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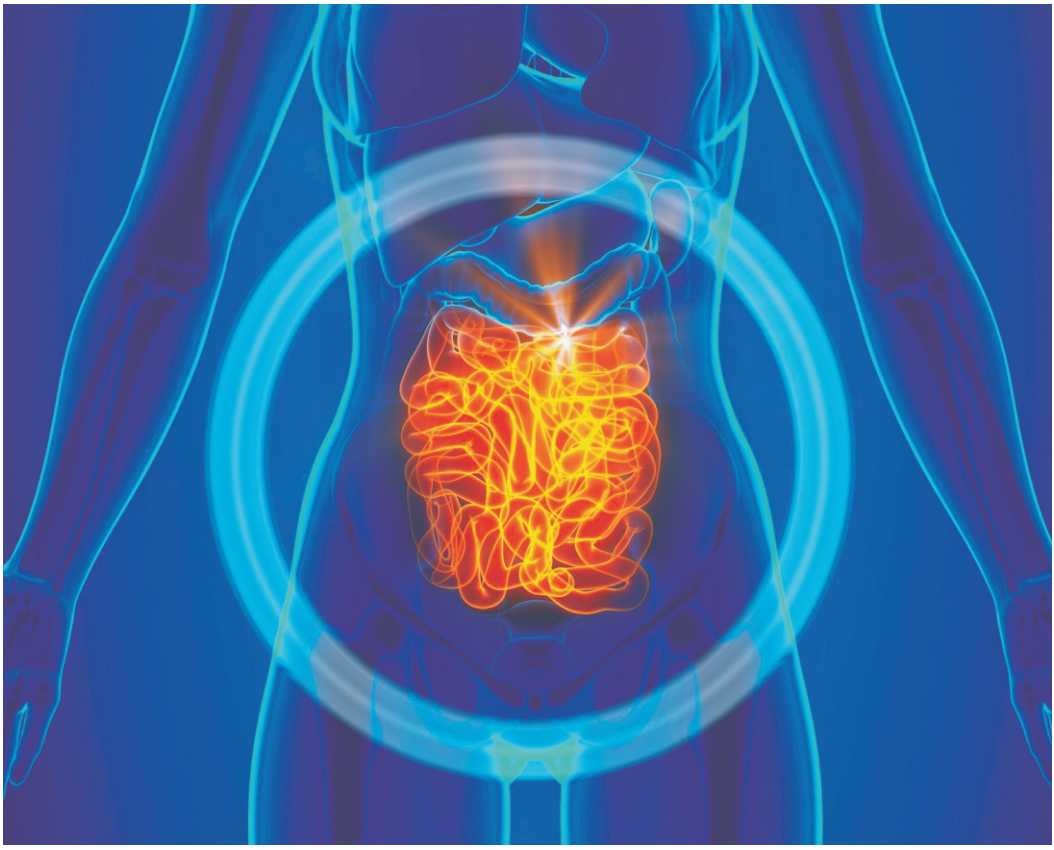

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The Endosymbiotic Archaea, Fructose Disease and Global Warming - Chronic Gastrointestinal Disease

Global warming induces endosymbiotic archaeal and RNA viroidal growth. The porphyrins form a template for the formation of RNA viroids, DNA viroids, prions, isoprenoids and polysaccharides. They can symbiose together to form primitive archaea. The archaea can further induce HIF alpha, aldose reductase and fructolysis resulting in further porphyrinogenesis and archaeal self replication. The primitive archaeal DNA is integrated along with RNA viroids which are converted to their corresponding DNA by the action of redox stress induced HERV reverse transcriptase into the human genome by the redox stress induced HERV integrase. The archaeal DNA sequences that are integrated into the human genome forms endogenous archaeal human genomic sequences akin to HERV sequences and can function as jumping genes regulating genomic DNA flexibility. The integrated endogenous genomic archaeal sequences can get expressed in the presence of redox stress forming endosymbiotic archaeal particles which can function as a new organelle called the archaeaons. The archaeaon can express the fructolytic pathway constituting an organelle called the fructosome, cholesterol catabolic pathway and digoxin synthetic forming an organelle called the steroidelle, the shikimic acid pathway forming an organelle called the neurotransminoid, antioxidant vitamin E and vitamin C synthetic organelle called the vitaminocyte as well as the glycosaminoglycan synthetic organelle called glycosaminoglycoid. The archaea can secrete capsulated RNA viroidal particles which can function as blocking RNAs modulating cell metabolism and such archaeaon organelle are called viroidelle. The archaea suppresses pyruvate dehydrogenase and promotes fructolysis resulting in accumulation of pyruvate which enters the GABA shunt pathway producing succinyl CoA and glycine, the substrates for porphyrin synthesis. Porphyrin forms a template for the formation of RNA viroids, DNA viroids, prions and isoprenoids which can symbiose together to form an archaea. Thus endosymbiotic archaea have an abiogenic replication. The archaeaon concerned with GABA shunt pathway and

porphyrinogenesis are called porphyrinoids. The archaeaon colony forms a network with different areas showing differential specialization of function - fructosoids, steroidelle, vitaminocyte, viroidelle, neurotransminoid, porphyrinoids and glycosaminoglycoids. This forms a living organized structure within human cells and tissues regulating their function and reducing the human body to zombie working under the directions of the organized archaeal colony. The organized archaeal colony has abiogenetic replication and is eternal. The endosymbiotic actinidic archaea forms the basis of life and can be considered as the third element in the cell. It regulates the cell, the neuro-immune-endocrine system and the conscious / unconscious brain. The endosymbiotic actinidic archaea can be called as the elixir of life. A definite population of endosymbiotic actinidic archaea is required for the existence and survival of life. A higher density of endosymbiotic actinidic archaeal population can lead to human disease. Thus actinidic archaea are important for survival of human life and can be considered as crucial to it. Symbiosis by actinidic archaea is the basis of evolution of humans and primates. The increase in endosymbiotic archaeal growth can lead to the induction of homo neanderthalis. This endosymbiotic archaea induced neanderthalisation of the species leads to human disease like metabolic syndrome X, neurodegenerations, schizophrenia and autism, autoimmune disease and cancer. The reduction in endosymbiotic archaeal growth by a high fibre, high medium chain triglyceride and legume protein ketogenic diet, antibiotics from higher plants like Curcuma longa, Emblica officianalis, Allium sativum, Withania somnifera, Moringa pterygosperma and Zingeber officianalis and transplantation of colonic microflora from normal homo sapien population can lead to deneanderthalisation of species and treatment of the above mentioned diseased states. The colonic microflora of neanderthalised diseased states like metabolic syndrome X, neurodegenerations, schizophrenia and autism, autoimmune disease and cancer when transferred to the normal homo sapien species leads to generation and induction of homo

neanderthalis. Thus primate and human evolution is symbiotic event which can be induced the modulating symbiotic archaeal growth. Human populations can be divided into matrilineal Neanderthal population in South Indian Dravidians, Celts, Basques, Jews and Berbers and the Cro-Magnon population seen in Africa and Europe. The symbiotic archaeal colonization decides which species - Neanderthal or Cro-Magnon to which the society belongs to. It is tempting to postulate symbiotic microflora and archaea determining the family behavior and traits as well as societal and caste behavior and traits. The cell has been postulated by Margulis to be a symbiotic association of bacteria and viruses. Similarly, the family, the caste, the community, nationalities and the species itself is determined by archaeal and other bacterial symbiosis.

Symbiosis by microorganisms especially archaea drives the evolution of the species. In such a case symbiosis can be induced by transfer of microflora symbionts and evolution induced. Endosymbiosis by archaea as well as archaeal symbionts in the gut can modulate the genotype, the phenotype, the social class and the racial group of the individual. The symbiotic archaea can have horizontal and vertical transmission. Endosymbiotic archaeal growth leads to neanderthalisation of the species. The neanderthalised species is matrilineal society and includes the Dravidians, the Celts, the Basques and the Berbers. The inhibition of the endosymbiotic archaeal growth leads to evolution of the homo sapiens. This includes the Africans, Aryan invaders of North India and the Aryan derived European population. Symbiosis mediated evolution depends on the gut flora and the diet. This has been demonstrated in the drosophila pseudoobscura. The drosophila mates only with other individuals eating the same diet. When the drosophila gut microflora is altered by feeding antibiotics they mate with other individuals eating different diets. The diet consumed by the drosophila regulates its gut microflora and mating habits. The combination of the human genome and the symbiotic microbial genome is called the

hologenome. The hologenome especially its symbiotic microbial component drives human evolution as well as animal evolution. The evolutionary distance between species of wasp depends on the gut microflora. The human gut microflora regulates the endocrine, genetic and neuronal systems. Humans and primate evolution depends on endosymbiotic archaea and gut microflora. The endosymbiotic archaeal growth determines the racial differences between the matrilineal Harappan / Dravidian societies and the patriarchal Aryan society. The matrilineal Harappan / Dravidian society was neanderthalic and had increased endosymbiotic archaeal growth. Endosymbiotic archaeal growth and neanderthalisation can lead to autoimmune disease, metabolic syndrome X, neurodegeneration, cancer, autism and schizophrenia. The Neanderthal gut flora and endosymbiotic archaea was determined by the non vegetarian ketogenic high fat high protein diet consumed by them in the Eurasian steppes. The homo sapiens including the classical Aryan tribes and African ate a high fibre diet and had lower archaeal growth both endosymbiotic and gut. The dietary fibre intake determines the microbial diversity of the gut. The high fibre intake is associated with increased generation of short chain fatty acids - butyric acid by the gut flora. Butyrate is a HDAC inhibitor and leads to increased generation and incorporation of endogenous retroviral sequences. The high dietary fibre intake related increased HERV sequences leads to increased synaptic connectivity and a dominant frontal cortex as seen in homo sapien species. The neanderthalic species consume a ketogenic non vegetarian high fat high protein low fibre diet. This leads to decreased generation of endogenous HERV sequences and reduced genomic flexibility in neanderthalic species. This produces smaller cerebral cortex and a dominant cerebellar cortex in the neanderthalic brain. The homo neanderthalic species by the low dietary fibre intake starve their microbial self. This leads to increased endosymbiotic and gut archaeal growth. The mucous membrane lining the gut becomes thinned out as the gut bacteria eats

up the mucous lining of the gut. This results in leakage of endotoxin and archaea from the gut to the blood breaching the barrier and produces a chronic immunostimulatory inflammatory state which forms the basis of autoimmune disease, metabolic syndrome, neurodegeneration, oncogenic and psychiatric disorders. The Neanderthal species eat a low fibre diet and have a deficiency of microbiota accessed carbohydrate generating short chain fatty acid. There is a deficiency of butyrate generated in the gut from the dietary fibre which can produce suppression of the chronic inflammatory process. The Neanderthals have got the fermentation by-product deficiency syndrome. The induction of neanderthalic species depends on the low fibre intake induced high archaeal density endosymbiotic and the gut microflora. The homo sapiens species consume a high fibre diet generating large amounts of short chain fatty acid butyrate which inhibits endosymbiotic and gut archaeal growth. The microbial self of the homo sapien species is more diverse than that of the neanderthalic species and the archaeal population density is less. This results in a protection against chronic inflammation and the induction of diseases like autoimmune disease, metabolic syndrome, neurodegeneration, oncogenic and psychiatric disorders. The homo sapien species have a higher intake of dietary fibre contributing to around 40 g/day and a diverse microbial gut flora with less of archaeal population density. The butyrate generated from dietary fibre produces an immunosuppressive state. Thus the symbiotic microflora with less of archaeal density induces a homo sapien species. This can be demonstrated by experimental induction of evolution. A high fibre high MCT diet as well as antibiotics derived from higher plants and fecal microbiota transfer from sapien species can inhibit the Neanderthal metabolonomics and phenotype and induce the evolution of homo sapiens. A low fibre high fat high protein diet as well as fecal microbiota transfer from the Neanderthal species can produce Neanderthal metabolonomics and phenotype inducing the evolution of homo neanderthalis.

Transfer of colonic microflora predominantly archaea and modulation of endosymbiotic archaea by a paleo diet and antibiotics from higher plants can lead to interconversion of human species between homo neanderthalis and homo sapiens. The hologenome especially the microbial flora endosymbiotic/gut drives human and animal evolution and can be experimentally induced. Symbiotic microflora drives evolution. Every animal, every human species, different communities, different races and different caste have their signature endosymbiotic and gut microflora which can be transmitted vertically and horizontally. Thus symbiosis drives human and animal evolution.

