GLOBAL WARMING

Archaea and Viroid Induced Symbiotic Human Evolution – Vitaminocyte Organelle and Brain Evolution

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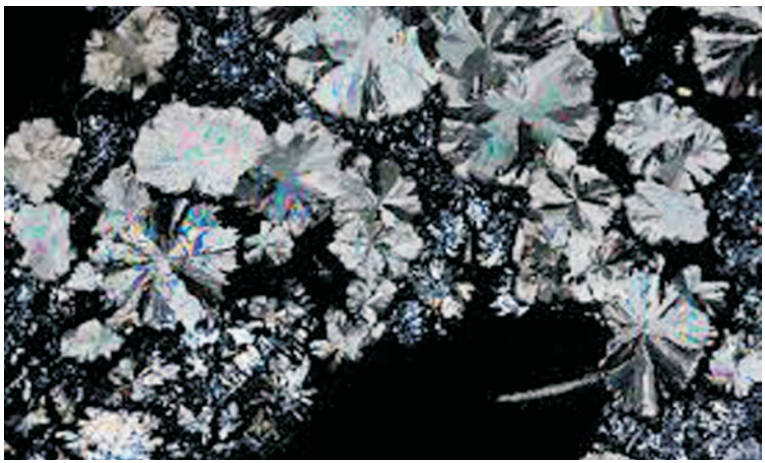

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Chapter 1

The Vitaminocyte and Endogenous Human Genomic Archaeal Sequence Expression

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.

Fructolysis in the archaeaon vitaminocyte can contribute to vitamin C and vitamin E synthesis. The Neanderthals have a higher density of archaeal symbiosis resulting in increasing number of vitaminocyte organelle. This results in increased synthesis endogenous ascorbic acid and tocopherol in Neanderthals which function as free radical scavengers. Free radicals are important in neuronal function and NMDA activity. Free radicals increase NMDA activity. Free radicals are also important as messengers of human endogenous retroviruses. Free radicals mediate the expression and reintegration into the genome where it functions as jumping genes contributing to genomic plasticity and dynamicity. Genomic dynamicity is consequently absent in Neanderthals due to higher synthesis of ascorbic acid and tocopherol by the vitaminocyte and free radical deficiency. Genomic dynamicity and HERV sequences contribute to development of synaptic connectivity, formation of cerebral cortex and brain size. This leads onto defective NMDA transmission, cerebral cortical dysfunction and cerebellar dominance in Neanderthals. The brain size in Neanderthals is bigger than the newer species of homo sapiens. The homo sapiens on the other hand has less of archaeal symbiotic density and fewer archaeal vitaminocyte organelle. The gene for vitamin C synthesis is already mutated in all human species and in the presence of decreased density of archaeal vitaminocyte organelle in homo sapiens there is deficiency of ascorbic

acid and tocopherols in homo sapiens. This results in reduced free radical scavenging, increased free radicals in the system, increased expression and reintegration of HERV sequences in to the genome. There is increased genomic dynamicity and plasticity and a dominant cerebral cortical function in homo sapien population and a smaller brain size. Thus the archaeal symbiosis and the resultant vitaminocyte organelle decides the human species type, brain size, cerebral cortical versus cerebellar dominance and the human consciousness.

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 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 D1,3-biphosphoglycerate which is then converted to 3-phosphoglycerate. The 3-phosphglycerate 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 catabolized 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.

The endosymbiotic archaea gets integrated into the human genome by the action of HERV integrase. This forms human genomic endosymbiotic archaeal sequences which can regulate genomic function. The redox stress and osmotic stress of global warming can induce the expression of endogenous genomic archaeal sequences. This results in induction of the shikimic acid pathway. The redox and osmotic stress of global warming results in induction of aldose reductase which converts glucose to sorbitol. Sorbitol is acted upon by sorbitol dehydrogenase converting sorbitol to fructose. Fructose enters the fructolytic pathway by the action of the enzymes fructokinase and aldolase B. The fructosylation of glycolytic enzymes blocks the glycolytic pathway. The fructosylated glycolytic enzymes become antigenic and antibodies are developed against glycolytic enzymes suppressing glycolysis further. The endosymbiotic archaea synthesize digoxin depletes intracellular magnesium

blocking the glycolytic pathway. This results in utilization of glycolytic metabolites phosphoenol pyruvate for the shikimic acid pathway.

The shikimic acid is converted to tyrosine from which parahydroxy phenyl pyruvate is generated. The parahydroxy phenyl pyruvate is converted to homogentisate. The fructolysis by the action of the enzymes fructokinase and aldolase B generates glyceraldehyde 3-phosphate and pyruvate which is then converted to 1-deoxy D-xylulose 5-phosphate which is then converted to 3-isopentenyl pyrophosphate and dimethyl allyl pyrophosphate. The homo gentisate and 3-isopentenyl pyrophosphate/dimethyl allyl pyrophosphate combines to form 2-methyl 6-phytyl benzoquinone which is converted to alpha tocopherol. The 2-methyl 6-phytyl benzoquinone is converted to 2,3-dimethyl 6-phyto benzoquinone and then gamma tocopherol. Thus the archaeaon vitaminocyte is capable of vitamin E synthesis.

The archaeaon vitaminocyte is capable of synthesizing vitamin C or ascorbate. Ascorbate is synthesized from UDP D-glucose which is converted to UDP D-glucuronic acid. D-glucouronic acid is acted upon by aldoketoreductases and aldehyde reductase to generate L-gulonate. L-gulonate is acted by lactonase to generate L-gulonolactone. L-gulonolactone is acted upon by L-gulonolactone oxidase to generate ascorbic acid. The GULO sequence in humans is mutated. The expression of endogenous genomic archaeal sequences consequent to redox and osmotic stress of global warming induces L-gulo oxidase inducing vitamin C synthesis. Thus endogenous genomic archaeal sequences expression can induce vitamin C synthesis.

The shikimic acid pathway induced by expression of endogenous genomic archaeal sequences can also induce pantothenic acid synthesis. Pantothenic acid is involved in the synthesis of coenzyme A.

Thus the global warming induced redox stress and osmotic stress induces the expression of endogenous genomic archaeal sequences and new archaeaon organelle with specialized function called the vitaminocyte with a predominant antioxidant function.

Table 1

	Serum fructose		**Serum fructokinase**		**Aldolase B**		**Total GAG**	
	Mean	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**
Normal	2.50	0.195	8.5	0.405	3.50	1.304	3.50	0.707
Sy X	21.20	5.201	18.91	2.942	8.01	1.244	18.46	4.623
CAD	31.40	3.212	21.18	2.267	9.02	0.667	21.41	1.653
CVA	29.98	4.002	24.96	3.829	11.72	1.397	21.65	2.755
DCM/EMF	32.04	4.955	21.37	2.050	10.89	1.344	20.12	2.855
Tumour	27.94	3.732	22.29	1.237	9.46	1.386	20.89	1.651
Schizo	31.14	4.446	22.19	2.634	11.63	3.081	21.50	1.714
Autism	28.66	5.089	24.09	2.146	12.30	1.621	22.60	3.054
AD	33.13	2.754	19.87	1.646	11.37	1.406	22.97	3.662
PD	30.24	4.551	22.72	1.955	11.93	2.999	20.13	1.507
MS	29.88	5.150	22.29	1.641	10.87	1.895	23.47	2.878
Lupus	33.11	4.509	20.24	1.639	11.59	0.767	20.62	3.504
CRF	30.24	3.209	22.52	3.196	11.76	1.596	20.55	2.164
ILD	32.04	5.295	22.37	1.585	11.84	0.963	21.49	1.544
COPD	26.68	4.266	21.78	2.253	10.62	1.703	22.84	2.965
BA	33.59	3.938	22.45	2.472	11.30	0.783	23.50	3.225
Cirrhosis	32.53	6.737	23.00	1.722	10.49	1.373	20.57	1.878
IBD	31.75	5.236	21.89	2.292	11.63	1.304	22.46	4.030
MAO	31.53	4.507	22.07	2.324	11.32	1.343	23.89	2.936
IBS	29.90	4.299	22.52	1.995	10.93	1.498	22.09	2.797
PUD	32.49	6.487	21.89	3.431	10.85	1.606	25.27	3.693
EMF	30.79	4.740	21.47	3.056	11.65	1.427	20.54	2.192
CCP	31.16	3.635	22.42	3.126	10.49	1.476	17.94	2.276
MNG	32.24	5.864	20.46	2.864	9.82	1.135	21.42	2.662
Muc ANG	30.40	6.405	23.30	4.089	11.08	1.360	22.16	3.543
DBJD	33.06	5.970	22.42	3.714	11.21	1.660	17.76	3.556
Spondylosis	32.70	4.430	21.92	1.840	14.10	2.423	26.80	3.679
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
Sy X	262.40	32.790	0.82	0.143	6.21	0.452	2.20	0.583
CAD	252.44	35.388	0.85	0.085	9.00	0.485	2.23	0.567
CVA	297.64	36.410	0.79	0.081	9.34	1.641	2.02	0.303
DCM/EMF	302.00	25.166	0.77	0.151	9.26	1.048	1.41	0.310
Tumour	277.60	34.613	0.80	0.136	7.88	0.847	1.45	0.415
Schizo	244.00	31.383	0.72	0.102	8.65	0.701	1.35	0.319
Autism	284.30	19.743	0.87	0.072	8.14	0.538	1.35	0.218
AD	244.70	22.106	0.82	0.121	8.74	0.687	1.70	0.361
PD	284.30	19.945	0.83	0.090	8.90	0.579	2.03	0.232
MS	289.89	23.406	0.74	0.115	9.59	0.783	1.80	0.402
Lupus	294.00	39.903	0.78	0.161	8.34	0.712	1.81	0.691
CRF	272.10	31.057	0.86	0.101	7.76	0.798	1.67	0.363
ILD	292.10	26.337	0.78	0.135	8.40	0.442	1.72	0.360
COPD	306.40	24.419	0.74	0.136	9.62	0.952	1.63	0.440
BA	293.80	31.555	0.72	0.134	9.51	1.059	2.10	0.572
Cirrhosis	271.80	37.818	0.79	0.150	8.12	0.747	1.67	0.377
IBD	287.50	20.414	0.77	0.102	9.44	0.924	1.30	0.223
MAO	316.20	31.283	0.76	0.103	9.32	0.864	1.41	0.307
IBS	279.10	27.606	0.77	0.095	9.68	1.060	1.44	0.350
PUD	285.70	22.628	0.76	0.126	9.77	0.957	1.14	0.134
EMF	270.10	28.792	0.81	0.079	8.76	0.881	1.31	0.329
CCP	293.00	28.111	0.78	0.145	8.30	0.966	1.31	0.265
MNG	262.70	30.324	0.83	0.091	8.04	0.667	1.55	0.493
Muc ANG	275.40	30.351	0.77	0.138	8.83	0.633	1.47	0.466
DBJD	282.60	27.573	0.79	0.136	8.28	0.978	1.89	0.315
Spondylosis	295.30	16.600	0.72	0.108	10.21	1.310	1.54	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
Sy X	0.51	0.185	17.04	3.556	1.73	0.371
CAD	0.55	0.154	16.06	6.811	1.78	0.349
CVA	0.66	0.182	21.79	4.567	1.50	0.307
DCM/EMF	0.49	0.197	18.68	4.585	1.54	0.471
Tumour	0.42	0.182	19.93	2.421	1.39	0.253
Schizo	0.40	0.142	22.02	11.954	1.31	0.235
Autism	0.20	0.060	19.27	2.201	1.20	0.205
AD	0.38	0.205	18.87	3.899	1.37	0.305
PD	0.42	0.208	20.11	3.220	1.44	0.342
MS	0.39	0.124	18.93	6.447	1.78	0.355
Lupus	0.42	0.116	18.59	3.721	1.48	0.258
CRF	0.55	0.220	17.06	3.449	1.32	0.358
ILD	0.52	0.202	18.80	3.221	1.41	0.355
COPD	0.59	0.159	18.14	3.500	1.71	0.509
BA	0.36	0.177	15.33	3.212	1.72	0.277
Cirrhosis	0.48	0.273	18.60	2.915	1.52	0.287
IBD	0.43	0.163	17.06	4.366	1.40	0.298
MAO	0.44	0.230	19.08	3.396	1.48	0.220
IBS	0.57	0.242	19.99	2.637	1.39	0.289
PUD	0.51	0.221	20.63	5.116	1.42	0.329
EMF	0.42	0.182	14.55	3.133	1.24	0.239
CCP	0.50	0.149	17.82	2.889	1.44	0.234
MNG	0.47	0.151	17.59	2.469	1.44	0.270
Muc ANG	0.36	0.114	18.63	3.147	1.48	0.271
DBJD	0.54	0.211	22.48	4.638	1.33	0.302
Spondylosis	0.40	0.134	19.91	5.099	1.49	0.282
F value	14.091		21.073		58.769	
p value	< 0.01		< 0.01		< 0.01	

