Ravikumar Kurup & Parameswara Achutha Kurup

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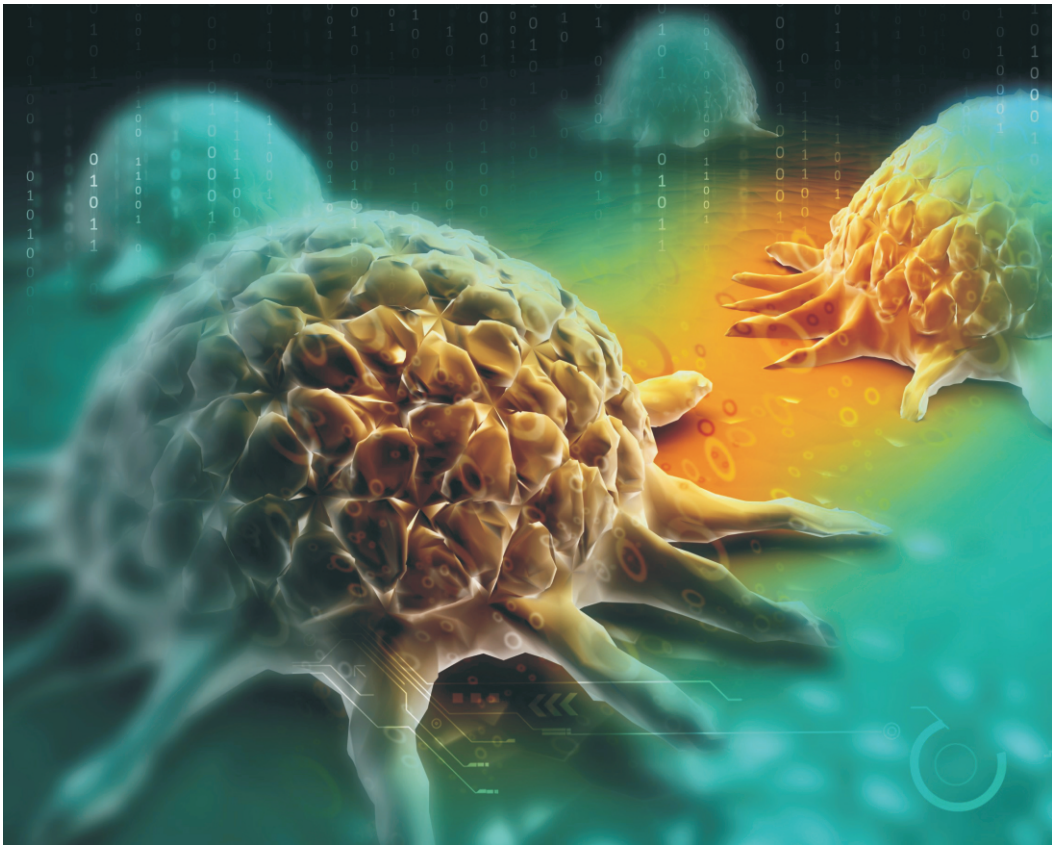

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The Endosymbiotic Archaea, Fructose Disease, Oncogenesis and Global Warming

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.

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

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 civilisation - 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 2C methyl erythritol phosphate. 2C methyl erythritol phosphate can be synthesized from erythrose 4-phosphate a metabolite of the shikimic acid pathway. DXP combines with MEP to form isopentenyl pyrophosphate which is converted to cholesterol. Cholesterol is catabolised by archaeal cholesterol oxidases to generate digoxin. The digoxin sugars digitoxose and rhamnose are synthesized by the upregulated pentose phosphate pathway. Glycolytic suppression leads to upregulation of the pentose phosphate pathway. The expressed archaeaon organelle concerned with cholesterol catabolism and digoxin synthesis is called the steroidelle. The suppression of glycolysis and stimulation of fructolysis results in upregulation

of the hexosamine pathway. Fructose is converted to fructose 6-phosphate by ketohexokinases. The fructose 6-phosphate is converted to glucosamine 6-phosphate by the action of glutamine fructose 6-phosphate amidotransferase (GFAT). Glucosamine 6- phosphate is converted to UDP N-acetyl glucosamine which is then converted to N-acetyl glucosamine and various amino sugars. UDP glucose is converted to UDP D-glucuronic acid. UDP D-glucuronic acid is converted to glucuronic acid. This forms the uronic acid synthetic pathway. Uronic acids and hexosamines form repeating units of glycosaminoglycans. In the setting of glycolytic suppression and fructolytic metabolism fructolysis leads to increase synthesis of hexosamines and GAG synthesis. The GAG synthesizing archaeaon particles are called the glycosaminoglycoids. The expressed archaeaon particles are capable of synthesizing antioxidant vitamin C and E. The UDP D-glucose is converted to UDP D-glucuronic acid. UDP D-glucuronic acid is converted to D-glucuronic acid. D-glucuronic acid is converted to L-gulonate by enzyme aldoketoreductases. L-gulonate is converted to L-gulonolactone by lactonase. L-gulonolactone is converted to ascorbic acid by the action of archaeal L-gulo oxidase. The vitamin E is synthesized from shikimate which is converted to tyrosine and then to parahydroxy phenyl pyruvic acid. Parahydroxy phenyl pyruvic acid is converted to homogentisate. Homogentisate is converted to 2-methyl 6-phytyl benzoquinone which is converted to alpha tocopherol. 2-methyl 6-phytyl benzoquinone is converted to 2,3-methyl 6-phytyl benzoquinone and gamma tocopherol. Vitamin E can also be synthesized by the DXP pathway. Glyceraldehyde 3-phosphate and pyruvate combined to form 1-deoxy D-xylulose 5-phosphate which is converted to 3-isopentenyl pyrophosphate. 3-isopentenyl pyrophosphate and dimethyl allyl pyrophosphate combined to form 2-methyl 6-phytyl benzoquinone which is converted to tocopherols. The ubiquinone another important membrane antioxidant and part of the mitochondrial electron transport chain is synthesized

by the shikimic acid pathway and DXP pathway. The isoprenoid moiety of ubiquinone is contributed from the DXP pathway and the rest of it by tyrosine catabolism. The tyrosine is generated by the shikimic acid pathway. The archaeaon particles concerned with the synthesis of vitamin C, vitamin E and ubiquinone which are all antioxidants are called the vitaminocyte.