This can be interpreted on the basis of Villarreal hypothesis of group identity and cooperativity of RNA collectives. Archaeal symbiosis in the gut and in the tissue spaces determines speciation of human beings as homo sapiens and homo neanderthalis. The endosymbiotic archaea can secrete RNA viroids and viruses and there is a viroid-archaeal host relationship between the two. A dynamic state of virus lysis and persistence can occur in archaea suggesting that viral addiction can occur in archaea. The RNA viroids in the archaea coordinate their behavior by information exchange, modulation and innovation generating new sequence based content. This occurs due to a phenomenon of symbiosis in contrast to the concept of survival of the fittest. The generation of new RNA viroidal sequences is a result of practical competence of living agents to generate new sequences by symbiosis and sharing. This represents highly productive RNA viroidal quasi-species consortia for the evolution, conservation and plasticity of genomic environments. The behavioural motives of the RNA are single stem loop structures. They have self folding and group building capabilities depending upon functional needs. The evolution process depends upon what Villareal calls RNA stem loop consortia. The whole entity can function only if participatory groups of RNA viroids can get their function coordinated. There is competent denovo generation of new sequences by

cooperative action and not by competition. These RNA viroidal group consortia can contribute to the host identity, group identity and group immunity. The term used for this is RNA viroidal sociological behavior. The RNA viroids can build groups that invade the archaea and compete as a group for limited resources such host genomes. A key behavioural motif is able to integrate a persistent life style into the archaeal colony with the addiction module forming competing viroidal groups that are counter balancing each other together with the archaeal/host immune system. This leads to creation of an identity for the archaeal colony and the homo neanderthalis host. Viroids can kill their host and also colonize their host without disease and protect the host from similar viruses and viroids. Together with lysis and protection we see a viroid colonized host that is both symbiotic and innovative acquiring new competent codes. Thus the viroid-host relationship is a pervasive, ancient force in the origin and evolution of life. Cumulative evolution at the level of RNA viroids is like a ratchet effect used for transmission of cultural memes. This learning accumulates so that every new generation must not repeat all innovative thoughts and techniques. Quasi-species of RNA viroids are cooperative and exclusive of other quasi-species. They have group recognition differentiating self-groups and non-self-groups allowing for quasi-species to promote the emergence of group identity. With group identity via counter related addiction modules two opposing components must be present and work coherently and define the group as a whole. Biological identity is constituted by dynamic interaction of cooperative groups. Virus addiction module is an essential strategy for existence of life in the virosphere. Viruses are transmissible and can persist in specific host population leading to a form of group immunity / identity since identical but uncolonized host population remains susceptible to a killing action of lytic viruses. In this way we see that viruses are necessary providing opposing functions for addiction (persistence/protection and lytic/killing). Viroids can

function as consortia, an essential interacting group and provide a mechanism from which consortial function could emerge in the origin of protobiotic life. Genetic parasites can act as a group (qs-c). But for this group to be coherent they must attain group identity and this is typically via an addiction strategy. Antiviral and proviral system in the archaea will themselves emerge in the host from virus derived information. The archaeal viruses themselves provide the critical function required for antiviral defence. The opposing functions are the basis of addiction modules. Thus the emergence of group identity becomes an essential and early event in the emergence of life. This is coherent to the basically group behavior of RNA viroids in archaea. This group selection and group identity are needed to create information coherence and network formation and to establish a system of communication - code competent interactions. This identity serves as information also for the ones that do not share this identity. This is the beginning of self/non-self differentiating capability. In this way viroids promote the emergence of group identity in archaeal colonies and host humans. The archaeal colony identity depends upon the colonizing set of RNA viroids producing a coherent network that is inclusive opposing functions and favours the persistence of parasite derived new information. On the basis of population-based functions of RNA DNA can be considered as a habitat for consortia RNA. Thus RNA viroids of the archaea are involved in complex multicellular identity. This is called as the Gangen hypothesis by Villarreal. The Gangen describes the emergence of commonly shared code use, group membership and collective living function of RNA viroids. Communication is a code depended interaction and transmission of infectious code defines the origin of the virosphere. This issue refers to the idea of collective of RNA viroids with inherent toxic and antitoxic features should be able to transmit or communicate these agents and their features to a nearby competing population. It strongly favours the survival of RNA viroidal

population with compatible addiction modules that will inhibit agent toxicity and allow persistence of new agents. This is thus the survival of the persistently colonized set which is an inherently symbiotic and consortial process. It also promotes increasing complexity and identity/immunity of the host collective via a new agent colonization, and stable addition. Thus the transmission of RNA agents attains both communication and recognition of group membership. In this way the emergence of the virosphere must had been an early event in the origin of life and group identity. Viruses and viroids are genetic parasites and the most abundant living entities on earth. The virosphere is a network of infectious genetic agents. Evolution, conservation and plasticity of genetic identities are the result of cooperative consortia of RNA viroids that are competent to communicate. Thus the archaeal viroidal consortia can symbiotically share and communicate producing new sequences and give an identity to the archaeal colony. The low fibre diet and extreme temperatures of the Eurasian steppes leads to archaeal multiplication and induction of the homo neanderthalis species. The archaeal colony's characteristics are determined by the cooperative consortia of RNA viroids in the archaea and the archaeal colony identity determines the homo neanderthalis identity. Thus the archaeal colonies with their quasi-species consortia of RNA viroids determine the homo neanderthalis identity. The new sequence generation by the RNA viroidal consortia's symbiotic sharing character contributes to the diversity in the behavior and creativity of the homo neanderthalis population. The archaeal RNA viruses and viroids and the archaeal colonies themselves protect the homo neanderthalis population from retroviral infections. Thus the homo neanderthalis population is retroviral resistant and the quasi-species consortia of archaea and archaeal viroids gives them a group identity as retroviral resistant. Thus the quasi-species consortia of archaea and RNA viroids give homo neanderthalis colonies their identity and idea of self. The homo neanderthalis is

resistant to retroviral infection like the Australian aboriginals and the endogenous retroviral sequences in the Neanderthal genome are limited. This leads to lack of plasticity and dynamicity of the human genome and the cerebral cortex in ill-developed with a dominant impulsive cerebellar cortex in the homo neanderthalis population. This produces the impulsive creative surrealistic spiritual neanderthalic brain. As the extreme of temperature goes off and the ice age ends the archaeal population density also comes down. This also can result from the consumption of a high fibre diet in the African continent. The high fibre diet digested by clostridial clusters in the colon promotes butyrate synthesis and butyrate will induce HDAC inhibition and expression of retroviral sequences in the primate genome. This leads to increase in endogenous retroviral sequences in the human genome, increasing genomic dynamicity and the evolution of complicated cerebral cortex dominant brain with its complex synaptic connectivity in the homo sapiens. This leads onto a logical, commonsensical, pragmatic and practical homo sapien brain. The homo sapiens due to lack of archaea and the RNA viroids are susceptible retroviral infection. Thus the archaeal colonies and RNA viroidal quasi-species consortia determine the evolution of the human species and the brain networks. Thus extremes of temperature, fibre intake, archaeal colony density, RNA viroidal quasi-species, group identity and retroviral resistance decides on the evolution of homo sapiens and homo neanderthalis as well as the brain networks. The present extremes of temperature and low fibre intake in civilized society can lead to increase in archaeal population densities and quasi-species RNA viroidal networks generating a new homo neanderthalis in a new neanderthalic anthropocene age as opposed to the present homo sapien anthropocene age. The archaeal population densities and quasi-species RNA viroidal networks determine homo sapien / homo neanderthalis species, racial, caste, community, national, sexual, metabolic, phenotypic, immune, genotypic and individual

identity. The archaea secretes the trephone digoxin which can edit the RNA viroids and generate new sequences. Archaeal dipolar magnetite and porphyrins in the setting of digoxin induced membrane sodium potassium ATPas inhibition can produce a pumped phonon system mediated quantal perceptive state and quantal communication in the RNA viroidal symbiotic system generating new sequences by steroidal digoxin enzymatic editing action. This gives rise to archaeal RNA viroidal quasi-species symbiotic diversity and identity to species, race, caste, sex, culture, individual and national identity.

The roots of Western civilisational disease can be related to the starvation of the colonic microflora. The colonic microflora depends upon complex carbohydrates derived from dietary fibre. The processed food of high protein, fat and sugars is digested and absorbed in the stomach and small intestine. A very little of it reaches the colon and widespread use of antibiotics in medicine has produced mass extinction of the colonic microflora. The colonic microflora is extremely diverse and the diversity is lost. There are 100 trillion bacteria in the colon belonging to 1200 species. They regulate the immune system by inducing the T-regulatory cells. A high fibre diet contributes to colonic microbiota diversity. Interaction with farm animals like cows and dogs also contributes to the colonic microflora diversity. The typical Western diet of high fat, high protein and sugars decreases the colonic microbiota diversity and increase colonic/endosymbiotic archaea producing methanogenesis. The colonic archaea feed upon the mucous lining of the colon and produces leakage of archaea into the blood and tissue system producing endosymbiotic archaea. This results in a chronic inflammatory state. The high fibre diet of Africans, South Americans and Indians produces increased colonic microbiota diversity and increase in clostridial clusters generating SCFA in the gut. High fibre diet is protective against metabolic syndrome and diabetes mellitus. Metabolic syndrome is related to degeneration, cancer, neuropsychiatric illness and

autoimmune disease. A high fibre diet of upto 40 g/day can be called as a gut diet. The colonic microflora especially the clostridial cluster digests the fibre generating short chain fatty acids which regulates immunity and metabolism. High fibre diet increases the colonic mucus secretion and the thickness of the mucus lining. A high fibre diet produces increase in clostridial clusters and mucous secretion. This produces a strong gut blood barrier and prevents metabolic endotoxemia which produces a chronic inflammatory response. High dietary fibre intake and the diversity of the colonic microflora with prominent SCFA producing clostridial clusters are interrelated. The clostridial clusters metabolise the complex carbohydrate in dietary fibre to short chain fatty acids butyrate, propionate and acetate. They increase the T-regulatory function. A high fibre diet increases the bacteroides and reduces the firmecutes of the colonic microflora. A high fibre diet is associated with a low body-mass index. A low fibre diet produces increase in colonic archaeal growth as well as endosymbiotic tissue and blood archaea. This produces more of methanogenesis rather than short chain fatty acid synthesis contributing to immune activation. A low fibre diet is associated a high body-mass index and chronic systemic inflammation. Germ-free mice show cardiac, pulmonary and liver atrophy. Gut microflora is required for the generation of organ systems. The gut microflora is also required for generation of T-regulatory cells. High fibre intake produces more colonic microbiota diversity and increase in clostridial clusters and fermentation by products like butyrate which suppresses inflammation and increases T-regulatory cells. A low fibre diet produces increase in archaeal growth, methanogenesis, destruction of the mucus lining and leakage of the colonic archaea producing endosymbiotic tissue and blood archaea. This produces an immune hyperreactivity contributing to the modern plagues of civilization - metabolic syndrome, schizophrenia, autism, cancer, autoimmunity and degenerations. The gut microbiota drives human evolution. The humans

don't host the gut microbiota but the gut microbiota host us. The human system forms an elaborate culture laboratory for the propagation and survival of the microbiota. The human system is induced by the microbiota for their survival and growth. The human system exists for the microbiota and not the other way round. The same mechanism holds good in plant systems. Plant started the colonized earth as they started symbiosing with bacteria in the roots systems which can derive nutrients from the soil. Human beings form a mobile culture laboratory for the more effective propagation and survival of the microbiota. The microbiota induces the formation of specialized immune cells called innate lymphoid cells. The innate lymphoid cells will direct the lymphocytes not to attack the beneficial bacteria. Thus the endosymbiotic archaea and the gut archaea induce human, primate and animal evolution to generate structures for them to survive and propagate. The source of endosymbiotic archaea, the third element of life is the colonic archaea that leaks into the tissue spaces and blood systems due to breach in the gut blood barrier. The increase in colonic archaea is due to the starvation of the gut microbiota consequent to a low fibre diet. This results in increase in colonic archaeal growth and destruction of clostridial clusters and bacteroides. The increase colonic archaeal growth in the presence of gut starvation due to low fibre diet eats up the mucus lining and produces breakages in the gut blood barrier. The colonic archaea enters the blood stream and produces endosymbiosis generating endosymbiotic archaea and various new organelle - fructosoids, steroidelle, vitaminocyte, viroidelle, neurotransminoid, porphyrinoids and glycosaminoglycoids.

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.

The increase in endogenous EDLF, a potent inhibitor of membrane Na^+-K^+ ATPase, can decrease this enzyme activity. The results showed increased endogenous EDLF synthesis as evidenced by increased HMG CoA reductase activity, which functions as the rate limiting step of the isoprenoid pathway. Studies in our laboratory have demonstrated that EDLF is synthesized by the isoprenoid pathway. The endosymbiotic archaeal sequences in the human genome get expressed by redox stress and osmotic stress of global warming. This results in induction of HIF alpha which will upregulate fructolysis and glycolysis. In the setting of redox stress all glucose gets converted to fructose by the induction of enzymes aldose reductase and sorbitol dehydrogenase. Aldose reductase converts glucose to sorbitol and sorbitol dehydrogenase converts sorbitol to fructose. Since fructose is preferentially phosphorylated by ketohexokinases the cell is depleted of ATP and glucose phosphorylation comes

to a halt. Fructose becomes the dominant sugar that is metabolized by fructolysis in expressed archaeal particles in the cell functioning as organelle called fructosoids. The fructose is phosphorylated to fructose 1-phosphate which is acted upon by aldolase B which converts it into glyceraldehyde 3-phosphate and dihydroxy acetone phosphate. Glyceraldehyde 3-phosphate is converted to D 1,3-biphosphoglycerate which is then converted to 3-phosphoglycerate. The 3-phosphoglycerate is converted to 2-phosphoglycerate. 2-phosphoglycerate is converted to phosphoenol pyruvate by the enzyme enolase. Phosphoenol pyruvate is converted to pyruvate by the enzyme pyruvic kinase. The archaeaon induces HIF alpha which upregulates fructolysis and glycolysis but inhibits pyruvate dehydrogenase. The forward metabolism of pyruvate is stopped. The dephosphorylation of phosphoenol pyruvate is inhibited in the setting of pyruvic kinase inhibition. Phosphoenol pyruvate enters the shikimic acid pathway where it is converted to chorismate. The shikimic acid is synthesized by a pathway starting from glyceraldehyde 3-phosphate. Glyceraldehyde 3-phosphate combines with the pentose phosphate pathway metabolite sedoheptulose 7-phosphate which is converted to erythrose 4-phosphate. The pentose phosphate pathway is upregulated in the presence of the suppression of glycolytic pathway. Erythrose 4-phosphate combines with phosphoenol pyruvate to generate shikimic acid. Shikimic acid combines with another molecule of phosphoenol pyruvate to generate chorismate. The chorismate is converted to prephenic acid and then to parahydroxy phenyl pyruvic acid. Parahydroxy phenyl pyruvic acid is converted to tyrosine and tryptophan as well as neuroactive alkaloids. The shikimic acid pathway is structured in expressed archaeaon organelle called the neurotransminoid. The fructolytic intermediates glyceraldehydes 3-phosphate and pyruvate are the starting points of the DXP pathway of cholesterol synthesis. Glyceraldehyde 3-phosphate combines with pyruvate to form 1-deoxy D-xylulose phosphate

