Ravikumar Kurup & Parameswara Achutha Kurup

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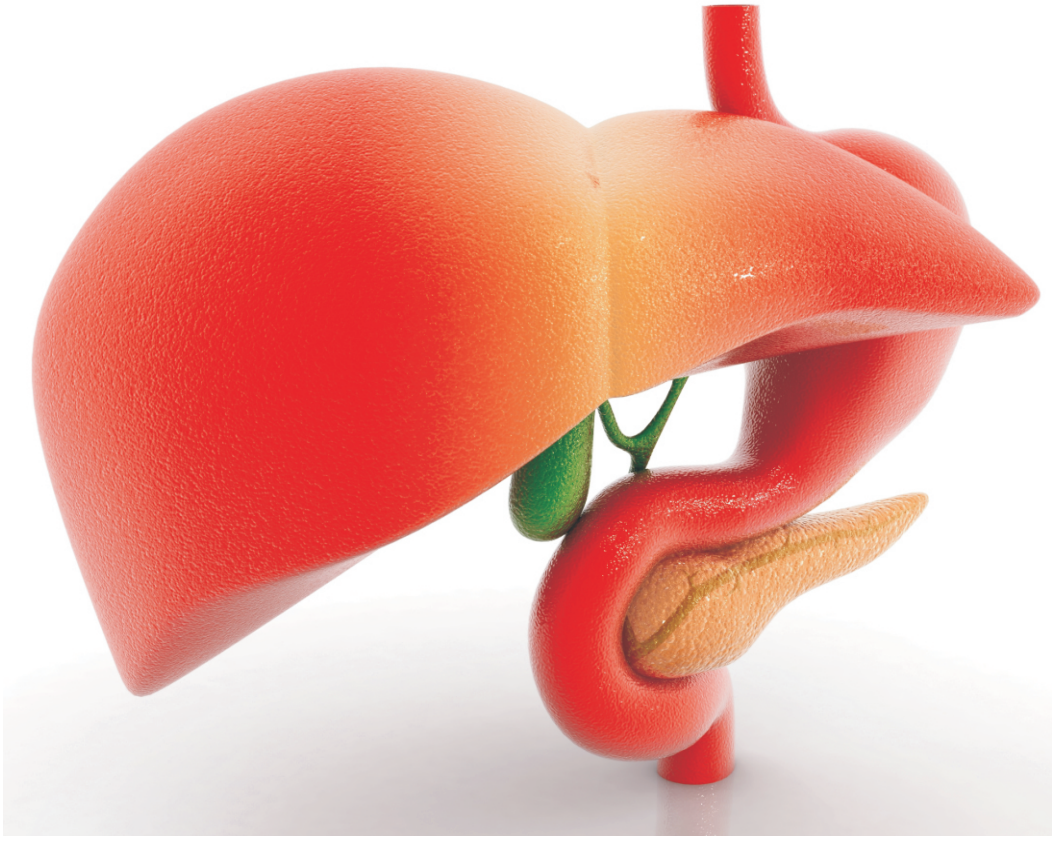

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Ravikumar Kurup

Parameswara Achutha Kurup

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Contents

1

The Endosymbiotic Archaea, Fructose Disease and Global Warming - Chronic Heaptic 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 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 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.

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 stearoyl 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 organise 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. Glutame 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 seretion 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 bypasses 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 percent 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, 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
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
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
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 Hepatic 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.

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

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.

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 gastro-intestinal and liver disease.

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3

Archaeal Digoxin Mediated Model for Cirrhosis Liver

The cardinal pathologic features of cirrhosis reflect irreversible chronic injury of the hepatic parenchyma and include extensive fibrosis in association with the formation of regenerative nodules. These features result from hepatocyte necrosis, collapse of the supporting reticulin network with subsequent connective tissue deposition, distortion of the vascular bed, and nodular regeneration of remaining liver parenchyma. The causes of cirrhosis include alcoholic, post viral or post necrotic. The finding of increased concordance of alcoholic liver disease among monozygotic twins compared to dizygotic twins ingesting excessive amounts of alcohol suggests that genetic factors may contribute, to the genesis of cirrhosis. The alcoholic cirrhosis passes through three pathological states - alcoholic fatty liver, alcoholic hepatitis and alcoholic cirrhosis. The isoprenoid pathway is a key regulatory pathway in the cell. It produces two metabolites important in the genesis of cirrhosis - digoxin and cholesterol. Archaeal digoxin by producing membrane Na^+-K^+ ATPase inhibition can contribute to intracellular hypomagnesemia which can upregulate connective tissue synthesis. The cholesterol pathway and lipoprotein synthesis can contribute to the genesis of fatty liver. Archaeal digoxin can also modulate tryptophan and tyrosine transport. Tyrosine can contribute to the synthesis of endogenous morphines. Alcoholic addiction, an important etiological factor for cirrhosis has been related to an endogenous morphine deficiency syndrome. Tryptophan catabolism can lead to the generation of quinolinic acid important in the pathogenesis of hepatic coma. It was therefore considered pertinent to study the isoprenoid pathway related biochemical cascade in alcoholic cirrhosis of the liver to find out whether changes in the pathway can modulate the predisposition to cirrhosis liver. As hypothalamic archaeal digoxin can modulate synaptic transmission of multiple neurotransmitter systems, the pathway was also assessed in individuals with differing hemispheric dominance to find out the role of hemispheric dominance in the pathogenesis of cirrhosis.