Global warming induces endosymbiotic archaeal and RNA viroidal growth. The endosymbiotic archaea and the generated RNA viroids induce aldose reductase which converts glucose to sorbitol. The archaeal polysaccharides and lipopolysaccharides as well as viroids and viruses can induce aldose reductase. Sorbitol is acted upon by sorbitol dehydrogenase to generate fructose which enters fructolytic pathway. Aldose reductase is also induced by the osmotic stress of global warming and redox stress. Aldose reductase is induced by inflammatory and immune stimulation. Archaeal synthesized endogenous digoxin can produce intracellular redox stress and activate NFKB which produces immune activation. Both redox stress and immune activation can activate aldose reductase which converts glucose to fructose. Hypoxic stress or anerobic conditions induces HIF alpha which activates ketohexokinase C which phosphorylates fructose. Fructose is acted upon by fructokinase which converts fructose to fructose 1-phosphate. Fructose 1-phosphate is converted to dihydroxy acetone phosphate and glyceraldehydes 3-phosphate which is converted to pyruvate, acetyl CoA and citrate. Citrate is used for lipid synthesis. Fat deposition occurs in the visceral organs like the liver, heart and kidney. There is no subcutaneous fat deposit. Fructose metabolism bypasses phosphofructokinase which is inhibited by citrate and ATP. Fructose metabolism is therefore not under the regulatory control of the enzyme phosphofructokinase. Fructose transport and metabolism is not regulated by insulin. Fructose is transported by glut 5 receptor. Fructose does not increase insulin secretion and therefore does not activate lipoprotein lipase. This results

in visceral 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.

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% of the ATP generated by metabolism is used for maintaining the sodium potassium pump. This results in membrane ATPase inhibition generated hibernatory state. The glyceraldehydes 3-phosphate generated by fructolysis can be converted to the pyruvate and acetyl CoA used for cholesterol synthesis. The cholesterol that is synthesized is used for digoxin synthesis. Digoxin also has got aglycone part which contains sugars like digitoxose and rhamnose. Digitoxose and rhamnose are generated by the fructose induced flux and upgradation of the pentose phosphate pathway.

Thus fructolysis results in a hyperdigoxinemic state and membrane sodium potassium ATPase inhibition. This results in cell protection and hibernation.

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

The global warming results in endosymbiotic archaeal growth. Archaea can induce aldose reductase which converts glucose to fructose. Fructolysis promotes flux along the pentose phosphate pathway generating nucleic acids and glycosaminoglycans. Fructolysis also generates glyceraldehydes 3-phosphate and further pyruvate. The pyruvate can enter the pyruvate carboxylase scheme generating gluconeogenesis and glycogen synthesis. Thus fructolysis can produce glycogen storage. Pyruvate can be converted to citrate for lipid synthesis. Pyruvate can also be converted to acetyl CoA for cholesterol synthesis. The flux along the pentose phosphate pathway generates the digoxin sugars, digitoxose and rhamnose. Cholesterol can be converted to digoxin producing a hyperdigoxinemic state. Digoxin produces membrane sodium potassium ATPase inhibition. The selective phosphorylation of fructose by fructokinase depletes the cell of ATP producing membrane sodium potassium ATPase inhibition. This results in the generation of a hibernatory state. The fructolysis generated pyruvate can get converted to glutamate which can enter

the GABA shunt pathway producing succinyl CoA and glycine for porphyrin synthesis. Porphyrins can form self replicating porphyrions or act as a template for the formation of RNA viroids, DNA viroids and prions which can symbiose to form archaea. Thus the archaea are capable of self replicating on porphyrin templates. The fructolysis thus produces a hibernatory syndrome with fat, glycogen and nucleic acid synthesis and storage. Fructolysis results in the generation of a hibernatory species, the homo neanderthalis. The fructolysis generated membrane sodium potassium ATPase inhibition results in cell hibernation and ATP sparing. The lack of ATP and digoxin induced membrane sodium potassium ATPase inhibition results in cortical inhibition and cerebellar dominance. This produces a somnolent state and a cerebellar cognitive affective disorder. The porphyrions generated by fructolysis produces quantal perception and cerebellar dominance. The storage of glycogen, fat and GAG results in obesity. The cerebellar cognitive affective syndrome results in a hypersexual state. The fructolysis and fructose can activate NFKB producing immune activation. The fructosylation of glycolytic and mitochondrial proteins suppresses the body's normal energetic which depends upon glycolysis and mitochondrial oxidative phosphorylation. Fructosylation of proteins results in blockade of glycolysis and mitochondrial oxidative phosphorylation. The body's energy needs are produced by fructolysis, porphyrin array mediated electron transport chain and ATP synthesis as well as membrane sodium potassium ATPase inhibition relation ATP synthesis. This produces a new species by archaeal symbiosis consequent to global warming - the homo neanderthalis. This can be called as the tropical hibernatory syndrome consequent to global warming.