(DOXP) which is then converted to 2-C methyl erythritol phosphate. 2-C methyl erythritol phosphate can be synthesized from erythrose 4-phosphate a metabolite of the shikimic acid pathway. DXP combines with MEP to form isopentenyl pyrophosphate which is converted to cholesterol. Cholesterol is catabolised by archaeal cholesterol oxidases to generate digoxin. The digoxin sugars digitoxose and rhamnose are synthesized by the upregulated pentose phosphate pathway. Glycolytic suppression leads to upregulation of the pentose phosphate pathway. The expressed archaeaon organelle concerned with cholesterol catabolism and digoxin synthesis is called the steroidelle. The suppression of glycolysis and stimulation of fructolysis results in upregulation of the hexosamine pathway. Fructose is converted to fructose 6-phosphate by ketohexokinases. The fructose 6-phosphate is converted to glucosamine 6-phosphate by the action of glutamine fructose 6-phosphate amidotransferase (GFAT). Glucosamine 6-phosphate is converted to UDP N-acetyl glucosamine which is then converted to N-acetyl glucosamine and various amino sugars. UDP glucose is converted to UDP D-glucuronic acid. UDP D-glucuronic acid is converted to glucuronic acid. This forms the uronic acid synthetic pathway. Uronic acids and hexosamines form repeating units of glycosaminoglycans. In the setting of glycolytic suppression and fructolytic metabolism fructolysis leads to increase synthesis of hexosamines and GAG synthesis. The GAG synthesizing archaeaon particles are called the glycosaminoglycoids. The expressed archaeaon particles are capable of synthesizing antioxidant vitamin C and E. The UDP D-glucose is converted to UDP D-glucuronic acid. UDP D-glucuronic acid is converted to D-glucuronic acid. D-glucuronic acid is converted to L-gulonate by enzyme aldoketoreductases. L-gulonate is converted to L-gulonolactone by lactonase. L-gulonolactone is converted to ascorbic acid by the action of archaeal L-gulo oxidase. The vitamin E is synthesized from shikimate which is converted to tyrosine and then to parahydroxy phenyl

pyruvic acid. Parahydroxy phenyl pyruvic acid is converted to homogentisate. Homogentisate is converted to 2-methyl 6-phytyl benzoquinone which is converted to alpha tocopherol. 2-methyl 6-phytyl benzoquinone is converted to 2,3-methyl 6-phytyl benzoquinone and gamma tocopherol. Vitamin E can also be synthesized by the DXP pathway. Glyceraldehyde 3-phosphate and pyruvate combined to form 1-deoxy D-xylulose 5-phosphate which is converted to 3-isopentenyl pyrophosphate. 3-isopentenyl pyrophosphate and dimethyl allyl pyrophosphate combined to form 2-methyl 6-phytyl benzoquinone which is converted to tocopherols. The ubiquinone another important membrane antioxidant and part of the mitochondrial electron transport chain is synthesized by the shikimic acid pathway and DXP pathway. The isoprenoid moiety of ubiquinone is contributed from the DXP pathway and the rest of it by tyrosine catabolism. The tyrosine is generated by the shikimic acid pathway. The archaeaon particles concerned with the synthesis of vitamin C, vitamin E and ubiquinone which are all antioxidants are called the vitaminocyte.

Global warming induces endosymbiotic archaeal and RNA viroidal growth. The endosymbiotic archaea and the generated RNA viroids induce aldose reductase which converts glucose to sorbitol. The archaeal polysaccharides and lipopolysaccharides as well as viroids and viruses can induce aldose reductase. Sorbitol is acted upon by sorbitol dehydrogenase to generate fructose which enters fructolytic pathway. Aldose reductase is also induced by the osmotic stress of global warming and redox stress. Aldose reductase is induced by inflammatory and immune stimulation. Archaeal synthesized endogenous digoxin can produce intracellular redox stress and activate NFKB which produces immune activation. Both redox stress and immune activation can activate aldose reductase which converts glucose to fructose. Hypoxic stress or anerobic conditions induces HIF alpha which activates ketohexokinase C which phosphorylates fructose. Fructose is acted upon by fructokinase which converts

fructose to fructose 1-phosphate. Fructose 1-phosphate is converted to dihydroxy acetone phosphate and glyceraldehydes 3-phosphate which is converted to pyruvate, acetyl CoA and citrate. Citrate is used for lipid synthesis. Fat deposition occurs in the visceral organs like the liver, heart and kidney. There is no subcutaneous fat deposit. Fructose metabolism bypasses phosphofructokinase which is inhibited by citrate and ATP. Fructose metabolism is therefore not under the regulatory control of the enzyme phosphofructokinase. Fructose transport and metabolism is not regulated by insulin. Fructose is transported by glut-5 receptor. Fructose does not increase insulin secretion and therefore does not activate lipoprotein lipase. This results in visceral adipogeneis. Fructose induces ChREBP and SREBP elements. This results in increased hepatic lipogenesis by the induction of the enzyme fatty acid synthase, acetyl CoA carboxylase and steroyl CoA desaturace. This increases fatty acids and cholesterol synthesis. Fructose is a lipophilic carbohydrate. Fructose can be converted to glycerol 3-phosphate and fatty acids involved in triglyceride synthesis. Fructose administration leads to increase in triglycerides and VLDL. Fructose consumption leads to insulin resistance, fat accumulation in visceral organs like liver, heart and kidney, insulin resistance, dyslipidemia with increased triglycerides, VLDL and LDL as well as the metabolic syndrome. The metabolic syndrome X can be considered as a fructolytic syndrome. Fructose will increase lipid storage and promote insulin resistance. Fructose can fructosylate proteins producing dysfunction. Fructose has no effect upon ghrelin and leptin in the brain and can lead to increased feeding behaviour. Glucose decreases ghrelin and increases leptin levels. This leads to suppression of appetite. Thus fructose can modulate eating behaviour leading onto obesity. Fructose results in NFKB activation and TNF alpha secretion. TNF alpha can modulate the insulin receptor producing insulin resistance and metabolic

syndrome X. Fructose can also lead to leptin resistance and obesity. There is an epidemic of metabolic syndrome X in relation to global warming.

Fructose can activate the sympathetic nervous system. This leads to hypertension and increase in heart rate. Fructose is involved in left ventricular hypertrophy, increase in left ventricular mass and decrease in left ventricular ejection fraction in hypertension. Fructose suppresses the parasympathetic nervous system. Fructose acts as a key inducer for uncontrolled proliferation and hypertrophy of the cardiac musculature consequent to hypertension. The heart uses beta oxidation of fatty acids to generate energy. In the setting of anerobic glycolysis consequent to myocardial infarction and hypertensive hypertrophy of the heart, there is induction of HIF alpha. This produces increase in ketohexokinase C in the heart which phosphorylates fructose. Ketohexokinase C is a predominant liver enzyme as fructose metabolism is primarily focused in the liver. In the setting of anerobic glycolysis ketohexokinase C is also produced in the brain and the heart. Ketohexokinase A is the predominant enzyme in the heart and brain. In the setting of anerobic glycolysis ketohexokinase A which preferentially metabolizes glucose is converted to ketohexokinase C metabolizing fructose by the mechanism of RNA splicing. Anerobic conditions can induce HIF alpha which activates the splicing factor SF3B1. Thus HIF alpha induced by glycolysis induces SF3B1 which induces ketohexokinase C producing fructolysis in the heart. The fructose is converted to lipids, glycogen and glycosaminoglycans in the heart producing cardiac hypertrophy. Fructose metabolism is not under regulatory control of the key enzyme phosphofructokinase by citrate and ATP. The fructolytic pathway functions as a rogue pathway not under any regulatory control. Fructose is a key contributor. The sympathetic overactivity and parasympathetic blockade consequent to fructose can produce immune activation. The sympathetic overactivity and parasympathetic blockade can lead to dysregulation of the nervous system.

Fructose can activate NFKB and tumour necrosis factor alpha. The vagal blockade produced by fructose also leads to increase in immune activation. Fructose can inhibit neutrophilic phagocytosis. Increased fructose ingestion can lead to immune activation and respiratory diseases like chronic bronchitis, COPD and bronchial asthma as well as interstitial lung disease. This immune activation induced by fructose is called as fructositis. Fructosylated proteins can serve as autoantigens. Fructosylated proteins can bind to RAGE receptors producing immune activation. Global warming induced fructose disease is the basis of the epidemic of autoimmune disease rising with the global warming.

Fructose increases flux through the pentose phosphate pathway. This increases the availability of hexose sugars like ribose for nucleic acid synthesis. This increases DNA synthesis. There is also consequent increase in protein synthesis. The tumour cells can slurp up fructose. Tumour cells utilise fructose for proliferation. The fetal cells like tumour cells also utilize fructose for proliferation. Fructose can promote metastatic deposits. The tumour cells use fructose differently from glucose. Cancer cells utilize fructose to support proliferation and metastasis. Fructose increases nucleic acid synthesis. Fructose can help the cancer cells to grow fast by inducing the transketolase enzyme and the pentose phosphate pathway. Fructose administration increases redox stress, DNA damage and cell inflammation all contributing to oncogenesis. Fructose is the most abundant sugar in the fetal tissues and is important in the development of fetus by promoting cell proliferation. Fructose is 20-times more concentrated in the fetal blood than glucose. Sperm cells and ova also use fructose for metabolism and energy. Thus all rapidly proliferating cells - cancer cells, fetal cells and reproductive cells depends upon fructolysis. Fructose is the principal diet of the cancer cells. Global warming and archaeal growth results in HIF alpha induction. HIF alpha induces tumour growth. HIF alpha also increases glycolysis. But archaeal induced HIF alpha also induces aldose reductase which

converts glucose to fructose and metabolism proceeds along the fructolytic pathway. Fructosylation of glycolytic enzymes brings glycolysis to a halt. Fructosylation of mitochondrial PT pore hexokinase can result in PT pore dysfunction and cell proliferation. The fructolytic pathway is the principal energetic pathway for rapidly proliferating cancer cells, fetal cells and stem cells. The global warming will induce the Warburg phenotype of the fructolytic variety. This leads to an epidemic of cancer. There is an epidemic of cancer in relation to global warming. The fructolytic pathway can lead to increased DNA synthesis and RNA synthesis due to flux via the pentose phosphate pathway. The fructolytic pathway can be directed to the GABA shunt generating succinyl CoA and glycine. These are substrates for porphyrin templates to form RNA viroids. The archaeal induced redox stress can induce endogenous HERV expression and reverse transcriptase expression. The RNA viroids are converted by HERV reverse transcriptase to corresponding DNA and integrated into the genome by HERV integrase. The integrated RNA viroid related DNA can function as jumping genes producing genomic plasticity and genomic change.

Fructose as said before induces the thiamine dependent transketolase flux. It increases both the oxidative and non oxidative pentose phosphate pathway. This increases nucleic acids and glycosaminoglycan synthesis. Fructose is converted to fructose 1-phosphate which is acted upon by aldolase B converting it into glyceraldehyde and dihydroxy acetone phosphate. Glyceraldehyde is converted glyceraldehyde 3-phosphate by triokinase. DHAP can be converted to glyceraldehyde 3-phosphate by the enzyme triose phosphate isomerase. Glyceraldehyde 3-phosphate can be converted to pyruvate. This pyruvate can be channeled to gluconeogenesis and glycogen storage by the action of the enzyme pyruvate carboxylase. This results in the conversion of glyceraldehyde 3-phosphate to pyruvate and via pyruvate carboxylase to glucose 1-phosphate. Glucose 1-phosphate is converted to glycogen polymers. Thus fructolysis

results in glycogen storage. The pyruvate that is generated by fructolysis is converted to glutamate which can enter the GABA shunt pathway. The GABA shunt pathway generates glycine and succinyl CoA which are substrates for ALA synthesis. Thus fructolysis stimulates porphyrin synthesis. The porphyrins can self organize to form supramolecular arrays called porphyrions. Porphyrions can self replicate by using other porphyrions as templates. Porphyrions can have energetic and ATP synthesis by electron or photon transport. Porphyrions are dipolar molecules and in the setting of digoxin induced membrane sodium potassium ATPase inhibition can generate a pumped phonon system induced quantal state and quantal perception. They can function as quantal computers with information storage. The porphyrions are basic self replicating living structures. The porphyrins can act as a template for the formation RNA, DNA and proteins. The RNA viroids, the DNA viroids and proteins generated by abiogenesis on porphyrin templates can self organize to form primitive archaea. The archaea are thus capable of abiogenic replication on porphyrin templates. The archaea can induce HIF alpha and further aldose reductase induction promoting fructolysis.

Fructose is an addictive substance. Fructose affects the hedonic centres in the brain concerned with pleasure and reward. In the addiction scale fructose is more addictive then cocaine and cannabis. Fructose decreases BDNF. Low BDNF produces changes in the brain resulting in schizophrenia and depression. Fructose can also produce chronic inflammation involved in schizophrenia. The fructolytic pathway is important in the genesis of psychiatric disorders. The increased fructolysis can lead to fructosylation of lipoproteins especially apoprotein E and apoprotein B. Apo B can undergo lysine fructosylation leading to defective LDL and cholesterol uptake by the brain. This results in autism and schizophrenia. Fructolysis leads to cholesterol depletion of the brain. Cholesterol is required for the formation of synaptic connections and cerebral

cortex. This leads to cerebral cortical atrophy and cerebellar dominance in the presence of cholesterol depletion. This can contribute to the genesis of the cerebellar cognitive affective syndrome, the basis of schizophrenia and autism. There is an epidemic of schizophrenia and autism correlating with global warming. Fructosylation of LDL and brain cholesterol depletion can lead to dysfunction in synaptic transport. There is more release of glutamate into the synaptic from the presynaptic neuron consequent to a presynaptic neuron membrane dysfunction as a result of cholesterol depletion. This contributes to glutamate excitotoxicity. Glutamate excitotoxicity can contribute to neuronal degeneration. Fructose can also produce zinc deficiency. Increased fructose intake produces zinc depletion leading to defective formation of metallothionines leading to defective heavy metal excretion. This leads to mercury, cadmium and aluminium toxicity in the brain leading to psychiatric disorders like autism and degenerations like Alzheimer's disease. Zinc deficiency consequent to fructose excess can lead to copper excess. The zinc containing neurons in the cerebral cortex are called the gluzinergic neurons. The cerebral cortex especially the prefrontal cortex will atrophy producing cerebellar and brain stem dominance. Copper is required for the dominance of subcortical cognitive structures. Fructose ingestion can also lead to calcium deficiency which can produce defective calcium signaling. Fructose ingestion leads to fructolysis and the generation of reactive species 3-deoxyglucosone important in mallard reachion and fructosylation of neuronal proteins leading to their defective function. Neuropsychiatric disorders and neurodegenerative disorders can be described as fructose diseases. Topiramate a fructose analogue is used to treat motor neuron disease. Fructose biphosphate aldolase B mutation has been seen in schizophrenia, bipolar disorders and depression. 6-phosphofructo 2-kinase and fructose 2,6-biphosphotase abnormalities have been seen in schizophrenia. Fructose metabolism abnormalities have been noted

in schizophrenia, manic depressive psychosis and autism. Fructose inhibits brain plasticity. Fructose inhibits the ability of neurons to communicate with each other. The wiring and re-wiring of neurons is inhibited. Fructose leads to a neuronal disconnection syndrome.