Results

(1) The activity of HMG CoA reductase and the concentration of digoxin and dolichol were increased in the patient group. The concentration of serum ubiquinone, the activity of erythrocyte membrane Na^+-K^+ ATPase and serum magnesium were decreased in the patient group.

(2) The concentration of serum tryptophan, quinolinic acid and serotonin were increased in the plasma while that of tyrosine, dopamine and noradrenaline were decreased in the patient group.

(3) Nicotine and strychnine were detected in the plasma of the patient group and were undetectable in control serum. Morphine was not detected in the plasma of the patient group while it was present in the control group.

(4) 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 group. The concentration of total hexose, fucose and sialic acid were increased in the glycoproteins of the serum in the patient group.

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

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

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

(8) 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 also 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 also 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 Cirrhosis Liver

The archaeaon steroidelle DXP pathway and the upregulated pentose phosphate pathway contribute to digoxin synthesis. The results showed that HMG CoA reductase activity, serum digoxin and dolichol were increased in cirrhosis liver while serum ubiquinone was reduced. Previous studies in this laboratory have demonstrated incorporation of ‘4C-acetate in to digoxin in rat brain indicating that acetyl CoA is the precursor for digoxin biosynthesis in

mammals also. The elevated HMG CoA reductase activity correlates well with elevated digoxin levels and reduced RC membrane Na^+-K^+ ATPase activity. The increase in endogenous digoxin, a potent inhibitor of membrane Na^+-K^+ ATPase, can decrease this enzyme activity. The inhibition of Na^+-K^+ ATPase by digoxin is known to cause an increase in intracellular calcium resulting from increased Na^+-Ca^{++} exchange, increased entry of calcium via the voltage gated calcium channel and increased release of calcium from intracellular endoplasmic reticulum calcium stores. This increase in intracellular calcium by displacing magnesium from its binding sites causes a decrease in the functional availability of magnesium. This decrease in the availability of magnesium can cause decreased mitochondrial ATP formation which along with low magnesium can cause further inhibition of Na^+-K^+ ATPase, since ATP-magnesium complex is the actual substrate for this reaction. Cytosolic free calcium is normally buffered by two mechanisms, ATP dependent calcium extrusion from cell and ATP dependent sequestration of calcium within the endoplasmic reticulum. The magnesium related mitochondrial dysfunction results in defective calcium extrusion from the cell. There is thus a progressive inhibition of Na^+-K^+ ATPase activity first triggered by digoxin. Low intracellular magnesium and high intracellular calcium consequent to Na^+-K^+ ATPase inhibition appear to be crucial to the pathogenesis of cirrhosis liver. Serum magnesium was found to be reduced 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 on to a mitochondrial

dysfunction. This leads on 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.

Archaeal Digoxin and Regulation of Neurotransmitter Synthesis and Function in Relation to Cirrhosis Liver

The archaeaon neurotransminoid shikimic acid pathway contributes to tryptophan and tyrosine synthesis and catabolism generating neurotransmitters and neuroactive alkaloids. Digoxin, apart from affecting cation transport is also reported to influence the transport of various metabolites across cellular membranes, including amino acids and various neurotransmitters. The results showed that the concentration of tryptophan, quinolinic acid and serotonin were found to be higher in the plasma of patients with cirrhosis liver while that of tyrosine, dopamine and norepinephrine were lower. Thus there is an increase in tryptophan and its catabolites and a reduction in tyrosine and its catabolites in the serum of cirrhosis liver patients. This could be due to the fact that digoxin can regulate neutral amino acid transport system with preferential promotion of tryptophan transport over tyrosine. The decrease in membrane Na^+-K^+ ATPase activity in cirrhosis liver could be due to the fact that the hyperpolarising neurotransmitters (dopamine and noradrenaline) are reduced and the depolarising neuroactive compounds (serotonin and quinolinic acid) are increased. These abnormalities can contribute to the neurological complications of liver failure in cirrhosis. Reduced tyrosine levels can lead on to reduced dopamine synthesis contributing to the extrapyramidal syndrome and altered sensorium in liver failure consequent to cirrhosis. Increased quinolinic acid and serotonin levels can contribute to NMDA excitotoxicity as both are NMDA agonists. Quinolinic acid mediated NMDA excitotoxicity is important in the pathogenesis of neuronal dysfunction in hepatic failure.

