parameters while addition of rutile increased their levels but the extent of change was more in patient's sera as compared to controls. The results are expressed in tables 1-7 as percentage change in the parameters after 1 hour incubation as compared to the values at zero time.

Table 1. *Effect of rutile and antibiotics on muramic acid and serotonin.*

Group	Muramic acid % change (Increase with Rutile)		Muramic acid % change (Decrease with Doxy+Cipro)		5 HT % (Increase without Doxy)		5 HT % (Decrease with Doxy)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Normal	4.41	0.15	18.63	0.12	4.34	0.15	18.24	0.37
ASTH	23.45	1.79	66.32	3.63	22.56	2.46	62.70	4.53
CBE	23.20	1.57	66.65	4.26	22.12	2.44	63.69	5.14
ILD	22.95	1.61	65.76	4.01	22.92	1.99	66.55	4.55
F value	403.394		680.284		348.867		364.999	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 2. *Effect of rutile and antibiotics on free DNA and RNA.*

Group	DNA % change (Increase with Rutile)		DNA % change (Decrease with Doxy)		RNA % change (Increase with Rutile)		RNA % change (Decrease with Doxy)	
Normal	4.37	0.15	18.39	0.38	4.37	0.13	18.38	0.48
ASTH	23.17	1.49	63.96	5.72	23.21	1.72	66.40	3.69
CBE	22.98	1.50	65.13	4.87	23.15	1.62	66.48	4.17
ILD	22.79	2.20	64.26	6.02	22.60	1.64	66.86	4.21
F value	337.577		356.621		427.828		654.453	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 3. *Effect of rutile and antibiotics on HMG CoA reductase and PAH.*

Group	HMG CoA R % change (Increase with Rutile)		HMG CoA R % change (Decrease with Doxy)		PAH % change (Increase with Rutile)		PAH % change (Decrease with Doxy)	
Normal	4.30	0.20	18.35	0.35	4.45	0.14	18.25	0.72
ASTH	22.03	2.58	60.73	5.55	23.22	1.67	62.06	2.05
CBE	22.28	2.10	65.21	3.81	23.31	1.70	64.38	5.67
ILD	22.75	2.75	62.71	6.04	22.98	2.01	63.91	4.86
F value	319.332		199.553		391.318		257.996	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 4. *Effect of rutile and antibiotics on digoxin and bile acids.*

Group	Digoxin (ng/ml) (Increase with Rutile)		Digoxin (ng/ml) (Decrease with Doxy+Cipro)		Bile acids % change (Increase with Rutile)		Bile acids % change (Decrease with Doxy)	
Normal	0.11	0.00	0.054	0.003	4.29	0.18	18.15	0.58
ASTH	0.49	0.07	0.199	0.022	23.38	2.13	64.52	6.49
CBE	0.55	0.04	0.219	0.038	23.19	1.72	64.25	6.19
ILD	0.50	0.07	0.183	0.029	22.77	1.97	64.79	5.78
F value	135.116		71.706		290.441		203.651	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 5. *Effect of rutile and antibiotics on pyruvate and hexokinase.*

Group	Pyruvate % change (Increase with Rutile)		Pyruvate % change (Decrease with Doxy)		Hexokinase % change (Increase with Rutile)		Hexokinase % change (Decrease with Doxy)	
Normal	4.34	0.21	18.43	0.82	4.21	0.16	18.56	0.76
ASTH	21.26	2.04	55.44	7.92	22.20	2.41	64.44	5.78
CBE	21.53	2.15	58.30	8.80	22.90	2.07	67.17	4.33
ILD	20.89	2.28	58.84	9.44	22.54	2.57	65.57	5.41
F value	321.255		115.242		292.065		317.966	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 6. *Effect of rutile and antibiotics on hydrogen peroxide and delta amino levulinic acid.*

Group	H_2O_2 % (Increase with Rutile)		H_2O_2 % (Decrease with Doxy)		ALA % (Increase with Rutile)		ALA % (Decrease with Doxy)	
Normal	4.43	0.19	18.13	0.63	4.40	0.10	18.48	0.39
ASTH	22.90	1.51	63.27	4.96	23.43	1.57	66.30	3.57
CBE	23.43	1.74	64.28	7.33	22.76	2.20	67.63	3.52
ILD	23.30	1.47	60.35	7.93	22.63	1.63	67.24	3.42
F value	380.721		171.228		372.716		556.411	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 7. *Effect of rutile and antibiotics on ATP synthase and cytochrome F420.*

Group	ATP synthase % (Increase with Rutile)		ATP synthase % (Decrease with Doxy)		CYT F420 % (Increase with Rutile)		CYT F420 % (Decrease with Doxy)	
Normal	4.40	0.11	18.78	0.11	4.48	0.15	18.24	0.66
ASTH	22.94	1.94	66.18	4.15	22.39	1.75	64.24	8.55
CBE	23.32	1.74	65.67	4.16	22.78	2.23	62.58	8.62
ILD	23.33	1.35	66.83	3.27	21.95	1.56	53.17	7.20
F value	449.503		673.081		306.749		130.054	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Discussion

There was increase in cytochrome F420 indicating archaeal growth in interstitial lung disease, chronic bronchitis emphysema and bronchial asthma. The archaea can synthesize and use cholesterol as a carbon and energy source.[14, 15] The archaeal origin of the enzyme activities was indicated by antibiotic induced suppression. The study indicates the presence of actinide based archaea with an alternate actinide based enzymes or metalloenzymes in the system as indicated by rutile induced increase in enzyme activities.[16] There was also an increase in archaeal HMG CoA reductase activity indicating increased cholesterol synthesis

by the archaeal mevalonate pathway. The archaeal beta hydroxyl steroid dehydrogenase activity indicating digoxin synthesis and archaeal cholesterol hydroxylase activity indicating bile acid synthesis were increased.[7] The archaeal cholesterol oxidase activity was increased resulting in generation of pyruvate and hydrogen peroxide.[15] The pyruvate gets converted to glutamate and ammonia by the GABA shunt pathway. The archaeal aromatization of cholesterol generating PAH, serotonin and dopamine was also detected.[17] The archaeal glycolytic hexokinase activity and archaeal extracellular ATP synthase activity were increased. The archaea can undergo magnetite and calcium carbonate mineralization and can exist as calcified nanoforms.[18] There was an increase in free RNA indicating self replicating RNA viroids and free DNA indicating generation of viroid complementary DNA strands by archaeal reverse transcriptase activity. The actinides modulate RNA folding and catalyse its ribozymal action. Digoxin can cut and paste the viroidal strands by modulating RNA splicing generating RNA viroidal diversity. The viroids are evolutionarily escaped archaeal group I introns which have retrotransposition and self splicing qualities.[19] Archaeal pyruvate can produce histone deacetylase inhibition resulting in endogenous retroviral (HERV) reverse transcriptase and integrase expression. This can integrate the RNA viroidal complementary DNA into the noncoding region of eukaryotic noncoding DNA using HERV integrase as has been described for borna and ebola viruses.[20] The noncoding DNA is lengthened by integrating RNA viroidal complementary DNA with the integration going on as a continuing event. The archaea genome can also get integrated into human genome using integrase as has been described for trypanosomes.[21] The integrated viroids and archaea can undergo vertical transmission and can exist as genomic parasites.[20, 21] This increases the length and alters the grammar of the noncoding region producing memes or memory of acquired characters.[22] The viroidal complementary DNA can function as

jumping genes producing a dynamic genome important in HLA gene expression. This modulation of HLA gene expression by viroidal complementary DNA can result in autoimmune diseases. The RNA viroids can regulate mRNA function by RNA interference.[19] The phenomena of RNA interference can modulate T cell and B cell function and euchromatin/heterochromatin expression. RNA viroidal mRNA interference plays a role in the pathogenesis of autoimmune diseases like interstitial lung disease, chronic bronchitis emphysema and bronchial asthma.

The presence of muramic acid, HMG CoA reductase and cholesterol oxidase activity inhibited by antibiotics indicates the presence of bacteria with mevalonate pathway. The bacterial with mevalonate pathway include streptococcus, staphylococcus, actinomycetes, listeria, coxiella and Borrelia.[23] The bacteria and archaea with mevalonate pathway and cholesterol catabolism had a evolutionarily advantage and constitutes the isoprenoidal clade organism with the archaea evolving into mevalonate pathway gram positive and gram negative organism through horizontal gene transfer of viroidal and virus genes.[24] The isoprenoidal clade prokaryotes develop into other groups of prokaryotes via viroidal/virus as well as eukaryotic horizontal gene transfer producing bacterial speciation.[25] The RNA viroids and its complementary DNA developed into cholesterol enveloped RNA and DNA viruses like herpes, retrovirus, influenza virus, borna virus, cytomegalo virus and Ebstein Barr virus by recombining with eukaryotic and human genes resulting in viral speciation. Bacterial and viral species are ill defined and fuzzy with all of them forming one common genetic pool with frequent horizontal gene transfer and recombination. Thus the multi and unicellular eukaryote with its genes serves the purpose of prokaryotic and viral speciation. The multicellular eukaryote developed so that their endosymbiotic archaeal colonies could survive and

forage better. The multicellular eukaryotes are like bacterial biofilms. The archaea and bacteria with a mevalonate pathway uses the extracellular RNA viroids and DNA viroids for quorum sensing and in the generation of symbiotic biofilm like structures which develop into multicellular eukaryotes.[26, 27] The endosymbiotic archaea and bacteria with mevalonate pathway still uses the RNA viroids and DNA viroids for the regulation of muticellular eukaryote. Pollution is induced by the primitive nanoarchaea and mevalonate pathway bacteria synthesised PAH and methane leading on to redox stress. Redox stress leads to sodium potassium ATPase inhibition, inward movement of plasma membrane cholesterol, defective SREBP sensing, increased cholesterol synthesis and nanoarchaeal/mevalonate pathway bacterial growth.[28] Redox stress leads on to viroidal and archaeal multiplication. Redox stress can also lead to HERV reverse transcriptase and integrase expression. The noncoding DNA is formed of integrating RNA viroidal complementary DNA and archaea with the integration going on as a continuing event. The archaeal pox like dsDNA virus forms evolutionarily the nucleus. The integrated viroidal, archaeal and mevalonate pathway bacterial sequences can undergo vertical transmission and can exist as genomic parasites. The genomic integrated archaea, mevalonate pathway bacteria and viroids form a genomic reserve of bacteria and viruses which can recombine with human and eukaryotic genes producing bacterial and viral speciation. Bacteria and viruses have been related to the pathogenesis of interstitial lung disease, chronic bronchitis emphysema and bronchial asthma.[29, 30] The change in the length and grammar of the noncoding region produces eukaryotic speciation and individuality.[31] Changes in the length of noncoding region especially human endogenous retroviruses can lead onto autoimmune diseases.[32] The integration of nanoarchaea, mevalonate pathway prokaryotes and viroids in to the eukaryotic and human genome produces a chimera which can multiply producing biofilm like multicellular structures having a mixed

archaeal, viroidal, prokaryotic and eukaryotic characters which is a regression from the multicellular eukaryotic tissue This results in a new neuronal, metabolic, immune and tissue phenotype or microchimeras leading to human diseases like interstitial lung disease, chronic bronchitis emphysema and bronchial asthma. The microchimeras formed can lead to autoantigens and autoimmune diseases.

Archaea and RNA viroid can bind the TLR receptor induce NFKB producing immune activation and cytokine TNF alpha secretion. The archaeal DXP and mevalonate pathway metabolites can bind γδ TCR and digoxin induced calcium signalling can activate NFKB producing chronic immune activation.[2, 33] The archaeal cholesterol aromatase generated PAH can produce immune activation. The archaea and viroid induced chronic immune activation and generation of superantigens can lead on to autoimmune disease. Immune activation has been related to the pathogenesis of interstitial lung disease, chronic bronchitis emphysema and bronchial asthma.[29, 30] PAH has also been related to the pathogenesis of interstitial lung disease, chronic bronchitis emphysema and bronchial asthma.

The archaea and viroids can regulate the nervous system including the NMDA synaptic transmission.[2] NMDA can be activated by digoxin induced calcium oscillations, PAH and viroid induced RNA interference.[2] The cholesterol ring oxidase generated pyruvate can be converted by the GABA shunt pathway to glutamate. The archaeal cholesterol aromatase can generate serotonin.[17] Glutamatergic and serotoninergic transmission can lead to immune activation. Serotonin can produce bronchospasm leading onto bronchial asthma. The higher degree of integration of the archaea into the genome produces increased digoxin synthesis producing right hemispheric dominance and lesser degree producing left hemispheric dominance.[2] Right hemispheric dominance

can lead to autoimmune diseases like interstitial lung disease, chronic bronchitis emphysema and bronchial asthma.[2]

Archaea, viroids and digoxin can induce the host AKT PI3K, AMPK, HIF alpha and NFKB producing the Warburg metabolic phenotype.[34] The increased glycolytic hexokinase activity, decrease in blood ATP, leakage of cytochrome C, increase in serum pyruvate and decrease in acetyl CoA indicates the generation of the Warburg phenotype. There is induction of glycolysis, inhibition of PDH activity and mitochondrial dysfunction resulting in inefficient energetics. The lymphocytes depend on glycolysis for their energy needs. The increased glycolysis induced by the Warburg phenotype leads to immune activation. Lactic acid generated by increased glycolysis leads to immune stimulation. Cholesterol oxidase activity, increased glycolysis related NADPH oxidase activity, bacterial porphyrin induced redox stress and mitochondrial dysfunction generates free radicals important in the pathogenesis of interstitial lung disease, chronic bronchitis emphysema and bronchial asthma. The accumulated pyruvate enters the GABA shunt pathway and is converted to citrate which is acted upon by citrate lyase and converted to acetyl CoA, used for cholesterol synthesis.[34] The pyruvate can be converted to glutamate and ammonia which is oxidised by archaea for energy needs. The increased cholesterol substrate leads to increased archaeal growth and digoxin synthesis leading to metabolic channelling to the mevalonate pathway. Hyperdigoxinemia is important in the pathogenesis of autoimmune diseases like interstitial lung disease, chronic bronchitis emphysema and bronchial asthma.[2] Digoxin can increase lymphocytic intracellular calcium which leads on to induction of NFKB and immune activation.[2] The archaeal cholesterol atabolism can deplete the lymphocytic cell membranes of cholesterol resulting in alteration of lymphocytic cell membrane microdomains related receptors producing immune activation. The archaeal bile

acids can bind GPCR and modulate D2 regulating the conversion of T4 to T3. T3 activates uncoupling proteins reducing redox stress. Bile acids can also activate NRF ½ inducing NQO1, GST, HOI reducing redox stress. Bile acids can bind PXR inducing the bile acid shunt pathway of cholesterol detoxification. Bile acids can bind macrophage GPCR and VDR producing immunosuppression and inhibiting NFKB. This helps to modulate the archaea and viroid induced chronic immune activation. Bile acids are thus protective compounds and put a break on the archaea and viroid induced changes.[35] Thus the actinide, viroid and mevalonate pathway bacteria induced metabolic, genetic, immune and neuronal transmission changes can lead onto interstitial lung disease, chronic bronchitis emphysema and bronchial asthma.