Fructose can increase flux via the pentose phosphate pathway and hexosamine pathway leading to glycosaminoglycan synthesis. Glycosaminoglycan accumulation in the tissues can produce mucopolysaccharidosis and fibrosis. Increased heparan sulphate accumulation in the brain leads to formation of amyloids plaques and Alzheimer's disease. Connective tissue accumulation in the lung leads to interstitial lung disease, in the kidneys it produces tubular atrophy and a chronic renal failure similar to meso-American nephropathy. Connective tissue accumulation in the heart can lead to a restrictive cardiomyopathy. Accumulation of GAG especially hyaluronic acid in bones and joints leads to osteoarthritis and spondylosis. GAG accumulation in the endocrine organs can produce thyroid dysfunction resulting in MNG and thyroiditis, pancreatic dysfunction producing chronic calcific pancreatitis and adrenal dysfunction producing hypoadrenalism. Accumulation of GAG in the vascular tissues can result in mucoid angiopathy contributing to coronary artery disease and stroke. The accumulation of lipids due to the fructolytic pathway along with glycosaminoglycans can lead to fatty liver. This can later lead onto cirrhosis of the liver. Fructose is the principal culprit for fatty liver and cirrhosis. The glycine synthesized from the fructolytic intermediate phosphoglycerate can play a role inhibiting fatty liver. There is an epidemic of chronic renal failure due to tubular fibrosis, mucoid angiopathic vascular diseases, cardiomyopathy, multiple endocrine failures, cirrhosis of the liver, interstitial lung disease, degenerative bone and joint diseases and degenerative brain disease like Alzheimer's disease and Parkinson's disease as a consequence of global warming.

The increasing growth of archaea results in increased secretion of archaeal RNA viroids. They can interrupt mRNA function and dysregulates cell metabolism. This is by the mechanism of mRNA blockade. The viroidal RNA can combine with proteins generating prion proteins. This produces a protein conformation defect. This produces a prion protein disease. Abnormal protein conformation of beta amyloid, alpha synuclein, ribonuceloproteins, islet associated amyloid polypeptide and tumour suppressor protein can lead to an epidemic of Alzheimer's disease due to beta amyloid accumulation, alpha synuclein accumulation producing Parkinson's disease, prion like ribonucleoproteins producing motor neuron disease, metabolic syndrome X due to defective insulin secretion as a result of IAPP and abnormal prion like tumour suppressor protein producing tumours. These prion diseases induced by archaeal RNA viroids are also transmissible. Thus global warming related fructolysis leads to archaeal induced RNA viroidal mediated prion disease and amyloidosis. This raises the spectacle of a Cassandra syndrome of human extinction.

Fructose is phosphorylated to fructose 1-phosphate by ketohexokinase C or fructokinase. Fructose 1-phosphate is converted to glyceraldehyde which is then converted to glyceraldehyde 3-phosphate and dihydroxy acetone phosphate (DHAP). Fructose 1-phosphate is cleaved to DHAP and glyceraldehyde 3-phosphate. DHAP can enter the glycolytic pathway or can go to gluconeogenetic pathway. DHAP generated from fructose 1-phosphate by the action of aldolase B is acted upon by triose phosphate isomerase converting it into glyceraldehydes 3-phosphate. Glyceraldehyde 3-phosphate can be fructolysed to pyruvate and acetyl CoA. Acetyl CoA can be used for cholesterol synthesis for storage. The pyruvate generated from glyceraldehydes 3-phosphate can be converted to the citrate which can be used for fatty acid synthesis by the action of enzymes acetyl CoA carboxylase, fatty acid synthase and malonate dehydrogenase. Glyceraldehyde is acted upon by alcohol

dehydrogenase which converts it into glycerol. Glycerol is acted upon by glycerolkinase converting it into glycerol phosphate used for phosphoglyceride and triglyceride synthesis. Glyceraldehyde can also be acted upon by triokinase converting it into glyceraldehydes 3-phosphate which is then converted to DHAP by triose phosphate isomerase. Glyceral phosphate and dihydroxy acetone phosphate are interconvertible by the action of the enzyme glycerol phosphate dehydrogenase. Glycerol and fatty acids generated by fructolysis contribute to lipid synthesis and fat is stored. Fructose does not increase insulin secretion and doesn't need insulin for transport into the cell. Fructose is transported by the fructose transporter GLUT 5. Ketohexokinase C is exclusively seen in the liver which is the principal site of fructose metabolism. In the presence of hypoxia and anerobic states, there is induction of HIF alpha which can induce ketohexokinase C or fructokinase in the liver, kidney, gastrointestinal tract, brain and heart. Fructose 1-phosphate bye-passes the enzyme phosphofructokinase which is the key regulatory enzyme the glycolytic pathway. Phosphofructokinase is inhibited by ATP and citrate. Thus stress induced fructolysis is an unregulated pathway not amenable to metabolic switches. Fructose does not depend upon insulin for its transport and fructolysis. Therefore fructolysis is not under insulin or endocrine control. It is an unregulated pathway.

The phosphorylation of fructose depletes the cell of ATP. Ketohexokinases preferentially phosphorylate fructose over glucose if it is available. In the presence of redox stress, osmotic stress and archaea/viroids aldose reductase is induced converting all the glucose to fructose. Glycolytic pathway comes to a halt as no ATP is available for phosphorylation of glucose and glucose as such gets converted to fructose. The fructose phosphorylation depletes the cell of ATP. ATP is converted to ADP and AMP which is deaminated to produce uric acid. Fructose increases flux in the pentose phosphate pathway increasing

nucleic acid synthesis. Purine degradation results in hyperuricemia. Thus fructolysis results in increase in uric acid accumulation in the body. Uric acid will suppress the mitochondrial oxidative phosphorylation as well as produce endothelial dysfunction. The depletion of ATP by fructose phosphorylation results in membrane sodium potassium ATPase inhibition. This results in reduced energy needs of the cell as 80% of the ATP generated by metabolism is used for maintaining the sodium potassium pump. This results in membrane ATPase inhibition generated hibernatory state. The glyceraldehydes 3-phosphate generated by fructolysis can be converted to the pyruvate and acetyl CoA used for cholesterol synthesis. The cholesterol that is synthesized is used for digoxin synthesis. Digoxin also has got aglycone part which contains sugars like digitoxose and rhamnose. Digitoxose and rhamnose are generated by the fructose induced flux and upgradation of the pentose phosphate pathway. Thus fructolysis results in a hyperdigoxinemic state and membrane sodium potassium ATPase inhibition. This results in cell protection and hibernation.

Fructose produces flux along the pentose phosphate pathway and hexosamine pathway. This results in GAG and nucleic acid synthesis. Fructose is converted to fructose 1-phosphate which is then converted to ribulose 5-phosphate. Ribulose 5-phosphate is acted upon by an isomerase converting it into xylulose 5-phosphate and ribose 5-phosphate. Xylulose 5-phosphate and ribose 5-phosphate interact to produce glyceraldehydes 3-phosphate and sedoheptulose 7-phosphate which is then converted to fructose 6-phosphate and erythrose 4-phosphate. The pentose phosphate pathway generates ribose for nucleic acid synthesis. The pathway also generates hexosamines for GAG synthesis. The pentose phosphate pathway also produces digitoxose and rhamnose for digoxin synthesis.

The global warming results in endosymbiotic archaeal growth. Archaea can induce aldose reductase which converts glucose to fructose. Fructolysis

promotes flux along the pentose phosphate pathway generating nucleic acids and glycosaminoglycans. Fructolysis also generates glyceraldehydes 3-phosphate and further pyruvate. The pyruvate can enter the pyruvate carboxylase scheme generating gluconeogenesis and glycogen synthesis. Thus fructolysis can produce glycogen storage. Pyruvate can be converted to citrate for lipid synthesis. Pyruvate can also be converted to acetyl CoA for cholesterol synthesis. The flux along the pentose phosphate pathway generates the digoxin sugars, digitoxose and rhamnose. Cholesterol can be converted to digoxin producing a hyperdigoxinemic state. Digoxin produces membrane sodium potassium ATPase inhibition. The selective phosphorylation of fructose by fructokinase depletes the cell of ATP producing membrane sodium potassium ATPase inhibition. This results in the generation of a hibernatory state. The fructolysis generated pyruvate can get converted to glutamate which can enter the GABA shunt pathway producing succinyl CoA and glycine for porphyrin synthesis. Porphyrins can form self replicating porphyrions or act as a template for the formation of RNA viroids, DNA viroids and prions which can symbiose to form archaea. Thus the archaea are capable of self replicating on porphyrin templates. The fructolysis thus produces a hibernatory syndrome with fat, glycogen and nucleic acid synthesis and storage. Fructolysis results in the generation of a hibernatory species, the homo neanderthalis. The fructolysis generated membrane sodium potassium ATPase inhibition results in cell hibernation and ATP sparing. The lack of ATP and digoxin induced membrane sodium potassium ATPase inhibition results in cortical inhibition and cerebellar dominance. This produces a somnolent state and a cerebellar cognitive affective disorder. The porphyrions generated by fructolysis produces quantal perception and cerebellar dominance. The storage of glycogen, fat and GAG results in obesity. The cerebellar cognitive affective syndrome results in a hypersexual state. The fructolysis and fructose can activate NFKB producing immune

activation. The fructosylation of glycolytic and mitochondrial proteins suppresses the body's normal energetic which depends upon glycolysis and mitochondrial oxidative phosphorylation. Fructosylation of proteins results in blockade of glycolysis and mitochondrial oxidative phosphorylation. The body's energy needs are produced by fructolysis, porphyrin array mediated electron transport chain and ATP synthesis as well as membrane sodium potassium ATPase inhibition relation ATP synthesis. This produces a new species by archaeal symbiosis consequent to global warming - the homo neanderthalis. This can be called as the tropical hibernatory syndrome consequent to global warming.

This can be called also as a fructose disease. Endosymbiotic archaea and viroids induce aldose reductase and converts body glucose to fructose leading to preferential fructose phosphorylation by ketohexokinase C. Fructolysis results in fructose 1-phosphate being acted upon by aldolase B resulting in the formation of glyceraldehyde and dihydroxy acetone phosphate. Glyceraldehyde can be converted to glyceraldehyde 3-phosphate and this contributes to pyruvate formation. Pyruvate enters the GABA shunt resulting in the formation of succinyl CoA and glycine. They are substrates for porphyrin synthesis and porphyrion formation. The porphyrins form a template for the formation of RNA viroids, DNA viroids, prions, isoprenoids and polysaccharides. They can symbiose together to form primitive archaea. The archaea can further induce HIF alpha, aldose reductose and fructolysis resulting in further porphyrinogenesis and archaeal self replication. The archaea by methanogenesis contributes to global warming which leads to further archaeal growth and a vicious cycle with no regulatory switches. The fructolytic pathway induced by archaea by-passes regulatory enzyme phosphofructokinase and is practically unregulated. Fructolytic pathway contributes to glycogen, lipids, cholesterol, hexose sugars and mucopolysaccharides synthesis and storage. This leads onto a

hibernatory state and archaeal symbiosis induced species change resulting in neanderthalisation of the homo sapien species. The digoxin and fructose phosphorylation induced ATP depletion leads to membrane sodium potassium ATPase inhibition, sparing of ATP and tissue hibernation as most of the energy needs of the body are for the working of the sodium potassium pump. The cholesterol that is synthesized by fructolysis is catabolized cholesterol oxidases for archaeal energetics. Archaea also derives its energy from a primitive form of electron transport chain functioning in self replicating porphyrin arrays. The archaeal digoxin induced sodium potassium ATPase inhibition can lead to membrane ATP synthesis. The archaea and the new human species phenotype derive its energy from the above mentioned mechanism. The glycolytic enzymes and the mitochondrial PT pore hexokinase are fructosylated making them dysfunction. The fructosylated glycolytic enzymes lead to generation of antiglycolytic enzyme antibodies and disease states. The human body's principal method of energetics tissue glycolysis and oxidative phosphorylation comes to a grinding halt. The human body is taken over by the overgrowth of endosymbiotic archaea and assumes hibernatory state with accumulation of glycogen, lipids, mucopolysaccharides and nucleic acids. The catabolic pathways for energy generation related to glucose, glycolysis and oxphos scheme stops. The human body can depend upon ketogenesis from fat and proteins. The upregulated fructolytic pathway generates phosphoglycerate which converted to phosphoserine and glycine. They can be converted to other amino acids and used for ketogenesis. The body assumes a high BMI index and obesity with visceral fat storage and adiposity akin to the Neanderthal metabolic phenotype. Digoxin induced membrane sodium potassium ATPase inhibition results in cortical dysfunction. The brain porphyrins can form a quantal pumped phonon system resulting in quantal perception and low level EMF absorption. This leads to prefrontal cortex atrophy and cerebellar dominance. Fructose itself

leads to sympathetic hyperactivity and parasympathetic blockade. This leads onto a functional form of cerebellar cognition and quantal perception resulting in a new brain phenotype. The cerebellar cognitive syndrome leads to a robotic human phenotype. The phenotype is impulsive, has extrasensory perception and has less of speech production. Communication is by symbolic acts. The cerebellar phenotype doesn't have a cortical control and contributes to surrealistic behavior patterns. This produces impulsive behavior and an epidemic of surrealism where the rational prefrontal cortex becomes extinct. This leads to extremes of spirituality, violent and terroristic behavior and hypersexual states contributing to a state of trancedence underlined and reinforced by quantal perception. Cerebellar phenotype owing to its quantal perception behaves as a community and not as an individual. This creates new social and psychological phenotypes. Fructose induces NFKB and immune activation. This results in an immune activatory phenotype. Cultured T-reg cells on high fructose diet have 62% less IL-40 secretion than controls. This results in a hyperimmune state with fructosylated proteins acting as antigens. The fructolytic pathway can lead to increased DNA synthesis and RNA synthesis due to flux via the pentose phosphate pathway. The fructolytic pathway can be directed to the GABA shunt generating succinyl CoA and glycine. These are substrates for porphyrin templates to form RNA viroids. The archaeal induced redox stress can induce endogenous HERV expression and reverse transcriptase expression. The RNA viroids are converted by HERV reverse transcriptase to corresponding DNA and integrated into the genome by HERV integrase. The integrated RNA viroid related DNA can function as jumping genes producing genomic plasticity and genomic change. This produces a new genotype. Fructosylation of body proteins and enzymes results in a protein processing defect resulting in loss of protein function. The human cell function due to protein fructosylation, protein processing defects and protein conformational