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 cirrhosis liver showed the presence of strychnine and nicotine but morphine was absent. The absence of morphine in patients with cirrhosis liver is also significant. Endogenous morphine deficiency has been related to alcoholic addiction. This could be a contributory factor for cirrhosis liver. The presence of strychnine in patients with cirrhosis liver is important. Strychnine displaces glycine from its binding site. The glycine is free to bind to the glycine sensitive site of the NMDA receptor producing NMDA excitotoxicity important in neuronal dysfunction in cirrhosis.

Archaeal Digoxin and Regulation of Golgi Body / Lysosomal Function in Relation to Cirrhosis Liver

The archaeaon glycosaminoglycoid and fructosoid contributes to glycoconjugate synthesis and catabolism by the process of fructolysis. The low magnesium levels consequent to membrane Na^{+}-K^{+} ATPase inhibition can affect the metabolism of glycosaminoglycans, glycoproteins and glycolipids. The elevation in the level of dolichol consequent to its increased synthesis, may suggest its increased availability of N-glycosylation of proteins. Decrease in intracellular magnesium can produce changes in collagen and elastin biosynthesis and produce replacement fibrosis. In magnesium deficiency the glycolysis, citric acid cycle and oxidative phosphorylation are blocked and more glucose 6-phosphate is channelled for the synthesis of glycosaminoglycans (GAG). The results showed an increase in the concentration of serum total GAG, and carbohydrate components of glycoproteins (hexose, fucose and sialic acid) in cirrhosis liver. The increase in the carbohydrate components of serum glycoproteins - total hexose, fucose and sialic acid was not to the same extent in cirrhosis liver suggesting a qualitative change in glycoprotein structure. In

cirrhosis liver the percentage change in total hexose, fucose and sialic acid when compared to control is 54.3%, 20% and 33% respectively. The pattern of change in individual GAG in the serum was different. The concentration of hyaluronic acid, heparan sulphate, heparin, dermatan sulphate and chondroitin sulphates were increased in the serum of cirrhosis liver patients. The activity of GAG degrading enzymes (beta glucuronidase, beta N-acetyl hexosaminidase, hyaluronidase and cathepsin-D) were increased in the serum of cirrhosis liver patients. The activities of glycohydrolases - beta galactosidase, beta fucosidase and beta glucosidase were increased in the serum of cirrhosis liver patients. 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 may be due to their possible resistance to cleavage by glycohydrolases 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. The upregulated connective tissue macromolecular synthesis consequent to hypomagnesemia can predispose to cirrhosis liver.

The protein processing defect can result in defective glycosylation of exogenous viral glycoprotein antigens with consequent defective formation of MHC-viral 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 which is dysfunctional in the presence of magnesium deficiency. This results in defective transport of MHC class-1 viral glycoprotein antigen complex to the antigen presenting cell surface for recognition by CD_4 or CD_8 cell. 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 post necrotic cirrhosis of the liver. This can also contribute to defective immunity and increased predisposition to bacterial infections especially due to pneumococcus and mycobacterium tuberculosis in cirrhosis liver. Increased intracellular calcium activates calcium dependent calcineurin signal transduction pathway which can produce T-cell activation and secretion of interleukin - 3, 4, 5, 6, 8 and TNF alpha (Tumour necrosis factor alpha). This can also explain the immune activation and infiltration of inflammatory cell noticed in the alcoholic hepatitis stage of cirrhosis liver. TNF alpha can also bring about apoptosis of the cell. It binds to its receptor and activates caspase-9. Caspase-9 activation can produce hepatocyte apoptosis. Membrane Na^{+}-K^{+} ATPase inhibition can produce immune activation and is reported to increase CD_4/CD_8 ratios as exemplified by the action of lithium. A number of fucose and sialic acid containing natural ligands are involved in the trafficking of leukocytes and adhesion of the lymphocyte producing leukocyte trafficking and extravasation in to the perivascular space as has been described in cirrhosis liver. In the alcoholic hepatitis stage the damaged hepatocytes contained mallory bodies or alcoholic hyaline. These are clumps of perinuclear, deeply eosinophilic material believed to represent aggregated intermediate filaments. Digoxin by producing magnesium depletion intracellularly can interfere with the function of the cytoskeletal proteins leading on to the intermediate filament aggregation.