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Chapter 2

The Endosymbiotic Archaea, Fructose Disease and Global Warming

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 adipogenesis. Fructose induces ChREBP and SREBP elements. This results in increased hepatic lipogenesis by the induction of the enzyme fatty acid synthase, acetyl CoA carboxylase and steroyl CoA desaturace. This increases fatty acids and cholesterol synthesis. Fructose is a lipophilic carbohydrate. Fructose can be converted to glycerol 3-phosphate and fatty acids involved in

triglyceride synthesis. Fructose administration leads to increase in triglycerides and VLDL. Fructose consumption leads to insulin resistance, fat accumulation in visceral organs like liver, heart and kidney, insulin resistance, dyslipidemia with increased triglycerides, VLDL and LDL as well as the metabolic syndrome. The metabolic syndrome X can be considered as a fructolytic syndrome. Fructose will increase lipid storage and promote insulin resistance. Fructose can fructosylate proteins producing dysfunction. Fructose has no effect upon ghrelin and leptin in the brain and can lead to increased feeding behaviour. Glucose decreases ghrelin and increases leptin levels. This leads to suppression of appetite. Thus fructose can modulate eating behaviour leading onto obesity. Fructose results in NFKB activation and TNF alpha secretion. TNF alpha can modulate the insulin receptor producing insulin resistance and metabolic syndrome X. Fructose can also lead to leptin resistance and obesity. There is an epidemic of metabolic syndrome X in relation to global warming.

Fructolysis in the archaeaon vitaminocyte can contribute to vitamin C and vitamin E synthesis. The Neanderthals have a higher density of archaeal symbiosis resulting in increasing number of vitaminocyte organelle. This results in increased synthesis endogenous ascorbic acid and tocopherol in Neanderthals which function as free radical scavengers. Free radicals are important in neuronal function and NMDA activity. Free radicals increase NMDA activity. Free radicals are also important as messengers of human endogenous retroviruses. Free radicals mediate the expression and reintegration into the genome where it functions as jumping genes contributing to genomic plasticity and dynamicity. Genomic dynamicity is consequently absent in Neanderthals due to higher synthesis of ascorbic acid and tocopherol by the vitaminocyte and free radical deficiency. Genomic dynamicity and HERV sequences contribute to development of synaptic connectivity, formation of cerebral cortex and brain size. This leads onto defective NMDA transmission, cerebral cortical

dysfunction and cerebellar dominance in Neanderthals. The brain size in Neanderthals is bigger than the newer species of homo sapiens. The homo sapiens on the other hand has less of archaeal symbiotic density and fewer archaeal vitaminocyte organelle. The gene for vitamin C synthesis is already mutated in all human species and in the presence of decreased density of archaeal vitaminocyte organelle in homo sapiens there is deficiency of ascorbic acid and tocopherols in homo sapiens. This results in reduced free radical scavenging, increased free radicals in the system, increased expression and reintegration of HERV sequences in to the genome. There is increased genomic dynamicity and plasticity and a dominant cerebral cortical function in homo sapien population and a smaller brain size. Thus the archaeal symbiosis and the resultant vitaminocyte organelle decides the human species type, brain size, cerebral cortical versus cerebellar dominance and the human consciousness.

Fructose can activate the sympathetic nervous system. This leads to hypertension and increase in heart rate. Fructose is involved in left ventricular hypertrophy, increase in left ventricular mass and decrease in left ventricular ejection fraction in hypertension. Fructose suppresses the parasympathetic nervous system. Fructose acts as a key inducer for uncontrolled proliferation and hypertrophy of the cardiac musculature consequent to hypertension. The heart uses beta oxidation of fatty acids to generate energy. In the setting of anerobic glycolysis consequent to myocardial infarction and hypertensive hypertrophy of the heart, there is induction of HIF alpha. This produces increase in ketohexokinase C in the heart which phosphorylates fructose. Ketohexokinase C is a predominant liver enzyme as fructose metabolism is primarily focused in the liver. In the setting of anerobic glycolysis ketohexokinase C is also produced in the brain and the heart. Ketohexokinase A is the predominant enzyme in the heart and brain. In the setting of anerobic glycolysis ketohexokinase A which preferentially metabolizes glucose is

converted to ketohexokinase C metabolizing fructose by the mechanism of RNA splicing. Anerobic conditions can induce HIF alpha which activates the splicing factor SF3B1. Thus HIF alpha induced by glycolysis induces SF3B1 which induces ketohexokinase C producing fructolysis in the heart. The fructose is converted to lipids, glycogen and glycosaminoglycans in the heart producing cardiac hypertrophy. Fructose metabolism is not under regulatory control of the key enzyme phosphofructokinase by citrate and ATP. The fructolytic pathway functions as a rogue pathway not under any regulatory control. Fructose is a key contributor. The sympathetic overactivity and parasympathetic blockade consequent to fructose can produce immune activation. The sympathetic overactivity and parasympathetic blockade can lead to dysregulation of the nervous system.

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

Fructose increases flux through the pentose phosphate pathway. This increases the availability of hexose sugars like ribose for nucleic acid synthesis. This increases DNA synthesis. There is also consequent increase in protein synthesis. The tumour cells can slurp up fructose. Tumour cells utilise fructose for proliferation. The fetal cells like tumour cells also utilize fructose for proliferation. Fructose can promote metastatic deposits. The tumour cells use fructose differently from glucose. Cancer cells utilize fructose to support

proliferation and metastasis. Fructose increases nucleic acid synthesis. Fructose can help the cancer cells to grow fast by inducing the transketolase enzyme and the pentose phosphate pathway. Fructose administration increases redox stress, DNA damage and cell inflammation all contributing to oncogenesis. Fructose is the most abundant sugar in the fetal tissues and is important in the development of fetus by promoting cell proliferation. Fructose is 20-times more concentrated in the fetal blood than glucose. Sperm cells and ova also use fructose for metabolism and energy. Thus all rapidly proliferating cells - cancer cells, fetal cells and reproductive cells depends upon fructolysis. Fructose is the principal diet of the cancer cells. Global warming and archaeal growth results in HIF alpha induction. HIF alpha induces tumour growth. HIF alpha also increases glycolysis. But archaeal induced HIF alpha also induces aldose reductase which converts glucose to fructose and metabolism proceeds along the fructolytic pathway. Fructosylation of glycolytic enzymes brings glycolysis to a halt. Fructosylation of mitochondrial PT pore hexokinase can result in PT pore dysfunction and cell proliferation. The fructolytic pathway is the principal energetic pathway for rapidly proliferating cancer cells, fetal cells and stem cells. The global warming will induce the Warburg phenotype of the fructolytic variety. This leads to an epidemic of cancer. There is an epidemic of cancer in relation to global warming. The fructolytic pathway can lead to increased DNA synthesis and RNA synthesis due to flux via the pentose phosphate pathway. The fructolytic pathway can be directed to the GABA shunt generating succinyl CoA and glycine. These are substrates for porphyrin templates to form RNA viroids. The archaeal induced redox stress can induce endogenous HERV expression and reverse transcriptase expression. The RNA viroids are converted by HERV reverse transcriptase to corresponding DNA and integrated into the genome by HERV integrase. The integrated RNA viroid related DNA can function as jumping genes producing genomic plasticity and genomic change.

Fructose as said before induces the thiamine dependent transketolase flux. It increases both the oxidative and non oxidative pentose phosphate pathway. This increases nucleic acids and glycosaminoglycan synthesis. Fructose is converted to fructose 1-phosphate which is acted upon by aldolase B converting it into glyceraldehyde and dihydroxy acetone phosphate. Glyceraldehyde is converted glyceraldehyde 3-phosphate by triokinase. DHAP can be converted to glyceraldehyde 3-phosphate by the enzyme triose phosphate isomerase. Glyceraldehyde 3-phosphate can be converted to pyruvate. This pyruvate can be channeled to gluconeogenesis and glycogen storage by the action of the enzyme pyruvate carboxylase. This results in the conversion of glyceraldehyde 3-phosphate to pyruvate and via pyruvate carboxylase to glucose 1-phosphate. Glucose 1-phosphate is converted to glycogen polymers. Thus fructolysis results in glycogen storage. The pyruvate that is generated by fructolysis is converted to glutamate which can enter the GABA shunt pathway. The GABA shunt pathway generates glycine and succinyl CoA which are substrates for ALA synthesis. Thus fructolysis stimulates porphyrin synthesis. The porphyrins can self organize to form supramolecular arrays called porphyrions. Porphyrions can self replicate by using other porphyrions as templates. Porphyrions can have energetic and ATP synthesis by electron or photon transport. Porphyrions are dipolar molecules and in the setting of digoxin induced membrane sodium potassium ATPase inhibition can generate a pumped phonon system induced quantal state and quantal perception. They can function as quantal computers with information storage. The porphyrions are basic self replicating living structures. The porphyrins can act as a template for the formation RNA, DNA and proteins. The RNA viroids, the DNA viroids and proteins generated by abiogenesis on porphyrin templates can self organize to form primitive archaea. The archaea are thus capable of abiogenic replication on porphyrin templates. The archaea can induce HIF alpha and further aldose reductase induction promoting fructolysis.