Global warming can lead to osmotic stress consequent to dehydration. The increase in actinidic archaeal growth leads to cholesterol catabolism and digoxin synthesis. Digoxin produces membrane sodium potassium ATPase inhibition and increase in intracellular calcium producing mitochondrial dysfunction. This results in oxidative stress. The oxidative stress and osmotic stress can induce the enzyme aldose reductase which converts glucose to fructose. Fructose has got a low km value for ketokinase as compared to glucose. Therefore fructose gets phosphorylated more to fructose phosphate and the cell is depleted of ATP. The cell depletion of ATP leads to oxidative stress and chronic inflammation consequent to induction of NFKB. Oxidative stress can open the mitochondrial PT pore producing release of cyto C and activation of the caspase cascade of cell death. The fructose phosphate can enter the pentose phosphate pathway synthesizing ribose and nucleic acid. The depletion of cellular ATP results in generation of AMP and ADP which are acted upon by deaminases causing hyperuricemia. Uric acid can produce endothelial dysfunction and vascular disease. Uric acid can also produce mitochondrial dysfunction. The fructose

phosphate can enter the glucosamine pathway synthesizing GAG and producing mucopolysaccharide accumulation. Fructose can fructosylate proteins making them antigenic and producing an autoimmune response. This can lead to global warming related pulmonary diseases.

References

[1] Valiathan M. S., Somers, K., Kartha, C. C. (1993). *Endomyocardial Fibrosis.* Delhi: Oxford University Press.

[2] Kurup R., Kurup, P. A. (2009). *Hypothalamic digoxin, cerebral dominance and brain function in health and diseases*. New York: Nova Science Publishers.

[3] Hanold D., Randies, J. W. (1991). Coconut cadang-cadang disease and its viroid agent, *Plant Disease,* 75, 330-335.

[4] Edwin B. T., Mohankumaran, C. (2007). Kerala wilt disease phytoplasma: Phylogenetic analysis and identification of a vector, *Proutista moesta*, *Physiological and Molecular Plant Pathology*, 71(1-3), 41-47.

[5] Eckburg P. B., Lepp, P. W., Relman, D. A. (2003). Archaea and their potential role in human disease, *Infect Immun*, 71, 591-596.

[6] Adam Z. (2007). Actinides and Life's Origins, *Astrobiology*, 7, 6-10.

[7] Schoner W. (2002). Endogenous cardiac glycosides, a new class of steroid hormones, *Eur J Biochem*, 269, 2440-2448.

[8] Davies P. C. W., Benner, S. A., Cleland, C. E., Lineweaver, C. H., McKay, C. P., Wolfe-Simon, F. (2009). Signatures of a Shadow Biosphere, *Astrobiology*, 10, 241-249.

[9] Richmond W. (1973). Preparation and properties of a cholesterol oxidase from nocardia species and its application to the enzymatic assay of total cholesterol in serum, *Clin Chem*, 19, 1350-1356.

[10] Snell E. D., Snell, C. T. (1961). *Colorimetric Methods of Analysis.* Vol 3A. New York: Van Nostrand.

[11] Glick D. (1971). *Methods of Biochemical Analysis.* Vol 5. New York: Interscience Publishers.

[12] Colowick, Kaplan, N. O. (1955). *Methods in Enzymology.* Vol 2. New York: Academic Press.

[13] Maarten A. H., Marie-Jose, M., Cornelia, G., van Helden-Meewsen, Fritz, E., Marten, P. H. (1995). Detection of muramic acid in human spleen, *Infection and Immunity*, 63(5), 1652-1657.

[14] Smit A., Mushegian, A. (2000). Biosynthesis of isoprenoids via mevalonate in Archaea: the lost pathway, *Genome Res*, 10(10), 1468-84.

[15] Van der Geize R., Yam, K., Heuser, T., Wilbrink, M. H., Hara, H., Anderton, M. C. (2007). A gene cluster encoding cholesterol catabolism in a soil actinomycete provides insight into Mycobacterium tuberculosis survival in macrophages, *Proc Natl Acad Sci USA*, 104(6), 1947-52.

[16] Francis A. J. (1998). Biotransformation of uranium and other actinides in radioactive wastes, *Journal of Alloys and Compounds*, 271(273), 78-84.

[17] Probian C., Wülfing, A., Harder, J. (2003). Anaerobic mineralization of quaternary carbon atoms: Isolation of denitrifying bacteria on pivalic acid (2,2-Dimethylpropionic acid), *Applied and Environmental Microbiology*, 69(3), 1866-1870.

[18] Vainshtein M., Suzina, N., Kudryashova, E., Ariskina, E. (2002). New Magnet-Sensitive Structures in Bacterial and Archaeal Cells, *Biol Cell*, 94(1), 29-35.

[19] Tsagris E. M., de Alba, A. E., Gozmanova, M., Kalantidis, K. (2008). Viroids, *Cell Microbiol*, 10, 2168.

[20] Horie M., Honda, T., Suzuki, Y., Kobayashi, Y., Daito, T., Oshida, T. (2010). Endogenous non-retroviral RNA virus elements in mammalian genomes, *Nature*, 463, 84-87.

[21] Hecht M., Nitz, N., Araujo, P., Sousa, A., Rosa, A., Gomes, D. (2010). Genes from Chagas parasite can transfer to humans and be passed on to children. Inheritance of DNA Transferred from American Trypanosomes to Human Hosts, *PLoS ONE*, 5, 2-10.

[22] Flam F. (1994). Hints of a language in junk DNA, *Science*, 266, 1320.

[23] Horbach S., Sahm, H., Welle, R. (1993). Isoprenoid biosynthesis in bacteria: two different pathways? *FEMS Microbiol Lett*, 111, 135-140.

[24] Gupta R. S. (1998). Protein phylogenetics and signature sequences: a reappraisal of evolutionary relationship among archaebacteria, eubacteria, and eukaryotes, *Microbiol Mol Biol Rev*, 62, 1435-1491.

[25] Hanage W., Fraser, C., Spratt, B. (2005). Fuzzy species among recombinogenic bacteria, *BMC Biology*, 3, 6-10.

[26] Webb J. S., Givskov, M., Kjelleberg, S. (2003). Bacterial biofilms: prokaryotic adventures in multicellularity, *Curr Opin Microbiol*, 6(6), 578-85.

[27] Whitchurch C. B., Tolker-Nielsen, T., Ragas, P. C., Mattick, J. S. (2002). Extracellular DNA Required for Bacterial Biofilm Formation. *Science*, 295(5559), 1487.

[28] Chen Y., Cai, T., Wang, H., Li, Z., Loreaux, E., Lingrel, J. B. (2009). Regulation of intracellular cholesterol distribution by Na/K-ATPase, *J Biol Chem*, 284(22), 14881-90.

[29] Fauci A. S. (1998). *Harrison's Principles of Internal Medicine*. New York: McGraw-Hill.

[30] Crystal R. G. (1996). *The Lung: Scientific Foundations*. Philadelphia: Lippincott-Raven.

[31] Poole A. M. (2006). Did group II intron proliferation in an endosymbiont-bearing archaeon create eukaryotes? *Biol Direct*, 1, 36-40.

[32] Villarreal L. P. (2006). How viruses shape the tree of life, *Future Virology*, 1(5), 587-595.

[33] Eberl M., Hintz, M., Reichenberg, A., Kollas, A., Wiesner, J., Jomaa, H. (2010). Microbial isoprenoid biosynthesis and human γδ T cell activation, *FEBS Letters*, 544(1), 4-10.

[34] Wallace D. C. (2005). Mitochondria and Cancer: Warburg Addressed, *Cold Spring Harbor Symposia on Quantitative Biology*, 70, 363-374.

[35] Lefebvre P., Cariou, B., Lien, F., Kuipers, F., Staels, B. (2009). Role of Bile Acids and Bile Acid Receptors in Metabolic Regulation, *Physiol Rev,* 89(1), 147-191.

6

The Actinidic Archaea Related Lemurian Syndrome - Endomyocardial Fibrosis, Chronic Calcific Pancreatitis and Multinodular Goitre

Introduction

Actinidic beach sands have been postulated to play a pivotal role in abiogenesis. Chronic calcific pancreatitis (CCP), endomyocardial fibrosis (EMF), multinodular goitre (MNG) and mucoid angiopathy along with the root wilt disease of coconut is endemic to Kerala with its radioactive actinide beach sands. The Actinides like rutile producing intracellular magnesium deficiency due to actinide-magnesium exchange sites in the cell membrane has been implicated in the etiology of EMF.[1-3] Endogenous digoxin, a steroidal glycoside which functions as a membrane sodium-potassium ATPase inhibitor has also been related to its etiology of EMF, CCP, MNG and mucoid angiopathy.[4] Digoxin produces intracellular magnesium deficiency which results in acidic mucopolysaccharide accumulation of the vascular, cardiac and endocrine tissues contributing to the pathogenesis. Organisms like phytoplasmas and viroids have also been demonstrated to play a role in the etiology of root wilt disease of coconut which is co-endemic in Kerala.[5, 6] The possibility of endogenous digoxin synthesis by actinide based primitive organism like archaea with a mevalonate pathway and cholesterol catabolism was considered.[7-9] The role of RNA viroids in the etiopathogenesis of EMF, CCP, MNG and mucoid angiopathy was also explored. Davies has put forward the concept of a shadow biosphere of organisms with alternate biochemistry present in earth itself.[10] An actinide dependent shadow biosphere of archaea and viroids in the above mentioned disease states is described.[7]

The group of diseases are seen in particular geographic areas of the world near the equator - South India, South America, South Africa and Australia.[1-3] These geographic areas are rich in placer deposits containing monazite, illmenite, rutile

and thorium. These areas peninsular India, Africa, Australia, South America and Antarctica formed part of one single pre-historic continent in Southern ocean and Indian ocean called Lemuria by geologists. The evolution of primates and homo sapiens occurred in the rift valley of Africa part of this pre-historic continent. Metal actinides in beach sands have been postulated to play a role in abiogenesis. Actinide mineral like rutile, monazite and illmenite by surface metabolism would have contributed to abiogenesis. A hypothesis of cholesterol as the primal prebiotic molecule synthesised on actinide surfaces with all other biomolecules arising from it and a self replicating cholesterol lipid organism as the initial life form is presented. Actinide dependent organism would have contributed to primate and human evolution. It is also possible that actinidic organisms would also have contributed to the destruction of the Lemurian supercontinent. This paper postulates that the co-existence of EMF, CCP and MNG in the above mentioned geographic areas points to the possibility of these land masses being joined together has one single land mass - Lemuria.

Actinidic archaea has been related to global warming and human diseases. The growth of endosymbiotic actinidic archaea in relation to climate change and global warming leads to neanderthalisation of the humans. Neanderthal metabolonomics include the Warburg phenotype and cholesterol catabolism resulting in hyperdigoxinemia. Digoxin produced by archaeal cholesterol catabolism produces neanderthalisation. The neanderthalisation of the human brain due to endosymbiotic archaeal overgrowth results in prefrontal cortical atrophy and cerebellar hyperplasia. This leads on to dysautonomia with sympathetic hyperactivity and parasympathetic neuropathy in these disorders.

Global warming can lead to osmotic stress consequent to dehydration. The increase in actinidic archaeal growth leads to cholesterol catabolism and digoxin synthesis. Digoxin produces membrane sodium potassium ATPase inhibition

and increase in intracellular calcium producing mitochondrial dysfunction. This results in oxidative stress. The oxidative stress and osmotic stress can induce the enzyme aldose reductase which converts glucose to fructose. Fructose has got a low km value for ketokinase as compared to glucose. Therefore fructose gets phosphorylated more to fructose phosphate and the cell is depleted of ATP. The cell depletion of ATP leads to oxidative stress and chronic inflammation consequent to induction of NFKB. Oxidative stress can open the mitochondrial PT pore producing release of cyto C and activation of the caspase cascade of cell death. The fructose phosphate can enter the pentose phosphate pathway synthesizing ribose and nucleic acid. The depletion of cellular ATP results in generation of AMP and ADP which are acted upon by deaminases causing hyperuricemia. Uric acid can produce endothelial dysfunction and vascular disease. Uric acid can also produce mitochondrial dysfunction. The fructose phosphate can enter the glucosamine pathway synthesizing GAG and producing mucopolysaccharide accumulation. Fructose can fructosylate proteins making them antigenic and producing an autoimmune response. This can lead to the global warming related Lemurian syndrome of EMF, CCP, MNG and mucoid angiopathy.