This can be called also as a fructose disease. Endosymbiotic archaea and viroids induce aldose reductase and converts body glucose to fructose leading to preferential fructose phosphorylation by ketohexokinase C. Fructolysis results in fructose 1-phosphate being acted upon by aldolase B resulting in the

formation of glyceraldehyde and dihydroxy acetone phosphate. Glyceraldehyde can be converted to glyceraldehyde 3-phosphate and this contributes to pyruvate formation. Pyruvate enters the GABA shunt resulting in the formation of succinyl CoA and glycine. They are substrates for porphyrin synthesis and porphyrion formation. The porphyrins form a template for the formation of RNA viroids, DNA viroids, prions, isoprenoids and polysaccharides. They can symbiose together to form primitive archaea. The archaea can further induce HIF alpha, aldose reductose and fructolysis resulting in further porphyrinogenesis and archaeal self replication. The archaea by methanogenesis contributes to global warming which leads to further archaeal growth and a vicious cycle with no regulatory switches. The fructolytic pathway induced by archaea by-passes regulatory enzyme phosphofructokinase and is practically unregulated. Fructolytic pathway contributes to glycogen, lipids, cholesterol, hexose sugars and mucopolysaccharides synthesis and storage. This leads onto a hibernatory state and archaeal symbiosis induced species change resulting in neanderthalisation of the homo sapien species. The digoxin and fructose phosphorylation induced ATP depletion leads to membrane sodium potassium ATPase inhibition, sparing of ATP and tissue hibernation as most of the energy needs of the body are for the working of the sodium potassium pump. The cholesterol that is synthesized by fructolysis is catabolized cholesterol oxidases for archaeal energetics. Archaea also derives its energy from a primitive form of electron transport chain functioning in self replicating porphyrin arrays. The archaeal digoxin induced sodium potassium ATPase inhibition can lead to membrane ATP synthesis. The archaea and the new human species phenotype derive its energy from the above mentioned mechanism. The glycolytic enzymes and the mitochondrial PT pore hexokinase are fructosylated making them dysfunction. The fructosylated glycolytic enzymes lead to generation of antiglycolytic enzyme antibodies and disease states. The human body’s

principal method of energetics tissue glycolysis and oxidative phosphorylation comes to a grinding halt. The human body is taken over by the overgrowth of endosymbiotic archaea and assumes hibernatory state with accumulation of glycogen, lipids, mucopolysaccharides and nucleic acids. The catabolic pathways for energy generation related to glucose, glycolysis and oxphos scheme stops. The human body can depend upon ketogenesis from fat and proteins. The upregulated fructolytic pathway generates phosphoglycerate which converted to phosphoserine and glycine. They can be converted to other amino acids and used for ketogenesis. The body assumes a high BMI index and obesity with visceral fat storage and adiposity akin to the Neanderthal metabolic phenotype. Digoxin induced membrane sodium potassium ATPase inhibition results in cortical dysfunction. The brain porphyrins can form a quantal pumped phonon system resulting in quantal perception and low level EMF absorption. This leads to prefrontal cortex atrophy and cerebellar dominance. Fructose itself leads to sympathetic hyperactivity and parasympathetic blockade. This leads onto a functional form of cerebellar cognition and quantal perception resulting in a new brain phenotype. The cerebellar cognitive syndrome leads to a robotic human phenotype. The phenotype is impulsive, has extrasensory perception and has less of speech production. Communication is by symbolic acts. The cerebellar phenotype doesn’t have a cortical control and contributes to surrealistic behavior patterns. This produces impulsive behavior and an epidemic of surrealism where the rational prefrontal cortex becomes extinct. This leads to extremes of spirituality, violent and terroristic behavior and hypersexual states contributing to a state of trancedence underlined and reinforced by quantal perception. Cerebellar phenotype owing to its quantal perception behaves as a community and not as an individual. This creates new social and psychological phenotypes. Fructose induces NFKB and immune activation. This results in an immune activatory phenotype. Cultured T-reg cells

on high fructose diet have 62% less IL-40 secretion than controls. This results in a hyperimmune state with fructosylated proteins acting as antigens. The fructolytic pathway can lead to increased DNA synthesis and RNA synthesis due to flux via the pentose phosphate pathway. The fructolytic pathway can be directed to the GABA shunt generating succinyl CoA and glycine. These are substrates for porphyrin templates to form RNA viroids. The archaeal induced redox stress can induce endogenous HERV expression and reverse transcriptase expression. The RNA viroids are converted by HERV reverse transcriptase to corresponding DNA and integrated into the genome by HERV integrase. The integrated RNA viroid related DNA can function as jumping genes producing genomic plasticity and genomic change. This produces a new genotype. Fructosylation of body proteins and enzymes results in a protein processing defect resulting in loss of protein function. The human cell function due to protein fructosylation, protein processing defects and protein conformational defects comes to a grinding halt. Fructolytic pathway generates porphyrin arrays induced ATP production, membrane sodium potassium ATPase inhibition induced ATP synthesis and fructolysis induced ATP generation. This provides energy for porphyrin template induced archaeal replication. The digoxin and fructose phosphorylation induced ATP depletion produces cell membrane sodium potassium ATPase inhibition and a hibernatory state. This leads onto a somnolent sleepy state. The cholesterol catabolism by cholesterol oxidases for archaeal energetics leads to defective sex hormone synthesis. This leads onto an asexual androgynous state. The cerebellar cognitive syndrome due to prefrontal cortical atrophy consequent to porphyrion induced low level EMF perception produces a hypersexual state. This results in male-female equidominance and changes in sexual behavior of the population. Thus the fructose disease consequent to global warming results in a new neuronal, immune, metabolic, sexual, social phenotype. The human body is converted to a zombie for the

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

and the vicious irreversible cycle proceeds. The uncontrolled growth of archaea leads to still further global warming. The world of endosymbiotic eternal archaea takes over and persists during the extremophilic climatic changes of global warming. The human beings exist as neanderthalic zombies serving archaeal multiplication. The homo sapiens gets converted to a new phenotype, genotype, immunotype, metabolonomic type and brain type. This is called as hibernatory zombie related to global warming - homo neoneanderthalis.