Fructose is an addictive substance. Fructose affects the hedonic centres in the brain concerned with pleasure and reward. In the addiction scale fructose is more addictive then cocaine and cannabis. Fructose decreases BDNF. Low BDNF produces changes in the brain resulting in schizophrenia and depression. Fructose can also produce chronic inflammation involved in schizophrenia. The fructolytic pathway is important in the genesis of psychiatric disorders. The increased fructolysis can lead to fructosylation of lipoproteins especially apoprotein E and apoprotein B. Apo B can undergo lysine fructosylation leading to defective LDL and cholesterol uptake by the brain. This results in autism and schizophrenia. Fructolysis leads to cholesterol depletion of the brain. Cholesterol is required for the formation of synaptic connections and cerebral cortex. This leads to cerebral cortical atrophy and cerebellar dominance in the presence of cholesterol depletion. This can contribute to the genesis of the cerebellar cognitive affective syndrome, the basis of schizophrenia and autism. There is an epidemic of schizophrenia and autism correlating with global warming. Fructosylation of LDL and brain cholesterol depletion can lead to dysfunction in synaptic transport. There is more release of glutamate into the synaptic from the presynaptic neuron consequent to a presynaptic neuron membrane dysfunction as a result of cholesterol depletion. This contributes to glutamate excitotoxicity. 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 secretion as a result of IAPP and abnormal prion like tumour suppressor protein producing tumours. These prion diseases induced by archaeal RNA viroids are also transmissible. Thus global warming related fructolysis leads to archaeal induced RNA viroidal mediated prion disease and amyloidosis. This raises the spectacle of a Cassandra syndrome of human extinction.

Fructose is phosphorylated to fructose 1-phosphate by ketohexokinase C or fructokinase. Fructose 1-phosphate is converted to glyceraldehyde which is then converted to glyceraldehyde 3-phosphate and dihydroxy acetone phosphate

(DHAP). Fructose 1-phosphate is cleaved to DHAP and glyceraldehyde 3-phosphate. DHAP can enter the glycolytic pathway or can go to gluconeogenetic pathway. DHAP generated from fructose 1-phosphate by the action of aldolase B is acted upon by triose phosphate isomerase converting it into glyceraldehydes 3-phosphate. Glyceraldehyde 3-phosphate can be fructolysed to pyruvate and acetyl CoA. Acetyl CoA can be used for cholesterol synthesis for storage. The pyruvate generated from glyceraldehydes 3-phosphate can be converted to the citrate which can be used for fatty acid synthesis by the action of enzymes acetyl CoA carboxylase, fatty acid synthase and malonate dehydrogenase. Glyceraldehyde is acted upon by alcohol dehydrogenase which converts it into glycerol. Glycerol is acted upon by glycerolkinase converting it into glycerol phosphate used for phosphoglyceride and triglyceride synthesis. Glyceraldehyde can also be acted upon by triokinase converting it into glyceraldehydes 3-phosphate which is then converted to DHAP by triose phosphate isomerase. Glyceral phosphate and dihydroxy acetone phosphate are interconvertible by the action of the enzyme glycerol phosphate dehydrogenase. Glycerol and fatty acids generated by fructolysis contribute to lipid synthesis and fat is stored. Fructose does not increase insulin secretion and doesn't need insulin for transport into the cell. Fructose is transported by the fructose transporter GLUT-5. Ketohexokinase C is exclusively seen in the liver which is the principal site of fructose metabolism. In the presence of hypoxia and anerobic states, there is induction of HIF alpha which can induce ketohexokinase C or fructokinase in the liver, kidney, gastrointestinal tract, brain and heart. Fructose 1-phosphate by-passes the enzyme phosphofructokinase which is the key regulatory enzyme the glycolytic pathway. Phosphofructokinase is inhibited by ATP and citrate. Thus stress induced fructolysis is an unregulated pathway not amenable to metabolic switches. Fructose does not depend upon insulin for its transport and fructolysis.

Therefore fructolysis is not under insulin or endocrine control. It is an unregulated pathway.

The phosphorylation of fructose depletes the cell of ATP. Ketohexokinases preferentially phosphorylate fructose over glucose if it is available. In the presence of redox stress, osmotic stress and archaea/viroids aldose reductase is induced converting all the glucose to fructose. Glycolytic pathway comes to a halt as no ATP is available for phosphorylation of glucose and glucose as such gets converted to fructose. The fructose phosphorylation depletes the cell of ATP. ATP is converted to ADP and AMP which is deaminated to produce uric acid. Fructose increases flux in the pentose phosphate pathway increasing nucleic acid synthesis. Purine degradation results in hyperuricemia. Thus fructolysis results in increase in uric acid accumulation in the body. Uric acid will suppress the mitochondrial oxidative phosphorylation as well as produce endothelial dysfunction. The depletion of ATP by fructose phosphorylation results in membrane sodium potassium ATPase inhibition. This results in reduced energy needs of the cell as 80 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 result in obesity. The cerebellar cognitive affective syndrome results in a hypersexual state. The fructolysis and fructose can activate NFKB producing immune activation. The fructosylation of glycolytic and mitochondrial proteins suppresses the body's normal energetic which depends upon glycolysis and mitochondrial oxidative phosphorylation. Fructosylation of proteins results in blockade of glycolysis and mitochondrial oxidative phosphorylation. The body's energy needs are produced by fructolysis, porphyrin array mediated electron transport chain and ATP synthesis as well as membrane sodium potassium ATPase inhibition relation ATP synthesis. This produces a new species by archaeal symbiosis consequent to global warming - the homo neanderthalis. This can be called as the tropical hibernatory syndrome consequent to global warming.

This can be called also as a fructose disease. Endosymbiotic archaea and viroids induce aldose reductase and converts body glucose to fructose leading to preferential fructose phosphorylation by ketohexokinase C. Fructolysis results in fructose 1-phosphate being acted upon by aldolase B resulting in the formation of glyceraldehyde and dihydroxy acetone phosphate. Glyceraldehyde can be converted to glyceraldehyde 3-phosphate and this contributes to pyruvate formation. Pyruvate enters the GABA shunt resulting in the formation of succinyl CoA and glycine. They are substrates for porphyrin synthesis and

porphyrion formation. The porphyrins form a template for the formation of RNA viroids, DNA viroids, prions, isoprenoids and polysaccharides. They can symbiose together to form primitive archaea. The archaea can further induce HIF alpha, aldose reductose and fructolysis resulting in further porphyrinogenesis and archaeal self replication. The archaea by methanogenesis contributes to global warming which leads to further archaeal growth and a vicious cycle with no regulatory switches. The fructolytic pathway induced by archaea by-passes regulatory enzyme phosphofructokinase and is practically unregulated. Fructolytic pathway contributes to glycogen, lipids, cholesterol, hexose sugars and mucopolysaccharides synthesis and storage. This leads onto a hibernatory state and archaeal symbiosis induced species change resulting in neanderthalisation of the homo sapien species. The digoxin and fructose phosphorylation induced ATP depletion leads to membrane sodium potassium ATPase inhibition, sparing of ATP and tissue hibernation as most of the energy needs of the body are for the working of the sodium potassium pump. The cholesterol that is synthesized by fructolysis is catabolized cholesterol oxidases for archaeal energetics. Archaea also derives its energy from a primitive form of electron transport chain functioning in self replicating porphyrin arrays. The archaeal digoxin induced sodium potassium ATPase inhibition can lead to membrane ATP synthesis. The archaea and the new human species phenotype derive its energy from the above mentioned mechanism. The glycolytic enzymes and the mitochondrial PT pore hexokinase are fructosylated making them dysfunction. The fructosylated glycolytic enzymes lead to generation of antiglycolytic enzyme antibodies and disease states. The human body's principal method of energetics tissue glycolysis and oxidative phosphorylation comes to a grinding halt. The human body is taken over by the overgrowth of endosymbiotic archaea and assumes hibernatory state with accumulation of glycogen, lipids, mucopolysaccharides and nucleic acids. The catabolic

pathways for energy generation related to glucose, glycolysis and oxphos scheme stops. The human body can depend upon ketogenesis from fat and proteins. The upregulated fructolytic pathway generates phosphoglycerate which converted to phosphoserine and glycine. They can be converted to other amino acids and used for ketogenesis. The body assumes a high BMI index and obesity with visceral fat storage and adiposity akin to the Neanderthal metabolic phenotype. Digoxin induced membrane sodium potassium ATPase inhibition results in cortical dysfunction. The brain porphyrins can form a quantal pumped phonon system resulting in quantal perception and low level EMF absorption. This leads to prefrontal cortex atrophy and cerebellar dominance. Fructose itself leads to sympathetic hyperactivity and parasympathetic blockade. This leads onto a functional form of cerebellar cognition and quantal perception resulting in a new brain phenotype. The cerebellar cognitive syndrome leads to a robotic human phenotype. The phenotype is impulsive, has extrasensory perception and has less of speech production. Communication is by symbolic acts. The cerebellar phenotype doesn't have a cortical control and contributes to surrealistic behavior patterns. This produces impulsive behavior and an epidemic of surrealism where the rational prefrontal cortex becomes extinct. This leads to extremes of spirituality, violent and terroristic behavior and hypersexual states contributing to a state of trancedence underlined and reinforced by quantal perception. Cerebellar phenotype owing to its quantal perception behaves as a community and not as an individual. This creates new social and psychological phenotypes. Fructose induces NFKB and immune activation. This results in an immune activatory phenotype. Cultured T-reg cells on high fructose diet have 62% less IL-40 secretion than controls. This results in a hyperimmune state with fructosylated proteins acting as antigens. The fructolytic pathway can lead to increased DNA synthesis and RNA synthesis due to flux via the pentose phosphate pathway. The fructolytic pathway can be