Materials and Methods

Informed consent of the subjects and the approval of the ethics committee were obtained for the study. The following groups were included in the study: - endomyocardial fibrosis, chronic calcific pancreatitis, multinodular goitre and mucoid angiopathy. There were 10 patients in each group and each patient had an age and sex matched healthy control selected randomly from the general population. The blood samples were drawn in the fasting state before treatment was initiated. Plasma from fasting heparinised blood was used and the

experimental protocol was as follows (I) Plasma+phosphate buffered saline, (II) same as I+cholesterol substrate, (III) same as II+rutile 0.1 mg/ml, (IV) same as II+ciprofloxacine and doxycycline each in a concentration of 1 mg/ml. Cholesterol substrate was prepared as described by Richmond.[11] Aliquots were withdrawn at zero time immediately after mixing and after incubation at 37 ℃ for 1 hour. The following estimations were carried out: - Cytochrome F420, free RNA, free DNA, muramic acid, polycyclic aromatic hydrocarbon, hydrogen peroxide, serotonin, pyruvate, ammonia, glutamate, cytochrome C, hexokinase, ATP synthase, HMG CoA reductase, digoxin and urease.[12-15] Cytochrome F420 was estimated flourimetrically (excitation wavelength 420 nm and emission wavelength 520 nm). Polycyclic aromatic hydrocarbon was estimated by measuring hydrogen peroxide liberated by using glucose reagent. The statistical analysis was done by ANOVA.

Results

The parameters checked as indicated above were: - cytochrome F420, free RNA, free DNA, muramic acid, polycyclic aromatic hydrocarbon, hydrogen peroxide, serotonin, pyruvate, ammonia, glutamate, cytochrome C, hexokinase, ATP synthase, HMG CoA reductase, digoxin and urease. Plasma of control subjects showed increased levels of the above mentioned parameters with after incubation for 1 hour and addition of cholesterol substrate resulted in still further significant increase in these parameters. The plasma of patients showed similar results but the extent of increase was more. The addition of antibiotics to the control plasma caused a decrease in all the parameters while addition of rutile increased their levels. The addition of antibiotics to the patient's plasma caused a decrease in all the parameters while addition of rutile increased their levels but the extent of change was more in patient's sera as compared to

controls. The results are expressed in tables 1-7 as percentage change in the parameters after 1 hour incubation as compared to the values at zero time.

Table 1. *Effect of rutile and antibiotics on muramic acid and serotonin.*

Group	Muramic acid % (Increase without Doxy)		Muramic acid % (Decrease with Doxy)		5 HT % (Increase without Doxy)		5 HT % (Decrease with Doxy)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Normal	4.41	0.15	18.63	0.12	4.34	0.15	18.24	0.37
Muc Angio	24.43	0.81	68.72	2.77	24.32	1.09	65.80	5.14
EMF	22.28	1.52	64.05	2.79	22.82	1.56	64.61	4.95
CCP	23.07	1.46	64.68	3.86	22.89	1.50	64.19	6.51
MNG	23.85	1.69	66.43	3.17	22.72	1.64	63.91	4.93
F value	403.394		680.284		348.867		364.999	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 2. *Effect of rutile and antibiotics on free DNA and RNA.*

Group	DNA % change (Increase with Rutile)		DNA % change (Decrease with Doxy)		RNA % change (Increase with Rutile)		RNA % change (Decrease with Doxy)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Normal	4.37	0.15	18.39	0.38	4.37	0.13	18.38	0.48
Muc Angio	22.27	1.49	63.99	4.03	22.27	1.49	69.25	2.33
EMF	22.29	2.05	58.70	7.34	22.29	2.05	67.03	5.97
CCP	21.19	2.18	61.63	7.68	21.19	2.18	62.99	5.47
MNG	22.93	2.08	63.49	5.01	23.19	1.74	65.68	4.06
F value	337.577		356.621		427.828		654.453	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 3. *Effect of rutile and antibiotics on HMG CoA reductase and PAH.*

Group	HMG CoA R % change (Increase with Rutile)		HMG CoA R% change (Decrease with Doxy)		PAH % change (Increase with Rutile)		PAH % change (Decrease with Doxy)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Normal	4.30	0.20	18.35	0.35	4.45	0.14	18.25	0.72
Muc Angio	24.44	0.90	59.90	4.74	23.90	1.36	63.29	6.86
EMF	22.92	1.48	61.91	7.56	23.73	1.38	65.20	6.20
CCP	23.27	1.96	63.09	9.21	22.85	1.71	66.14	3.58
MNG	23.65	1.88	64.78	6.62	23.79	1.19	64.24	3.96
F value	319.332		199.553		391.318		257.996	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 4. *Effect of rutile and antibiotics on digoxin and urease.*

Group	Digoxin (ng/ml) (Increase with Rutile)		Digoxin (ng/ml) (Decrease with Doxy+Cipro)		Urease % change (Increase with Rutile)		Urease % change (Decrease with Doxy)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Normal	0.11	0.00	0.054	0.003	4.29	0.18	18.15	0.58
Muc Angio	0.53	0.03	0.224	0.041	23.37	1.55	63.99	4.03
EMF	0.51	0.05	0.213	0.033	23.41	1.41	58.70	7.34
CCP	0.47	0.05	0.212	0.028	22.44	2.00	61.63	7.68
MNG	0.51	0.06	0.227	0.040	22.15	1.79	65.49	7.28
F value	135.116		71.706		290.441		203.651	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 5. *Effect of rutile and antibiotics on pyruvate and hexokinase.*

Group	Pyruvate % change (Increase with Rutile)		Pyruvate % change (Decrease with Doxy)		Hexokinase % change (Increase with Rutile)		Hexokinase % change (Decrease with Doxy)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Normal	4.34	0.21	18.43	0.82	4.21	0.16	18.56	0.76
Muc Angio	22.27	1.49	61.94	5.49	23.67	1.65	69.25	2.33
EMF	22.29	2.05	62.37	5.05	21.66	1.94	67.03	5.97
CCP	21.19	2.18	54.82	8.70	22.27	2.18	62.99	5.47
MNG	19.73	2.27	59.36	7.53	22.51	2.32	62.70	3.24
F value	321.255		115.242		292.065		317.966	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 6. *Effect of rutile and antibiotics on hydrogen peroxide and delta amino levulinic acid.*

Group	H_2O_2 % (Increase with Rutile)		H_2O_2 % (Decrease with Doxy)		ALA % (Increase with Rutile)		ALA % (Decrease with Doxy)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Normal	4.43	0.19	18.13	0.63	4.40	0.10	18.48	0.39
Muc Angio	23.64	1.50	60.44	6.83	22.27	1.49	59.90	4.74
EMF	23.29	1.67	60.52	5.38	22.29	2.05	61.91	7.56
CCP	23.38	1.79	57.37	7.45	21.19	2.18	63.09	9.21
MNG	22.00	1.77	61.39	7.47	22.71	1.82	66.13	3.83
F value	380.721		171.228		372.716		556.411	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 7. *Effect of rutile and antibiotics on ATP synthase and cytochrome F420.*

Group	ATP synthase % (Increase with Rutile)		ATP synthase % (Decrease with Doxy)		CYT F420 % (Increase with Rutile)		CYT F420 % (Decrease with Doxy)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Normal	4.40	0.11	18.78	0.11	4.48	0.15	18.24	0.66
Muc Angio	23.45	1.52	67.05	4.84	23.72	1.76	58.92	5.46
EMF	23.37	1.31	63.97	3.62	22.70	1.87	60.46	8.06
CCP	22.53	1.92	66.31	3.10	21.31	1.37	57.32	8.41
MNG	23.39	1.14	68.11	3.02	22.17	2.01	65.15	6.46
F value	449.503		673.081		306.749		130.054	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Abbreviations

Muc Angio: Mucoid angiopathy

EMF: Endomyocardial fibrosis

CCP: Chronic calcific pancreatitis

MNG: Multinodular goitre

Discussion

There was increase in cytochrome F420 indicating archaeal growth in endomyocardial fibrosis, chronic calcific pancreatitis, multinodular goitre and mucoid angiopathy. The archaea can synthesise and use cholesterol as a carbon and energy source.[16, 17] The archaeal origin of the enzyme activities was indicated by antibiotic induced suppression. The study indicates the presence of actinide based archaea with an alternate actinide based enzymes or metalloenzymes in the system as indicated by rutile induced increase in enzyme activities.[18] There was also an increase in archaeal HMG CoA reductase activity indicating increased cholesterol synthesis by the archaeal mevalonate pathway. The archaeal beta hydroxyl steroid dehydrogenase activity indicating digoxin synthesis and archaeal cholesterol hydroxylase activity indicating bile acid synthesis were increased.[8] The archaeal cholesterol oxidase activity was increased resulting in generation of pyruvate and hydrogen peroxide.[17] The pyruvate gets converted to glutamate and ammonia by the GABA shunt pathway. The archaeal aromatization of cholesterol generating PAH, serotonin and dopamine was also detected.[19] The archaeal glycolytic hexokinase activity and archaeal extracellular ATP synthase activity were increased. There was an increase in free RNA indicating self replicating RNA viroids and free DNA indicating generation of viroid complementary DNA strands by archaeal reverse transcriptase activity. The actinides modulate RNA folding and catalyse its ribozymal action. Digoxin can cut and paste the viroidal strands by modulating RNA splicing generating RNA viroidal diversity. The viroids are evolutionarily escaped archaeal group I introns which have retrotransposition and self splicing qualities.[20] Archaeal pyruvate can produce histone deacetylase inhibition resulting in endogenous retroviral (HERV) reverse transcriptase and integrase expression. This can integrate the RNA viroidal complementary DNA into the

noncoding region of eukaryotic noncoding DNA using HERV integrase as has been described for borna and ebola viruses.[21] The noncoding DNA is lengthened by integrating RNA viroidal complementary DNA with the integration going on as a continuing event. The archaea genome can also get integrated into human genome using integrase as has been described for trypanosomes.[22] The integrated viroids and archaea can undergo vertical transmission and can exist as genomic parasites.[21, 22] This increases the length and alters the grammar of the noncoding region producing memes or memory of acquired characters.[23] The viroidal complementary DNA can function as jumping genes producing a dynamic genome and changing DNA sequences. The RNA viroids can regulate mRNA function by RNA interference.[20] The phenomena of RNA interference can modulate euchromatin/heterochromatin expression. RNA viroidal mRNA interference plays a role in the pathogenesis of endomyocardial fibrosis, chronic calcific pancreatitis, multinodular goitre and mucoid angiopathy. The viroidal RNA modulation of T cell and B cell function by mRNA interference can lead to immune activation. Monocytic infiltration of the vascular wall, cardiac and endocrine tissue can produce reactive connective tissue macromolecular deposition contributing to EMF, CCP, MNG and mucoid angiopathy. The viroidal RNA mediated mRNA interference can also inhibit insulin signalling and secretion leading onto CCP. The viroid RNA can inhibit thyroid hormone secretion and action by mRNA interference leading to increased TSH secretion and multinodular goitre.

The presence of muramic acid, HMG CoA reductase and cholesterol oxidase activity inhibited by antibiotics indicates the presence of bacteria with mevalonate pathway. The bacterial with mevalonate pathway include streptococcus, staphylococcus, actinomycetes, listeria, coxiella and borrelia.[24] The bacteria and archaea with mevalonate pathway and cholesterol catabolism

had a evolutionarily advantage and constitutes the isoprenoidal clade organism with the archaea evolving into mevalonate pathway gram positive and gram negative organism through horizontal gene transfer of viroidal and virus genes.[25] The isoprenoidal clade prokaryotes develop into other groups of prokaryotes via viroidal/virus as well as eukaryotic horizontal gene transfer producing bacterial speciation.[26] The RNA viroids and its complementary DNA developed into cholesterol enveloped RNA and DNA viruses like herpes, retrovirus, influenza virus, borna virus, cytomegalo virus and Ebstein Barr virus by recombining with eukaryotic and human genes resulting in viral speciation. Bacterial and viral species are ill defined and fuzzy with all of them forming one common genetic pool with frequent horizontal gene transfer and recombination. Thus the multi and unicellular eukaryote with its genes serves the purpose of prokaryotic and viral speciation. The multicellular eukaryote developed so that their endosymbiotic archaeal colonies could survive and forage better. The multicellular eukaryotes are like bacterial biofilms. The archaea and bacteria with a mevalonate pathway uses the extracellular RNA viroids and DNA viroids for quorum sensing and in the generation of symbiotic biofilm like structures which develop into multicellular eukaryotes.[27, 28] The endosymbiotic archaea and bacteria with mevalonate pathway still uses the RNA viroids and DNA viroids for the regulation of muticellular eukaryote. Pollution is induced by the primitive nanoarchaea and mevalonate pathway bacteria synthesised PAH and methane leading on to redox stress. Redox stress leads to sodium potassium ATPase inhibition, inward movement of plasma membrane cholesterol, defective SREBP sensing, increased cholesterol synthesis and nanoarchaeal/mevalonate pathway bacterial growth.[29] Redox stress leads on to viroidal and archaeal multiplication. Redox stress can also lead to HERV reverse transcriptase and integrase expression. The noncoding DNA is formed of integrating RNA viroidal complementary DNA and archaea

with the integration going on as a continuing event. The change in the length and grammar of the noncoding region produces eukaryotic speciation and individuality.[30] Thus actinidic nanoarchaea would have contributed to the evolution of the multicellular eukaryote, primates and humans. Changes in the length of noncoding region especially due to integration of viroid complementary DNA and archaea and the resulting jumping genes leads to new DNA sequences possibly contributing to EMF, CCP, MNG and mucoid angiopathy.[31] The integrated viroidal, archaeal and mevalonate pathway bacterial sequences can undergo vertical transmission and can exist as genomic parasites. The genomic integrated archaea, mevalonate pathway bacteria and viroids form a genomic reserve of bacteria and viruses which can recombine with human and eukaryotic genes producing bacterial and viral speciation. Archaea and mevalonate pathway bacteria can lead onto EMF, CCP, MNG and mucoid angiopathy. The persistent symbiosis leads to reparative connective tissue macromolecular deposition of acidic mucopolysaccharides, glycoproteins, collagen and elastin leading to fibrotic changes in the heart, vessel wall, thyroid and pancreas contributing to EMF, CCP, MNG and mucoid angiopathy.[4, 32] The integration of nanoarchaea, mevalonate pathway prokaryotes and viroids in to the eukaryotic and human genome produces a chimera which can multiply producing biofilm like multicellular structures having a mixed archaeal, viroidal, prokaryotic and eukaryotic characters which is a regression from the multicellular eukaryotic tissue. This results in a new metabolic and immune phenotype or microchimeras leading on to human diseases like EMF, CCP, MNG and mucoid angiopathy with a predilection to develop malignancy. Microchimeras can lead to cellular polyploidy important in malignant transformation and induction of carcinoma of thyroid and pancreas. The growth of archaea in the vascular, cardiac and endocrine tissues can result in calcification. The archaea can form calcified nanoarchaeal structures which can

exist as colonies in slime. The archaea can undergo magnetite and calcium carbonate mineralization and can exist as calcified nanoforms.[33] The calcified nanoarchaea can contribute to the tissue calcification noted in CCP, MNG and mucoid angiopathy.