Table 1

	Serum fructose		**Serum fructokinase**		**Aldolase B**		**Total GAG**	
	Mean	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**
Normal	2.50	0.195	8.50	0.405	3.50	1.304	3.50	0.707
Myeloma	32.04	4.955	21.37	2.050	10.89	1.344	20.12	2.855
Lymphoma	27.94	3.732	22.29	1.237	9.46	1.386	20.89	1.651
Glioma	29.88	5.150	22.29	1.641	10.87	1.895	23.47	2.878
F value	17.373		13.973		13.903		21.081	
p value	< 0.01		< 0.01		< 0.01		< 0.01	

Table 2

	Total TG		**Serum ATP levels**		**Uric acid**		**Anti-aldolase**	
	Mean	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**
Normal	124.00	3.688	2.50	0.405	5.70	0.369	7.50	1.704
Myeloma	302.00	25.166	0.77	0.151	9.26	1.048	1.41	0.310
Lymphoma	277.60	34.613	0.80	0.136	7.88	0.847	1.45	0.415
Glioma	289.89	23.406	0.74	0.115	9.59	0.783	1.80	0.402
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
Myeloma	0.49	0.197	18.68	4.585	1.54	0.471
Lymphoma	0.42	0.182	19.93	2.421	1.39	0.253
Glioma	0.39	0.124	18.93	6.447	1.78	0.355
F value	14.091		21.073		58.769	
p value	< 0.01		< 0.01		< 0.01	

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2

Archaeal Digoxin and Oncogenesis

Introduction

Changes involving the isoprenoid pathway have been described in neoplasms. The isoprenoid pathway produces key four metabolites important in cellular function - digoxin (an endogenous Na^+-K^+ ATPase inhibition), dolichol (important in N-glycosylation of proteins). ubiquinone (a component of the mitochondrial electron transport chain and membrane antioxidant) and cholesterol.

Alteration in membrane Na^+-K^+ ATPase has been described in oncogenesis suggesting a possible role for endogenous digoxin. An important feature of malignant transformation is loss of the cholesterol feedback inhibition mechanism that regulates cholesterol synthesis. Cancer cells seem to require an increase in the concentration of cholesterol and cholesterol precursors. Prevention of tumour-cell growth can be achieved by restricting either cholesterol availability or cholesterol synthesis. In vivo-and-cell-culture experiments have shown that lowering the plasma cholesterol concentration or intervening in the mevalonate pathway with HMG CoA reductase inhibitors decreases tumour growth. Another key protein in the internal signalling pathway that triggers cell growth is ras. ras is activated by hooking a 15 carbon farnesyl chain to ras by the enzyme farnesyl transferase. Farnesyl transferase inhibitors are used to block K-ras-driven tumours.

Digoxin by its inhibition of Na^+-K^+ ATPase can alter intracellular calcium / magnesium ratios in the cell leading to free radical generation. Alteration in ubiquinone which is a component of the mitochondrial electron transport chain and a membrane antioxidant, can also lead to mitochondrial dysfunction and free radical generation. Defects in structure and function of mitochondria have been described in neoplasms. Free radical mechanisms have been implicated in tumourogenesis. Free radicals are required for the action of the oncogene coded growth factors. Digoxin induced membrane Na^+-K^+ ATPase inhibition can

produce magnesium depletion leading to altered glycoconjugate metabolism. Altered glycoproteins and dolichol have been described in neoplasms. The dolichol pathway is important in N-glycosylation of protein. Altered glycosylation of serum transferrin has been reported in neoplastic lesions. Abnormal glycoconjugates have been described in neoplastic disorders. A number of fucose and sialic acids containing carbohydrate ligands are important in malignant cell transformation. Glycosylation inhibitors are used to treat neoplasms. In some tumours, interaction of tumour and host cells with adhesion and extracellular matrix molecules like heparan sulphate, proteoglycan and syndecan are important.

Digoxin has been reported to regulate the transport of amino acids, especially the neutral amino acids. Tryptophan metabolism has also been implicated in neoplastic disorders and immune activation. Interferons act by inducing the enzyme indoleamine 2,3-dioxygenase which catalyses the catabolism of tryptophan along the kynurenine pathway. This leads to tryptophan depletion and increase in the level of its metabolites kynurenine and quinolinic acid. Cachexia related to cancer has also been related to indoleamine 2,3-digoxygenase induction and depletion of tryptophan by enhancing its catabolism. The kynurenine pathway can also contribute to oncogenesis. Neurotransmitters could contribute to the regulation of the immune response. Elevated serotonin and reduced dopamine levels have been related to immune activation and immunoproliferation. Tryptophan and tyrosine catabolism could be important in this respect with regard to non-Hodgkin's lymphoma.

Global warming can lead to osmotic stress consequent to dehydration. The increase in actinidic archaeal growth leads to cholesterol catabolism and digoxin synthesis. Digoxin produces membrane sodium potassium ATPase inhibition and increase in intracellular calcium producing mitochondrial dysfunction. This results in oxidative stress. The oxidative stress and osmotic stress can induce the

enzyme aldose reductase which converts glucose to fructose. Fructose has got a low km value for ketokinase as compared to glucose. Therefore fructose gets phosphorylated more to fructose phosphate and the cell is depleted of ATP. The cell depletion of ATP leads to oxidative stress and chronic inflammation consequent to induction of NFKB. The fructose phosphate can enter the pentose phosphate pathway synthesizing ribose and nucleic acid. The depletion of cellular ATP results in generation of AMP and ADP which are acted upon by deaminases causing hyperuricemia. Uric acid can also produce mitochondrial dysfunction. The fructose phosphate can enter the glucosamine pathway synthesizing GAG and producing mucopolysaccharide accumulation. Fructose can fructosylate proteins making them antigenic and producing an autoimmune response. This can lead to global warming related cancer.