directed to the GABA shunt generating succinyl CoA and glycine. These are substrates for porphyrin templates to form RNA viroids. The archaeal induced redox stress can induce endogenous HERV expression and reverse transcriptase expression. The RNA viroids are converted by HERV reverse transcriptase to corresponding DNA and integrated into the genome by HERV integrase. The integrated RNA viroid related DNA can function as jumping genes producing genomic plasticity and genomic change. This produces a new genotype. Fructosylation of body proteins and enzymes results in a protein processing defect resulting in loss of protein function. The human cell function due to protein fructosylation, protein processing defects and protein conformational defects comes to a grinding halt. Fructolytic pathway generates porphyrin arrays induced ATP production, membrane sodium potassium ATPase inhibition induced ATP synthesis and fructolysis induced ATP generation. This provides energy for porphyrin template induced archaeal replication. The digoxin and fructose phosphorylation induced ATP depletion produces cell membrane sodium potassium ATPase inhibition and a hibernatory state. This leads onto a somnolent sleepy state. The cholesterol catabolism by cholesterol oxidases for archaeal energetics leads to defective sex hormone synthesis. This leads onto an asexual androgynous state. The cerebellar cognitive syndrome due to prefrontal cortical atrophy consequent to porphyrion induced low level EMF perception produces a hypersexual state. This results in male-female equidominance and changes in sexual behavior of the population. Thus the fructose disease consequent to global warming results in a new neuronal, immune, metabolic, sexual and social phenotype. The human body is converted to a zombie for the global warming related endosymbiotic archaea to thrive. The neuronal, metabolic, sexual and social phenotype creates the necessary environment endosymbiotic archaeal multiplication and the human body is converted to a zombie phenotype. This can be called as a hibernatory zombie syndrome. Due

to the new sexual and social phenotype with asexuality and hypersexuality and female-male equidominance the human population falls. The global warming and archaeal induction of HIF alpha resulting in the Warburg phenotype leads to changes in the metabolic scheme of the cells producing body cell transformation to stem cells. The stem cells depend upon glycolysis or fructolysis for energy needs. The Warburg phenotype produces an acidic pH which can result in conversion of body cells to stem cells. The stem cells conversion results in loss of tissue function. The cerebral cortex synaptic connectivity is lost and becomes dysfunction leading to subcortical cerebellar dominance. The immune stem cells proliferate producing an autoimmune disease. The various tissue cells the specialized function like neuron, nephron and muscle cell all because of stem cell conversion becomes dysfunctional. This produces a stem cell syndrome with human somatic cells being converted to stem cells with loss of function and uncontrolled proliferation. The fructosylation of proteins results in protein function defects. The fructosylation of LDL results in defective cholesterol transport to the cells. This results in steroidal hormone synthesis defects. Cholesterol is required for formation of synaptic connectivity and this leads to cerebral cortical dysfunction. The hemoglobin becomes fructosylated and oxygen transport is affected. This leads to hypoxia and anerobic states. The hypoxia and anerobic states induces HIF alpha and the Warburg fructolytic phenotype. The HIF alpha also induces aldose reductase converting glucose to fructose and inducing the fructolytic scheme. The fructolysis induced GABA shunt pathway and porphyrin synthesis results in further archaeal porphyrin template related replication. This results in further archaeal induced fructolysis and the vicious irreversible cycle proceeds. The uncontrolled growth of archaea leads to still further global warming. The world of endosymbiotic eternal archaea takes over and persists during the extremophilic climatic changes of global warming. The human beings exist as neanderthalic zombies serving

archaeal multiplication. The homo sapiens gets converted to a new phenotype, genotype, immunotype, metabolonomic type and brain type. This is called as hibernatory zombie related to global warming - homo neoneanderthalis.

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Chapter 3

Archaeaon and Vitamin C Synthesis -

The Vitaminocyte Organelle

Introduction

Ascorbic acid is not synthesized by primates and humans. Vitamin C is synthesized from monosaccharides especially mannose, galactose or glucose. Primates and humans have the mutated form of the enzyme L-gulonolactone oxidase and are therefore not able to synthesize vitamin C. Archaea are endosymbionts in the human cell and function as cellular organelle. Archaea have the vitamin C synthetic pathway. Therefore the human cell could be able to synthesize vitamin C using endosymbiotic archaea functioning as organelle.

Fructolysis in the archaeaon vitaminocyte can contribute to vitamin C and vitamin E synthesis. The Neanderthals have a higher density of archaeal symbiosis resulting in increasing number of vitaminocyte organelle. This results in increased synthesis endogenous ascorbic acid and tocopherol in Neanderthals which function as free radical scavengers. Free radicals are important in neuronal function and NMDA activity. Free radicals increase NMDA activity. Free radicals are also important as messengers of human endogenous retroviruses. Free radicals mediate the expression and reintegration into the genome where it functions as jumping genes contributing to genomic plasticity and dynamicity. Genomic dynamicity is consequently absent in Neanderthals due to higher synthesis of ascorbic acid and tocopherol by the vitaminocyte and free radical deficiency. Genomic dynamicity and HERV sequences contribute to development of synaptic connectivity, formation of cerebral cortex and brain size. This leads onto defective NMDA transmission, cerebral cortical dysfunction and cerebellar dominance in Neanderthals. The brain size in Neanderthals is bigger than the newer species of homo sapiens. The homo sapiens on the other hand has less of archaeal symbiotic density and fewer archaeal vitaminocyte organelle. The gene for vitamin C synthesis is already mutated in all human species and in the presence of decreased density of

archaeal vitaminocyte organelle in homo sapiens there is deficiency of ascorbic acid and tocopherols in homo sapiens. This results in reduced free radical scavenging, increased free radicals in the system, increased expression and reintegration of HERV sequences in to the genome. There is increased genomic dynamicity and plasticity and a dominant cerebral cortical function in homo sapien population and a smaller brain size. Thus the archaeal symbiosis and the resultant vitaminocyte organelle decides the human species type, brain size, cerebral cortical versus cerebellar dominance and the human consciousness.

Materials and Methods

10 normal individuals were drawn for the study. 10 ml of plasma from heparinised blood was taken for the study. The experimental protocols was as follows: (1) Plasma+buffered saline containing glucose 1 mg/ml with vitamin C concentration measured at 0 time and 2 hour time. (2) Plasma+doxy 1 mg/ml+buffered saline containing glucose 1 mg/ml with vitamin C concentration measured at 0 time and 2 hour time. Cytochrome F420 activity was also assessed.

Results

The vitamin C level were found to increase spontaneously from 9 mg/l at 0 time to 14 mg/l at 2 hr. in experimental protocol (1) containing plasma+buffered saline with glucose at 1 mg/ml. The solution also showed cytochrome F420 activity. The protocol (2) containing plasma+doxy+buffered saline containing glucose at 1 mg/ml had no vitamin C activity detected or cytochrome F420 activity detected. The archaeal endosymbiont or archaeaon could thus synthesize vitamin C.

Discussion

The study demonstrates that vitamin C is synthesized by endosymbiotic archaeaon. It functions as a vitaminocyte. The primates and humans lost the capacity to synthesize vitamin C. L-gulonolactone oxidase is deficient in humans. Vitamin C deficiency is a genetic disease. Vitamin C deficiency played an important role in human evolution. Vitamin C is an anti-oxidant. Its deficiency leads to free radical generation and modulation of monoaminergic and glutamatenergic neurotransmission and evolution of the cerebral cortex. The generation of free radicals may have played the role in conscious perception and the bigger size of the primate cerebral cortex as seen in homo sapiens. The capacity to generate vitamin C synthesis by endosymbiotic archaea may shrink the cerebral cortex and increase the cerebellar size leading onto the dominance of the unconscious brain as seen in homo neanderthalis. Vitamin C deficiency is implicated in disorders of consciousness like schizophrenia and autism.

Vitamin C deficiency leads to defective collagen synthesis and breaks in the vessel wall producing damage which is healed by adhesion of lipoprotein a to the vessel wall producing atherosclerosis. Atherosclerosis is a genetic vitamin C deficiency disease. This hypothesis was put forward by Linus Pauling. The capacity of endosymbiotic archaea to synthesize vitamin C may protect against it. Vitamin C is required for insulin secretion and its deficiency leads to diabetes mellitus and metabolic syndrome. Vitamin C deficiency leads to oncogenesis.

Vitamin C deficiency generates free radicals which can activate oncogenes producing cell proliferation. The defective collagen matrix that is formed can lead to metastasis. Oncogenesis can be considered as a vitamin C deficiency syndrome. Vitamin C is seen in high levels in lymphocytes. Vitamin C deficiency leads to immunosuppression and viral infections. Vitamin C is anti-viral agent. Vitamin C is required for lymphocyte function and its

deficiency leads to autoimmune disease. Vitamin C deficiency leads to free radical generation and cell death and neurodegeneration.

All the civilisational disorders of schizophrenia, autism, autoimmune disease, neurodegeneration, metabolic syndrome X, cancer and atherosclerosis. The archaeaon is the cellular organelle concerned with ascorbic acid synthesis and cyto protection. It can be considered as a vitaminocyte.[1-3]

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Chapter 4

Archaeaon - A New Cell Organelle - The Master Organelle of the Cell

Introduction

Endomyocardial fibrosis (EMF) along with the root wilt disease of coconut is endemic to Kerala with its radioactive actinide beach sands. Actinides like rutile, endogenous digoxin as well as organisms like phytoplasmas and viroids have been implicated in the etiology of these diseases.[1-4] Endogenous digoxin has been related to the pathogenesis of Schizophrenia, malignancy, metabolic syndrome X, autoimmune disease and neuronal degeneration.[4] The possibility of endogenous digoxin synthesis by actinide based primitive organism like archaea with a mevalonate pathway and cholesterol catabolism was considered.[5-8] An actinide dependent shadow biosphere of archaea and viroids in the above mentioned disease states is described.[7, 9] Metal actinides in beach sands have been postulated to play a role in abiogenesis.[7] A hypothesis of cholesterol as the primal prebiotic molecule synthesized on actinide surfaces with all other biomolecules arising from it and a self replicating cholesterol lipid organism as the initial life form is presented. The archaea exists as an endosymbiont in the human cell and can be considered as a cellular organelle. All cell organelle are basically endosymbionts according to the endosymbiotic theory of cell origin put forward by Lynn Margulis. The endosymbiotic archaea concerned cell regulation as well as neuro-immuno-endocrine-genetic-metabolic regulation is an organelle. The endosymbiotic archaeal organelle can be termed the archaeaon.