defects comes to a grinding halt. Fructolytic pathway generates porphyrin arrays induced ATP production, membrane sodium potassium ATPase inhibition induced ATP synthesis and fructolysis induced ATP generation. This provides energy for porphyrin template induced archaeal replication. The digoxin and fructose phosphorylation induced ATP depletion produces cell membrane sodium potassium ATPase inhibition and a hibernatory state. This leads onto a somnolent sleepy state. The cholesterol catabolism by cholesterol oxidases for archaeal energetics leads to defective sex hormone synthesis. This leads onto an asexual androgynous state. The cerebellar cognitive syndrome due to prefrontal cortical atrophy consequent to porphyrion induced low level EMF perception produces a hypersexual state. This results in male-female equidominance and changes in sexual behavior of the population. Thus the fructose disease consequent to global warming results in a new neuronal, immune, metabolic, sexual and social phenotype. The human body is converted to a zombie for the global warming related endosymbiotic archaea to thrive. The neuronal, metabolic, sexual and social phenotype creates the necessary environment endosymbiotic archaeal multiplication and the human body is converted to a zombie phenotype. This can be called as a hibernatory zombie syndrome. Due to the new sexual and social phenotype with asexuality and hypersexuality and female-male equidominance the human population falls. The global warming and archaeal induction of HIF alpha resulting in the Warburg phenotype leads to changes in the metabolic scheme of the cells producing body cell transformation to stem cells. The stem cells depend upon glycolysis or fructolysis for energy needs. The Warburg phenotype produces an acidic pH which can result in conversion of body cells to stem cells. The stem cells conversion results in loss of tissue function. The cerebral cortex synaptic connectivity is lost and becomes dysfunction leading to subcortical cerebellar dominance. The immune stem cells proliferate producing an autoimmune disease. The various tissue cells the

specialized function like neuron, nephron and muscle cell all because of stem cell conversion becomes dysfunctional. This produces a stem cell syndrome with human somatic cells being converted to stem cells with loss of function and uncontrolled proliferation. The fructosylation of proteins results in protein function defects. The fructosylation of LDL results in defective cholesterol transport to the cells. This results in steroidal hormone synthesis defects. Cholesterol is required for formation of synaptic connectivity and this leads to cerebral cortical dysfunction. The hemoglobin becomes fructosylated and oxygen transport is affected. This leads to hypoxia and anerobic states. The hypoxia and anerobic states induces HIF alpha and the Warburg fructolytic phenotype. The HIF alpha also induces aldose reductase converting glucose to fructose and inducing the fructolytic scheme. The fructolysis induced GABA shunt pathway and porphyrin synthesis results in further archaeal porphyrin template related replication. This results in further archaeal induced fructolysis and the vicious irreversible cycle proceeds. The uncontrolled growth of archaea leads to still further global warming. The world of endosymbiotic eternal archaea takes over and persists during the extremophilic climatic changes of global warming. The human beings exist as neanderthalic zombies serving archaeal multiplication. The homo sapiens gets converted to a new phenotype, genotype, immunotype, metabolonomic type and brain type. This is called as hibernatory zombie related to global warming - homo neoneanderthalis.

Table 1

	Serum fructose		Serum fructokinase		Aldolase B		Total GAG	
	Mean	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**
Normal	2.50	0.195	8.50	0.405	3.50	1.304	3.50	0.707
Cirrhosis	32.53	6.737	23.00	1.722	10.49	1.373	20.57	1.878
IBD	31.75	5.236	21.89	2.292	11.63	1.304	22.46	4.030
MAO	31.53	4.507	22.07	2.324	11.32	1.343	23.89	2.936
IBS	29.90	4.299	22.52	1.995	10.93	1.498	22.09	2.797
PUD	32.49	6.487	21.89	3.431	10.85	1.606	25.27	3.693
F value	17.373		13.973		13.903		21.081	
p value	< 0.01		< 0.01		< 0.01		< 0.01	

Table 2

	Total TG		Serum ATP levels		Uric acid		Anti-aldolase	
	Mean	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**
Normal	124.00	3.688	2.50	0.405	5.70	0.369	7.50	1.704
Cirrhosis	271.80	37.818	0.79	0.150	8.12	0.747	1.67	0.377
IBD	287.50	20.414	0.77	0.102	9.44	0.924	1.30	0.223
MAO	316.20	31.283	0.76	0.103	9.32	0.864	1.41	0.307
IBS	279.10	27.606	0.77	0.095	9.68	1.060	1.44	0.350
PUD	285.70	22.628	0.76	0.126	9.77	0.957	1.14	0.134
F value	16.378		59.169		14.166		55.173	
p value	< 0.01		< 0.01		< 0.01		< 0.01	

Table 3

	Anti-enolase		Anti-pyruvatekinase		Anti-GAPDH	
	Mean	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**
Normal	1.50	0.358	50.40	5.960	5.20	0.363
Cirrhosis	0.48	0.273	18.60	2.915	1.52	0.287
IBD	0.43	0.163	17.06	4.366	1.40	0.298
MAO	0.44	0.230	19.08	3.396	1.48	0.220
IBS	0.57	0.242	19.99	2.637	1.39	0.289
PUD	0.51	0.221	20.63	5.116	1.42	0.329
F value	14.091		21.073		58.769	
p value	< 0.01		< 0.01		< 0.01	

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2

Global Warming Induced Actinidic Archaea and Viroids Related Chronic Gastrointestinal 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 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 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 multicellular eukaryote.

Pollution is induced by the primitive nanoarchaea and mevalonate pathway bacteria synthesized 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 T_4 to T_3. T_3 activates uncoupling proteins reducing redox stress. Bile acids can also activate NRF½ 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 gastrointestinal and liver disease.

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3

Fructolysis, Archaeal Digoxin, Cerebral Dominance and Regulation of Gastrointestinal Function

Introduction

Global warming induces a genomic change in humans. Global warming induces endosymbiotic archaeal and RNA viroidal growth. The porphyrins form a template for the formation of RNA viroids, DNA viroids, prions, isoprenoids and polysaccharides. They can symbiose together to form primitive archaea. The archaea can further induce HIF alpha, aldose reductose and fructolysis resulting in further porphyrinogenesis and archaeal self replication. The primitive archaeal DNA is integrated along with RNA viroids which are converted to their corresponding DNA by the action of redox stress induced HERV reverse transcriptase into the human genome by the redox stress induced HERV integrase. The archaeal DNA sequences that are integrated into the human genome forms endogenous archaeal human genomic sequences akin to HERV sequences and can function as jumping genes regulating genomic DNA flexibility. The integrated endogenous genomic archaeal sequences can get expressed in the presence of redox stress forming endosymbiotic archaeal particles which can function as a new organelle called the archaeaons. The archaeaon can express the fructolytic pathway constituting an organelle called the fructosome, cholesterol catabolic pathway and digoxin synthetic forming an organelle called the steroidelle, the shikimic acid pathway forming an organelle called the neurotransminoid, antioxidant vitamin E and vitamin C synthetic organelle called the vitaminocyte as well as the glycosaminoglycan synthetic organelle called glycosaminoglycoid. The archaeaon secreting RNA viroids is called the viroidelle.

The increase in endogenous EDLF, a potent inhibitor of membrane Na^+-K^+ ATPase, can decrease this enzyme activity. The results showed increased endogenous EDLF synthesis as evidenced by increased HMG CoA reductase activity, which functions as the rate limiting step of the isoprenoid pathway. Studies in our laboratory have demonstrated that EDLF is synthesized by the

isoprenoid pathway. The endosymbiotic archaeal sequences in the human genome get expressed by redox stress and osmotic stress of global warming. This results in induction of HIF alpha which will upregulate fructolysis and glycolysis. In the setting of redox stress all glucose gets converted to fructose by the induction of enzymes aldose reductase and sorbitol dehydrogenase. Aldose reductase converts glucose to sorbitol and sorbitol dehydrogenase converts sorbitol to fructose. Since fructose is preferentially phosphorylated by ketohexokinases the cell is depleted of ATP and glucose phosphorylation comes to a halt. Fructose becomes the dominant sugar that is metabolized by fructolysis in expressed archaeal particles in the cell functioning as organelle called fructosoids. The fructose is phosphorylated to fructose 1-phosphate which is acted upon by aldolase B which converts it into glyceraldehyde 3-phosphate and dihydroxy acetone phosphate. Glyceraldehyde 3-phosphate is converted to D 1,3-biphosphoglycerate which is then converted to 3-phosphoglycerate. The 3-phosphoglycerate is converted to 2-phosphoglycerate. 2-phosphoglycerate is converted to phosphoenol pyruvate by the enzyme enolase. Phosphoenol pyruvate is converted to pyruvate by the enzyme pyruvic kinase. The archaeaon induces HIF alpha which upregulates fructolysis and glycolysis but inhibits pyruvate dehydrogenase. The forward metabolism of pyruvate is stopped. The dephosphorylation of phosphoenol pyruvate is inhibited in the setting of pyruvic kinase inhibition. Phosphoenol pyruvate enters the shikimic acid pathway where it is converted to chorismate. The shikimic acid is synthesized by a pathway starting from glyceraldehyde 3-phosphate. Glyceraldehyde 3-phosphate combines with the pentose phosphate pathway metabolite sedoheptulose 7-phosphate which is converted to erythrose 4-phosphate. The pentose phosphate pathway is upregulated in the presence of the suppression of glycolytic pathway. Erythrose 4-phosphate combines with phosphoenol pyruvate to generate shikimic acid. Shikimic acid combines with

another molecule of phosphoenol pyruvate to generate chorismate. The chorismate is converted to prephenic acid and then to parahydroxy phenyl pyruvic acid. Parahydroxy phenyl pyruvic acid is converted to tyrosine and tryptophan as well as neuroactive alkaloids. The shikimic acid pathway is structured in expressed archaeaon organelle called the neurotransminoid. The fructolytic intermediates glyceraldehydes 3-phosphate and pyruvate are the starting points of the DXP pathway of cholesterol synthesis. Glyceraldehyde 3-phosphate combines with pyruvate to form 1-deoxy D-xylulose phosphate (DOXP) which is then converted to 2-C methyl erythritol phosphate. 2-C methyl erythritol phosphate can be synthesized from erythrose 4-phosphate a metabolite of the shikimic acid pathway. DXP combines with MEP to form isopentenyl pyrophosphate which is converted to cholesterol. Cholesterol is catabolised by archaeal cholesterol oxidases to generate digoxin. The digoxin sugars digitoxose and rhamnose are synthesized by the upregulated pentose phosphate pathway. Glycolytic suppression leads to upregulation of the pentose phosphate pathway. The expressed archaeaon organelle concerned with cholesterol catabolism and digoxin synthesis is called the steroidelle. The suppression of glycolysis and stimulation of fructolysis results in upregulation of the hexosamine pathway. Fructose is converted to fructose 6-phosphate by ketohexokinases. The fructose 6-phosphate is converted to glucosamine 6-phosphate by the action of glutamine fructose 6-phosphate amidotransferase (GFAT). Glucosamine 6-phosphate is converted to UDP N-acetyl glucosamine which is then converted to N-acetyl glucosamine and various amino sugars. UDP glucose is converted to UDP D-glucuronic acid. UDP D-glucuronic acid is converted to glucuronic acid. This forms the uronic acid synthetic pathway. Uronic acids and hexosamines form repeating units of glycosaminoglycans. In the setting of glycolytic suppression and fructolytic metabolism fructolysis leads to increase synthesis of hexosamines and GAG synthesis. The GAG

synthesizing archaeaon particles are called the glycosaminoglycoids. The expressed archaeaon particles are capable of synthesizing antioxidant vitamin C and E. The UDP D-glucose is converted to UDP D-glucuronic acid. UDP D-glucuronic acid is converted to D-glucuronic acid. D-glucuronic acid is converted to L-gulonate by enzyme aldoketo reductases. L-gulonate is converted to L-gulonolactone by lactonase. L-gulonolactone is converted to ascorbic acid by the action of archaeal L-Gulo oxidase. The vitamin E is synthesized from shikimate which is converted to tyrosine and then to parahydroxy phenyl pyruvic acid. Parahydroxy phenyl pyruvic acid is converted to homogentisate. Homogentisate is converted to 2-methyl 6-phytyl benzoquinone which is converted to alpha tocopherol. 2-methyl 6-phytyl benzoquinone is converted to 2,3-methyl 6-phytyl benzoquinone and gamma tocopherol. Vitamin E can also be synthesized by the DXP pathway. Glyceraldehyde 3-phosphate and pyruvate combined to form 1-deoxy D-xylulose 5-phosphate which is converted to 3-isopentenyl pyrophosphate. 3-isopentenyl pyrophosphate and dimethyl allyl pyrophosphate combined to form 2-methyl 6-phytyl benzoquinone which is converted to tocopherols. The ubiquinone another important membrane antioxidant and part of the mitochondrial electron transport chain is synthesized by the shikimic acid pathway and DXP pathway. The isoprenoid moiety of ubiquinone is contributed from the DXP pathway and the rest of it by tyrosine catabolism. The tyrosine is generated by the shikimic acid pathway. The archaeaon particles concerned with the synthesis of vitamin C, vitamin E and ubiquinone which are all antioxidants are called the vitaminocyte.

The isoprenoid pathway is a key regulatory pathway in the cell. It produces cholesterol, an important component of cellular membranes. Dolichol is important in N-glycosylation of proteins and glycoprotein biosynthesis. Digoxin is an endogenous membrane Na^{+}-K^{+} ATPase inhibitor crucial in regulation of

synaptic transmission. Membrane Na^+-K^+ ATPase inhibition can lead to altered CD_4/CD_8 ratios an immune activation. Ubiquinone is a component of the mitochondrial electron transport chain.