This study was undertaken to assess the following parameters in Non-Hodgkin's Lymphoma (NHL) and CNS astrocytomas: (1) The isoprenoid pathway, (2) The tryptophan/tyrosine catabolic patterns, (3) Glycoconjugate metabolism, and (4) RBC membrane changes as a reflection of neoplastic cell membrane change (the isoprenoid pathway produces four metabolites which can regulate membrane function and structure-dolichol, digoxin, cholesterol and ubiquinone). A hypothesis implicating membrane Na^+-K^+ ATPase inhibition as pivotal to all these changes is also presented.

Results

(1) The activity of HMG CoA reductase and the concentration of digoxin and dolichol were increased in CNS astrocytmas and NHL when compared with controls. The concentration of serum ubiquinone, the activity of erythrocyte membrane Na^+-K^+ ATPase and serum magnesium were decreased.

(2) The concentration of serum tryptophan, quinolinic acid and serotonin was increased in the plasma while that of tyrosine, dopamine and noradrenaline was decreased in CNS astrocytomas and NHL.

(3) Nicotine could be detected in the plasma of patients with CNS astrocytomas and NHL but was not detectable in control serum. Morphine and strychnine was not detected in the plasma of these patients.

(4) The concentration of total glycosaminoglycans (GAG) increased in the serum of CNS astrocytomas and NHL patients. The concentration of heparan sulphate (HS) heparin (H), chondroitin sulphates (ChS) and hyaluronic acid was increased in NHL and CNS astrocytomas, while that of dermatan sulphate (OS) was decreased in CNS astrocytomas and increased in NHL. The concentration total hexose, fucose and sialic acid were increased in the glycoproteins of the serum in these patients. The concentration of gangliosides, glycosyl-diglycerides, cerebroside and sulphatide showed significant increase in the serum of these patients.

(5) The activity of glycosaminoglycan (GAG) degrading enzymes - beta glucuronidase, beta N-acetyl hexoseaminidase, hyaluronidase and cathepsin-D - was increased in CNS astrocytomas and NHL when compared to the controls. The activity of beta galactosidase, beta fucosidase and beta glucosidase increased in CNS astrocytomas and NHL patients.

(6) The concentration of total GAG and hexose and fucose residues of glycoproteins in the RBC membrane decreased significantly in CNS astrocytomas and NHL. The concentration of RBC membrane cholesterol was unaltered in CNS astrocytomas and NHL while that of phospholipid decreased. The ratio of RBC membrane cholesterol: phospholipids increased in CNS astrocytomas and NHL.

(7) Concentration of total serum cholesterol and LDL cholesterol was not significantly altered while HDL cholesterol showed a significant decrease in the plasma in CNS astrocytomas and NHL. Serum triglycerides and free fatty acids (FFA) increased in CNS astrocytomas and NHL.

(8) The activity of superoxide dismutase (SOD), catalase, glutathione reductase and glutathione peroxidase in the erythrocytes decreased significantly in CNS astrocytomas and NHL. The concentration of MDA, hydroperoxides, conjugated dienes and NO increased significantly. The concentration of glutathione was decreased and of alpha tocopherol was unaltered in CNS astrocytomas and NHL. Iron binding capacity and ceruloplasmin decreased significantly in CNS astrocytomas and NHL while albumin was reduced.

Discussion

Archaeal Digoxin and Membrane Na^+-K^+ ATPase Inhibition in Relation to Oncogenesis

The archaeaon steroidelle DXP pathway and the upregulated pentose phosphate pathway contribute to digoxin synthesis. The increase in endogenous digoxin, a potent inhibitor of membrane Na^+-K^+ ATPase can decrease this enzyme activity. In CNS astrocytomas and NHL there was significant inhibition of the RBC membrane Na^+-K^+ ATPase. The inhibition of Na^+-K^+ ATPase by digoxin is known to cause an increase in intracellular calcium resulting from increased Na^+-Ca^{++} exchange, increased entry of calcium via the voltage gated calcium channel and increased release of calcium from intracellular endoplasmic reticulum calcium stores. This increase in intracellular calcium by displacing magnesium from its binding sites causes a decrease in the functional availability of magnesium. The decrease in the availability of magnesium can cause decreased mitochondrial ATP formation which along with low

magnesium can cause further inhibition of Na^+-K^+ ATPase, since the ATP-magnesium complex is the actual substrate for this reaction. There is thus a progressive inhibition of Na^+-K^+ ATPase activity first triggered by digoxin. Low intracellular magnesium and high intracellular calcium consequent to Na^+-K^+ ATPase inhibition appear to be crucial to the pathophysiology of CNS astrocytomas and NHL. Serum magnesium was assessed in CNS astrocytomas and NHL and was found to be reduced. Increased intracellular calcium activates phospholipase C beta which results in increased production of diacyglycerol (DAG) with resultant activation of protein kinase C. The protein kinase C (PKC) activates the MAP kinase cascade resulting in cellular proliferation. The decreased intracellular magnesium can produce dysfunction of GTPase activity of the alpha - subunit of G-protein. This results in ras oncogene activation, as more of the ras is bound to GTP rather than GDP. Phosphorylation mechanisms are required for the activation of the tumour suppressor gene P_{53}. The activation of P_{53} is impaired owing to intracellular magnesium deficiency producing a phosphorylation defect. Intracellular magnesium depletion can produce defective phosphorylation of microtubule associated proteins (MAP) resulting in microtubule related spindle fibre dysfunction and chromosomal non-dysjunction. This produces the characteristic neoplastic cellular polyploidy and aneuploidy. Upregulation of the isoprenoid pathway can result in increased production of farnesyl phosphate which can farnesylate the ras oncogene producing its activation.