Archaea and RNA viroid can bind the TLR receptor induce NFKB producing immune activation and cytokine TNF alpha secretion. The archaeal DXP and mevalonate pathway metabolites can bind γδ TCR and digoxin induced calcium signalling can activate NFKB producing chronic immune activation.[4, 34] The archaea and viroid can induce chronic immune activation and generation of superantigens. The archaea and viroid induced chronic immune activation can lead to monocyte infiltration of the vessel wall, cardiac and endocrine tissues leading on to reparative connective tissue macromolecular deposition. Immune activation results in induction of NADPH oxidase which generates hydrogen peroxide. Cholesterol oxidase activity also generates hydrogen peroxide. Hydrogen peroxide can produce tissue injury in MNG, CCP, EMF and mucoid angiopathy contributing to reparative connective tissue macromolecular deposition. Immune activation can also produce insulin resistance. TNF alpha produced by chronic immune activation can modulate the insulin receptor producing insulin resistance.[35] Chronic immune activation and cholesterol oxidase generated hydrogen peroxide can induce neutral sphingomyelinase generating ceramide producing insulin resistance.[36] This can contribute to chronic calcific pancreatitis. Immune activation and NFKB induction can suppress the thyroid hormone receptor resulting in hypothyroidism and increased TSH levels contributing to thyroid gland enlargement and multinodular goitre. Immune activation and NFKB induction can suppress the nuclear receptors LXR, PXR and FXR. FXR suppression can also lead to insulin resistance as well as increased connective tissue MPS deposition in

vessel wall, cardiac tissue and endocrine tissue. LXR suppression by NFKB stimulates HMG CoA reductase activity and suppresses cholesterol 7 alpha hydroxylase activity.[37] This stimulates cholesterol synthesis and inhibits its degradation via the bile acid pathway. PXR suppression by NFKB prevents cholesterol detoxification via the bile acid shunt pathway.[38] Thus LXR and PXR suppression by NFKB produces acute cholesterol toxicity. The increased cholesterol in the system leads to still further archaeal multiplication and growth as they depend on cholesterol as a carbon and energy source.

Archaea, viroids and digoxin can induce the host AKT PI3K, AMPK, HIF alpha and NFKB producing the Warburg metabolic phenotype.[39] The increased glycolytic hexokinase activity, decrease in blood ATP, leakage of cytochrome C, increase in serum pyruvate and decrease in acetyl CoA indicates the generation of the Warburg phenotype. There is induction of glycolysis, inhibition of PDH activity and mitochondrial dysfunction resulting in inefficient energetics. Mitochondrial dysfunction owing to the Warburg's phenotype can contribute to ineffective glucose utilisation and CCP. The accumulated pyruvate enters the GABA shunt pathway and is converted to citrate which is acted upon by citrate lyase and converted to acetyl CoA, used for cholesterol synthesis.[39] The increased cholesterol substrate also leads to increased archaeal growth and digoxin synthesis due to metabolic channelling to the mevalonate pathway. The Warburg phenotype leads to increased lipid synthesis and defective beta oxidation of fatty acids. The myocardium depends on fatty acids beta oxidation for energetics. The defective beta oxidation of fatty acids leads to myocardial dysfunction and EMF. The Warburg phenotype leads to upregulated glycolysis and increase in the metabolite fructose 1,6 diphosphate which is channelled to the pentose phosphate pathway. This can generate UDP sugars used for mucopolysaccharide synthesis. This results in acidic MPS deposition in the

tissues leading onto EMF, CCP, MNG and mucoid angiopathy. The pyruvate can be converted to glutamate and ammonia which is oxidised by archaea for energy needs. Ammonia can stimulate membrane sodium-potassium ATPase, increase ATP utilisation and produce mitochondrial transmembrane potential changes leading to mitochondrial dysfunction. This causes defective glucose utilisation contributing to CCP. Archaeal urease can convert urea to ammonia and thiocyanate. Increase cyanide load in the system can lead to mitochondrial dysfunction.[3] Cyanide related mitochondrial dysfunction can produce EMF, CCP and MNG. It produces defective cardiac function, decreased glucose utilisation and impaired iodide transport into the thyroid follicular cells. The Warburg phenotype can also lead onto malignant transformation. The upregulated glycolysis results in increased mitochondrial PT pore hexokinase and cell proliferation producing carcinoma of thyroid and pancreas.

Digoxin can produce sodium-potassium ATPase inhibition and inward movement of plasma membrane cholesterol. This produces defective SREBP sensing, increased HMG CoA reductase activity and cholesterol synthesis.[29] The digoxin induced inward movement of plasma membrane cholesterol can alter membrane cholesterol/sphingomyelin ratio producing modified lipid microdomains.[40] The digoxin induced lipid microdomain modulation can regulate the GPCR couple adrenaline, noradrenaline, glucagon and neuropeptide receptors as well as protein tyrosine kinase linked insulin receptor. This can lead onto CCP. The digoxin mediated inhibition of nuclear membrane sodium-potassium ATPase can modulate nuclear membrane lipid microdomains and thyroxine DNA receptor function. This can lead onto hypothyroidism, increased TSH levels and thyroid gland enlargement contributing to MNG. Digoxin can produce intracellular hypercalcemia and hypomagnesemia. This can lead on to vasospasm and thrombosis. Intracellular hypercalcemia can

activate the G-protein coupled thrombin receptor and PAF receptor producing thrombosis. Intracellular magnesium deficiency can lead onto increased thrombin and ADP/collagen induced platelet aggregation. This leads onto the thrombotic state in mucoid angiopathy. The decreased intracellular magnesium can produce ATP synthase inhibition and the increased intracellular calcium can produce mitochondrial PT pore dysfunction. Mitochondrial dysfunction can contribute to decreased glucose utilisation in CCP and myocardial dysfunction in EMF. Digoxin can produce sodium-potassium ATPase inhibition and intracellular hypomagnesemia. The increased tissue rutile load can lead to rutile-magnesium exchange leading onto intracellular hypomagnesemia. Hypomagnesemia can lead onto upregulated connective tissue macromolecular synthesis contributing to MNG, CCP, EMF and mucoid angiopathy. Acidic MPS deposition in the vessel wall leads to a hose pipe narrowing of the entire vascular tree leading onto mucoid angiopathy. Acidic MPS, collagen and elastin deposition of the heart leads to EMF. Hyperdigoxinemia is important in the pathogenesis of EMF, CCP, MNG and mucoid angiopathy. Digoxin induced sodium-potassium ATPase inhibition results in an ATP sparing effect.[41] Eighty percent of the ATP generated is used to run the sodium-potassium ATPase pump. The digoxin inhibition of the sodium-potassium ATPase spares this ATP which is then used for lipid and cholesterol synthesis. Fat also fuels insulin resistance by binding to the toll receptor and producing immune activation and immune infiltration of the adipose tissue. Digoxin can also increase lymphocytic intracellular calcium which leads on to induction of NFKB and immune activation.[4] The archaeal cholesterol catabolism can deplete the lymphocytic cell membranes of cholesterol resulting in alteration of lymphocytic cell membrane microdomains related receptors producing immune activation, monocytic infiltration and reparative connective tissue macromolecular deposition.

NMDA can be activated by digoxin induced calcium oscillations, PAH and viroid induced RNA interference.[4] The cholesterol ring oxidase generated pyruvate can be converted by the GABA shunt pathway to glutamate. Glutamatergic transmission can lead to immune activation. Immune activation can lead to reparative connective tissue macromolecular deposition in EMF, CCP, MNG and mucoid angiopathy. The cholesterol aromatase generated serotonin is well known to produce connective tissue macromolecule especially collagen deposition producing the fibrotic changes in EMF, mucoid angiopathy, MNG and CCP. The archaeal cholesterol aromatase can generate PAH.[19] The PAH can also lead to insulin resistance and CCP. PAH can also inhibit thyroid hormone receptor function contributing to hypothyroidism, increased TSH, thyroid enlargement and MNG. Particulate pollution has been related to vascular thrombosis and can lead to mucoid angiopathy. PAH particles are also known to produce myocardial dysfunction. Thus the actinide, viroid and mevalonate pathway bacteria induced metabolic, genetic, immune and neuronal transmission changes can lead onto endemic EMF, CCP, MNG and mucoid angiopathy. The term archaea and viroid induced endemic cardiovascular and endocrine mucopolysaccharidoses can be used to describe this entity.

The metal actinides provide radiolytic energy, catalysis for oligomer formation and provide a coordinating ion for metalloenzymes all important in abiogenesis.[6] The metal actinide surfaces would by surface metabolism generate acetate which could get converted to acetyl CoA and then to cholesterol which functions as the primal prebiotic molecule self organizing into self replicating supramolecular systems, the lipid organism.[42] Cholesterol by radiolysis by actinides would have formed PAH generating PAH aromatic organism.[8] Cholesterol radiolysis would generate pyruvate which would get converted to amino acids, sugars, nucleotides, porphyrins, fatty acids and TCA acids.

Anastase and rutile surfaces can produce polymerization of amino acids, isoprenyl residues, PAH and nucleotides to generate the initial lipid organism, PAH organism, prions and RNA viroids which would have symbiosed to generate the archaeal protocell. The archaea evolved into gram negative and gram positive bacteria with a mevalonate pathway which had a evolutionary advantage and the symbiosis of archaea with gram negative organism generated the eukaryotic cell.[43] The data supports the persistence of an actinide and cholesterol based shadow biosphere which throws light on the actinide based origin of life and cholesterol as the premier prebiotic molecule. The presence of placer deposits and mineral sands containing monazite, illmenite, rutile and thorium in the Lemurian supercontinent would have made it the ideal place for the primitive cell, nanoarchaea, eukaryote, multicellular eukaryote, primates and humans to evolve. Anthropological studies have provided evidence for the evolution of primates and homosapiens in the rift valley of Kenya part of the prehistoric Lemurian continent.

Global warming can lead to osmotic stress consequent to dehydration. The increase in actinidic archaeal growth leads to cholesterol catabolism and digoxin synthesis. Digoxin produces membrane sodium potassium ATPase inhibition and increase in intracellular calcium producing mitochondrial dysfunction. This results in oxidative stress. The oxidative stress and osmotic stress can induce the enzyme aldose reductase which converts glucose to fructose. Fructose has got a low km value for ketokinase as compared to glucose. Therefore fructose gets phosphorylated more to fructose phosphate and the cell is depleted of ATP. The cell depletion of ATP leads to oxidative stress and chronic inflammation consequent to induction of NFKB. Oxidative stress can open the mitochondrial PT pore producing release of cyto C and activation of the caspase cascade of cell death. The fructose phosphate can enter the pentose phosphate pathway

synthesizing ribose and nucleic acid. The depletion of cellular ATP results in generation of AMP and ADP which are acted upon by deaminases causing hyperuricemia. Uric acid can produce endothelial dysfunction and vascular disease. Uric acid can also produce mitochondrial dysfunction. The fructose phosphate can enter the glucosamine pathway synthesizing GAG and producing mucopolysaccharide accumulation. Fructose can fructosylate proteins making them antigenic and producing an autoimmune response. This can lead to the global warming related Lemurian syndrome of MNG, CCP, EMF and mucoid angiopathy.