Archaeal Digoxin and Alteration in Membrane Structure and Membrane Formation in Relation to Cirrhosis Liver

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 magnesium deficiency can inhibit phospholipid synthesis. Phospholipid degradation is increased owing to an increase in intracellular calcium activating phospholipase A_2 and U. The membrane composition was assessed by, RBC membrane cholesterol: phospholipid ratio, carbohydrate residues of glycoproteins and total glycosaminoglycans. The cholesterol: phospholipid ratio of the RBC membrane was increased in cirrhosis liver patients. The concentration of total GAG, hexose and fucose of glycoprotein and cholesterol 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 off 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 magnesium 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. Increased released of lysosomal enzymes can contribute to tissue destruction and necrosis in cirrhosis of the liver. Alteration in RBC membrane can lead on to the acanthocytosis noticed in cirrhosis liver.

Archaeal Digoxin and Mitochondrial Dysfunction in Relation to CIrrhosis Liver

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 cirrhosis liver which may be the result of low tyrosine levels, reported in cirrhosis liver consequent to digoxin's effect in preferentially promoting tryptophan transport over tyrosine. The aromatic ring portion of ubiquinone is derived from the tyrosine. Ubiquinone, which is an important component of the mitochondrial electron transport chain also contributes to free radical scavenging. The increase in intracellular calcium can open the mitochondrial PT pore causing a collapse of the hydrogen gradient across the inner membrane and uncoupling of the respiratory chain. Intracellular magnesium, deficiency can lead to a defect in the function of ATP synthase. All this leads to a defect 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 radicals to form peroxynitrite. Increased generation of NO can lead onto 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 erytherna can be related to increased nitric oxide synthesis. Increased calcium also can 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 again. There was an increase in lipid peroxidation as evidenced from the increase in the concentration of MDA, conjugated dienes, hydroperoxides and NO with decreased antioxidant protection as indicated by a decrease in ubiquinone and reduced glutathione in cirrhosis liver. The activity of enzymes involved in free radical scavenging like superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase and catalase is decreased in cirrhosis liver suggesting reduced free radical scavenging. The peroxisomal membrane is defective owing to membrane Na^{+}-K^{+} ATPase inhibition related defect in membrane formation and leads to reduced catalase activity. Intracellular magnesium deficiency consequent to membrane Na^{+}-K^{+} ATPase inhibition can lead to inhibition of glutathione synthetase and glutathione peroxidase function. Thus the glutathione system of free radical scavenging is defective in the presence of membrane Na^{+}-K^{+} ATPase inhibition. Superoxide dismutase exists in a mitochondrial and cytoplasmic form. Opening of the mitochondrial PT pore produces hyperosmolality and matrix expansion rupturing the outer membrane, producing loss of the mitochondrial disniutase leading to a decrease in its activity. The reduction in catalase, superoxide dismutase (SOD), glutathione peroxidase and glutathione reductase suggests reduced free radical protection. Mitochondrial dysfunction related free radical generation has been implicated in the pathogenesis of tissue damage in cirrhosis liver.

Cell death is also mediated by increased intracellular Ca^{++} and ceramide related opening of the mitochondrial PT pore causing a collapse of the H^{+} gradient across the inner membrane and uncoupling of the respiratory chain. This also leads to volume dysregulation of mitochondria causing hyperosinolality of matrix and expansion of matrix space. The outer membrane of the mitochondria ruptures and releases AIF (apoptosis inducing factor) and

cyto C (cytochrome C) into the cytoplasm. This results in procaspase-9 activation to caspase-9 which produces cell death. Caspase-9 activates CAD (caspase activated deoxyribonuclease) which cleaves the nuclear membrane lamins and several proteins involved in cytoskeletal regulation like gelsolin which cleaves actin. 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.

Archaeal Digoxin and Regulation of Cell Division, Cell Proliferation and Neoplastic Transformation in Relation to Cirrhosis Liver - 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 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 GDP. Phosphorylation mechanisms are required for the activation of the tumour suppressor gene P_{53}. The activation of P_{53} is impaired owing to intracellular magnesium deficiency producing a phosphorylation defect. Upregulation of isoprenoid pathway can result in increased production of farnesyl phosphate which can farnesylate the ras oncogene producing its activation. The ubiquitin system of catabolic processing of processing of proteins is important in the DNA repair mechanism. In the presence of intracellular magnesium deficiency ubiquitin protein catabolic processing and DNA repair mechanisms are defective and this could contribute to oncogenesis.

Thus there is an increased tendency for neoplastic transformation in patients with cirrhosis liver. There is increased incidence of hepatomas in patients with cirrhosis liver.

Archaeal Digoxin and Hemispheric Dominance in Relation to Cirrhosis Liver

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 digoxin 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 levels of tyrosine and its catabolites and hyperdigoxinemia is suggestive of right hemispheric dominance. In left handed *I* right hemispheric dominant individuals the patterns were reversed. Cirrhosis liver occurs in right hemisphere dominant individuals and is a reflection of altered brain function occurring in right hemispheric dominant individuals.

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[1] Kurup RK, Kurup PA. *Hypothalamic Digoxin, Cerebral Dominance and Brain Function in Health and Diseases*. New York: Nova Medical Books, 2009.