Persistent helicobacter pylori infection, disordered histaminergic / cholinergic transmission and altered gastric mucoprotein secretion are important in the pathogenesis of peptic ulcer disease. Altered NMDA, dopaminergic, serotoninergic and cholinergic transmission have been implicated in the pathogenesis of IBS. In patients with IBD there are reports of the isolates of cell wall variants of Pseudomonas suggesting an infectious etiology for the disease. Patients with IBD have humoral antibodies to colon cells, to bacterial antigens such as E. coli, to lipopolysaccharide, and to foreign proteins such as cow's milk protein. Immune complexes also have been invoked to explain extraintestinal manifestations of IBD. Many abnormalities of cell-mediated immunity in the mucosa of patients with IBD have also been described. Membrane Na^+-K^+ ATPase inhibition can lead to an increase in intracellular calcium and a reduction in intracellular magnesium. Alteration in intracellular calcium/magnesium ratios can lead to vasospasm and mesenteric artery ischemia. Gallstones may occur in association with obesity and with increased activity of HMG CoA reductase the rate limiting enzymes of hepatic cholesterol synthesis. During micellation of vesicles, more phospholipid than cholesterol is transferred to mixed micelles, leading to unstable cholesterol - rich vesicles that aggregate into larger multilamellar vesicles from which cholesterol crystals aggregates. Nonmucin and mucin glycoproteins and lysine phosphatidyl choline appears to be pronucleating factors, while apolipoproteins AI and AII and other glycoproteins are antinucleating factors. Biliary sludge can develop with disorders that cause gall bladder hypomotility. The dolichol pathway is important in the connective tissue metabolic alterations of liver cirrhosis. The cholesterol pathway and lipoprotein synthesis can contribute to the genesis of fatty liver important in cirrhosis.

Digoxin can also modulate tryptophan and tyrosine transport. Tyrosine can contribute to the synthesis of endogenous morphine important in alcoholic addiction and tryptophan can generate quinolinic acid, important in the pathogenesis of hepatic encephalopathy. Altered mitochondrial function has been reported to contribute to Reye's syndrome.

Since digoxin can regulate multiple neurotransmitter systems it could also play a role in the genesis of hemispheric dominance. Hemispheric dominance has been related to systemic diseases. It was therefore considered pertinent to study the isoprenoidal pathway and its metabolites in gastrointestinal/hepatic disease as well as in individuals with differing hemispheric dominance to correlate changes in the isoprenoid pathway with hemispheric dominance and the pathogenesis of gastrointestinal/liver disease.

Materials and Methods

Nine sets of patients were chosen for the study. (1) 15 cases of acid peptic disease, (2) 15 cases of ulcerative colitis, (3) 15 cases of irritable bowel syndrome, (4) 15 cases of mesenteric artery occlusion, (5) 15 cases of patients with gallstones, (6) 15 cases of cryptogenic cirrhosis liver, (7) 15 cases of Reye's syndrome, (8) 15 cases of age and sex matched bihemispheric dominant controls, (9) 15 cases each of right hemispheric, left hemispheric and bihemispheric dominant individuals diagnosed by the dichotic listening test. The patient population's age ranged from 50 to 70 years. None of the subjects studied under medication at the time of removal of blood. All subjects included in the study were non-smokers (active or passive). Fasting blood was removed in citrate tubes from each of the number of patients mentioned above. RBCs were separated within one hour of collection of blood for the estimation of membrane Na^+-K^+ ATPase. Plasma was used for the analysis of various parameters. The methodology used in the study was as follows: All

biochemicals used in this study were obtained from M/s Sigma Chemicals, USA. Activity of HMQ CoA reductase of the plasma was determined by the method of Rao and Ramakrishnan by determining the ratio of HMG CoA to mevalonate. For the determination of the RBC Na^{+}-K^{+} ATPase activity of the erythrocyte membrane, the procedure described by Wallach and Kamat was used. Digoxin in the plasma was determined by the procedure described by Arun et al. For estimation of ubiquinone and dolichol in the plasma, the procedure described by Palmer et al. was used. Magnesium in the plasma was estimated by atomic absorption spectrophotometry. Tryptophan, tyrosine, serotonin and catecholamines were estimated by the procedures described in methods of biochemical analysis. Quinolinic acid content of plasma was estimated by HPLC (C_{18} column micro Bondapak^{TM} 4.6 x l50 mm), solvent system 0.01 M acetate buffer (pH 3.0) and methanol (6:4), flow rate 1.0 ml/minute and detection UV 250 nm). Morphine, strychnine and nicotine were estimated by the method described by Arun et al. Statistical analysis was done by 'ANOVA'.

Results

(1) The results showed that HMG CoA reductase activity, serum digoxin and dolichol were increased in IBD, mesenteric artery occlusion, APD, IBS, cirrhosis liver, gallstones and Reye's syndrome indicating upregulation of the isoprenoid pathway but serum ubiquinone, RBC membrane Na^{+}-K^{+} ATPase activity and serum magnesium were reduced.

(2) The results showed that the concentration of tryptophan, quinolinic acid, serotonin, strychnine and nicotine was found to be higher in the plasma of patients with IBD, mesenteric artery occlusion, APD, IBS, cirrhosis liver, gallstones and Reye's syndrome while that of tyrosine, dopamine, norepinephrine and morphine was lower.

(3) The concentration of total GAG increased in the serum of the patient group. The concentration of hyaluronic acid (HA), heparan sulphate (HS), heparin (H), dermatan sulphate (DS) and chondroitin sulphates (ChS) were increased in the patient groups. The concentration total hexose, fucose and sialic acid were increased in the glycoproteins of the serum in the patient groups.

(4) The activity of GAG degrading enzymes beta glucuronidase, beta N-acetyl hexosaminidase, hyaluronidase and cathepsin-D, were increased in the patient groups when compared to the controls. The activity of beta galactosidase, beta fucosidase and beta glucosidase increased in the patient groups.

(5) The concentration of total GAG, hexose and fucose in the RBC membrane decreased significantly in the patient groups. The concentration cholesterol increased and phospholipids decreased in the RBC membrane in the patient group and the cholesterol: phospholipid ratio in the RBC membrane increased significantly.

(6) The activity of superoxide dismutase (SOD), catalase, glutathione reductase and glutathione peroxidase in the erythrocytes decreased significantly in the patient groups. In the patient group the concentration of MDA, hydroperoxides, conjugated dienes and NO increased significantly. The concentration of reduced glutathione decreased in the patient groups.

(7) The results showed that HMG CoA reductase activity serum digoxin and dolichol were increased and ubiquinone reduced in left handed/right hemispheric dominant individuals. The results showed that HMG CoA reductase activity serum digoxin and dolichol were decreased and ubiquinone increased in right handed/left hemispheric dominant individuals. The results showed that the concentration of tryptophan,

quinolinic acid serotonin, strychnine and nicotine was found to be higher in the plasma of left handed/right hemispheric dominant individuals while that of tyrosine, dopamine, morphine and norepinephrine was lower. The results showed that the concentration of tryptophan, quinolinic acid serotonin, strychnine and nicotine was found to be lower in the plasma of right handed / left hemispheric dominant individuals while that of tyrosine, dopamine, morphine and norepinephrine was higher.

Discussion

Archaeal Digoxin and Membrane Na^+-K^+ ATPase Inhibition in Relation to GI / Hepatic Disease

The archaeaon steroidelle DXP pathway and the upregulated pentose phosphate pathway contribute to digoxin synthesis. In peptic ulcer disease there was significant inhibition of the RBC membrane Na^+-K^+ ATPase. The inhibition of Na^+-K^+ ATPase by EDLF is known to cause an increase in intracellular calcium resulting from increased Na^+-Ca^{++} exchange, increased entry of Ca^{++} via the voltage gated calcium channel and increased release of Ca^{++} from intracellular endoplasmic reticulum Ca^{++} stores. This increase in intracellular Ca^{++} by displacing Mg^{++} from its binding sites, causes a decrease in the functional availability of Mg^{++}. This decrease in the availability of Mg^{++} can cause decreased mitochondrial ATP formation which along with low Mg^{++} can cause further inhibition of Na^+-K^+ ATPase, since ATP-Mg^{++} complex is the actual substrate for this reaction. Cytosolic free calcium is normally buffered by two mechanisms, ATP dependent calcium extrusion from cells and ATP dependent sequestration of calcium within the endoplasmic reticulum. The intracellular Mg^{++} depletion related mitochondrial dysfunction results in defective calcium extrusion from the cell. There is thus a progressive inhibition of Na^+-K^+ ATPase activity first triggered by EDLF. Low intracellular Mg^{++} and

high intracellular Ca^{++} consequent to Na^{+}-K^{+} ATPase inhibition appear to be crucial to the pathophysiology of IBD, mesenteric artery occlusion, APD, IBS, cirrhosis liver, gallstones and Reye's syndrome. The intracellular positive Ca^{++} signal and negative Mg^{++} signal can regulate diverse cellular process. Ca^{++} on entry into the cell is used to charge up the internal endoplasmic reticulum stores which then release a burst of signal calcium responsible for activating a large variety of calcium dependent cellular processes. The information processing capability of the calcium signalling system is enhanced by amplitude and frequency modulation. The Ca^{++} is released from channels on internal ER individually or in small groups (blip/quark and puffs/sparks). Further diversity of calcium signalling is produced by compartmentalization as cytosolic calcium signal and nuclear calcium signal. Serum Mg^{++} was assessed in IBD, mesenteric artery occlusion, APD, IBS, cirrhosis liver, gallstones and Reye's syndrome and was found to be reduced. Increased intracellular parietal cell calcium and reduced intracellular magnesium can lead on to increased gastric acid secretion. Increased intracellular calcium can also activate the G-protein coupled receptor - histamine, which can lead to increased gastric acid secretion. Increased intracellular calcium can activate the gastrin and acetyl choline related gastric acid secretion. Increased intracellular calcium in the presynaptic neuron can promote cholinergic transmission. The increased presynaptic neuronal Ca^{++} can produce cyclic AMP dependent phosphorylation of synapsins resulting in increased neurotransmitter release into the synaptic junction and vesicular recycling. This promotes cholinergic vagal transmission promoting acid secretion and peptic ulcer formation. Low intracellular magnesium and high intracellular calcium in the smooth muscle cell can contribute to the disorder of bowel motility in IBS. Calcium channel blockers have been used to treat IBS. Magnesium can promote biliary secretion and in the presence of hypomagnesemia there is stagnation of biliary secretion.

Increase in intracellular calcium can activate G-protein coupled angiotensin receptor producing hypertension and G-protein coupled thrombin receptor and platelet activating factor producing thrombosis observed in abdominal angina and ischaemic colitis. Na^+-K^+ ATPase inhibition related increased intracellular smooth muscle calcium and decreased intracellular magnesium can contribute to vasospasm and ischaemia observed in abdominal angina and ischaemic colitis. Morphine can act as a vasodilator and its deficiency could contribute to the vasospasm. Thus increased secretion of hypothalamic or endothelial digoxin could lead to acute vasospasm and thrombosis. Thus a neural dysfunction could contribute to abdominal angina and ischaemic colitis. Na^+-K^+ ATPase inhibition induced hypomagnesemia related altered glycoprotein and glycosaminoglycan synthesis can contribute to arteriosclerosis. Increased intracellular calcium can open up the mitochondrial PT pore producing endothelial cell mitochondrial dysfunction. This results in altered membrane fluidity of endothelium and increased permeability of endothelial cells to lipoprotein. Increased intracellular calcium within the endothelial cell leads to fragmentation of elastic membrane and calcification. Increased intracellular calcium produces configuration change in arterial elastin, exposing the elastin's hydrophobic sites resulting in increased cholesterol absorption. Increased calcium within the arterial wall alters elastin synthesis, turnover and composition. Decreased intracellular magnesium can produce dysfunction of lipoprotein lipase producing defective catabolism of triglyceride 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 and increased triglycerides, risk factors for vascular disease. Magnesium deficiency has been reported to increase LDL cholesterol levels also. Nicotine administration is known to produce vasospasm. It can also produce autonomic ganglionic stimulation, adrenal medullary stimulation and carotid/aortic body

stimulation leading to hypertension. Nicotine administration has also been reported to produce significant changes in lipid metabolism. There is increased tissue cholesterogenesis, decreased hepatic degradation of cholesterol and increased triglyceride synthesis. The uptake of circulating triglyceride rich lipoprotein is decreased as revealed by decreased activity of extra hepatic lipoprotein lipase. Plasma LCAT activity is also reduced on nicotine administration. HDL cholesterol is decreased while the LDL-VLDL cholesterol is increased. All this can contribute to the atherosclerosis predisposing to abdominal angina and ischaemic colitis. Intracellular magnesium deficiency can lead to protein tyrosine kinase dysfunction and an insulin receptor defect. Increase in intracellular calcium and reduction in intracellular magnesium can lead to increased secretion of insulin from the beta cell of the islet of Langerhans. This leads to hyperinsulinism. The vascular tissues remain sensitive to insulin. Hyperinsulinism by its mitogenic action on the vascular smooth muscle cell can contribute to mesenteric artery atherosclerosis.

The increased digoxin synthesis in Reye's syndrome is significant. Digoxin administration in experimental animals has been reported to lead to brain oedema and vacuolar changes in the brain. The refractory brain oedema in Reye's syndrome could be due to increased digoxin levels.

Archaeal Digoxin and Regulation of Neurotransmitter Synthesis and Function in Relation to GI / Hepatic Disease

The archaeaon neurotransminoid shikimic acid pathway contributes to tryptophan and tyrosine synthesis and catabolism generating neurotransmitters and neuroactive alkaloids. There is an increase in tryptophan and its catabolites and a reduction in tyrosine and its catabolites in the serum of patients with IBD, mesenteric artery occlusion, APD, IBS, cirrhosis liver, gallstones and Reye's syndrome. This could be due to the fact that EDLF can regulate neutral amino

acid transport system with a preferential promotion of tryptophan transport over tyrosine. The decrease in membrane Na^{+}-K^{+} ATPase activity in IBD, mesenteric artery occlusion, APR IBS, cirrhosis liver, gallstones and Reye's syndrome could be due to the fact that the hyperpolarising neurotransmitters (dopamine, morphine and noradrenaline) are reduced and the depolarising neuroactive compounds (serotonin, strychnine, nicotine and quinolinic acid) are increased. Membrane Na^{+}-K^{+} ATPase inhibition could lead to an increase in intracellular calcium and reduction in intracellular magnesium in the vascular smooth muscle and vasospasm. This could lead to mesenteric artery occlusion. This particular neurotransmitter pattern could contribute to gall bladder hypomotility. Biliary sludge can develop with disorders that cause gall bladder hypomotility. Increased levels of endogenous nicotine also promote acid secretion and peptic ulcer formation.