The archaea can synthesise magnetite by biomineralization. The archaeal cholesterol catabolism can generate PAH. The archaea can exist as nanoarchaea and can have calcified nanoforms. The actinidic magnetotactic nanoarchaea and its secreted PAH organisms are extremophiles and survive in the interstellar space and can contribute to the interstellar grains and magnetic fields which play a role in the formation of the galaxies and star systems.[44] The cosmic dust grains occupy the intergalactic space and are thought to be formed of magnetotactic bacteria identified according to their spectral signatures. According to the Hoyle's hypothesis, the cosmic dust magnetotactic bacteria plays a role in the formation of the intergalactic magnetic field. A magnetic field equal in strength to about one millionth part of the magnetic field of earth exists throughout much of our galaxy. The magnetic files can be used to trace the spiral arms of the galaxy following a pattern of field lines that connect young stars and dust in which new stars are formed at a rapid rate. Studies have shown that a fraction of the dust particles have elongated shape similar to bacilli and they are systematically lined up in our galaxy. Moreover the direction of alignment is such that the long axes of the dust tend to be at right angles to the direction of the galactic magnetic field at every point. Magnetotactic bacteria

have the property to affect the degree of alignment that is observed. The fact that the magnetotactic bacteria appear to be connected to the magnetic field lines that thread through the spiral arms of the galaxy connecting one region of star formation to another support a role for them in star formation and in the mass distribution and rotation of stars. The nutrient supply for a population of interstellar bacteria comes from mass flows out of supernovas populating the galaxy. Giants arising in the evolution of such stars experience a phenomenon in which material containing nitrogen, carbon monoxide, hydrogen, helium, water and trace elements essential for life flows continuously outward into space. The interstellar bacteria need liquid water. Water exists only as vapour or solid in the interstellar space and only through star formation leading to associated planets and cometary bodies can there be access to liquid water. To control conditions leading to star formation is of paramount importance in cosmic biology. The rate of star formation is controlled by two factors: Too high a rate of star formation produces a destructive effect of UV radiation and destroys cosmic biology. Star formation as stated before produces water crucial for bacterial growth. Cosmic biology of magnetotactic bacteria and star formation are thus closely interlinked. Systems like solar systems do not arise in random condensation of blobs of interstellar gas. Only by a rigorous control of rotation of various parts of the system would galaxies and solar system evolved. The key to maintaining control over rotation seems to lie in the intergalactic magnetic field as indeed the whole phenomena of star formation. The intergalactic magnetic fields owes its origin to the lining up of magnetotactic bacteria and the cosmic biology of interstellar bacteria can prosper only by maintaining a firm grip on the interstellar magnetic field and hence on the rate of star formation and type of star system produced. This points to a cosmic intelligence or brain capable of computation, analysis and exploration of the universe at large - of magnetotactic bacterial networks. The origin of life on

earth according to the Hoyle's hypothesis would be by seeding of bacteria from the outer intergalactic space. Comets carrying microorganisms would have interacted with the earth. A thin skin of graphitized material around a single bacteria or clumps of bacteria can shield the interior from destruction by UV light. The sudden surge and diversification of species of plants and animals and their equally sudden extinction has seen from fossil records point to sporadic evolution produced by induction of fresh cometary genes with the arrival of each major new crop of comets.[45, 46] The interstellar PAH aromatic organism is formed from nanoarchaeal cholesterol catabolism. The PAH and cholesterol are the interconvertible primal prebiotic molecules. PAH aromatic organism and nanoarchaeal magnetite can have a wave particle existence and bridge the world of bosons and fermions. The nanoarchaea can form biofilms and the PAH aromatic organism can form a molecular quantum computing cloud in the biofilm which forms a interstellar intelligence regulating the formation of star systems and galaxies. The magnetite loaded nanoarchaeal biofilms and PAH aromatic organism quantal computing cloud can bridge the wave particle world functioning as the anthropic observer sensing gravity which orchestrates the reduction of the quantal world of possibilities in to the macroscopic world. The actinide based nanoarchaea can regulate the earth's carbon cycle by methanogenesis, nitrogen cycle by ammonia oxidation and rain formation by contributing the seeding nucleus. The earth's temperature and global warming and cooling are regulated by nanoarchaeal synthesised PAH from cholesterol and methanogenesis. The increased nanoarchaeal growth in ocean beds and soil leads to increased methane production and movement of the earth's crust producing tsunamis and massive earthquake leading to catastrophic mass extinction.[47] This nanoarchaeal growth in the Southern ocean and Indian ocean bed due to global warming induced by civilisational progress and human activity would have led to methane burps in the ocean bed contributing to

massive earthquakes leading onto Tsunamis. This would have led to catastrophic destruction of the Lemurian supercontinent. The migration of the Lemurian survivors into the Indian subcontinent Indus valley, the Nile valley and the Mesopotamian valley would have contributed to the origin of the Harappan, Sumerian and Egyptian civilization which have all evolved during the same period of human history.[48, 49] The eternal nanoarchaea survive and start the cycle of evolution once more. The actinide based nanoarchaea regulates the human system and biological universe.

The coexistence of EMF, CCP and MNG in South India, South Africa, Australia and South America is thus an indirect evidence for the existence of the Lemurian supercontinent containing these land masses. The actinidic nanoarcheal growth would have led to methane burps in the ocean bed contributing to earthquakes and Tsunamis producing extinction of the Lemurian supercontinent. It also supports the abiogenesis on radioactive actinidic beach sands through the process of surface metabolism. This gives support to the role of actinidic archaea as the third element that controls life and its role in the evolution of the multicellular eukaryote, primates and humans. Civilization and humans would have evolved in the placer deposits and actinidic sand rich pre-historic Lemurian supercontinent in the Indian and Southern ocean.[48,49]

References

[1] Sandhyamoni S. (1993). Mucoid vasculopathy - vascular lesions in autopsy studies, *Mod Pathology*, 6, 341-349.

[2] Balakrishnan V. (1987). *Chronic Pancreatitis in India*. Delhi: Indian Society of Pancreatology.

[3] Valiathan M. S., Somers, K., Kartha, C. C. (1993). *Endomyocardial Fibrosis.* Delhi: Oxford University Press.

[4] Kurup R., Kurup, P. A. (2009). *Hypothalamic digoxin, cerebral dominance and brain function in health and diseases*. New York: Nova Science Publishers.

[5] Hanold D., Randies, J. W. (1991). Coconut cadang-cadang disease and its viroid agent, *Plant Disease,* 75, 330-335.

[6] Edwin B. T., Mohankumaran, C. (2007). Kerala wilt disease phytoplasma: Phylogenetic analysis and identification of a vector, *Proutista moesta*, *Physiological and Molecular Plant Pathology*, 71(1-3), 41-47.

[7] Adam Z. (2007). Actinides and Life's Origins, *Astrobiology*, 7, 6-10.

[8] Schoner W. (2002). Endogenous cardiac glycosides, a new class of steroid hormones, *Eur J Biochem*, 269, 2440-2448.

[9] Eckburg P. B., Lepp, P. W., Relman, D. A. (2003). Archaea and their potential role in human disease, *Infect Immun*, 71, 591-596.

[10] Davies P. C. W., Benner, S. A., Cleland, C. E., Lineweaver, C. H., McKay, C. P., Wolfe-Simon, F. (2009). Signatures of a Shadow Biosphere, *Astrobiology*, 10, 241-249.

[11] Richmond W. (1973). Preparation and properties of a cholesterol oxidase from nocardia species and its application to the enzymatic assay of total cholesterol in serum, *Clin Chem*, 19, 1350-1356.

[12] Snell E. D., Snell, C. T. (1961). *Colorimetric Methods of Analysis.* Vol 3A. New York: Van Nostrand.

[13] Glick D. (1971). *Methods of Biochemical Analysis.* Vol 5. New York: Interscience Publishers.

[14] Colowick, Kaplan, N. O. (1955). *Methods in Enzymology.* Vol 2. New York: Academic Press.

[15] Maarten A. H., Marie-Jose, M., Cornelia, G., van Helden-Meewsen, Fritz, E., Marten, P. H. (1995). Detection of muramic acid in human spleen, *Infection and Immunity*, 63(5), 1652-1657.

[16] Smit A., Mushegian, A. (2000). Biosynthesis of isoprenoids via mevalonate in Archaea: the lost pathway, *Genome Res*, 10(10), 1468-84.

[17] Van der Geize R., Yam, K., Heuser, T., Wilbrink, M. H., Hara, H., Anderton, M. C. (2007). A gene cluster encoding cholesterol catabolism in a soil actinomycete provides insight into Mycobacterium tuberculosis survival in macrophages, *Proc Natl Acad Sci USA*, 104(6), 1947-52.

[18] Francis A. J. (1998). Biotransformation of uranium and other actinides in radioactive wastes, *Journal of Alloys and Compounds*, 271(273), 78-84.

[19] Probian C., Wülfing, A., Harder, J. (2003). Anaerobic mineralization of quaternary carbon atoms: Isolation of denitrifying bacteria on pivalic acid (2,2-Dimethylpropionic acid), *Applied and Environmental Microbiology*, 69(3), 1866-1870.

[20] Tsagris E. M., de Alba, A. E., Gozmanova, M., Kalantidis, K. (2008). Viroids, *Cell Microbiol*, 10, 2168.

[21] Horie M., Honda, T., Suzuki, Y., Kobayashi, Y., Daito, T., Oshida, T. (2010). Endogenous non-retroviral RNA virus elements in mammalian genomes, *Nature*, 463, 84-87.

[22] Hecht M., Nitz, N., Araujo, P., Sousa, A., Rosa, A., Gomes, D. (2010). Genes from Chagas parasite can transfer to humans and be passed on to children. Inheritance of DNA Transferred from American Trypanosomes to Human Hosts, *PLoS ONE*, 5, 2-10.

[23] Flam F. (1994). Hints of a language in junk DNA, *Science*, 266, 1320.

[24] Horbach S., Sahm, H., Welle, R. (1993). Isoprenoid biosynthesis in bacteria: two different pathways? *FEMS Microbiol Lett*, 111, 135-140.

[25] Gupta R. S. (1998). Protein phylogenetics and signature sequences: a reappraisal of evolutionary relationship among archaebacteria, eubacteria, and eukaryotes, *Microbiol Mol Biol Rev*, 62, 1435-1491.

[26] Hanage W., Fraser, C., Spratt, B. (2005). Fuzzy species among recombinogenic bacteria, *BMC Biology*, 3, 6-10.

[27] Webb J. S., Givskov, M., Kjelleberg, S. (2003). Bacterial biofilms: prokaryotic adventures in multicellularity, *Curr Opin Microbiol*, 6(6), 578-85.

[28] Whitchurch C. B., Tolker-Nielsen, T., Ragas, P. C., Mattick, J. S. (2002). Extracellular DNA Required for Bacterial Biofilm Formation. *Science*, 295(5559), 1487.

[29] Chen Y., Cai, T., Wang, H., Li, Z., Loreaux, E., Lingrel, J. B. (2009). Regulation of intracellular cholesterol distribution by Na/K-ATPase, *J Biol Chem*, 284(22), 14881-90.

[30] Poole A. M. (2006). Did group II intron proliferation in an endosymbiont-bearing archaeon create eukaryotes? *Biol Direct*, 1, 36-40.

[31] Villarreal L. P. (2006). How viruses shape the tree of life, *Future Virology*, 1(5), 587-595.

[32] Khovidhunkit W., Kim, M. S., Memon, R. A., Shigenaga, J. K., Moser, A. H., Feingold, K. R. (2004). Thematic review series: The Pathogenesis of Atherosclerosis. Effects of infection and inflammation on lipid and lipoprotein metabolism mechanisms and consequences to the host, *J Lipid Res*, 45(7), 1169 1196.

[33] Vainshtein M., Suzina, N., Kudryashova, E., Ariskina, E. (2002). New Magnet-Sensitive Structures in Bacterial and Archaeal Cells, *Biol Cell*, 94(1), 29-35.

[34] Eberl M., Hintz, M., Reichenberg, A., Kollas, A., Wiesner, J., Jomaa, H. (2010). Microbial isoprenoid biosynthesis and human γδ T cell activation, *FEBS Letters*, 544(1), 4-10.

[35] Cani P. D., Amar, J., Iglesias, M. A., Poggi, M., Knauf, C., Bastelica, D. (2007). Metabolic endotoxemia initiates obesity and insulin resistance, *Diabetes*, 56, 1761-1772.

[36] Memon R. A., Holleran, W. M., Moser, A. H., Seki, T., Uchida, Y., Fuller, J. (1998). Endotoxin and Cytokines Increase Hepatic Sphingolipid Biosynthesis and Produce Lipoproteins Enriched in Ceramides and Sphingomyelin, *Arterioscler Thromb Vasc Biol*, 18(8), 1257-1265.

[37] Carayol N., Chen, J., Yang, F., Jin, T., Jin, L., States, D. (2006). A dominant function of IKK/NF-kB signaling in global LPS-induced gene expression, *J Biol Chem*, 10, 1074.

[38] Kliewer S. A. (2005). Cholesterol detoxification by the nuclear pregnane X receptor, *Proc Natl Acad Sci USA*, 102(8), 2675-6.

[39] Wallace D. C. (2005). Mitochondria and Cancer: Warburg Addressed, *Cold Spring Harbor Symposia on Quantitative Biology*, 70, 363-374.

[40] Paila Y. D., Tiwari, S., Chattopadhyay, A. (2009). Are specific nonannular cholesterol binding sites present in G-protein coupled receptors? *Biochim Biophys Acta*, 1788(2), 295-302.

[41] Ebensperger G., Ebensperger, R., Herrera, E. A., Riquelme, R. A., Sanhueza, E. M., Lesage, F. (2005). Fetal brain hypometabolism during prolonged hypoxaemia in the llama, *J Physiol*, 567(3), 963 -975.

[42] Russell M. J., Martin, W. (2004). The rocky roots of the acetyl-CoA Pathway, *Trends in Biochemical Sciences*, 29, 7.

[43] Margulis L. (1996). Archaeal-eubacterial mergers in the origin of Eukarya: phylogenetic classification of life, *Proc Natl Acad Sci USA*, 93, 1071-1076.

[44] Tielens A. G. G. M. (2008). Interstellar Polycyclic Aromatic Hydrocarbon Molecules, *Annual Review of Astronomy and Astrophysics*, 46, 289-337.

[45] Wickramasinghe C. (2004). The universe: a cryogenic habitat for microbial life, *Cryobiology*, 48(2), 113-125.

[46] Hoyle F., Wickramasinghe, C. (1988). *Cosmic Life-Force.* London: J. M. Dent and Sons Ltd.

[47] Dun D. (2005). *The Black Silent*. New York: Pinnacle Books.

[48] Ramaswamy S. (2004). The Lost Land of Lemuria: Fabulous Geographies, Catastrophic Histories. Los Angeles: Trade paperback.

[49] Neild, Ted (2007). Supercontinent: Ten Billion Years in the Life of Our Planet. Boston: Harvard University Press.