4

Archaeal Digoxin Mediated Model for Reye's Syndrome

Reye's syndrome is characterised by vomiting and signs of progressive central nervous system damage, signs of hepatic injury, and hypoglycemia. There is a mitochondrial dysfunction and decrease in the activity of hepatic mitochondrial enzymes. The cause of Reye's syndrome is unknown although viral agents and drugs, especially salicylates, have been implicated. In fatal cases the liver is enlarged and yellow with striking diffuse fatty microvacuolization of cells. Peripheral zonal hepatic necrosis also has been present. Fatty changes of the renal tubular cells, cerebral edema and neuronal degeneration of the brain are the major extrahepatic changes. Electron-microscopic studies show structural alterations of mitochondria in liver, brain, and muscle.

The isoprenoid pathway is a key regulatory pathway in the cell. It produces 4 key metabolites important in regulation of cellular function - cholesterol, an important component of cellular membranes; ubiquinone, an important membrane antioxidant and component of the mitochondrial electron transport chain; dolichol, important in N-glycosylation of proteins and endosymbiotic archaeal digoxin, an endogenous membrane Na^+-K^+ ATPase inhibitor. Since mitochondrial dysfunction is important in the pathogenesis of Reye's syndrome it was considered pertinent to study the isoprenoid pathway in patients with Reye's syndrome. Hemispheric dominance can play a role in regulating cellular functions. Since digoxin can regulate multiple neurotransmitter systems, the pathway was also assessed in individuals with differing hemispheric dominance in order to find out the role of hemispheric dominance in the genesis of the disease.

Results

(1) The activity of HMG CoA reductase and the concentration of digoxin and dolichol were increased in Reye's syndrome. The concentration of serum ubiquinone, the activity of erythrocyte membrane Na^+-K^+ ATPase and serum magnesium were decreased.

(2) The concentration of serum tryptophan, quinolinic acid and serotonin was increased in the plasma while that of tyrosine, dopamine and noradrenaline was decreased in Reye's syndrome. Nicotine and strychnine were detected in the plasma of patients with Reye's syndrome but were not detectable in control serum. Morphine was not detected in the plasma of these patients.

(3) The activity of superoxide dismutase (SOD), catalase, glutathione reductase and glutathione peroxidase in the erythrocytes decreased significantly in Reye's syndrome. In Reye's syndrome concentration of MDA, hydroperoxides, conjugated dienes and NO increased significantly. The concentration of glutathione and of alpha tocopherol decreased in Reye's syndrome. Iron binding capacity, ceruloplasmin and albumin decreased significantly in Reye's syndrome.

(4) Concentration of total serum cholesterol was unaltered in Reye's syndrome. HOL cholesterol decreased significantly in Reye's syndrome. LDL cholesterol was also not significant. Plasma triglycerides were increased in Reye's syndrome. Concentration of free fatty acid increased in Reye's syndrome.

(5) 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 also showed that HMG CoA reductase activity, serum digoxin and dolichol were decreased and ubiquinone increased in right handed / left hemispheric dominant individuals.

(6) 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,

dopainine, morphine and norepinephrine was lower. The results also 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 Reye's Syndrome

The archaeaon steroidelle DXP pathway and the upregulated pentose phosphate pathway contribute to digoxin synthesis. The results showed that HMG CoA reductase activity, serum digoxin and dolichol were increased and serum ubiquinone was reduced in Reye's syndrome. Previous studies in this laboratory have demonstrated incorporation of ^{14}C-acetate into digoxin in the rat brain indicating that acetyl CoA is the precursor for digoxin biosynthesis in mammals also. The elevated HMG CoA reductase activity correlates well with elevated digoxin levels and reduced RBC membrane Na^+-K^+ ATPase activity. The increase in endogenous digoxin, a potent inhibitor of membrane Na^+-K^+ ATPase, can decrease this enzyme activity. The inhibition of Na^+-K^+ ATPase by digoxin is known to cause an increase in intracellular Ca^{++} resulting from increased Na^+-Ca^{++} exchange, increased entry of Ca^{++} via the voltage gated Ca^{++} 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. Cyrtosolic free calcium is normally buffered by 2 mechanisms, ATP dependent

calcium extrusion from cell and ATP dependent sequestration of calcium within the endoplasmic reticulum. The Mg^{++} 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 digoxin. Low intracellular Mg^{++} and high intracellular Ca^{++} consequent to Na^{+}-K^{+} ATPase inhibition appear to be crucial to the pathogenesis of Reye's syndrome. Serum Mg^{++} was found to be reduced in Reye's syndrome. 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 Reye's Syndrome