Fructolysis in the archaeaon vitaminocyte can contribute to vitamin C and vitamin E synthesis. The Neanderthals have a higher density of archaeal symbiosis resulting in increasing number of vitaminocyte organelle. This results in increased synthesis endogenous ascorbic acid and tocopherol in Neanderthals which function as free radical scavengers. Free radicals are important in neuronal function and NMDA activity. Free radicals increase NMDA activity. Free radicals are also important as messengers of human endogenous

retroviruses. Free radicals mediate the expression and reintegration into the genome where it functions as jumping genes contributing to genomic plasticity and dynamicity. Genomic dynamicity is consequently absent in Neanderthals due to higher synthesis of ascorbic acid and tocopherol by the vitaminocyte and free radical deficiency. Genomic dynamicity and HERV sequences contribute to development of synaptic connectivity, formation of cerebral cortex and brain size. This leads onto defective NMDA transmission, cerebral cortical dysfunction and cerebellar dominance in Neanderthals. The brain size in Neanderthals is bigger than the newer species of homo sapiens. The homo sapiens on the other hand has less of archaeal symbiotic density and fewer archaeal vitaminocyte organelle. The gene for vitamin C synthesis is already mutated in all human species and in the presence of decreased density of archaeal vitaminocyte organelle in homo sapiens there is deficiency of ascorbic acid and tocopherols in homo sapiens. This results in reduced free radical scavenging, increased free radicals in the system, increased expression and reintegration of HERV sequences in to the genome. There is increased genomic dynamicity and plasticity and a dominant cerebral cortical function in homo sapien population and a smaller brain size. Thus the archaeal symbiosis and the resultant vitaminocyte organelle decides the human species type, brain size, cerebral cortical versus cerebellar dominance and the human consciousness.

Materials and Methods

The following groups were included in the study: - endomyocardial fibrosis, Alzheimer's disease, multiple sclerosis, non-Hodgkin's lymphoma, metabolic syndrome X with cerebrovascular thrombosis and coronary artery disease, schizophrenia, autism, seizure disorder, Creutzfeldt Jakob's disease and acquired immunodeficiency syndrome. There were 10 patients in each group and each patient had an age and sex matched healthy control selected randomly from the

general population. The blood samples were drawn in the fasting state before treatment was initiated. Plasma from fasting heparinised blood was used and the experimental protocol was as follows (I) Plasma+phosphate buffered saline, (II) same as I+cholesterol substrate, (III) same as II+rutile 0.1 mg/ml, (IV) same as II+ciprofloxacine and doxycycline each in a concentration of 1 mg/ml. Cholesterol substrate was prepared as described by Richmond.[10] 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, polycyclic aromatic hydrocarbon, hydrogen peroxide, dopamine, serotonin, pyruvate, ammonia, glutamate, cytochrome C, hexokinase, ATP synthase, HMG CoA reductase, digoxin and bile acids.[11-13] 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. Informed consent of the subjects and the approval of the ethics committee were obtained for the study. The statistical analysis was done by ANOVA.

Results

Plasma of control subjects showed increased levels of the above mentioned parameters with after incubation for 1 hour and addition of cholesterol substrate resulted in still further significant increase in these parameters. The plasma of patients showed similar results but the extent of increase was more. The addition of antibiotics to the control plasma caused a decrease in all the parameters while addition of rutile increased their levels. The addition of antibiotics to the patient's plasma caused a decrease in all the parameters while addition of rutile increased their levels but the extent of change was more in patient's sera as compared to controls. The results are expressed in tables 1-7 as percentage change in the parameters after 1 hour incubation as compared to the values at zero time.

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

Group	CYT F420 % (Increase with Rutile)		CYT F420 % (Decrease with Doxy+Cipro)		PAH % change (Increase with Rutile)		PAH % change (Decrease with Doxy+Cipro)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Normal	4.48	0.15	18.24	0.66	4.45	0.14	18.25	0.72
Schizo	23.24	2.01	58.72	7.08	23.01	1.69	59.49	4.30
Seizure	23.46	1.87	59.27	8.86	22.67	2.29	57.69	5.29
AD	23.12	2.00	56.90	6.94	23.26	1.53	60.91	7.59
MS	22.12	1.81	61.33	9.82	22.83	1.78	59.84	7.62
NHL	22.79	2.13	55.90	7.29	22.84	1.42	66.07	3.78
DM	22.59	1.86	57.05	8.45	23.40	1.55	65.77	5.27
AIDS	22.29	1.66	59.02	7.50	23.23	1.97	65.89	5.05
CJD	22.06	1.61	57.81	6.04	23.46	1.91	61.56	4.61
Autism	21.68	1.90	57.93	9.64	22.61	1.42	64.48	6.90
EMF	22.70	1.87	60.46	8.06	23.73	1.38	65.20	6.20
F value	306.749		130.054		391.318		257.996	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

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

Group	DNA % change (Increase with Rutile)		DNA % change (Decrease with Doxy+Cipro)		RNA % change (Increase with Rutile)		RNA % change (Decrease with Doxy+Cipro)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Normal	4.37	0.15	18.39	0.38	4.37	0.13	18.38	0.48
Schizo	23.28	1.70	61.41	3.36	23.59	1.83	65.69	3.94
Seizure	23.40	1.51	63.68	4.66	23.08	1.87	65.09	3.48
AD	23.52	1.65	64.15	4.60	23.29	1.92	65.39	3.95
MS	22.62	1.38	63.82	5.53	23.29	1.98	67.46	3.96
NHL	22.42	1.99	61.14	3.47	23.78	1.20	66.90	4.10
DM	23.01	1.67	65.35	3.56	23.33	1.86	66.46	3.65
AIDS	22.56	2.46	62.70	4.53	23.32	1.74	65.67	4.16
CJD	23.30	1.42	65.07	4.95	23.11	1.52	66.68	3.97
Autism	22.12	2.44	63.69	5.14	23.33	1.35	66.83	3.27
EMF	22.29	2.05	58.70	7.34	22.29	2.05	67.03	5.97
F value	337.577		356.621		427.828		654.453	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

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

Group	HMG CoA R % change (Increase with Rutile)		HMG CoA R % change (Decrease with Doxy+Cipro)		ATP synthase % (Increase with Rutile)		ATP synthase % (Decrease with Doxy+Cipro)	
	Mean	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**
Normal	4.30	0.20	18.35	0.35	4.40	0.11	18.78	0.11
Schizo	22.91	1.92	61.63	6.79	23.67	1.42	67.39	3.13
Seizure	23.09	1.69	61.62	8.69	23.09	1.90	66.15	4.09
AD	23.43	1.68	61.68	8.32	23.58	2.08	66.21	3.69
MS	23.14	1.85	59.76	4.82	23.52	1.76	67.05	3.00
NHL	22.28	1.76	61.88	6.21	24.01	1.17	66.66	3.84
DM	23.06	1.65	62.25	6.24	23.72	1.73	66.25	3.69
AIDS	22.86	2.58	66.53	5.59	23.15	1.62	66.48	4.17
CJD	22.38	2.38	60.65	5.27	23.00	1.64	66.67	4.21
Autism	22.72	1.89	64.51	5.73	22.60	1.64	66.86	4.21
EMF	22.92	1.48	61.91	7.56	23.37	1.31	63.97	3.62
F value	319.332		199.553		449.503		673.081	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

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

Group	Digoxin (ng/ml) (Increase with Rutile)		Digoxin (ng/ml) (Decrease with Doxy+Cipro)		Bile Acids % change (Increase with Rutile)		Bile Acids % change (Decrease with Doxy+Cipro)	
	Mean	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**
Normal	0.11	0.00	0.054	0.003	4.29	0.18	18.15	0.58
Schizo	0.55	0.06	0.219	0.043	23.20	1.87	57.04	4.27
Seizure	0.51	0.05	0.199	0.027	22.61	2.22	66.62	4.99
AD	0.55	0.03	0.192	0.040	22.12	2.19	62.86	6.28
MS	0.52	0.03	0.214	0.032	21.95	2.11	65.46	5.79
NHL	0.54	0.04	0.210	0.042	22.98	2.19	64.96	5.64
DM	0.47	0.04	0.202	0.025	22.87	2.58	64.51	5.93
AIDS	0.56	0.05	0.220	0.052	22.29	1.47	64.35	5.58
CJD	0.53	0.06	0.212	0.045	23.30	1.88	62.49	7.26
Autism	0.53	0.08	0.205	0.041	22.21	2.04	63.84	6.16
EMF	0.51	0.05	0.213	0.033	23.41	1.41	58.70	7.34
F value	135.116		71.706		290.441		203.651	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

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

Group	Pyruvate % change (Increase with Rutile)		Pyruvate % change (Decrease with Doxy+Cipro)		Hexokinase % change (Increase with Rutile)		Hexokinase % change (Decrease with Doxy+Cipro)	
	Mean	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**
Normal	4.34	0.21	18.43	0.82	4.21	0.16	18.56	0.76
Schizo	20.99	1.46	61.23	9.73	23.01	2.61	65.87	5.27
Seizure	20.94	1.54	62.76	8.52	23.33	1.79	62.50	5.56
AD	22.63	0.88	56.40	8.59	22.96	2.12	65.11	5.91
MS	21.59	1.23	60.28	9.22	22.81	1.91	63.47	5.81
NHL	21.19	1.61	58.57	7.47	22.53	2.41	64.29	5.44
DM	20.67	1.38	58.75	8.12	23.23	1.88	65.11	5.14
AIDS	21.21	2.36	58.73	8.10	21.11	2.25	64.20	5.38
CJD	21.07	1.79	63.90	7.13	22.47	2.17	65.97	4.62
Autism	21.91	1.71	58.45	6.66	22.88	1.87	65.45	5.08
EMF	22.29	2.05	62.37	5.05	21.66	1.94	67.03	5.97
F value	321.255		115.242		292.065		317.966	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

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

Group	H_2O_2 % (Increase with Rutile)		H_2O_2 % (Decrease with Doxy+Cipro)		ALA %(Increase with Rutile)		ALA % (Decrease with Doxy+Cipro)	
	Mean	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**
Normal	4.43	0.19	18.13	0.63	4.40	0.10	18.48	0.39
Schizo	22.50	1.66	60.21	7.42	22.52	1.90	66.39	4.20
Seizure	23.81	1.19	61.08	7.38	22.83	1.90	67.23	3.45
AD	22.65	2.48	60.19	6.98	23.67	1.68	66.50	3.58
MS	21.14	1.20	60.53	4.70	22.38	1.79	67.10	3.82
NHL	23.35	1.76	59.17	3.33	23.34	1.75	66.80	3.43
DM	23.27	1.53	58.91	6.09	22.87	1.84	66.31	3.68
AIDS	23.32	1.71	63.15	7.62	23.45	1.79	66.32	3.63
CJD	22.86	1.91	63.66	6.88	23.17	1.88	68.53	2.65
Autism	23.52	1.49	63.24	7.36	23.20	1.57	66.65	4.26
EMF	23.29	1.67	60.52	5.38	22.29	2.05	61.91	7.56
F value	380.721		171.228		372.716		556.411	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 7. *Effect of rutile and antibiotics on dopamine and serotonin.*