7

Endemic Hyperdigoxinemia Related Cardiovascular and Endocrine Mucopolysaccharidoses Syndrome

Introduction

Kerala has a high incidence of endomyocardial fibrosis (EMF), chronic calcific pancreatitis (CCP), multinodular goitre (MNG) and mucoid angiopathic lesions presenting as coronary artery disease and thrombotic strokes. EMF claims 2.5% of all cardiac patients under 40 years who attend hospitals in Kerala. Kerala has the highest incidence of tropical pancreatitis in India. From 1980-1986 it accounted for 0.2% of total admissions and 7% of all diabetic admissions to the Trivandrum Medical College Hospital. MNG accounts for nearly 1.5% of total admissions in this hospital every year. Sandhyamoni has demonstrated a high incidence of mucoid angiopathic lesions in autopsy studies of the coronary and cerebral vessels with acid mucopolysaccharides accumulating in the tunica intima and media. There is magnesium deficiency in cardiac tissues of EMF patients. Magnesium deficiency is also a risk factor in the development of diabetes mellitus. In this context it has been reported that there are elevated levels of a hypothalamic endogenous membrane sodium potassium ATPase inhibitor, digoxin in the serum of diabetic patients. Membrane sodium potassium ATPase inhibition can lead to magnesium deficiency. Hypomagnesemia has been reported to produce upregulation of GAG synthesis in experimental models. Alteration in connective tissue metabolism may underlie EMF, CCP, MNG and mucoid angiopathy which are known to coexist in the very same geographic zone. Elevated digoxin levels and hypomagnesemia are known to contribute to insulin resistance. It has been reported that there is a high incidence of insulin resistance and metabolic syndrome x in Asian populations inhabiting the very same endemic zone.

Global warming leads to dehydration and osmotic stress. Global warming also leads to increased actinidic archaeal growth. Archaea catabolizes cholesterol and synthesizes digoxin. Digoxin can inhibit sodium potassium ATPase and increase intracellular calcium load producing mitochondrial PT pore dysfunction. This leads to oxidative stress. Osmotic stress and oxidative stress can induce the enzyme aldose reductase which converts glucose to fructose. Fructose has got a low km value for ketokinase as compared to glucose. Therefore fructose gets selectively phosphorylated to fructose phosphate which can be converted to glucosamine and galactosamine. Thus aldose reductase inhibition consequent to osmotic and oxidative stress of global warming can induce glycosaminoglycan synthesis. This study was undertaken to assess the following parameters in EMF, CCP, MNG and mucoid aniopathy-serum magnesium, serum total GAG, serum levels of various GAG fractions and serum digoxin levels. A hypothesis highlighting the pivotal role of endogenous digoxin in the pathogenesis of these disorders, which could be different spectra of a common insulin resistance state is also presented. This can lead to a global warming related Lemurian cardiovascular and endocrine syndrome.

Materials and Methods

Informed consent was obtained from all the patients as well as relatives of subjects included in the study. Necessary ethical clearance was also obtained for this study from the ethical committee of the Medical College Hospital, Trivandrum. Fifteen cases of EMF, CCP, MNG and mucoid angiopathic strokes and CAD from Department of Medicine, Cardiology and Gastroenterology of Medical College Hospital, Trivandrum were chosen for the study. The patients aged 25-50 years were selected randomly over a period of 2 years as and when they were admitted to the wards. They were all freshly diagnosed cases and

fasting blood was removed from them before any treatment was started as was from the equal number of age and sex matched healthy controls. The healthy normal controls were selected randomly from the general population of the Trivandrum district. Autopsy samples of heart tissue from EMF patients were supplied by the Sree Chitra Tirunal Institute for Medical Sciences and Technology. Autopsy samples of thyroid tissue from MNG cases were obtained from the Department of Pathology, Medical College Hospital, Trivandrum and autopsy samples of pancreatic tissue from chronic calcific pancreatitis patients were supplied by the Diagnostic and Research Centre, Trivandrum. Carotid arteries and aortic specimens with histopathologically demonstrated mucoid angiopathy were obtained from the Department of Forensic Pathology, Medical College, Alleppey. For comparison cardiac, thyroid, pancreas, aortic and carotid tissue from accident subjects (25-50 yrs) were used and these were also obtained from the Department of Forensic Pathology, Medical College, Alleppey. Concentration of total GAG and various GAG fractions were determined by methods described earlier. The tissue GAG was extracted by Folch's procedure. The dry defatted tissue was digested with papain and GAG was estimated as described before. Total cholesterol, HDL cholesterol and triglycerides were estimated in the serum by enzymatic methods. The kits were supplied by Sigma Chemicals, USA. Serum magnesium was determined by atomic absorption spectrophotometry. RBC membrane for estimation of sodium potassium ATPase was prepared according to the procedure of Blostein. For estimation of sodium potassium ATPase activity of the erythrocyte membrane, the procedure described by Wallach and Kamat was used. Digoxin in the serum was determined by the procedure by Wallah and Kamat was used. Digoxin in the serum was determined by the procedure described by Wallah and Kamat was used. Digoxin in the serum was determined by the procedure described by HPLC. Statistical analysis was carried out by ANOVA.

Results

1. Lipid profile of patients with EMF, CCP, MNG and mucoid angiopathy showed normal serum LDL cholesterol, low serum HDL cholesterol, elevated serum triglycerides and normal total serum cholesterol

2. Serum magnesium was decreased in patients with EMF, CCP, MNG and mucoid angiopathy

3. Serum total GAG was elevated in patients with EMF, CCP, MNG and mucoid angiopathy

4. The individual serum GAG fractions showed the following patterns in mucoid angiopathy - ChS forming 76.19% followed by DS forming 10% of GAG. The other fractions - HA, HS and H are present only in small amounts

5. Tissue total GAG was elevated in patients with EMF, CCP, MNG and mucoid angiopathy

6. RBC membrane sodium potassium ATPase activity was reduced in patients with EMF, CCP, MNG and mucoid angiopathy.

7. Serum digoxin level was elevated in patients with EMF, CCP, MNG and mucoid angiopathy.

Discussion

Endogenous digoxin like activity (EDLA) has been reported in several pathological conditions by reaction with digoxin antibodies. We have recently shown that the EDLA is in the fact due to the steroidal glycoside, digoxin itself.

Endogenous digoxin which is reported to be synthesized by the hypothalamus and other tissues, is a potent inhibitor of membrane sodium potassium ATPase. It is also reported that several plant sources contain digoxin like steroidal glycosides and the vegetarian diet consumed by populations in this geographic zone may be a rich source for digoxin. The increase in digoxin levels in the serum of these patients may therefore be due to increased endogenous synthesis and/or that derived from dietary sources. The decrease in membrane sodium potassium ATPase activity in the patients of CCP, EMF, MNG and mucoid angiopathy may be due to this increase in digoxin levels. The inhibition of membrane sodium potassium ATPase by digoxin is known to cuae an increase in intracellular calcium resulting from increased sodium calcium exchange, increased entry of calcium via the voltage gated calcium channel and increased release of calcium from intracellular endoplasmic reticulum calcium stores. This increase in intracellular calcium by displacing magnesium from its biding sites, causes a decrease in the functional availability of magnesium. The decrease in the availability of magnesium can cause decreased mitochondrial ATP formation which along with low magnesium can cause further inhibition of membrane sodium potassium ATPase, since the ATP-magnesium complex is the actual substrate for this reaction. Cytosolic free calcium is normally buffered by two mechanisms, ATP dependent calcium extrusion from the cell and ATP dependent sequestration of calcium within the endoplasmic reticulum. The magnesium related mitochondrial dysfunction results in defective calcium extrusion from the cell. There is thus a progressive inhibition of membrane sodium potassium ATPase activity first triggered by digoxin. Low intracellular magnesium and high intracellular calcium consequent to membrane sodium potassium ATPase inhibition appear to be crucial to the pathophysiology of these disorders. Membrane sodium potassium ATPase inhibition could in part be contributed to by the low level of background irradiation from the mineral

sands in Kerala coast which produces membrane disruption. Earlier it was postulated that the cerium from the mineral sands is ingested and is exchanged for magnesium leading to magnesium depletion had postulated a protein deficiency model for this group of disorders. But there is no nutritional data to support any but marginal protein deficiency in the Kerala population. It is interesting to note that intracellular magnesium deficiency can produce ribosomal disruption and inhibition of protein synthesis. Therefore protein deficiency could be a functional correlate of magnesium depletion. The population of Kerala consumes a high carbohydrate and high fibre diet. The total dietary fibre intake is around 20 g per day. Fibre has been reported to bind to magnesium producing magnesium depletion via the stools. Cyanide from dietary sources has also been implicated in the etiology of this group of disorders. Cyanide can produce inhibition of cytochrome oxidase and produce a mitochondrial dysfunction leading to ATP depletion and membrane sodium potassium ATPase inhibition. Serum magnesium was assessed in all these disorders and was found to be reduced.

Increased calcium within the cell can open the mitochondrial PT pore, disrupt the inner membrane hydrogen gradient and uncouple oxidative phosphorylation. This results in volume dysregulation of the mitochondrial matrix, hyperosmolality of the matrix, outer membrane rupture and release of cyto C and AIF (apoptosis inducing factor) into the cytosol. This activates procaspase 9 to caspase 9 which produces apoptosis and replacement fibrosis. The intracellular magnesium depletion related inhibition of glycolysis, citric acid cycle and oxidative posphorylation can channel more glucose-6 phosphate for the synthesis of GAG precursors. Magnesium deficiency in fact has been shown by us to result in glycosaminoglycan accumulation in tissues. Glysosaminoglycan accumulation has been described in these disorders, which can be explained as being due to

magnesium deficiency. Increase in beta cell calcium can contribute to increased insulin release from beta cells and hyperinsulinemia. Hypomagnesemia has been reported to markedly increase glucose stimulated insulin secretion by the perfused pancreas. Magnesium deficiency can also lead to insulin resistance. Magnesium translocation appears to be an early event in insulin action. Decrease in intracellular magnesium can block the phosphorylation reactions involved in protein tyrosine kinase receptor activity leading to insulin resistance. Elevated fibre content of the diet can also mimic the action of insulin leading to hyperinsulinism. On the other hand magnesium deficiency produced by dietary fibre can lead to insulin resistance. Insulin administration has been reported to lead to an upregulation of GAG synthesis. The lipid profile of the patient with EMF, MNG, CCP and mucoid angiopathy is similar to that obtained in the insulin resistance state. It is tempting to speculate that all these diverse group of disorders are due to insulin resistance.

Increase in intracellular calcium can activate the G-protein coupled signal transduction system of the contra-insulin hormones - glucagon, adrenaline, noradrenaline and the growth hormone via the growth hormone releasing factor. This results in increased production of glucose. Decrease in intracellular magnesium can lead to inhibition of glycolysis causing defective glucose utilization and hyperglycemia. Increase in intracellular calcium can open up the mitochondrial PT pore, disrupt the hydrogen gradient across the inner membrane and block mitochondrial oxidative phosphorylation. Intracellular magnesium deficiency can also lead to a ATP synthase defect. All this leads to defective glucose utilization and hyperglycemia. As already described above increased intracellular calcium and reduced intracellular magnesium can lead to hyperinsulinism and insulin resistance described in CCP. Again the increased intracellular calcium can activate the T cells via the calcium dependent

calcineurin pathway producing an increase in TNF alpha secretion. This results in immune activation and the inflammatory changes noticed in the pancreas and other tissues especially peripheral nerve in CCP. Increase in TNF alpha secretion. This results in immune activation and the inflammatory changes noticed in the pancreas and other tissues especially peripheral nerve in CCP. Increase in TNF alpha can also contribute to insulin resistance. Decrease in intracellular magnesium can result in a glycosylation defect since magnesium is a cofactor for formation of dolichol-1 phosphate required for N-glycosylation and nucleoside diphosphate sugars required for O-glycosylation. The defective glycoproteins may be responsible for micro and macroangiopathy of diabetes mellitus in CCP. Defectively processed N-glycosylated glycoproteins can also lead on to a defective insulin sensing mechanism of the beta cells. Intracellular magnesium deficiency can lead to upregulation of GAG synthesis and their accumulation in the pancreatic tissues. MPS accumulation in the pancreas has been described in CCP.

The intracellular deficiency of magnesium, which is required for protein transcription and translation, results in a nuclear and ribosomal dysfunction. The thyroid hormone receptor belongs to the steroid receptor family and has a DNA binding site. The intracellular magnesium deficiency results in a thyroid hormone receptor defect. This results in defective feed back inhibition to the hypothalamus and pituitary and increased TRH and TSH secretion. There is also increased activity of TSH and TRH owing to increased intracellular calcium and increased G protein coupled signal transduction of these hormones. The multinodular goiter arises owing to TSH dependent thyroid proliferation. The inhibition of sodium potassium ATPase produces inhibition of the sodium potassium ATPase coupled neutral amino acid tyrosine transport into the thyroid follicular cell. The iodide transport into the thyroid follicular cell also

depends on ATP. The intracellular magnesium depletion produces defective ATP synthesis and a mitochondrial dysfunction in the thyroid follicular cell. This results in defective iodide transport into the cell. Defective iodide and tyrosine transport into the cell can produce defects in thyroid hormone synthesis and the resulting hypothyroidism can lead on to increased TSH levels. The depleted intracellular magnesium can stimulate mucopolysaccharide biosynthesis and fibrosis of the thyroid gland. MPS accumulation has been demonstrated in the thyroid tissue in MNG.