The archaeaon neurotransminoid shikimic acid pathway contributes to tryptophan and tyrosine synthesis and catabolism generating neurotransmitters and neuroactive alkaloids. Digoxin, apart from affecting cation transport is also reported to influence the transport of various metabolites across cellular membranes, including amino acids and various neurotransmitters. Two of the amino acids in this respect are important, tryptophan, a precursor for strychnine and nicotine and tyrosine, a precursor for morphine. 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. The present study shows that the concentration of tryptophan, quinolinic acid, and serotonin was higher in the plasma of Reye's syndrome patients while that of tyrosine, dopamixie and norepinephrlne was lower. Serum of patients with Reye's syndrome showed the presence of nicotine and strychnine. Morphine was absent in the serum of these patients. Thus there is an increase in

tryptophan and its catabolites (serotonin, nicotine, strychnine and quinolinic acid) and a reduction in tyrosine and its catabolites (dopamine, norepinephrine and morphine) in the patient's serum. This could be due to the fact that digoxin can regulate neutral amino acid transport system with preferential promotion of tryptophan transport over tyrosine. Increased neuronal tryptophan load and reduced neuronal tyrosine load can upregulate tryptophan catabolism and down regulate the catabolism of tyrosine. The decrease in membrane Na^{+}-K^{+} ATPase activity in 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 as well to increased digoxin levels.

In the presence of hypomagnesemia, consequent to Na^{+}-K^{+} ATPase inhibition the Mg^{++} block on the NMDA receptor is removed leading to NMDA excitotoxicity. The increased levels of free fatty acids can contribute to NMDA excitotoxicity by binding Mg^{++}. This results in the formation of Mg^{++} soaps in the blood and hypomagnesemia. The increased presynaptic neuronal Ca^{++} can produce cyclic AMP dependent phosphorylation of synapsins resulting in increased glutamate 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 glutamate transporter (On the surface of the glial cell and presynaptic neuron) is coupled to a Na^{+} 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 of Na^{+}-K^{+} ATPase can promote excitatory glutamatergic transmission. Serotonin and quinolinic acid are NMDA agonist and positive modulators and could contribute to increased NMDA transmission. Strychnine by blocking glycinergic transmission contributes to the decreased inhibitory transmission in

the brain. Strychnine displaces glycine from its binding sites and the glycine is free to bind to the strychnine insensitive site of the NMDA receptor and promote excitatory NMDA transmission. 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.

Archaeal Digoxin and Mitochondrial Dysfunction in Relation to Reye's Syndrome

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 Reye's syndrome which may be the result of low tyrosine levels, consequent to digoxin's effect in preferentially promoting tryptophan transport over tyrosine. The aromatic ring portion of ubiquinone is derived from the 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 a defect in mitochondrial oxidative phosphorylation, incomplete reduction of oxygen and generation of superoxide ions 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 also can 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 again. There was an increase in lipid peroxidation as evidenced by the increase in the concentration of MDA, conjugated dienes, hydroperoxides and NO with decreased antioxidant protection as indicated by decrease in ubiquinone, reduced glutathione and alpha tocopherol in Reye's syndrome. The activity of enzymes involved in free radical scavenging like superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase and catalase is decreased in Reye's syndrome suggesting reduced free radical scavenging. In our study the iron binding capacity and serum ceruloplasmin are reduced suggesting increased amounts of free iron and copper, promoting free radical generation. Ceruloplasmin is a 132 KD monomeric copper oxidase which has been implicated in iron metabolism because of its catalytic oxidation of Fe^{2++} to Fe^{3++} (ferroxidase activity). In the presence of iron in Fe^{2++} form the conversion of H_2O_2 to hydroxyl radical is greatly increased. Low ceruloplasmin results in more of the iron to be in Fe^{2+} form. It has been shown that ceruloplasmin increases iron uptake by cells increasing the apparent affinity for the substrate by three times. Low ceruloplasmin levels can result in decreased iron uptake and this results in an increased amount of free iron. The intra cellular magnesium deficiency can produce ribosomal dysfunction and inhibition of protein synthesis as noted by a decrease in serum albumin in these cases. The low iron binding capacity and low serum ceruloplasmin levels may be a consequence of reduced ferritin and ceruloplasmin synthesis. The peroxisomal membrane is defective owing to membrane Na^{+}-K^{+} ATPase inhibition related defect in membrane formation and leads to reduced catalase activity. Glutathione is synthesized by the enzyme glutathione synthetase which needs magnesium and ATP. The low intracellular

Mg^{++} consequent to Na^{+}-K^{+} ATPase inhibition and the resulting low ATP can result in decreased synthesis of glutathione. Glutathione peroxidase, a selenium containing enzyme oxidises reduced glutathione (GSH) to oxidised glutathione (GSSG) which is then rapidly reduced to GSH by glutathione reductase. There is also a concommitant conversion of H_2O_2 to H_2O. The activity of glutathione reductase needs NADPH for the regeneration of GSH. This NADPH comes mostly from the pentose phosphate pathway. Intracellular magnesium deficiency due to membrane Na^{+}-K^{+} ATPase inhibition leads to decreased formation of glucose 6-phosphate and down regulation of the pentose phosphate pathway with consequent decreased generation of NADPH. Thus glutathione system of free radical scavenging is defective in the presence of membrane sodium potassium ATPase inhibition. Superoxide dismutase exists in a mitochondrial and cytoplasmic form. The opening of the mitochondrial PT pore produces hyperosmolality and matrix expansion rupturing the outer membrane producing loss of the mitochondrial dismutase and decrease in its activity. The reduction in catalase, superoxide dismutase (SOD), glutathione peroxidase and glutathione reductase suggests reduced free radical protection. 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.