Glutamate excitotoxicity can result from membrane Na^{+}-K^{+} ATPase inhibition. In the presence of hypomagnesmia, the Mg^{++} block on the NMDA receptor is removed leading to NMDA excitotoxicty. The increased presynaptic neuronal Ca^{++} can produce cyclic AMP dependent phosphorylation of synapsins resulting in increased neurotransmitter release into the synaptic junction and vesicular recycling. Increased intracellular Ca^{++} in the post synaptic neuron can also activate the Ca^{++} dependent NMDA signal transduction. The plasma membrane neurotransmitter transporter (on the surface of the glial cell and presynaptic neuron) is coupled to a sodium gradient which is disrupted by the inhibition of Na^{+}-K^{+} ATPase, resulting in decreased clearance of glutamate by presynaptic and glial uptake at the end of synaptic transmission. By these mechanisms, inhibition Na^{+}-K^{+} ATPase can promote glutamatergic transmission. The elevated levels of quinolinic acid, strychnine and serotonin can also contribute to NMDA excitotoxicity. Strychnine displaces glycine from its binding sites and inhibits glycinergic inhibitory transmission in the brain. The

glycine is free to bind to the strychnine insensitive site of the NMDA receptor and promote excitatory NMDA transmission. Quinolinic acid and serotonin are also positive modulators of the NMDA receptor. Increased glutamatergic transmission resulting in excitotoxicity has been implicated in the pathogenesis of IBS. Sensory abnormalities including visceral hypersensitivity after sensitizing stimulation has been described in IBS and has been correlated with NMDA (N-methyl-D-aspartate) excitotoxicity. Excess cholinergic transmission has been implicated in the pathogenesis of IBS as indicated by the use of anti-cholinergic agents in its management. The excess endogenous nicotine levels consequent to its increased synthesis from tryptophan described here is significant. Nicotine can promote cholinergic transmission by binding to central and peripheral nicotinic cholinergic receptors. This is important in the pathogenesis of IBS. The increase in serotonin can contribute to altered bowel motility in IBS. Serotonin blockers are useful in the treatment of IBS. Increased serotoninergic transmission could be important in the pathogenesis of IBS. This could be due to increased synthesis of serotonin from tryptophan as demonstrated in the study. Reduced morphine and dopamine levels can also contribute to the pathogenesis of IBS. Studies have shown that there is endogenous synthesis of morphine from tyrosine and dopamine in the human brain. The reduced morphine levels noted in IBS could be due to its reduced synthesis from tyrosine and dopamine. Kappa and opioid agonist are useful in the treatment of bowel motility disorders. Dopamine receptor modulators have also been used to treat IBS. The dopamine deficiency demonstrated in IBS owing to its reduced synthesis from tyrosine is important in this context.

NMDA excitotoxicity is important in the pathogenesis of hepatocerebral degeneration. Reduced tyrosine levels can lead to reduced dopamine synthesis contributing to the extrapyramidal syndrome and reduced alertness of acquired hepatocerebral degeneration. The increased nicotine synthesis from tryptophan

is also significant. Nicotine can promote cholinergic transmission contributing to the tremor of acquired hepatocerebral degeneration. The low level of dopamine consequent to its reduced synthesis owing to decreased tyrosine level is significant with respect to the predisposition to alcoholic addiction. Low levels of dopamine in addicts can lead to inhibition of the mesolimbic-mesocortical dopaminergic system and substance abuse. The low tyrosine levels noted in these patients leads to reduced synthesis of morphine. Morphine activates the mesolimbic-mesocortical DA (dopaminergic) system. It is known that mu opioid agonist can excite VTA (ventral tegmental area) DA neurons by hyperpolarisation of local interneurons. In morphine deficiency there is inhibition of mesolimbic-mesocortical dopaminergic system. It should also be noted that there is a hypothesis that might link alcohol addiction to this system as well. Alcohol may induce alteration of the chemical disposition of dopamine. In certain tissues such as the brain and its mesolimbic-mesocortical DA system, there is a relatively low aldehyde oxidizing ability. In such a context, alcohol biotransformation to its active metabolite, acetaldehyde, blocks the normal conversion of amine derived aldehyde to its corresponding acid, due to inhibition of aldehyde dehydrogenase. The intermediate aldehyde that accumulates is highly reactive and may condense with the parent amine present. In the case of DA and its aldehyde, which is 3,4 dihydroxyphenyl acetaldehyde, the condensation compound is tetrahydropapaveroline (Norlaudanosoline). Norlaudanosoline may go on after several steps to form morphine-like alkaloids with addictive potential and morphine itself. In such a cascade, it is hypothesized that alcohol could lead to endogenous production of morphine and morphine-like compounds to counteract the endogenous morphine deficiency. Increased glutamatergic transmission resulting in excitotoxicity has been implicated in addiction. Excitatory amino acids (EAA) can promote the release of dopamine in the nucleus accumbens. But there is also depolarisation

inactivation of DA neurons with excessive EAA stimulation. This results in inactivation of the mesolimbic-mesocortical dopaminergic system. Thus membrane Na^+-K^+ ATPase induced hypomagnesemia, serotonin, quinolinic acid and strychnine, all being positive modulators of the NMDA receptor, can contribute to alcoholic addiction. The same mechanism holds well in the case of excess nicotine synthesis from tryptophan noticed in alcoholic addiction. Nicotine can also produce a biphasic effect on mesolimbic-mesocortical dopaminergic neurons with initial activation followed by depolarisation inactivation of DA neurons. High levels of nicotine can produce permanent depolarisation inactivation of DA neurons of the mesolimbic-mesocortical dopamine system leading on to addiction. The increased synthesis of strychnine from tryptophan demonstrated in these cases is also significant with respect to addiction. Strychnine can block the glycinergic inhibitory transmission in the brain. This glycine is free to modulate NMDA transmission acting at the strychnine sensitive site of the NMDA receptor and promotes glutamatergic excitotoxicity. Activation of inhibitory GABA receptors expressed on VTA DA neurons results in inhibition of dopaminergic activity. The strychnine induced glutamatergic excitotoxicity and reduced inhibitory glycine/GABA transmission can inhibit dopaminergic activity in the mesolimbic-mesocortical dopaminergic system leading substance abuse and addiction. Increased NMDA excitotoxicity could contribute to the seizures in Reye's syndrome. NMDA excitotoxicity could also contribute to the neuronal degeneration observed in Reye's syndrome.

Quinolinic acid has been implicated in immune activation in other immune diseases like lupus and could contribute to the same in IBD. Serotonin, dopamine and noradrenaline receptors have been demonstrated in the lymphocytes. It has been reported that during immune activation serotonin is increased with the corresponding reduction in dopamine and noradrenaline in the brainstem monoaminergic nuclei. Thus elevated serotonin and reduced

noradrenaline and dopamine can contribute to the immune activation in IBD. We had already shown the presence of endogenous morphine in the brain of rats loaded with tyrosine and endogenous strychnine and nicotine in the brain of rats loaded with tryptophan. Serum of patients with IBD showed the presence of strychnine and nicotine but morphine was absent. The absence of morphine in patients with IBD is also significant. Morphine can inhibit the inflammatory response and the absence of morphine could contribute to an exaggeration of this response.

The schizoid neurotransmitter pattern of reduced dopamine, noradrenaline and morphine and increased serotonin, strychnine and nicotine is also noticed in IBD, mesenteric artery occlusion, APD, IBS, cirrhosis liver, gallstones and Reye's syndrome and could predispose their development. Quinolinic acid, an NMDA agonist can contribute to NMDA excitotoxicity reported in schizophrenia. Strychnine by blocking glycinergic transmission can contribute to the decreased inhibitory transmission in schizophrenia. Recent data suggest that the initial abnormality in schizophrenia involves a hypodopaminergic state and the low dopamine levels now observed agrees with this. Nicotine by interacting with nicotine receptors can facilitate the release of dopamine, promoting the dopaminergic transmission in the brain. This can explain the increased dopaminergic transmission in the presence of decreased dopamine levels. The increase serotoninergic activity and reduced noradrenergic outflow from locus coeruleus reported earlier in schizophrenia agrees with our finding of elevated serotonin and reduced noradrenaline levels. A schizoid neurotransmitter pattern can predispose to IBD, mesenteric artery occlusion, APD, IBS, cirrhosis liver, gallstones and Reye's syndrome. IBS patients have been reported to have an increased frequency of psychiatric diagnosis including personality disorders, anxiety, depression, hysteria and somatization.

Archaeal Digoxin and Regulation of Golgi Body / Lysosomal Function in Relation to GI / Hepatic Disease

The archaeaon glycosaminoglycoid and fructosoid contributes to glycoconjugate synthesis and catabolism by the process of fructolysis. The elevation in the level of dolichol may suggest its increased availability of N-glycosylation of proteins. Magnesium deficiency can lead to defective metabolism of sphinganine producing its accumulation which may lead to increased cerebroside and ganglioside synthesis. In Mg^{++} deficiency the glycolysis, citric acid cycle and oxidative phosphorylation are blocked and more glucose 6-phosphate is channelled for the synthesis of glycosaminoglycans (GAG). Intracellular Mg^{++} deficiency also results in defective ubiquitin dependent proteolytic processing of glycoconjugates as it requires Mg^{++} for its function. The increase in the activity of glycohydrolases and GAG degrading enzymes could be due to reduced lysosomal stability and consequent leakage of lysosomal enzymes into the serum. The increase in the concentration of carbohydrate components of glycoproteins and GAG in spite of increased activity of many glycohydrolases and GAG degrading enzymes may be due to their possible resistance to cleavage consequent to qualitative change in their structure. Proteoglycan complexes formed in the presence of altered Ca^{++}/Mg^{++} ratios intracellularly may be structurally abnormal and resistant to lysosomal enzymes and may accumulate. Alteration in glycoprotein and proteoglycans can alter the gastric mucosa and mucous secretion making it more susceptible to corrosive effects of pepsin. Thus the mucosal barrier which helps in defence against peptic ulcer disease is altered. Alteration in sulphated proteoglycan matrix of the neurotransmitter vesicles in the mast cell can produce breakage of the vesicles due to the structural instability and release histamine producing increased acid secretion and peptic ulcer formation.

Structurally abnormal glycoproteins and proteoglycans resist catabolism by lysosomal enzymes and accumulate leading on to arteriosclerosis. Interaction between heparan sulphate-proteoglycan and chondroitin sulphate-proteoglycan with lipoproteins and reduced proteolytic digestion of these complexes leading to their accumulation in the vascular wall can lead to atherogenesis. A number of fucose and sialic acid containing natural ligands are involved in trafficking of leukocytes and similar breaches in blood brain barrier and adhesion of the lymphocyte producing leukocyte trafficking and extravasation in to the perivascular space have been described in atherogenesis. Immune mechanisms have been postulated to contribute to the evolution of the atheromatous plaque. Altered cell surfaces of glycoproteins, glycolipids and GAG can lead to defective contact inhibition and smooth muscle cell proliferation contributing to anteriosclerosis and atherosclerosis.

The protein processing defect can result in defective glycosylation of MHC glycoprotein antigens. There is also defective formation of MHC - Helicobacter pylori glycoprotein antigen complex. The MHC linked peptide transporter, a P-glycoprotein which transports MHC-antigen complex to the antigen presenting cell surface, has an ATP binding site. The peptide transporter is dysfunctional in the presence of Mg^{++} deficiency. This results in defective transport of MHC class-1 Helicobacter pylori glycoprotein antigen complex to the antigen presenting cell surface for recognition by CD_4 or CD_8 cell. Defective presentation of exogenous helicobacter pylori glycoprotein antigen can explain the immune dysregulation and persistence of helicobacter pylori infection in peptic ulcer disease. A number of fucose and sialic acid containing natural ligands are involved in trafficking of leukocytes and could play a role in the genesis of the inflammatory response in peptic ulcer disease.

The fucoligand and sialoligands can also contribute to immune activation in IBD. Defective presentation of endogenous colonic glycoprotein antigen can

explain the immune dysregulation in IBD. Patients with IBD have humoral antibodies to the colonic cells. Immune complexes have also been involved to explain extraintestinal manifestations of IBD. Altered glycoconjugate synthesis can lead to the generation of new endogenous colonic antigens, setting up an autoimmune process. Defective presentation of exogenous bacterial glycoprotein antigens can produce immune evasion by the bacteria and bacterial persistence especially of pseudomonas in IBD.

Alteration in the sulphated proteoglycan matrix of the synaptic vesicles can alter neurotransmitter release into the synapse and produce a functional disorder like IBS. Altered glycoproteins, glycolipids and GAG of neuronal membrane can also contribute to IBS by producing disordered synaptic connectivity in the neuronal network in the bowel wall.

Previous reports of alteration in glycoproteins in neuronal degeneration include alpha synuclein in Parkinson's disease and beta amyloid in Alzheimer's disease. Structurally abnormal glycoproteins resist catabolism by lysosomal enzymes and accumulate in neuronal degeneration. Interaction between HS-proteoglycan and ChS-proteoglycan with neuronal proteins and reduced proteolytic digestion of these complexes can lead to their accumulation in the neurons. Defective ubiquitin dependent proteolytic processing of proteins consequent to intracellular magnesium deficiency can also lead to neuronal degeneration. Alteration in sulphated proteoglycan matrix of the synaptic vesicles can alter dopamine release into the synapse and contribute to the pathogenesis of acquired hepatocerebral degeneration. Altered glycoproteins, glycolipids and GAG of neuronal membrane can also contribute to acquired hepatocerebral degeneration by producing disordered synaptic connectivity in the nigrostriate pathways. The upregulated connective tissue macromolecular synthesis consequent to hypomagnesemia can predispose to cirrhosis liver by producing replacement fibrosis. Defective presentation of exogenous viral or

bacterial glycoprotein antigens can produce immune evasion by the virus / bacteria and viral / bacterial persistence as in the case of hepatitis virus B persistence in another type of cirrhosis - post necrotic cirrhosis of the liver. This can also contribute to defective immunity and increased predisposition to bacterial infections especially due to pneumococcus ad mycobacterium tuberculosis in cirrhosis liver.