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

The archaeaon neurotransminoid shikimic acid pathway contributes to tryptophan and tyrosine synthesis and catabolism generating neurotransmitters and neuroactive alkaloids. Digoxin, apart from affecting cation transport is also

reported to influence the transport of various metabolite across cellular membranes, including amino acids and various neurotransmitters. Two of the amino acids in this respect are important - tryptophan, a precursor for nicotine and strychnine and tyrosine a precursor for morphine. We have a already shown the presence of endogenous nicotine and strychnine in the brain of rats loaded with tryptophan and morphine in the brain of rats loaded with tyrosine. The results now obtained show that the concentration of tryptophan, quinolinic acid and serotonin was higher in the plasma of patients with CNS astrocytomas and NHL while that of tyrosine, dopamine and norepinephrine was lower. Serum of patients with CNS astrocytomas and NHL showed the presence of high amounts of nicotine in their serum. Morphine and strychnine were absent in the serum of these patients. Thus there is increase in tryptophan and its catabolites and a reduction in tyrosine and its catabolites in the patient's serum. This could be due to the fact that digoxin can regulate the neutral amino acid transport system with preferential promotion of tryptophan transport over tyrosine. The decrease in membrane Na^+-K^+ ATPase activity in all the disorders studied could be due to the fact that the hyperpolarising neurotransmitters (dopamine and noradrenaline) are reduced and the depolarising neuroactive compounds (serotonin, nicotine and quinolinic acid) are increased.

The neurotransmitter pattern of reduced dopamine and noradrenaline, and increased serotonin can contribute to cancer related psychosis. This neurotransmitter pattern is common to neoplasms (CNS astrocytomas and NHL) and schizophrenia (paper under publication). A schizoid state of mind can predispose the patients to the development of neoplasms. Alteration in natural killer cell activity has been reported in psychiatric disorders. Serotonin and acetyl choline promote cell proliferation and dedifferentiation by inhibiting denyl cyclase or by activating phospholipase-C (PLC). Nicotine by binding to the nicotinic receptor promotes cholinergic transmission. Dopamine and

noradrenaline elevate cyclic AMP levels and inhibit cell proliferation and differentiation. Increased quinolinic acid can lead to cancer related cachexia. Serotonin dopamine and noradrenaline receptors have been demonstrated is increased with the corresponding reduction in dopamine and noradrenaline in the brainstem monoaminergic nuclei. Thus elevated serotonin and reduced noradrenaline and dopamine can contribute to the immune activation and immunoproliferation in non-Hodgkin's lymphoma. Decreased morphine levels can lead to the increased metastatic property of tumours as morphine has a suppressing effect on tumour metastasis and tumour growth.

In the presence of hypomagnesemia, the magnesium block on the NMDA receptor is removed leading to NMDA excitotoxicity. The increased presynaptic neuronal calcium can produce cyclic AMP dependent phosphorylation of synapsins resulting in increased neurotransmitter release into the synaptic junction and vesicular recycling. Increased intracellular calcium in the post synaptic neuron can also activate the calcium dependent NMDA signal transduction. The plasma membrane neurotransmitter transporter (on the surface of the glial cell and presynaptic neuron) is coupled to a sodium gradient which is disrupted by the inhibition of Na^+-K^+ ATPase, resulting in decreased clearance of glutamate by presynaptic and glial uptake at the end of synaptic transmission. By these mechanisms, inhibition of Na^+-K^+ ATPase can promote glutamatergic transmission. The elevated levels of quinolinic acid and serotonin can also contribute to NMDA excitotoxicity. Quinolinic acid and serotonin are positive modulators of the NMDA receptor. Increased glutamatergic transmission resulting in excitotoxicity has been implicated in cellular proliferation. Excitatory amino acids like glutamate can act as trophic factors and promote cellular proliferations.

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

The archaeaon glycosaminoglycoid and fructosoid contributes to glycoconjugate synthesis and catabolism by the process of fructolysis. The membrane Na^+-K^+ ATPase related Magnesium depletion can affect the metabolism of glycosaminoglycans, glycoproteins and glycolipids. The elevation in the level of dolichol may suggest its increased availability for N-glycosylation of proteins. Magnesium deficiency can lead to defective metabolism of sphinganine, producing its accumulation which may lead to increased cerebroside and ganglioside synthesis. In Magnesium deficiency the glycolysis, citric acid cycle and oxidative phosphorylation are blocked and more glucose 6-phosphate is channelled for the synthesis of glycosaminoglycans (GAG). The results now obtained show an increase in the concentration of serum total GAG, glycolipids (ganglioside, glycosyl-diglyceride, cerebrosides and sulphatides) and carbophydrate components of glycoproteins (hexose, fucose and sialic acid) in CNS astrocytomas and NHL. The increase in the carbohydrate components - total hexose, fucose and sialic acid - in CNS astrocytomas and NHL was not to the same extent suggesting qualitative change in glycoprotein structure. The pattern of change in individual GAG was that HA, H, HS, ChS and DS (except in CNS astrocytomas where DS was reduced) increased in the serum in CNS astrocytomas and NHL. The activity of GAG degrading enzymes (beta glucuronidase, beta N-acetyl hexosaminidase, hyaluronidase and cathepsin-D) and that of glycohydrolases (beta galactosidase, beta fucosidase and beta glucosidase) showed significant increase in the serum in CNS astrocytomas and NHL. Intracellular magnesium deficiency also results in defective ubiquitin dependent proteolytic processing of glycoconjugates as it requires magnesium for its function. The increase in the activity of glycohydrolases and GAG degrading enzymes could be due to reduced

lysosomal stability and consequent leakage of lysosomal enzymes into the serum. The increase in the concentration of carbohydrate components of glycoproteins and GAG in spite of increased activity of many glycohydrolases may be due to their possible resistance to cleavage by glycohydrolases consequent to qualitative change in their structure. Proteoglycan complexes formed in the presence of altered calcium/magnesium ratios intracellularly may be structurally abnormal and resistant to lysosomal enzymes and may accumulate.