CCP and MNG are precancerous states. CCP has been found to lead to carcinoma of the pancreas and multinodular goitre is a predisposing factor for thyroid malignancies. Membrane sodium potassium ATPase inhibition can lead to oncogenesis. Intracellular calcium activates phospholipase C beta which results in increased production of diacylglycerol (DAG) with resultant activation of protein kinase C. The protein kinase C (PKC) activates the MAP kinase cascade resulting in cellular proliferation. The decreased intracellular magnesium can produce dysfunction of GTPase activity of the alpha-subunit of G protein. This results in RAS oncogene activation, as more of the RAS is bound to GTP rather than GDP. Phosphorylation mechanisms are required for the activation of the tumour suppressor gene P_{53}. The activation of P_{53} is impaired owing to intracellular magnesium deficiency producing a phosphorylation defect.

Membrane sodium potassium ATPase inhibition can produce a decrease in the intramyocardial cell magnesium and an increase in the intramyocardial cell calcium. The increase in intramyocardial cell calcium can open the mitochondrial PT pore, destroy the hydrogen gradient across the inner membrane and uncouple oxidative phosphorylation. The decrease in intramyocardial cell magnesium can inhibit ATP synthase and produce a

defective mitochondrial oxidative phosphorylation. This results in a myocardial mitochondrial dysfunction and increased generation of free radicals due to incomplete reduction of molecular oxygen. Free radicals can produce damage to myocardium. The opening of the mitochondrial PT pore can produce osmotic dysregulation and hyperosmolality of the mitochondria, rupture the outer mitochondrial membrane and release AIF (apoptosis inducing factor) and cyto C in to the cytosol. This activates procaspase 9 to caspase 9 producing myocardial apoptosis and replacement fibrosis. The decrease in intracellular magnesium can result in increased channelling of glucose 6-phosphate to the synthesis of GAG precursors and increased glycosaminoglycan biosynthesis. Decrease in intracellular magnesium can produce changes in collagen and elastin biosynthesis and result in replacement fibrosis. MPS accumulation has been demonstrated in EMF tissues by previous studies. The increase in intracellular calcium can produce T cell activation via the calcium dependent calcineurin pathway releasing TNF alpha, from the activated T cell. Elevated levels of TNF alpha have been related to myocardial dysfunction. Impairment of calcium homeostasis, decrease in magnesium ATPase activity and troponin I phosphorylation, cytokine expression especially TNF alpha and aberrant induction of apoptosis have been described in cardiomyopathies. The basic defect in cardiomyopathy is thus interstitial/endocardial fibrosis and MPS/elastin deposition which can occur in magnesium deficiency. Increase in intracellular calcium can activate the G protein coupled signal transduction system of the platelet activating factor and thrombin. Magnesium deficiency can produce increased platelet aggregation and release reaction and thrombosis resulting in the formation of a LV or RV thrombus which can get fibrosed leading on to endocardial fibrosis.

Membrane sodium potassium ATPase inhibition induced hypomagnesemia related increased glycosaminoglycan synthesis can contribute to mucoid angiopathy. Increased intracellular calcium within the endothelial cell leads to fragmentation of the elastic membrane and calcification. Increased calcium within the arterial wall alters elastin synthesis, turnover and composition. Increase in arterial wall cellular calcium can open the mitochondrial PT pore, produce osmotic dysregulation and hyperosmolality of the mitochondrial matrix, rupture the outer membrane and release cyto C and AIF to the cytosol producing vascular wall cellular apoptosis. In mucoid angiopathy there is a uniform hose pipe like narrowing of large, medium sized and small sized arteries with deposition of acidic mucopolysaccharides in the tunica intima and media. Increase in intracellular calcium can activate the G-protein coupled thrombin receptor and platelet activating factor producing the thrombosis observed in mucoid angiopathy. Decreased intracellular magnesium can lead to increased thrombin and ADP/collagen induced platelet aggregation. Membrane sodium potassium ATPase inhibition related increased smooth muscle calcium and decreased magnesium can contribute to the vasospasm and ischaemia observed in mucoid angiopathic, stroke and CAD. Decreased intracellular magnesium can produce dysfunction of lipoprotein lipase producing defective catabolism of triglycerides rich lipoproteins and hypertriglyceridemia. In hypomagnesemia, lecithin cholesterol acyl transferase (LCAT) is defective and there is reduced formation of cholesterol esters in HDL. This results in reduced HDL cholesterol levels described in mucoid angiopathy. The increase in intracellular calcium can activate phospholipase A_2 producing increased amounts of arachidonic acid for thromboxane A_2 synthesis via the cyclooxygenase pathway. This can lead on to increased platelet aggregation and thrombosis in mucoid angiopathy.

MNG, CCP, EMF and mucoid angiopathy belong to the same geoendemic zone. The study shows that they share the same etiological factors of causation.

1. Low membrane sodium potassium ATPase and magnesium depletion consequent to increased digoxin from exogenous or endogenous sources

2. Hypomagnesemia related elevated GAG synthesis

3. Digoxin induced hypomagnesemia related insulin resistance state/hyperinsulinism producing elevated GAG synthesis.

Therefore these disorders could be termed as the endemic hyperdigoxinemia related cardiovascular and endocrine mucopolysaccharidoses syndrome. Global warming leads to dehydration and osmotic stress. Global warming also leads to increased actinidic archaeal growth. Archaea catabolizes cholesterol and synthesizes digoxin. Digoxin can inhibit sodium potassium ATPase and increase intracellular calcium load producing mitochondrial PT pore dysfunction. This leads to oxidative stress. Osmotic stress and oxidative stress can induce the enzyme aldose reductase which converts glucose to fructose. Fructose has got a low km value for ketokinase as compared to glucose. Therefore fructose gets selectively phosphorylated to fructose phosphate which can be converted to glucosamine and galactosamine. Thus aldose reductase inhibition consequent to osmotic and oxidative stress of global warming can induce glycosaminoglycan synthesis. The fructose phosphorylation depletes the cell of ATP. This results in inhibition of glucose phosphorylation, glycolysis and mitochondrial oxidative phosphorylation. The depletion of cellular ATP results in oxidative stress. Oxidative stress can open the mitochondrial PT pore, release cytochrome c and activate the caspase cascade of cell death. Oxidative stress generated by cellular depletion of ATP consequent to fructose phosphorylation and digoxin induced mitochondrial dysfunction can produce

further aldose reductase induction. This results in more conversion of glucose to fructose. The fructose can produce mitochondrial dysfunction on its own. The fructose can also fructosylate proteins making them antigenic and the oxidative stress induced by fructose phosphorylation and depletion of cellular ATP can activate NFKB producing immune activation. The fructose phosphate can get converted to glucosamine and galactosamine increasing GAG synthesis. This results in increase in heparan sulphate which can combine with proteins producing amyloidosis. Thus the cell death, glycosaminoglycan synthesis, amyloidogenesis, immune activation and autoimmunity produced by fructosemia or fructositis can contribute to mucoid angiopathy, endomyocardial fibrosis, chronic calcific pancreatitis and multinodular goitre. This can be called a global warming related mucopolysaccharidotic syndrome.

References

[1] Kurup R. A. and Kurup P. A. (2007). Hypothalamic digoxin, cerebral dominance and brain function in health and diseases. New York: Nova Biomedical Books.

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Endosymbiotic Actinidic Archaea and Viroidal Induced Warburg Phenotype Can Be Reversed by a Modified Vegetarian High Fiber, High Medium Chain Triglyceride Ketogenic Diet

Introduction

Actinidic archaea has been related to the pathogenesis of schizophrenia, malignancy, metabolic syndrome x, autoimmune disease and neuronal degeneration. An actinide dependent shadow biosphere of archaea and viroids in the above mentioned disease states is described. The actinidic archaeal and viroid induced Warburg phenotype contributes to the pathology of the disease states mentioned. The possibility of administration of high medium chain triglyceride, high fiber ketogenic diet on actinide based primitive organism like archaea with a mevalonate pathway and cholesterol catabolism was considered in these disease states.[1-10] The effect of a high medium chain triglyceride and a high fiber modified vegetarian ketogenic diet on the Warburg phenotype was also studied.

The ketogenic diet is a high-fat, adequate-protein, low-carbohydrate diet that in medicine is used primarily to treat difficult-to-control (refractory) epilepsy in children. The diet mimics aspects of starvation by forcing the body to burn fats rather than carbohydrates. However, if there is very little carbohydrate in the diet, the liver converts fat into fatty acids and ketone bodies. The ketone bodies pass into the brain and replace glucose as an energy source. An elevated level of ketone bodies in the blood, a state known as ketosis, leads to a reduction in the frequency of epileptic seizures. The ketogenic diet results in adaptive changes to brain energy metabolism that increases the energy reserves; ketone bodies are a more efficient fuel than glucose, and the number of mitochondria is increased. This may help the neurons to remain stable in the face of increased energy demand during a seizure, and may confer a neuroprotective effect.[10-15]

Dietary fiber and medium chain triglycerides have antiviral and antibacterial effects. A low carbohydrate diet generates lesser glucose for the body and inhibits glycolysis. Dietary fiber generates short chain fatty acids butyrate and propionate which are immunosuppressive. The decrease in cytokines has inhibitory effect on the generation of the Warburg phenotype. The results of the study on the effect of a high fiber, high MCT vegetarian ketogenic diet on the actinidic archaea and viroid induced Warburg phenotype are presented in this paper.[10-15]

Materials and Methods

The following groups were included in the study: - endomyocardial fibrosis, Alzheimer's disease, multiple sclerosis, non-Hodgkin's lymphoma, metabolic syndrome x with cerebrovascular thrombosis and coronary artery disease, schizophrenia, autism, seizure disorder, Creutzfeldt Jakob's disease and acquired immunodeficiency syndrome. There were 10 patients in each group and each patient had an age and sex matched healthy control selected randomly from the general population. The blood was drawn from the (1) in freshly diagnosed cases in the fasting state before treatment was initiated and (2) after a 15-days modified high fiber, high MCT vegetarian ketogenic diet of medium chain triglycerides (150 g of coconut oil), fiber (45 g of banana stem fiber) and vegetable proteins (black gram protein 100 g/day) with 50 g of carbohydrate (black gram polysaccharide). The blood samples were drawn in the fasting state before treatment was initiated. Plasma from fasting heparinised blood was used and the experimental protocol was as follows (I) Plasma+phosphate buffered saline, (II) same as I+cholesterol substrate, (III) same as II+rutile 0.1 mg/ml, (IV) same as II+ciprofloxacine and doxycycline each in a concentration of 1 mg/ml. Cholesterol substrate was prepared as described by Richmond.[16]

Aliquots were withdrawn at zero time immediately after mixing and after incubation at 37 ℃ for 1 hour. The following estimations were carried out: - Cytochrome F420, free RNA, free DNA, hexokinase activity and archaeal cholesterol oxidase activity as measured by hydrogen peroxide liberation.[17-19] Cytochrome F420 was estimated flourimetrically (excitation wavelength 420 nm and emission wavelength 520 nm). Informed consent of the subjects and the approval of the ethics committee were obtained for the study. The statistical analysis was done by ANOVA.

Results

Plasma of control subjects showed increased levels of the above mentioned parameters with after incubation for 1 hour and addition of cholesterol substrate resulted in still further significant increase in these parameters. The plasma of patients showed similar results but the extent of increase was more. The addition of antibiotics to the control plasma caused a decrease in all the parameters while addition of rutile increased their levels. The addition of antibiotics to the patient's plasma caused a decrease in all the parameters while addition of rutile increased their levels but the extent of change was more in patient's sera as compared to controls. The results are expressed in tables 1-5 as percentage change in the parameters after 1 hour incubation as compared to the values at zero time. The patients on modified ketogenic diet showed a decrease in all the parameters. Vegetarian ketogenic diets based on high fiber and high medium chain triglycerides has a inhibitory effect on the growth of archaea and viroids as well as archaeal cholesterol oxidase activity. The vegetarian ketogenic diet with its high fiber and high MCT content reversed the Warburg phenotype has indicated by a reduction in hexokinase activity.

Table 1. *Effect of rutile, antibiotics and ketogenic diet on cytochrome F420.*

Group	CYT F420 % (Increase with Rutile)		CYT F420 % (Decrease with Doxy+Cipro)		CYT F420 %(Decrease with Ketogenic diet)	
	Mean	± SD	Mean	± SD	Mean	± SD
Normal	4.48	0.15	18.24	0.66	18.25	0.72
Schizo	23.24	2.01	58.72	7.08	59.49	4.30
Seizure	23.46	1.87	59.27	8.86	57.69	5.29
AD	23.12	2.00	56.90	6.94	60.91	7.59
MS	22.12	1.81	61.33	9.82	59.84	7.62
NHL	22.79	2.13	55.90	7.29	66.07	3.78
DM	22.59	1.86	57.05	8.45	65.77	5.27
AIDS	22.29	1.66	59.02	7.50	65.89	5.05
CJD	22.06	1.61	57.81	6.04	61.56	4.61
Autism	21.68	1.90	57.93	9.64	64.48	6.90
EMF	22.70	1.87	60.46	8.06	65.20	6.20
F value	306.749		130.054		257.996	
P value	< 0.001		< 0.001		< 0.001	

Table 2. *Effect of rutile, antibiotics and ketogenic diet on free RNA.*

Group	RNA % change (Increase with Rutile)		RNA % change (Decrease with Doxy+Cipro)		RNA % change (Decrease with Ketogenic diet)	
	Mean	± SD	Mean	± SD	Mean	± SD
Normal	4.37	0.13	18.38	0.48	18.15	0.58
Schizo	23.59	1.83	65.69	3.94	57.04	4.27
Seizure	23.08	1.87	65.09	3.48	66.62	4.99
AD	23.29	1.92	65.39	3.95	62.86	6.28
MS	23.29	1.98	67.46	3.96	65.46	5.79
NHL	23.78	1.20	66.90	4.10	64.96	5.64
DM	23.33	1.86	66.46	3.65	64.51	5.93
AIDS	23.32	1.74	65.67	4.16	64.35	5.58
CJD	23.11	1.52	66.68	3.97	62.49	7.26
Autism	23.33	1.35	66.83	3.27	63.84	6.16
EMF	22.29	2.05	67.03	5.97	58.70	7.34
F value	427.828		654.453		203.651	
P value	< 0.001		< 0.001		< 0.001	