Group	DOPAMINE % (Increase with Rutile)		DOPAMINE % (Decrease with Doxy+Cipro)		5 HT % change (Increase with Rutile)		5 HT % change (Decrease with Doxy+Cipro)	
	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
Schizo	21.88	1.19	66.28	3.60	23.02	1.65	67.61	2.77
Seizure	22.29	1.33	65.38	3.62	22.13	2.14	66.26	3.93
AD	23.66	1.67	65.97	3.36	23.09	1.81	65.86	4.27
MS	22.92	2.14	67.54	3.65	21.93	2.29	63.70	5.63
NHL	23.81	1.90	66.95	3.67	23.12	1.71	65.12	5.58
DM	24.10	1.61	65.78	4.43	22.73	2.46	65.87	4.35
AIDS	23.43	1.57	66.30	3.57	22.98	1.50	65.13	4.87
CJD	23.70	1.75	68.06	3.52	23.81	1.49	64.89	6.01
Autism	22.76	2.20	67.63	3.52	22.79	2.20	64.26	6.02
EMF	22.28	1.52	64.05	2.79	22.82	1.56	64.61	4.95
F value	403.394		680.284		348.867		364.999	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Discussion

There was increase in cytochrome F420 indicating archaeal growth. The archaea exists as endosymbionts in the human cell and can be considered as a cell organelle. The other cell organelle also has a microbial origin. The mitochondria are of rickettsial origin. The nucleus is derived phylogenetically from the pox virus. The peroxisome is of acinetobacter origin. The symbiotic theory of cell origin was put forward by Lynn Margulis. The archaea can synthesize and use cholesterol as a carbon and energy source.[6, 14] The archaeal origin of the enzyme activities was indicated by antibiotic induced suppression. The study indicates the presence of actinide based archaea with an alternate actinide based enzymes or metalloenzymes in the system as indicated by rutile induced increase in enzyme activities.[15] There was also an increase in archaeal HMG CoA reductase activity indicating increased cholesterol synthesis by the

archaeal mevalonate pathway. The archaeal beta hydroxyl steroid dehydrogenase activity indicating digoxin synthesis and archaeal cholesterol hydroxylase activity indicating bile acid synthesis were increased.[8] The archaeal cholesterol oxidase activity was increased resulting in generation of pyruvate and hydrogen peroxide.[14] 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.[16] 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.[17] There was an increase in free RNA indicating self replicating RNA viroids and free DNA indicating generation of viroid complementary DNA strands by archaeal reverse transcriptase activity. The 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.[18] Archaeal pyruvate can produce histone deacetylase inhibition resulting in endogenous retroviral (HERV) reverse transcriptase and integrase expression. This can integrate the RNA viroidal complementary DNA into the noncoding region of eukaryotic non coding DNA using HERV integrase as has been described for borna and ebola viruses.[19] 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.[20] The integrated viroids and archaea can undergo vertical transmission and can exist as genomic parasites.[19, 20] This increases the length and alters the grammar of the noncoding region producing memes or memory of acquired characters as well as eukaryotic speciation and individuality.[21] The

viroidal complementary DNA can function as jumping genes producing a dynamic genome important in storage of synaptic information, HLA gene expression and developmental gene expression. The RNA viroids can regulate mRNA function by RNA interference.[18] The phenomena of RNA interference can modulate T-cell and B-cell function, insulin signalling lipid metabolism, cell growth and differentiation, apoptosis, neuronal transmission and euchromatin / heterochromatin expression.

The archaea and viroids can regulate the nervous system including the NMDA/GABA thalamo-cortico-thalamic pathway mediating conscious perception.[4, 22] NMDA/GABA receptors can be modulated by digoxin induced calcium oscillations resulting NMDA/GAD activity induction, PAH increasing NMDA activity and inducing GAD as well as viroid induced RNA interference.[4] The cholesterol ring oxidase generated pyruvate can be converted by the GABA shunt pathway to glutamate and GABA. The dipolar PAH and archaeal magnetite in the setting of digoxin induced sodium potassium ATPase inhibition can produce a pumped phonon system mediated Frohlich model superconducting state [22] inducing quantal perception with nanoarchaeal sensed gravity producing the orchestrated reduction of the quantal possibilities to the macroscopic world.[4, 22] The archaea can regulate limbic lobe transmission with archaeal cholesterol aromatase/ring oxidase generated norepinephrine, dopamine, serotonin and acetyl choline.[16] 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.[4] The increased integration of archaea into the neuronal genome can produce increased cholesterol oxidase and aromatase mediated monoamine and NMDA transmission producing Schizophrenia and Autism. Archaea and RNA viroid can bind the TLR receptor induce NFKB producing immune activation and cytokine TNF alpha secretion. The archaeal DXP and mevalonate pathway

metabolites can bind γδ TCR and digoxin induced calcium signalling can activate NFKB producing chronic immune activation.[4, 23] The archaea and viroid induced chronic immune activation and generation of superantigens can lead on to autoimmune disease. Archaea, viroids and digoxin can induce the host AKT PI3K, AMPK, HIF alpha and NFKB producing the Warburg metabolic phenotype.[24] 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 and metabolic syndrome. The archaea and viroid generated cytokines can lead to TNF alpha induced insulin resistance and metabolic syndrome X. The accumulated pyruvate enters the GABA shunt pathway and is converted to citrate which is acted upon by citrate lyase and converted to acetyl CoA, used for cholesterol synthesis.[24] 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 bile acids are steroidal hormones which can bind GPCR and modulate D_2 regulating the conversion of T_4 to T_3 which activates uncoupling proteins, can activate NRF½ inducing NQO1, GST, HOI reducing redox stress, can bind FXR regulating insulin receptor sensitivity and bind PXR inducing the bile acid shunt pathway of cholesterol detoxification.[25] The archaea and viroid induced monocyte activation and Warburg phenotype induced increased cholesterol synthesis leads to atherogenesis. The Warburg phenotype induced increased mitochondrial PT pore hexokinase, archaeal PAH and viroid induced RNA interference can lead on to malignant transformation. The digoxin and PAH induced increased intracellular calcium can lead to PT pore dysfunction, cell death and neuronal degeneration.[4] The archaeal

cholesterol catabolism can deplete the cell membranes of cholesterol resulting in organelle dysfunction and degeneration. The RNA viroids can recombine with HERV sequences and get encapsulated in microvesicles contributing to the retroviral state. The prion protein conformation is modulated by RNA viroid binding producing Prion Disease. The archaeal digoxin and rutile induced magnesium depletion can lead MPS deposition and produce EMF, CCP, MNG and mucoid angiopathy.[4]

The metal actinides provide radiolytic energy, catalysis for oligomer formation and provide a coordinating ion for metalloenzymes all important in abiogenesis.[7] The metal actinide surfaces would by surface metabolism generate acetate which could get converted to acetyl CoA and then to cholesterol which functions as the primal prebiotic molecule self organizing into self replicating supramolecular systems, the lipid organism.[9, 26, 27] Cholesterol by radiolysis by actinides would have formed PAH generating PAH aromatic organism.[9] Cholesterol radiolysis would generate pyruvate which would get converted to amino acids, sugars, nucleotides, porphyrins, fatty acids and TCA acids. Anastase and rutile surfaces can produce polymerization of amino acids, isoprenyl residues, PAH and nucleotides to generate the initial lipid organism, PAH organism, prions and RNA viroids which would have symbiosed to generate the archaeal protocell. The archaea evolved into gram negative and gram positive bacteria with a mevalonate pathway which had a evolutionary advantage and the symbiosis of archaea with gram negative organism generated the eukaryotic cell.[28] The data supports the persistence of an actinide and cholesterol based shadow biosphere which throws light on the actinide based origin of life and cholesterol as the premier prebiotic molecule. The archaea exists as an endosymbiont in the human cell and can be considered as a cellular organelle. All cell organelle are basically endosymbionts according to the endosymbiotic theory of cell origin put forward by Lynn Margulis. The

endosymbiotic archaea concerned cell regulation as well as neuro-immuno-endocrine-genetic-metabolic regulation is an organelle. The endosymbiotic archaeal organelle can be termed the archaeaon.

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Chapter 5

Archaeal Digoxin and Mitochondrial Function - Relation to Free Radical Metabolism

Introduction

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

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

Studies in our laboratory have demonstrated that EDLF is synthesized by the isoprenoid pathway. The endosymbiotic archaeal sequences in the human genome get expressed by redox stress and osmotic stress of global warming. This results in induction of HIF alpha which will upregulate fructolysis and glycolysis. In the setting of redox stress all glucose gets converted to fructose by the induction of enzymes aldose reductase and sorbitol dehydrogenase. Aldose reductase converts glucose to sorbitol and sorbitol dehydrogenase converts sorbitol to fructose. Since fructose is preferentially phosphorylated by ketohexokinases the cell is depleted of ATP and glucose phosphorylation comes to a halt. Fructose becomes the dominant sugar that is metabolized by fructolysis in expressed archaeal particles in the cell functioning as organelle called fructosoids. The fructose is phosphorylated to fructose 1-phosphate which is acted upon by aldolase B which converts it into glyceraldehyde 3-phosphate and dihydroxy acetone phosphate. Glyceraldehyde 3-phosphate is converted to D1,3-biphosphoglycerate which is then converted to 3-phosphoglycerate. The 3-phosphglycerate 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 glyceraldhyde 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 catabolized by archaeal cholesterol oxidases to generate digoxin. The digoxin sugars digitoxose and rhamnose are synthesized by the upregulated pentose phosphate pathway. Glycolytic suppression leads to upregulation of the pentose phosphate pathway. The expressed archaeaon organelle concerned with cholesterol catabolism and digoxin synthesis is called the steroidelle. The suppression of glycolysis and stimulation of fructolysis results in upregulation of the hexosamine pathway. Fructose is converted to fructose 6-phosphate by ketohexokinases. The fructose 6-phosphate is converted to glucosamine 6-phosphate by the action of glutamine fructose 6-phosphate amidotransferase (GFAT). Glucosamine 6-phosphate is converted to UDP N-acetyl glucosamine which is then converted to N-acetyl glucosamine and various amino sugars. UDP glucose is converted to UDP D-glucuronic acid. UDP D-glucuronic acid is converted to glucuronic acid. This forms the uronic acid synthetic pathway. Uronic acids and hexosamines form repeating units of glycosaminoglycans. In the setting of glycolytic suppression and fructolytic metabolism fructolysis

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

Fructolysis in the archaeaon vitaminocyte can contribute to vitamin C and vitamin E synthesis. The Neanderthals have a higher density of archaeal symbiosis resulting in increasing number of vitaminocyte organelle. This results

in increased synthesis endogenous ascorbic acid and tocopherol in Neanderthals which function as free radical scavengers. Free radicals are important in neuronal function and NMDA activity. Free radicals increase NMDA activity. Free radicals are also important as messengers of human endogenous retroviruses. Free radicals mediate the expression and reintegration into the genome where it functions as jumping genes contributing to genomic plasticity and dynamicity. Genomic dynamicity is consequently absent in Neanderthals due to higher synthesis of ascorbic acid and tocopherol by the vitaminocyte and free radical deficiency. Genomic dynamicity and HERV sequences contribute to development of synaptic connectivity, formation of cerebral cortex and brain size. This leads onto defective NMDA transmission, cerebral cortical dysfunction and cerebellar dominance in Neanderthals. The brain size in Neanderthals is bigger than the newer species of homo sapiens. The homo sapiens on the other hand has less of archaeal symbiotic density and fewer archaeal vitaminocyte organelle. The gene for vitamin C synthesis is already mutated in all human species and in the presence of decreased density of archaeal vitaminocyte organelle in homo sapiens there is deficiency of ascorbic acid and tocopherols in homo sapiens. This results in reduced free radical scavenging, increased free radicals in the system, increased expression and reintegration of HERV sequences in to the genome. There is increased genomic dynamicity and plasticity and a dominant cerebral cortical function in homo sapien population and a smaller brain size. Thus the archaeal symbiosis and the resultant vitaminocyte organelle decides the human species type, brain size, cerebral cortical versus cerebellar dominance and the human consciousness.