Cell death is also mediated by increased intracellular Ca^{++} and ceramide related opening of the mitochondrial PT pore causing a collapse of the H^{+} gradient across the inner membrane and uncoupling of the respiratory chain. This also leads to volume dysregulation of mitochondria causing hyperosmolality of matrix and expansion of matrix space. The outer membrane of the mitochondria ruptures and releases AIF (apoptosis inducing factor) and cyto C. This results in procaspase-9 activation to caspase-9 which produces cell death. Caspase-9 activates CAD (caspase activated deoxyribonuclease) which

cleaves the nuclear membrane lamins and several proteins involved in cytoskeletal regulation like gelsolin which cleaves actin. Apoptosis could contribute to hepatic dysfunction and hepatic necrosis in Reye's syndrome. Apoptosis can also contribute to neuronal cell death 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 Reye's Syndrome

The archaeaon related organelle - steroidelle, neurotransminoid and vitaminocyte contribute to hemispheric dominance. Thus the altered mitochondrial function in Reye's syndrome could be due to a defective isoprenoid pathway. The biochemical pattern in Reye's syndrome is correlated with those obtained in right hemispheric dominance. In right hemispheric dominant individuals there is an upregulated isoprenoid pathway and increased digoxin synthesis. In left hemispheric dominant individuals there is a downregulated isoprenoid pathway and reduced digoxin synthesis. Hemispheric dominance could decide the predisposition to the development of Reye's syndrome.

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5

Archaeal Digoxin Mediated Model for Gallstones

Gallstones are crystalline structures formed by concretion or accretion of normal or abnormal bile constituents. Cholesterol and mixed stones account for 80% of total stones. Mixed and cholesterol gallstones usually Contains more than 70% cholesterol monohydrate plus an admixture of calcium salts, bile acids and bile pigments, proteins, fatty acids, and phospholipids. There are several important mechanism in the formation of lithogenic bile. The most important is increased biliary secretion of cholesterol. This may occur in association with obesity and with increased activity of HMG CoA reductase the rate limiting enzymes of hepatic cholesterol synthesis. Lithogenic bile may also result from decreased hepatic secretion of bile salts and phospholipids, which may follow impaired hepatic synthesis. Patients with gallstones also tend to have reduced activity of hepatic cholesterol 7-alpha hydroxylase, the rate limiting enzyme for primary bile acid synthesis.

Thus an excess of biliary cholesterol in relation to bile acids and phospholipids may be due to hypersecretion of cholesterol, hyposecretion of bile acids, or both. While cholesterol saturation of bile is an important prerequisite for gallstone formation it is not sufficient by itself. An important abnormality is defective vesicle formation. Ordinary cholesterol and phospholipid are secreted into bile as unilamellar bilayered vesicles, which are unstable and are converted along with bile acids, into other lipid aggregates such as micelles. 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 crystal aggregates.

A third important mechanism is nucleation of cholesterol monohydrate crystals which is greatly accelerated in human lithogenic bile; it is this feature rather than the degree of cholesterol supersaturation that distinguishes lithogenic from normal gallbladder bile. Accelerated nucleation of cholesterol

monohydrate in bile may be due to either an excess of pronucleating factors or a deficiency of antinucleating factors. Non-mucin and mucin glycoproteins and lysine phosphatidyl choline appear to be pronucleating factors, while apolipoproteins Al and All and other glycoproteins are antinucleating factors.

A fourth important mechanism in cholesterol gallstone formation concerns biliary sludge. The presence of biliary sludge implies two abnormalities (1) The normal balance between gall bladder mucin secretion and elimination has become deranged, (2) Nucleation of biliary solutes has occurred. Biliary sludge can develop with disorders that cause gall bladder hypomotility.

The isoprenoid pathway is an important metabolic pathway regulating cell metabolism. It produces three important components - cholesterol, dolichol and endosymbiotic archaeal digoxin. Cholesterol is an important component of gallstones. Dolichol is important in N-glycosylation and synthesis of mucoproteins. Mucoproteins are important pronucleating factors. Archaeal digoxin is an important endogenous regulator of neurotransmitter transport and can modulate gallbladder contractility. Therefore it was considered pertinent to study the isoprenoid pathway it patients presenting with gallstones.