Table 3. *Effect of rutile, antibiotics and ketogenic diet on DNA.*

Group	DNA % change (Increase with Rutile)		DNA % change (Decrease with Doxy+Cipro)		DNA % change (Decrease with Ketogenic diet)	
	Mean	± SD	Mean	± SD	Mean	± SD
Normal	4.37	0.15	18.39	0.38	18.78	0.11
Schizo	23.28	1.70	61.41	3.36	67.39	3.13
Seizure	23.40	1.51	63.68	4.66	66.15	4.09
AD	23.52	1.65	64.15	4.60	66.21	3.69
MS	22.62	1.38	63.82	5.53	67.05	3.00
NHL	22.42	1.99	61.14	3.47	66.66	3.84
DM	23.01	1.67	65.35	3.56	66.25	3.69
AIDS	22.56	2.46	62.70	4.53	66.48	4.17
CJD	23.30	1.42	65.07	4.95	66.67	4.21
Autism	22.12	2.44	63.69	5.14	66.86	4.21
EMF	22.29	2.05	58.70	7.34	63.97	3.62
F value	337.577		356.621		673.081	
P value	< 0.001		< 0.001		< 0.001	

Table 4. *Effect of rutile, antibiotics and ketogenic diet on hexokinase activity.*

Group	Hexokinase % change (Increase with Rutile)		Hexokinase % change (Decrease with Doxy+Cipro)		Hexokinase % change (Decrease with Ketogenic diet)	
	Mean	± SD	Mean	± SD	Mean	± SD
Normal	4.21	0.16	18.56	0.76	18.43	0.82
Schizo	23.01	2.61	65.87	5.27	61.23	9.73
Seizure	23.33	1.79	62.50	5.56	62.76	8.52
AD	22.96	2.12	65.11	5.91	56.40	8.59
MS	22.81	1.91	63.47	5.81	60.28	9.22
NHL	22.53	2.41	64.29	5.44	58.57	7.47
DM	23.23	1.88	65.11	5.14	58.75	8.12
AIDS	21.11	2.25	64.20	5.38	58.73	8.10
CJD	22.47	2.17	65.97	4.62	63.90	7.13
Autism	22.88	1.87	65.45	5.08	58.45	6.66
EMF	21.66	1.94	67.03	5.97	62.37	5.05
F value	292.065		317.966		115.242	
P value	< 0.001		< 0.001		< 0.001	

Table 5. *Effect of rutile, antibiotics and ketogenic diet on cholesterol oxidase activity.*

Group	Cholesterol oxidase activity % (Increase with Rutile)		Cholesterol oxidase activity % (Decrease with Doxy+Cipro)		Cholesterol oxidase activity % (Decrease with Ketogenic diet)	
	Mean	± SD	Mean	± SD	Mean	± SD
Normal	4.43	0.19	18.13	0.63	18.48	0.39
Schizo	22.50	1.66	60.21	7.42	66.39	4.20
Seizure	23.81	1.19	61.08	7.38	67.23	3.45
AD	22.65	2.48	60.19	6.98	66.50	3.58
MS	21.14	1.20	60.53	4.70	67.10	3.82
NHL	23.35	1.76	59.17	3.33	66.80	3.43
DM	23.27	1.53	58.91	6.09	66.31	3.68
AIDS	23.32	1.71	63.15	7.62	66.32	3.63
CJD	22.86	1.91	63.66	6.88	68.53	2.65
Autism	23.52	1.49	63.24	7.36	66.65	4.26
EMF	23.29	1.67	60.52	5.38	61.91	7.56
F value	380.721		171.228		556.411	
P value	< 0.001		< 0.001		< 0.001	

Discussion

There was increase in cytochrome F420 indicating archaeal growth. The archaea can synthesize and use cholesterol as a carbon and energy source as indicated by cholesterol oxidase activity.[20-22] The archaeal origin of the enzyme activities was indicated by antibiotic induced suppression. The study indicates the presence of actinide based archaea with an alternate actinide based enzymes or metalloenzymes in the system as indicated by rutile induced increase in enzyme activities.[20-22] The archaeal cholesterol oxidase activity was increased resulting in generation of hydrogen peroxide.[20-22] The archaeal glycolytic hexokinase activity were increased. The archaea can undergo magnetite and calcium carbonate mineralization and can exist as calcified nanoforms.[17] There was an increase in free RNA indicating self replicating RNA viroids and free

DNA indicating generation of viroid complementary DNA strands by archaeal reverse transcriptase activity. The high fiber and high MCT modified vegetarian ketogenic diet can block archaeal and viroidal multiplication. Fiber and MCT have a antiarchaeal and antiviroidal effect.[11-15]

Archaea can induce the host AKT PI3K, AMPK, HIF alpha and NFKB producing the Warburg metabolic phenotype.[10] The increased glycolytic hexokinase activity indicates the generation of the Warburg phenotype. A high fiber and high MCT modified vegetarian ketogenic diet can inhibit hexokinase activity and glycolysis and reverse the Warburg phenotype. The generation of the Warburg phenotype is due to activation of HIF alpha. This stimulates anaerobic glycolysis, inhibits pyruvate dehydrogenase, inhibits mitochondrial oxidative phosphorylation, stimulates heme oxygenase, stimulates VEGF and activates nitric oxide synthase. The low carbohydrate diet generates less of glucose and inhibits the glycolytic pathway. This reverses the Warburg phenotype. The high fiber intake generates short chain fatty acids butyrate and propionate. Short chain fatty acids bind to lymphocyte GPCR receptors and are immunosuppressive. The reduction in cytokine generation inhibits the Warburg phenotype. The antiarchaeal and antiviroidal action of MCT and dietary fiber also inhibits the generation of the Warburg phenotype.[11-15]

The Warburg phenotype generates malignant, autoimmune, neurodegenerative, metabolic syndrome x and schizophrenic pathologies. The Warburg phenotype can lead to increased cell proliferation and malignant transformation. The mitochondrial PT pore hexokinase is increased leading onto cell proliferation. There is induction of glycolysis, inhibition of PDH activity and mitochondrial dysfunction resulting in inefficient energetics and metabolic syndrome. The archaea and viroid generated cytokines can lead to TNF alpha induced insulin resistance and metabolic syndrome x. The increase in glycolysis

can activate glyceraldehyde 3 phosphate dehydrogenase which gets translocated to the nucleus after polyadenylation. The PARP enzyme is activated by glycolysis mediated redox stress. This can produce nuclear cell death and neuronal degeneration. The increase in the glycolytic enzyme fructose 1,6 diphosphatase increases the pentose phosphate pathway. This generates NADPH which activates NOX. NOX activation is related to NMDA activation and glutamate excitotoxicity. This leads onto neuronal degeneration.[10]

The increase in glycolysis activates the enzyme fructose 1,6 diphosphatase which activates the pentose phosphate pathway liberating NADPH. This increases NOX activity generating free radical stress and H_2O_2. Free radical stress is related to insulin resistance and metabolic syndrome x. Free radicals can activate NFKB producing immune activation and autoimmune disease. Free radicals can open the mitochondrial PT pore, produce release of cyto C and activate the caspase cascade. This produces cell death and neuronal degeneration. The free radicals can activate NMDA receptor and induce the enzyme GAD generating GABA. This activates the NMDA/GABA thalamo-cortico-thalamic pathway mediating conscious perception. Increased free radical generation can also initiate schizophrenia. Free radicals can also produce oncogene activation and malignant transformation. Free radicals can produce HDAC inhibition and HERV generation. The encapsulation of HERV particles in phospholipids vesicles can mediate the generation of the acquired immunodeficiency syndrome. Free radicals can also promote atherogenesis.[10]

The lymphocytes depend on glycolysis for its energy needs. The increase in glycolysis owing to the induction of Warburg phenotype can lead to immune activation. Immune activation can lead to autoimmune disease. TNF alpha can activate the NMDA receptor leading to glutamate excitotoxicity and neuronal degeneration. TNF alpha activating NMDA receptor can contribute to

schizophrenia. TNF alpha can induce expression of HERV particles contributing to generation of acquired immunodeficiency syndrome. Immune activation has also been related to malignant transformation mediated by NFKB. TNF alpha can also act upon the insulin receptor producing insulin resistance. NOX activation consequent to the generation of the Warburg phenotype also activates the insulin receptor. Thus there is a hyperinsulinemic state leading on to metabolic syndrome x.[10]

Thus the induction of the Warburg phenotype can lead to malignancy, autoimmune disease, metabolic syndrome x, neuropsychiatric disease and neuronal degeneration. The Warburg phenotype leads to inhibition of pyruvate dehydrogenase and accumulation of pyruvate. The accumulated pyruvate enters the GABA shunt pathway and is converted to citrate which is acted upon by citrate lyase and converted to acetyl CoA, used for cholesterol synthesis. The pyruvate can be converted to glutamate and ammonia which is oxidised by archaea for energy needs. The increased cholesterol substrate leads to increased archaeal growth and further induction of the Warburg phenotype.[10]

A ketogenic diet is normal diet of the primitive hunter-gatherer humans. It is based upon a low carbohydrate, high saturated fat and high protein diet. In this study, a modified ketogenic diet was used. It included high medium chain triglycerides from coconut oil, high fiber from banana stem, high black gram protein and low black gram polysaccharide as source of carbohydrate. It was a modified vegetarian ketogenic diet high in MCT and fiber. This diet has got an antiviroidal and antiarchaeal activity and can reverse the Warburg phenotype, the basis of diverse malignant, autoimmune, neurodegenerative, metabolic syndrome x and schizophrenic pathologies.[11-15]

References

[1] Hanold D., Randies, J. W. (1991). Coconut cadang-cadang disease and its viroid agent, *Plant Disease,* 75, 330-335.

[2] Valiathan M. S., Somers, K., Kartha, C. C. (1993). *Endomyocardial Fibrosis.* Delhi: Oxford University Press.

[3] Edwin B. T., Mohankumaran, C. (2007). Kerala wilt disease phytoplasma: Phylogenetic analysis and identification of a vector, *Proutista moesta*, *Physiological and Molecular Plant Pathology*, 71(1-3), 41-47.

[4] Kurup R., Kurup, P. A. (2009). *Hypothalamic digoxin, cerebral dominance and brain function in health and diseases*. New York: Nova Science Publishers.

[5] Eckburg P. B., Lepp, P. W., Relman, D. A. (2003). Archaea and their potential role in human disease, *Infect Immun,* 71, 591-596.

[6] Smit A., Mushegian, A. (2000). Biosynthesis of isoprenoids via mevalonate in Archaea: the lost pathway, *Genome Res,* 10(10), 1468-84.

[7] Adam Z. (2007). Actinides and Life's Origins, *Astrobiology*, 7, 6-10.

[8] Schoner W. (2002). Endogenous cardiac glycosides, a new class of steroid hormones, *Eur J Biochem,* 269, 2440-2448.

[9] Davies P. C. W., Benner, S. A., Cleland, C. E., Lineweaver, C. H., McKay, C. P., Wolfe-Simon, F. (2009). Signatures of a Shadow Biosphere, *Astrobiology,* 10, 241-249.

[10] Wallace D. C. (2005). Mitochondria and Cancer: Warburg Addressed, *Cold Spring Harbor Symposia on Quantitative Biology,* 70, 363-374.

[11] Liu, Y. M. (2008). Medium-chain triglyceride (MCT) ketogenic therapy. *Epilepsia,*;49 S(8), 33-6.

[12] Gasior, M., Rogawski, M. A., Hartman, A. L. (2006). Neuroprotective and disease-modifying effects of the ketogenic diet. *Behav Pharmacol,* 17(5-6), 431-9.

[13] Maalouf, M., Rho, J. M., Mattson, M. P. (2009). The neuroprotective properties of calorie restriction, the ketogenic diet, and ketone bodies. *Brain Res Rev*, 59(2), 293-315.

[14] Barbary, O. M., El-Sohaimy, S. A., El-Saadani, M. A., Zeitoun, A. M. A. (2010). Antioxidant, antimicrobial and anti-HCV activities of lignan extracted from flaxseed. *Research Journal of Agriculture and Biological Sciences*, 6(3), 247-256.

[15] Lieberman, S., Enig, M. G., Preuss, H. G. (2006). A review of monolaurin and lauric acid. Natural virucidal and Bactericidal agents. *Alternative and Complementary Therapies*. 1, 310-314.

[16] Richmond W. (1973). Preparation and properties of a cholesterol oxidase from nocardia species and its application to the enzymatic assay of total cholesterol in serum, *Clin Chem*, 19, 1350-1356.

[17] Snell E. D., Snell, C. T. (1961). *Colorimetric Methods of Analysis.* Vol 3A. New York: Van Nostrand.

[18] Glick D. (1971). *Methods of Biochemical Analysis.* Vol 5. New York: Interscience Publishers.

[19] Colowick, Kaplan, N. O. (1955). *Methods in Enzymology.* Vol 2. New York: Academic Press.

[20] Van der Geize R., Yam, K., Heuser, T., Wilbrink, M. H., Hara, H., Anderton, M. C. (2007). A gene cluster encoding cholesterol catabolism in a soil actinomycete provides insight into Mycobacterium tuberculosis survival in macrophages, *Proc Natl Acad Sci USA*, 104(6), 1947-52.

[21] Francis A. J. (1998). Biotransformation of uranium and other actinides in radioactive wastes, *Journal of Alloys and Compounds*, 271(273), 78-84.

[22] Probian C., Wülfing, A., Harder, J. (2003). Anaerobic mineralization of quaternary carbon atoms: Isolation of denitrifying bacteria on pivalic acid (2,2-Dimethylpropionic acid), *Applied and Environmental Microbiology*, 69(3), 1866-1870.

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