Altered mucoproteins can contribute to the formation of gallstones. Nonmucin and mucin glycoproteins and lysine phosphatidyl choline appears to be pronucleating factors. Thus altered mucoproteins and glycoproteins of the bile can lead to the formation of gallstones.

Archaeal Digoxin and Alteration in Membrane Structure and Membrane Formation in Relation to GI / Hepatic Disease

The archaeaon steroidelle, glycosaminoglycoid and fructosoid contribute to cell membrane formation synthesizing cholesterol by the DXP pathway and glycosaminoglycans by fructolysis. The alteration in the isoprenoid pathway specifically, cholesterol as well as changes in glycoproteins and GAG can affect cellular membranes. The upregulation of isoprenoid pathway can lead to increased cholesterol synthesis and Mg^{++} deficiency can inhibit phospholipid synthesis. Phospholipid degradation is increased owing to an increase in intracellular calcium activating phosphase A_2 and D. The cholesterol-phospholipid ratio of the RBC membrane was increased in peptic ulcer disease. The concentration of total GAG, hexose and fucose content of glycoprotein decreased in the RBC membrane and increased in the serum suggesting their reduced incorporation into the membrane and defective membrane formation. The glycoproteins, GAG and glycolipids of cellular membrane are formed in the endoplasmic reticulum, which is then budded of as a vesicle which fuses with the golgi complex. The glycoconjugates are then transported via the golgi

channel and the golgi vesicle fuses with the cell membrane. This trafficking depends upon GTPases and lipid kinases which are crucially dependent on magnesium and are defective in Mg^{++} deficiency. The change in membrane structure produced by alteration in glycoconjugates and cholesterol-phospholipid ratio can produce changes in the conformation of Na^{+}-K^{+} ATPase resulting in further membrane Na^{+}-K^{+} ATPase inhibition. The same changes can affect the structure of organelle membrane. This results in defective lysosomal stability and leakage of glycohydrolases and GAG degrading enzymes into the serum. Defective lysosomal stability could lead to increased release of lysosomal enzymes which can produce destruction of the gastric mucosa. Alteration in the gastric mucous membrane structure can also predispose inflammation and peptic ulceration. Defective peroxisomal membranes lead to catalase dysfunction which has been documented in peptic ulcer disease.

This change in membrane structure and function can alter endothelial structure leading to platelet aggregation, platelet thrombin and atherogenesis. The same changes can affect the structure of organelle membrane. Altered lysosomal stability consequent to a change in the membrane can lead to plaque rupture. Lysosomal stability is important in the genesis of IBD as lysosomal enzymes can contribute to tissue destruction.

Increased release of lysosomal enzymes can contribute to tissue destruction and necrosis in cirrhosis of the liver. Alteration in RBC membrane can lead to the acanthocytosis noticed in cirrhosis liver. Altered lysosomal stability and function of lysosomal enzymes can contribute to acquired hepatocerebral degeneration. This can also result from altered structure of neuronal membranes.

Archaeal Digoxin and Mitochondrial Dysfunction in Relation to GI / Hepatic Disease

The archaeaon vitaminocyte contributes to the synthesis of ubiquinone and mitochondrial electron transport chain function. The mitochondrial function related free radical generation is regulated by the archaeaon vitaminocyte synthesized tocopherol and ascorbic acid. The concentration of ubiquinone decreased significantly in APD which may be the result of low tyrosine levels, reported in peptic ulcer disease, consequent to EDLF's effect in preferentially promoting tryptophan transport over tyrosine. The aromatic ring portion of ubiquinone is derived from tyrosine. Ubiquinone, which is an important component of the mitochondrial electron transport chain, is a membrane antioxidant and contributes to free radical scavenging. The increase in intracellular Ca^{++} can open the mitochondrial PT pore causing a collapse of the H^{+} gradient across the inner membrane and uncoupling of the respiratory chain. Intracellular Mg^{++} deficiency can lead to a defect in the function of ATP synthase. All this leads to defects in mitochondrial oxidative phosphorylation, incomplete reduction of oxygen and generation of superoxide ion which produces lipid peroxidation. Ubiquinone deficiency also leads to reduced free radical scavenging. The increase in intracellular calcium may lead to increased generation of NO by inducing the enzyme nitric oxide synthase which combines with superoxide radical to form peroxynitrite. Increased calcium can also activate phospholipase A_2 resulting in increased generation of arachidonic acid which can undergo increased lipid peroxidation. Increased generation of free radicals like the superoxide ion and hydroxyl radical can produce lipid peroxidation and cell membrane damage which can further inactivate Na^{+}-K^{+} ATPase, triggering the cycle of free radical generation once again. Mg^{++} deficiency can affect glutathione synthetase and glutathione reductase function. The mitochondrial superoxide dismutase leaks out and becomes dysfunctional

with calcium related opening of the mitochondrial PT pore and outer membrane rupture. The peroxisomal membrane is defective owing to membrane Na^{+}-K^{+} ATPase inhibition related defect in membrane formation and leads to reduced catalase activity. Free radicals can produce mucosal damage and ulceration as well as lymphocyte activation and immune infiltration in peptic ulcer disease.

The increased intracellular calcium related opening of the mitochondrial PT pore also leads to volume dysregulation of the mitochondria causing hyperosmolality of the matrix and expansion of the matrix space. The outer membrane of the mitochondria ruptures and releases apoptosis inducing factor and cytochrome C into the cytoplasm. This results in activation of caspase-9 and caspase-3. Caspase-9 can produce apoptosis of the cell. Increased apoptosis can produce mucosal damage in peptic ulcer disease.

Mitochondrial dysfunction related free radical generation has been implicated in the pathogenesis of atherosclerosis. Increased free radical production can produce oxidise LDL. Oxidised LDL is toxic to the macrophages. The macrophages rupture, releasing the lysosomal enzymes which rupture the plaque producing mesenteric artery occlusion. In addition to these the macrophage lysosomes are already unstable consequent to their altered membrane structure. This is an additional contributory factor for plaque rupture.

Apoptosis has been implicated in the genesis of atheromatous lesion as well as in neuronal death following as vascular occlusion. The synthesis of NO in abdominal angina and ischaemic colitis with increased NO synthesis - is a paradox. Probably NO synthesis occurs as a late event in vascular thrombosis. Initially the increase in intracellular calcium and reduction of intracellular magnesium leads to the formation of a platelet thrombi and vasospasm. Later after a time lag there is induction of nitric oxide synthase and vascular damage owing to generation of the toxic free radical peroxynitrite (resulting from

combination of NO with hydroxyl radical). NO is therefore more of a toxic free radical damaging the vascular endothelium rather than a vasodilator.

Mitochondrial dysfunction related free radical generation has been implicated in the pathogenesis of the IBD. Free radicals can produce immune activation and contribute to the pathogenesis of IBD.

Mitochondrial dysfunction related free radical generation has been implicated in the pathogenesis of Reye's syndrome. Free radicals and mitochondrial dysfunction can also produce degenerative changes in the neurons.

Increased generation of' NO can lead to vasodilatation and the hyperdynamic circulation noticed in hepatic failure consequent to cirrhosis. Many of the cutaneous abnormalities of hepatic failure in cirrhosis like spider naevi and palmar erythema can be related to increased nitric oxide synthesis. Mitochondrial dysfunction related free radical generation has been implicated in the pathogenesis of tissue damage in cirrhosis liver. Mitochondrial dysfunction and free radical generation have been implicated in neuronal degeneration. Mitochondrial dysfunction can remove the magnesium block of the NMDA receptor contributing to NMDA excitotoxicity. Hepatocyte apoptosis has been reported to occur in cirrhosis liver. We have been able to demonstrate neuronal degeneration and apoptosis in digoxin injected rat brain. Neuronal apoptosis can contribute to acquired hepatocerebral degeneration.

Archaeal Digoxin and Regulation of Cell Division, Cell Proliferation and Neoplastic Transformation in Relation to GI / Hepatic Disease - Relation to Immune Activation

The archaeaon fructosoid contributes to fructolysis and immune activation. Fructose can contribute to induction of NFKB and immune activation. The archaeaon steroidelle synthesized digoxin induces NFKB producing immune activation. Increased intracellular calcium activates the calcium dependent

calcineurin signal transduction pathway which can produce T-cell activation and secretion of interleukin-3,4,5,6 and TNF alpha (Tumour necrosis factor alpha). TNF alpha binds to its receptor TNFR1 and activates the transcription factors HF-kB and AP-l leading to the induction of proinflammatory and immunomodulatory genes. This can also explain the immune activation contributing to gastritis and inflammation in peptic ulcer disease. TNF alpha can also bring about apoptosis of the cell. It binds to its receptor and activates caspase-9, an ICE protease which converts IL-1 beta precursor to IL-1 beta. IL-1 beta produces apoptosis of the mucosal cells in peptic ulcer disease. Increased intracellular calcium activates phospholipase C beta which results in increased production of diacyglycerol (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 GOP. 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. Upregulation of isoprenoid pathway can result in increased production of farnesyl phosphate which can farnesylate the ras oncogene producing its activation. Ubiquitin system of catabolic processing of proteins is important in DNA repair mechanism. In the presence of intracellular magnesium deficiency ubiquitin system of protein catabolic processing and DNA repair mechanisms are defective and this could contribute to oncogenesis. Thus there is increased tendency for gastric carcinoma and gastric lymphoma in peptic ulcer disease associated with Helicobacter pylori infections.

This membrane Na^{+}-K^{+} ATPase inhibition related immune activation can contribute to the genesis of the atheromatous plaque in mesenteric artery

occlusion. Monoclorial cell invasion in to the vascular wall occurs in the initial phases of atherogenesis. This smooth muscle proliferative tendency and oncogerlic activation consequent to hyperdigoxinemia and membrane Na^{+}-K^{+} ATPase inhibition can contribute to arteriosclerosis occurring in abdominal angina and ischaemic colitis.

This can also explain the immune activation in IBD. Increased concentration of mucosal IgG cells and changes in subsets of T-cells, suggesting antigenic stimulation have been described in IBD. Activation of mucosal immune cells results in complex expression of cytokines, which may contribute to the mucosal inflammatory response. There is increased tendency for neoplastic transformation in patients with IBD. There is also increased incidence of colonic carcinoma in patients with IBD. This could be related to membrane Na^{+}-K^{+} ATPase inhibition related oncogene activation.

Immune activation has been described in IBS. Stress induced inflammatory response in the enteric wall is important in its pathogenesis. Membrane Na^{+}-K^{+} ATPase inhibition can also contribute to the stress induced enteric inflammation.

Membrane Na^{+}-K^{+} ATPase inhibition can also explain the immune activation and infiltration of inflammatory cell noticed in the alcoholic hepatitis stage of cirrhosis liver.

Archaeal Digoxin and Lipid Metabolism - in Relation to GI / Hepatic Disease

The archaeaon steroidelle contributes to lipid synthesis and metabolism. In gallstones there is increased cholesterol synthesis as noticed by increased HMG CoA reductase activity. This leads to cholesterol supersaturation of bile. Mg^{++} deficiency can inhibit phospholipid synthesis. Phospholipid degradation is increased owing to an increase in intracellular calcium activating phospholipase A_2 and D. Phospholipid secretion in the bile is thus reduced. Thus there is an

excess of biliary cholesterol in relation to phospholipids. This leads to the formation of unstable cholesterol rich vesicles which aggregate to form large multilamellar vesicles from which cholesterol crystals aggregate. This could be the third important factor contributing to the formation of gallstones.

In cirrhosis liver decreased intracellular magnesium can produce dysfunction of lipoprotein lipase leading to defective catabolism of triglycerides rich lipoproteins and hypertriglyceremia. In hypomagnesemia Lecithin cholesterol acyl transferase (LCAT) is defective and there is reduced formation of cholesterol esters in HDL. Magnesium deficiency has been reported to increase LDL cholesterol levels also. Increased intracellular calcium consequent to membrane Na^+-K^+ ATPase inhibition can open up the mitochondrial PT pore leading to a mitochondrial dysfunction. This leads to defective mitochondrial beta oxidation of fatty acids and triglyceride accumulation. All these changes in lipid metabolism produced by digoxin can contribute to alcoholic fatty liver.

In Reye's syndrome the mitochondrial dysfunction can lead to reduced beta oxidation of fatty acids. This leads to fatty acid accumulation in cells. The digoxin induced hypomagnesemia can inhibit the function of lipoprotein lipase. Lipoprotein lipase is concerned with triglyceride catabolism. This leads to accumulation of triglycerides within the cells. This could be the basis for fatty micro vacuolization in renal tubular cells and liver cells in Reye's syndrome. The lipid abnormality in Reye's syndrome of increased triglyceride and low HDL cholesterol is similar to that obtained in syndrome X and insulin resistance states.

Archaeal Digoxin and Hemispheric Dominance in Relation to GI / Hepatic Disease

The archaeaon related organelle - steroidelle, neurotransminoid and vitaminocyte contribute to hemispheric dominance. In left handed / right hemispheric dominant individuals there was a derangement of the isoprenoid

pathway. They had an upregulated HMG CoA reductase activity with increased EDLF and dolichol levels and reduced ubiquinone levels. The RBC membrane Na^+-K^+ ATPase activity was reduced and serum magnesium depleted. The left handed / right hemispheric dominant individuals had increased levels of tryptophan, serotonin, quinolinic acid, strychnine and nicotine while the levels of tyrosine, dopamine, noradrenaline and morphine were lower. Thus an upregulated isoprenoid pathway, increased level of tryptophan and its catabolites, decreased level of tyrosine and its catabolites and hyperEDLFemia is suggestive of right hemispheric dominance. Peptic ulcer disease occurs in right hemisphere dominant individuals and is a reflection of altered brain function. Hemispheric dominant has been correlated with the pathogenesis of systemic diseases.

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