Results

(1) The results showed that HMG C0A reductase activity, serum digoxin and dolichol were increased in patients with gallstones indicating upregulation of the isoprenoid pathway but serum ubiquinone, RBC sodium-potassium ATPase activity and serum magnesium were reduced.

(2) The results showed that the concentration of tryptophan, quinolinic acid, strychnine, nicotine and serotonin was found to be higher in the plasma of patients with gallstones while that of tyrosine, dopamine, morphine and norepinephrine was lower.

(3) The results show an increase in the concentration of serum carbohydrate components of glycoproteins (hexose, fucose and sialic acid) in patients with gallstones. The increase in the carbohydrate components - total hexose, fucose and sialic acid - in patients with gallstones was not to the same extent suggesting qualitative change in glycoprotein structure. The activity of glycohydrolases (beta galactosidase, beta fucosidase and beta glucosidase) showed significant increase in the serum of patients with gallstones.

(4) The cholesterol: phospholipid ratio of the RBC membrane was increased in patients with gallstones.

(5) The results showed that HMO CoA reductase activity serum digoxin and dolichol were increased and ubiquinone reduced in left handed / right hemispheric dominant individuals. The results also 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 also 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 Gall Stones

The archaeaon steroidelle DXP pathway and the upregulated pentose phosphate pathway contribute to digoxin synthesis. The study shows an upregulated Isoprenoid pathway in gallstones with Increased HMG CoA reductase activity. Also the digoxin and dolichol levels were high and serum magnesium and RBC Na^{+}-K^{+} ATPase activity reduced. Digoxin has been demonstrated to be synthesized by the isoprenoid pathway.

The increase in endogenous digoxin, a potent inhibitor or membrane Na^{+}-K^{+} ATPase, can decrease this enzyme activity. In gallstones, there was significant inhibition of the RBC membrane Na^{+}-K^{+} ATPase. The inhibition of Na^{+}-K^{+} ATPase by digoxin 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 cell and ATP dependent sequestration of calcium within the endoplasmic reticulum. The Mg^{++} 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 digoxin. Low intracellular Mg^{++} and high intracellular Ca^{++} consequent to Na^{+}-K^{+} ATPase inhibition appear to be crucial to the pathophysiology of gallstones. Serum Mg^{++} was assessed in gallstones and was found to be reduced.

Magnesium can promote biliary secretion and in the presence of hypomagnesemia there is stagnation of biliary secretion.

Archaeal Digoxin and Regulation of Neurotransmitter Synthesis and Function in Relation to Gallstones

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 gallstones. This could be due to the fact that digoxin can regulate neutral amino acid transport system with preferential promotion of tryptophan transport over tyrosine. The decrease in membrane Na^+-K^+ ATPase activity in patients with gallstones 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. This particular neurotransmitter pattern could contribute to gall bladder hypomotility. Biliary sludge can develop with disorders that cause gall bladder hypomotility.

Thus in the right hemisphere dominant hyperdigoxinemic state there is upregulated serotoninergic, cholinergic and glutamatergic transmission and downregulated dopaminergic, glycinergic and noradrenergic transmission. The same neurotransmitter pattern is seen in patients developing gallstones. Gallstones thus have a tendency to develop in right hemispheric dominant individuals.

Archaeal Digoxin and Regulation of Golgi Body / Lysosomal Function in Relation to Gallstones

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. 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 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 in spite of increased activity of many glycohydrolases may be due to their possible resistance to cleavage by glycohydrolases consequent to qualitative change in their structure. Altered mucoproteins can contribute to formation of gallstones. Non-mucin and mucin glycoproteins and lysine phosphatidyl choline appear to be pronucleating factors. Thus altered mucoproteins and glycoproteins of the bile can lead on to the formation of gallstones.

Archaeal Digoxin and Alteration in Membrane Structure and Membrane Formation in Relation to Gall Stones

The archaeaon steroidelle, glycosaminoglycoid and fructosoid contribute to cell membrane formation synthesizing cholesterol by the DXP pathway and glycosaminoglycans by fructolysis. 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 the 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.

Archaeal Digoxin and Hemispheric Dominance in Relation to Gall Stones

The archaeaon related organelle - steroidelle, neurotransminoid and vitaminocyte contribute to hemispheric dominance. Thus the isoprenoid pathway upregulation and digoxin can contribute to the genesis of gallstones by three mechanisms. (1) Increased cholesterol and decreased phospholipid in the bile, (2) Altered biliary mucoproteins, and (3) Altered gall bladder motility. The upregulatory isoprenoid pathway and elevated digoxin is seen in right hemispheric dominant individuals. Thus right hemispheric dominance can lead on to the formation of gallstones. Hemispheric dominance has been associated with several systemic diseases.

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