Two substances, which are products of the isoprenoid pathway, can participate in lipid peroxidation. One is digoxin, which by inhibiting membrane Na^{+}-K^{+} ATPase causes increase in intracellular Ca^{++}, and depletion of intracellular Mg^{++} both contributing to increase in lipid peroxidation.

Ubiquinone, another product of the pathway, is a powerful membrane antioxidant and its deficiency can also result in defective electron transport and generation of reactive oxygen species.

In view of this and also in the light of some preliminary reports on alteration in lipid peroxidation in neuropsychiatric disorders, a study was undertaken on the following aspects in some of these disorders (primary generalised epilepsy, schizophrenia, multiple sclerosis, Parkinson's disease and CNS glioma): (1) concentration of digoxin, ubiquinone, activity of HMG CoA reductase and RBC membrane Na^+-K^+ ATPase, (2) activity of enzymes involved in free radical scavenging, (3) parameters of lipid peroxidation and (4) antioxidant status.

The result obtained indicates an increase in the concentration of archaeal digoxin and activity of HMG CoA reductase, decrease in ubiquinone levels and in the activity of membrane Na^+-K^+ ATPase [There oxides and NO with decreased antioxidant protection as indicated by decrease in ubiquinone, vitamin E and reduced glutathione in schizophrenia, Parkinson's disease and glutathione reductase is decreased in the above diseases]. However, there is no evidence of any increase in lipid peroxidation in epilepsy in MS. The role of increased operation of the isoprenoid pathway as evidenced by alteration in the concentration of digoxin and ubiquinone in the generation of free radicals and protection against them in these disorders is discussed.

Apart from cholesterol, the isoprenoid or mevalonate pathway produces digoxin (a potent inhibitor of Na^+-K^+ ATPase) and ubiquinone (a cell membrane antioxidant and a component of the mitochondrial electron transport chain). Endogenous digoxin, reported to be synthesized by the hypothalamus is known to be altered in many neuropsychiatric disorders. Increased serum digoxin levels have been observed by us in primary generalised epilepsy, schizophrenia,

Parkinson's disease and multiple sclerosis. Involvement of endogenous digoxin like activity (EDLA) has also been reported by others in the brain in manic depressive psychosis and epilepsy. Digoxin by its inhibitory action on membrane Na^+-K^+ ATPase is known to cause an increase in intracellular calcium contributing to calcium mediated free radical generation of which NO is an example. NO combines with superoxide radical to form peroxynitrite which promotes lipid peroxidation. Increased intracellular calcium leads to opening of the mitochondrial PT pore resulting in uncoupling of the oxidative phosphorylation chain and consequent increased free radical generation. Intracellular calcium also activates phospholipase A_2 leading to increased generation of arachidonic acid and consequent increased lipid peroxidation. Further, inhibition of membrane sodium potassium ATPase by digoxin apart from increasing intracellular calcium also leads to intracellular magnesium depletion. Magnesium deficiency can affect mitochondrial electron transport and oxidative phosphorylation resulting in incomplete reduction of molecular oxygen and generation of reactive oxygen species.

Ubiquinone, another product of the isoprenoid pathway, which apart from its role in electron transport pathway which apart from - its role in electron transport is a powerful membrane and its deficiency can contribute to decreased antioxidant protection. Its deficiency can also contribute to defective electron transport leading to generation of reactive oxygen species like superoxide and hydrogen peroxide. Decreased ubiquinone levels have been reported in Parkinson's disease, schizophrenia, multiple sclerosis and epilepsy. It is therefore evident that alteration of the isoprenoid pathway can affect free radical generation and be damaging.

In connection to this, free radical damage has been implicated in the pathogenesis of Parkinson's disease, neoplasm and immune mediated disorders like multiple sclerosis. Increased lipid peroxidation and decreased activity of

superoxide dismutase (SOD) have been reported in the blood of epileptic patients. There is also a report of abnormal lipid peroxidation and activity of critical antioxidant enzymes and free radical damage in schizophrenia.

In Parkinson's disease the free radical generation has been reported to be due to formation of H_2O_2 from dopamine by the action of monoamine oxidase and the subsequent reaction of H_2O_2 with iron to generate the hydroxyl radical by the Fenton reaction. A critical role for iron in free radical generation has been suggested in neurodegenerations like Parkinson's disease and Alzheimer's disease. Another report associates manganese toxicity promoting autooxidation of catecholamines and free radical generation in Parkinson's disease. An altered free radical defence mechanism like decreased levels of antioxidant enzymes and antioxidants has been suggested for the free radical damage in neurodegenerative disorders. Increased formation of NO which forms peroxynitrite with superoxide promoting lipid peroxidation has also been reported in neurodegeneration.

The interrelationship between neuronal degeneration, psychiatric manifestation, immune activation and malignant transformation disorders has been well documented in literature. Autoantibodies have been demonstrated in multiple sclerosis, motor neuron disease, paraneoplastic disease and schizophrenia. Psychosis has been described in MS, Alzheimer's disease, Parkinson's disease and in neoplastic disorders. The relationship between Hodgkin's lymphoma and MS and lymphoma coexisting with MND has been documented in literature. A family with coexistence of many of these disorders has been reported by us. This interrelationship is probably dependent upon a central dysfunction which could play a role in the pathophysiology of these diseases. A dysfunction of the isoprenoid pathway with consequent aberration in free radical generation with damage may be a possibility in this respect. Support for this view comes from the reports on the alteration in some of the

products of this pathway in a few neuropsychiatric disorders. In view of this the following aspects have been studied in some neuropsychiatric disorders: the activity of the major regulatory steps in the isoprenoid of this pathway, plasma digoxin and ubiquinone levels, RBC membrane sodium potassium ATPase activity, parameters of lipid peroxidation-activity of enzymes involved in free radical scavenging, concentration of various antioxidants, concentration of products of lipid peroxidation, viz. malondialdehyde, conjugated dienes and hydroperoxides, concentration of NO, ceruloplasmin and iron binding capacity and concentration of serum magnesium and tyrosirle (since tyrosine is the precursor for melanin polymers which entrap free radicals and is also required for the synthesis of the ring system of ubiquinone).

The disorders studied include Parkinson's disease, primary generalised epilepsy, schizophrenia, multiple sclerosis and CNS glioma.

Results

HMG CoA Reductase RBC Membrane Na^+-K^+ ATPase Activity, Concentration of Digoxin and Ubiquinone

Activity of HMG CoA reductase in the plasma showed significant increase in epilepsy, schizophrenia, PD and glioma but not in MS when compared to the controls. Concentration of digoxin increased significantly in the plasma in all of these disorders when compared to controls except in glioma. Level of ubiquinone decreased in the serum in all these disorders when compared to controls except in the case of glioma. Activity of RBC membrane Na^+-K^+ ATPase activity also decreased significantly in all the disorders studied.

SOD, Catalase, Glutathione Reductase and Glutathione Peroxidase in the Erythrocytes

The activity of these enzymes decreased significantly in schizophrenia, Parkinson's disease and CNS glioma when compared to controls. None of these enzyme activities showed any significant alteration in primary generalized epilepsy and MS.

Malondialdehyde (MDA), Hydroperoxides, Conjugated Dienes, Glutathione, Alpha Tocopherol, NO, Iron Binding Capacity and Ceruloplasmin

None of these parameters was affected in primary generalized epilepsy and MS when compared to controls. In schizophrenia, Parkinson's disease and CNS glioma, concentration of MDA, hydroperoxides, conjugated dienes and NO increased significantly. Glutathione levels decreased significantly in schizophrenia, Parkinson's disease and CNS glioma. Concentration of alpha tocopherol decreased only in Parkinson's disease. Iron binding capacity decreased significantly only in Parkinson's disease and CNS glioma while concentration of ceruloplasmin decreased in schizophrenia, Parkinson's disease and CNS glioma.

Serum Albumin, Magnesium and Tyrosine

Concentration of albumin, magnesium and tyrosine showed significant decrease in the serum in all the disorders studied when compared to controls (except in the case of CNS glioma).

Discussion

Archaeal Digoxin and Membrane Na^{+}-K^{+} ATPase Inhibition in Relation to Mitochondrial Function

The archaeaon steroidelle DXP pathway and the upregulated pentose phosphate pathway contribute to digoxin synthesis. The results obtained indicate an upgradation of the isoprenoid (mevalonate) pathway in most of these disorders as is evident from the increased activity of HMG CoA reductase. This enzyme catalyses a major rate limiting step in this pathway ie, conversion of HMG CoA to mevalonate and the level of activity of this enzyme can be taken as a measure of the operation of this pathway. Two products of this pathway are important from the point of free radical generation and damage. One is digoxin which is now known to be synthesized in the mammalian hypothalamus and is a very potent inhibitor of membrane Na^{+}-K^{+} ATPase. Inhibition of this enzyme is known to be associated with increased intracellular calcium and decreased intracellular magnesium concentration. The increase in intracellular calcium results from increased Na^{+}-Ca^{++} exchange, increased entry of Ca^{++} via voltage gated Ca^{++} channels and increased release of Ca^{++} from intracellular endoplasmic reticulum Ca^{++}. This increase in intracellular Ca^{++} by displacing Mg^{++} from its binding sites causes a decrease in functional availability of Mg^{++}. Increased intracellular Ca^{++} also brings about increased leakage of Mg^{++} from the cells (Mg^{++} being easily permeable). Renal tubular Mg^{++} re-absorption is also decreased in the presence of increased Ca^{++} with consequent increased renal excretion of Mg^{++}. Intestinal absorption of Mg^{++} is also decreased in the presence of high intracellular Ca^{++}. The consequence of both increased intracellular calcium and decreased intracellular magnesium is to increase free radical generation and damage, as will be discussed later.