The protein processing defect can result in defective glycosylation of endogenous tumour antigens and exogenous viral glycoprotein antigens with consequent defective formation of the MHC-antigen complex. The MHC linked peptide transporter, a P-glycoprotein which transports the MHC-antigen complex to the antigen presenting cell surface, has an ATP binding site. There is dysfunction of this in the presence of magnesium deficiency. This results in defective transport of MHC class-1 glycoprotein antigen complex to the antigen presenting cell surface for recognition by the CD_4/CD_8 cell/NK cell. Defective presentation of exogenous viral antigens can produce immune evasion by the virus leading to viral persistence and oncogenesis consequent to viral oncogenesis. This is especially true in the case of Non-Hodgkin's lymphoma (both T-cell and B-cell type) where the ebstein barr virus has been linked to the pathogenesis. Defective presentation of endogenous tumour antigens can lead on to loss of NK cell (natural killer cell) immunosurveillance and oncogenesis. Altered cell surface glycoproteins, glycolipids and Gag can lead to defective contact inhibition and oncogenesis. A number of fucose and sialic acids containing natural ligands have been implicated in neoplastic transformation and metastasis as also immune activation and lymphocytic proliferation.

Archaeal Digoxin and Alteration in Membrane Structure and Membrane Formation in Relation to Oncogenesis

The archaeaon steroidelle, glycosaminoglycoid and fructosoid contribute to cell membrane formation synthesizing cholesterol by the DXP pathway and glycosaminoglycans by fructolysis. The alteration in the isoprenoid pathway specifically, cholesterol as well as changes in glycoproteins and GAG can affect cellular membranes. The upregulation of the isoprenoid pathway can lead to increased cholesterol synthesis and magnesium deficiency can inhibit phospholipid synthesis. Phospholipid degradation is increased owing to increase in intracellular calcium activating phospholipid degradation is increased owing to increase in intracellular calcium activating phospholipase A_2 and D. The RBC membrane cholesterol was unchanged while the phospholipids were reduced resulting in an increased cholesterol phospholipid ratio. The concentration of total GAG, hexose and fucose residues of glycoprotein decreased in the RBC membrane and increased in the serum suggesting their reduced incorporation into the membrane and defective membrane formation. The glycoproteins, GAG and glycolipids of the cellular membrane are formed in the endoplasmic reticulum, which is then budded off as a vesicle which fuses with the golgi complex. The glycoconjugates are then transported via the golgi channel and the golgi vesicle fuses with the cell membrane. This trafficking depends upon GTPases and lipid kinases which are crucially dependent on magnesium and are defective in magnesium deficiency. The change in membrane structure produced by alteration in glycoconjugates and cholesterol phospholipid ratio can produce changes in the conformation of Na^+-K^+ ATPase resulting in further membrane Na^+-K^+ ATPase inhibition. Similar changes can affect the structure of the organelle membrane. This results in defective lysosomal stability and leakage of glycohydrolases and GAG degrading

enzymes into the serum. Defective peoxisomal membranes lead to catalase dysfunction which has been documented in CNS astrocytomas and NHL.

Archaeal Digoxin and Mitochondrial Dysfunction in Relation to Oncogenesis

The archaeaon vitaminocyte contributes to the synthesis of ubiquinone and mitochondrial electron transport chain function. The mitochondrial function related free radical generation is regulated by the archaeaon vitaminocyte synthesized tocopherol and ascorbic acid. The concentration of ubiquinone decreased significantly in most of the cases which may be the result of low tyrosine levels, reported in CNS astrocytomas and NHL consequent to digoxin's effect in preferentially promoting tryptophan transport over tyrosine. The aromatic ring portion of ubiquinone is derived from the tyrosine. Ubiquinone, which is important and contributes to free radical scavenging. The increase in intracellular calcium can open the mitochondrial PT pore causing a collapse of the hydrogen gradient across the inner membrane and uncoupling of the respiratory chain. Intracellular magnesium deficiency can lead to a defect in the function of ATP synthase. All this leads to a defect in mitochondrial oxidative phosphorylation, incomplete reduction of oxygen and generation of the superoxide ion which produces lipid peroxidation. Ubiquinone deficiency also leads to reduced free radical scavenging. The increase in intracellular calcium may lead to increased generation of NO by inducing the enzyme nitric oxide synthase which combines with the superoxide radical to form peroxynitrite. Increased calcium also can activate phospholipase A_2 resulting in increased generation of arachidonic acid which can undergo increased lipid peroxidation. Increased generation of free radicals like the superoxide ion, and hydroxyl radical can produce lipid peroxidation and cell membrane damage which can further inactivate Na^+-K^+ ATPase triggering the cycle of free radical generation

again. The free radicals and scavenging enzymes were estimated in all these disorders. There was increase in lipid peroxidation as evidenced from the increase in the concentration of MDA, conjugated dienes, hydroperoxides and NO with decreased antioxidant protection as indicated by decrease in ubiquinone and reduced glutathione in CNS astrocytoma and NHL. The activity of enzymes involved in free radical scavenging like superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase and catalase is decreased in CNS astrocytoma and NHL suggesting reduced free radical scavenging. Alpha tocopherol values were unchanged in both neoplasms. 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+} form, the conversion of H_2O_2 to hydroxyl radical is greatly increased. Low ceruloplasmin results in more of the iron to be in Fe^{2+} form. It has been shown that ceruloplasmin increases iron uptake by cells increasing the apparent affinity for the substrate by three times. Low ceruloplasmin levels can result in decreased iron uptake and this results in an increased amount of free iron. The intra cellular magnesium deficiency can produce ribosomal dysfunction and inhibition of protein synthesis. The low iron binding capacity and low serum ceruloplasmin levels may be a consequence of reduced ferritin and ceruloplasmin synthesis. The peroxisomal membrane is defective owing to the membrane Na^+-K^+ ATPase inhibition related defect in membrane formation and leads to reduced catalase activity. Glutathione is synthesized by the enzyme glutathione synthetase which needs magnesium and ATP. The low intracellular magnesium 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 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. Opening of the mitochondrial PT pore produces hyperosmolality and matrix expansion rupturing the outer membrane producing loss of the mitochondrial dismutase and a decrease in its activity. The reduction in catalase, superoxide dismutase (SOD), glutathione peroxidase and glutathione reductase suggests reduced free radical protection. Mitochondrial dysfunction related free radical generation has been implicated in the pathogenesis of the oncogenesis. Free radicals are required for the action of growth factors and promote cellular proliferation.