The increase in the concentration of digoxin obtained in these studied disorders (except in glioma) may be the result of increased activity of HMG CoA reductase and increased channelling of intermediates for its synthesis in the hypothalamus. In this connection it has been shown in this lab that administration of ^{14}C acetate to rats resulted in incorporation of label into digoxin indicating that acetyl CoA is the precursor for digoxin also.

Archaeal Digoxin and Regulation of Tyrosine/Tryptophen Metabolism in Relation to Mitochondrial Function

The archaeaon neurotransminoid shikimic acid pathway contributes to tryptophan and tyrosine synthesis and catabolism generating neurotransmitters and neuroactive alkaloids. The decrease in membrane Na^+-K^+ ATPase activity obtained in all these cases may be the result of increased levels of digoxin except in glioma. In glioma inhibition of this enzyme activity takes place even though the digoxin level is not increased. The lack of increase in digoxin in spite of increased activity of HMG CoA reductase in this case is probably due to more substrates being channelled for the synthesis of other products. For example, in glioma there is increase in the concentration of dolichol (another product of the isoprenoid pathway). The inhibition of membrane Na^+-K^+ ATPase activity in glioma in spite of digoxin being unaltered may be due to other substances. In this connection serotonin and quinolinic acid, both products of tryptophan catabolism, have been reported to inhibit this enzyme activity. Increase in the concentration of both these substances has been observed in glioma in this lab. In MS even though there is no significant alteration in the activity of HMG CoA reductase, digoxin in increased. This may again be due to more of the intermediates of the isoprenoid pathway being utilised for digoxin synthesis rather than for other substances of this pathway.

However the concentration of ubiquinone, another product of the isoprenoid pathway, shows decrease in these disorders except in glioma. This is probably due to the fact that the isoprenoid pathway provides only the side chain of ubiquinone, while its ring structure is derived from the aromatic amino acids particularly tyrosine. The decrease in the concentration of tyrosine in the serum in all these studied disorders may result in its decreased utilisation for the synthesis of the ring structure of ubiquinone thus explaining its decreased level in spite of increased operation of the isoprenoid pathway. In glioma, tyrosine levels are not significantly altered and this may explain the lack of alteration in ubiquinone concentration in this case. Digoxin has also been reported to have an inhibitory effect on neutral amino acid transport especially that of tyrosine and this may be the reason for the low tyrosine concentration observed in these disorders.

Archaeal Digoxin and Free Radical Metabolism

The results of studies on lipid peroxidation indicate an increase in free radical generation in schizophrenia, Parkinson's disease and CNS glioma as is evident from the increased concentration of MDA, hydroperoxides and conjugated dienes. NO, another important participant in cellular lipid peroxidation, is also increased in these disorders. However there is no evidence of any increase in lipid peroxidation in primary generalised epilepsy and MS. NO is formed from arginine by the action of nitric oxide synthase which requires calcium for its activation. The increase in intracellular calcium may lead to increased generation of NO which combines with the superoxide radical to form peroxynitrite. Peroxynitrite is known to promote lipid peroxidation. The decrease in SOD which breaks down the superoxide radical in many of these disorders may result in more of the superoxide radical being available to combine with NO.

In addition to increased generation of free radical, there appears to be a decrease in antioxidant protection in many of the disorders studied. This is particularly evident in the case of schizophrenia, Parkinson's disease and glioma where there is both increased free radical generation and decreased antioxidant protection. The activity of enzymes which participates in free radical scavenging like SOD, catalase, glutathione reductase and glutathione peroxidase shows a similar decrease in schizophrenia, Parkinson's disease and glioma. There is also decrease in the level of antioxidants-reduced glutathione, vitamin E and ubiquinone in Parkinson's disease and decrease in reduced glutathione in schizophrenia. The level of iron binding capacity is decreased in Parkinson's disease and glioma while ceruloplasmin is decreased in schizophrenia, Parkinson's disease and glioma. The decrease in iron binding capacity may indicate more free iron being available to catalyse the Fenton's reaction. The decrease in ceruloplasmin in schizophrenia, Parkinson's disease and glioma may indicate availability of more free Cu to participate in free radical generation.

The isoprenoid pathway can influence free radical generation and damage via digoxin and ubiquinone. As discussed earlier the decrease in ubiquinone can result in less antioxidant protection since ubiquinone is a very important cell membrane antioxidant. Ubiquinone also affects the generation of reactive oxygen species like superoxide and hydrogen peroxide. Being a component of the mitochondrial electron transport chain, its deficiency can result in defective electron transport and consequent incomplete reduction of molecular oxygen to form reactive oxygen species.

Archaeal Digoxin and Mitochondrial Function

Digoxin as mentioned earlier by its inhibitory effect on membrane Na^+-K^+ ATPase, contributes to increase in intracellular calcium and decrease in

intracellular magnesium. Increased calcium can result in opening of the mitochondrial PT pore resulting in collapse of the proteon gradient across the inner membrane and consequent uncoupling of oxidative phosphorylation. This also results in increase in generation of reactive oxygen species. The role of calcium on NO generation has already been discussed. Increased calcium also can activate phospholipase A_2 resulting in increased generation of arachidonic acid which can undergo increased lipid peroxidation. Apart from calcium, decreased intracellular magnesium resulting from Na^+-K^+ ATPase inhibition by digoxin can also contribute to increased generation of free radicals. Magnesium is a cofactor for ATP synthesis taking place during coupling of electron flow to oxidative phosphorylation. The deficiency of magnesium can affect electron transport with consequent incomplete reduction of molecular oxygen to free reactive oxygen species.

Increased generation of free radicals like the superoxide ion, and hydroxyl radical can produce cell membrane damage. This damage to the cell membrane can further inactivate membrane Na^+-K^+ ATPase with entry of more calcium into the cell and further triggering of the mechanisms described above. The free radical related Na^+-K^+ ATPase inhibition can produce membrane depolarisation and opening of the voltage gated calcium channels resulting in increased intracellular calcium load. This Na^+-K^+ ATPase inhibition leads to free radical generation, which in turn produces further enzyme inhibition.

Free radical mediated mitochondrial dysfunction can result in decreased production of ATP. Cytosolic free calcium is normally buffered by two mechanisms: ATP dependent calcium extrusion from cell ATP dependent subquestration of calcium within the endoplasmic reticulum. The free radical related mitochondrial dysfunction results in defective extrusion of calcium from the cell. This calcium overload in the cell can trigger further free radical production.

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+} (feroxidase activity). In the presence of iron in Fe^{2+} from 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. Another recent study has 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 intracellular magnesium deficiency can produce ribosomal dysfunction and inhibition of protein synthesis as noted by the 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. Nigral iron accumulation in PD is primarily within neuromelanin granules. Neuromelanin binds to iron and is relatively protective. Neuromelanin is synthesized from tyrosine and digoxin related tyrosine transport defect may lead to decreased neuromelanin synthesis. 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 concomitant 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 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. 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 SOD, glutathione peroxidase and glutathione reductase suggests reduced free radical protection.

Archaeal Isoprenoids and Mitochondrial Protein Glycosylation

Apart from involvement in the free radical generation and antioxidant protection, the isoprenoid pathway may also contribute to the pathogenesis of neurological disorders in other ways. Dolichol, a product of the isoprenoid pathway is involved in protection glycosylation. Increase in serum dolichol has been observed by us in many neuropsychiatric disorders which may be the result of it being less utilised for the formation of dolichol 1-phosphate due to magnesium deficiency. This may result in altered protein glycosylation patterns. In this connection altered glycoprotein accumulation in the serum and brain has been reported in Alzheimer's disease, epilepsy, and schizophrenia. Defective N-glycosylated proteins can manifest as alteration in immune response. In the case of endogenous myelin glycoprotein antigen, defective glycosylation can cause its defective loading to HLA class-I or II molecules resulting in defective transport of the complex to the antigen presenting cell surface for recognition by CD_8 cell. A defective MHC class-1 restricted CD_8 response to myelin has been reported in MS. Defective glycoproteins can also lead to defective contact inhibition and cell proliferation leading to CNS glioma. Defective glycoproteins can also result in disordered synaptic connectivity and functional disorders like epilepsy and schizophrenia.

Archaeal Digoxin and Disease Pathology

The increase in digoxin can have the following consequence: - increased calcium can activate proteases, lipases and endonucleuses which can damage cell membrane, DNA and cytoskeleton of cell. Digoxin has been reported to inhibit glutamate transport via the dicarboxylate carrier system into the glial cells. This can result in synaptic accumulation of glutamate and increased NMDA transmission. The Na^{+}-K^{+} ATPase inhibitory action of digoxin can deplete the cells of Mg^{++} thus removing the magnesium-block on the NMDA receptor. All these lead to increased glutamatergic transmission and glutamate excitotoxicity. Glutamate excitotoxic mechanism is crucial in epileptogenesis, schizophrenia and neuronal degeneration. Digoxin has been shown to promote dopamine release by both exocytic and carrier mediated process in the rat brain and to inhibit serotonin uptake by mouse brain synaptosomes. The monoamine neurotransmitters dopamine, noradrenaline, adrenaline and serotonin act via the cyclic AMP/cyclic GMP/inositol second messenger system. Digoxin, by increasing cytosolic calcium, can activate the signal transduction system of these second messengers. Hyperdopaminergic transmission in the mesolimbic system has been shown to produce the psychotic symptoms of schizophrenia. Schizophrenia thus could be related to hypothalamic archaeal digoxin hypersecretion. Digoxin by its Na^{+}-K^{+} ATPase inhibitory action can prevent neuronal membrane repolarisation resulting in paroxysmal depolarization shift and epileptogenesis. The inhibition of Na^{+}-K^{+} ATPase caused by digoxin and the consequent Ca^{++} activation of inositol mediated signal transduction is also involved in ras oncogene activation. The increased cytosolic Ca^{++} caused by digoxin can upregulate the Ca^{++} mediated signal transduction system involved in T-cell activation. Immune activation may play a role in disorders like MS and neuronal degeneration. The question of how the upregulation of the isoprenoid pathway takes place in these disorders is important. Our studies have shown that

there is increased tryptophan catabolism in these disorders, resulting in increased levels of serotonin and quinolinic acid. Both these are known inhibitors of membrane Na^{+}-K^{+} ATPase. The Mg^{++} depletion resulting from this inhibition can cause stimulation of HMG CoA reductase and upregulation of the isoprenoid pathway with increase in digoxin synthesis. The endogenous digoxin can further inhibit membrane Na^{+}-K^{+} ATPase. Thus the inhibition of this enzyme proceeds in a cascade like fashion.

Thus apart from its role in generation of free radicals, the isoprenoid pathway can also influence the pathogenesis of various neuropsychiatric disorders.

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