The increased intracellular calcium and ceramide related opening of the mitochondrial PT pore also lead to volume dysregulation of the mitochondria causing hyperosmolality of the matrix and expansion of the matrix space. The outer membrane of the mitochondria ruptures and releases cytochrome C into the cytoplasm. This results in activation of caspase-3. Caspase-3 activation can cleave and inactivate P_{21} involved in linking DNA duplication to cell division resulting in a polyploidal cell and oncogenesis.

Archaeal Digoxin and Regulation of Cell Division, Cell Proliferation and Neoplastic Transformation in Relation to Oncogenesis - Relation to Immune Activation

The archaeaon fructosoid contributes to fructolysis and immune activation. Fructose can contribute to induction of NFKB and immune activation. The archaeaon steroidelle synthesized digoxin induces NFKB producing immune activation. Increased intracellular calcium activates the calcium dependent calcineurin signal transduction pathway which can produce T-cell activation and secretion of interleukin-3, 4, 5, 6 and TNF alpha. This can explain the immune activation in Non-Hodgkin's lymphoma and paraneoplastic syndromes. Membrane Na^{+}-K^{+} ATPase inhibition can produce immune activation and is reported to increase CD_4/CD_8 ratios as exemplified by the action of lithium. Defective presentation of glycoprotein neuronal antigens to the CD_4 and CD_8 cell can explain the immune dysregulation and autoimmunity describe in paraneoplastic syndromes.

Thus the defective isoprenoid pathway can promote oncogenesis by the following mechanisms, (1) Altered calcium/magnesium ratios promoting ras oncogene activation and defective function of the P_{53} tumour suppressor gene, (2) Protein processing defect and defective presentation of tumour antigens and defective immunosurveillance. This can also lead to defective contact inhibition. Defective processing of viral glycoprotein antigens and their presentation can lead to viral persistence and oncogenesis, (3) Mitochondrial defect and free radical generation. This also leads to caspase-3 activation and cleaving of P_{21} protein which couples cell division to DNA duplication, (4) Intracellular magnesium depletion can produce defective phosphorylation of MAP (microtubule associated proteins) resulting in microtubule related spindle fibre dysfunction and cellular polyploidy and aneuploidy, (5) Digoxin related tryptophan/tyrosine transport defect leading to increase in neurotransmitters that

promote cell proliferation (nicotine and serotonin) and decrease in neurotransmitters that inhibits cell proliferation (dopamine and noradrenaline). This also leads to quinolinic acid related cachexia and immunoproliferation, and (6) Increased production of famesyl phosphate leading to farnesylation of ras oncogene and its activation.

References

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Archaeal Digoxin, Hemispheric Chemical Dominance and Oncogenesis - Evidence from Multiple Myeloma

Introduction

Changes involving the isoprenoid pathway have been described in neoplasms. The isoprenoid pathway produces four key metabolites important in cellular function - digoxin (an endogenous Na^+-K^+ ATPase inhibitor), dolichol (important in N-glycosylation of proteins), ubiquinone (a component of the mitochondrial electron transport chain and membrane antioxidant) and cholesterol.

Alteration in membrane Na^+-K^+ ATPase has been described in oncogenesis suggesting a possible role for endogenous digoxin. An important feature of malignant transformation is loss of the cholesterol feedback inhibition mechanism that regulates cholesterol synthesis. Cancer cells seem to require an increased concentration of cholesterol and cholesterol precursors. Prevention of tumour-cell growth can be achieved by restricting either cholesterol availability or cholesterol synthesis. In vivo-and-cell-culture experiments have shown that lowering the plasma cholesterol concentration or intervening in the mevalonate pathway with HMG CoA reductase inhibitors decreases tumour growth. Another key protein in the internal signalling pathway that triggers cell growth is ras. ras is activated by hooking a 15 carbon farnesyl chain to ras by the enzyme farnesyl transferase. Farnesyl transferase inhibitors are used to block K-ras-driven tumours.

Digoxin, by its inhibition of Na^+-K^+ ATPase, can alter intracellular calcium / magnesium ratios in the cell leading to free radical generation. Alteration in ubiquinone which is a component of the mitochondrial electron transport chain and a membrane antioxidant can also lead to mitochondrial dysfunction and free radical generation. Defects in structure and function of mitochondria have been described in neoplasms. Free radical mechanisms have been implicated in tumourogenesis. Free radicals are required for the action of the oncogene coded growth factors. Digoxin induced membrane Na^+-K^+ ATPase inhibition can

produce magnesium depletion leading to altered glycoconjugate metabolism. Altered glycoproteins and dolichol have been described in neoplasms. The dolichol pathway is important in N-glycosylation of protein. Altered glycosylation of serum transferrin has been reported in neoplastic lesions. Abnormal glycoconjugates have been described in neoplastic disorders. A number of fucose and sialic acids containing carbohydrate ligands are important in malignant cell transformation. Glycosylation inhibitors are used to treat neoplasms. In multiple myeloma, interaction of tumour and host cells with adhesion and extracellular matrix molecules like heparan sulphate proteoglycan and syndecan are important.

Digoxin has been reported to regulate the transport of amino acids, especially the neutral amino acids. Tryptophan metabolism has also been implicated in neoplastic disorders and immune activation. lnterferons act by inducing the enzyme indoleamine 2,3-dioxygenase which catalyses the catabolism of tryptophan along the kynurenine pathway. This leads to tryptophan depletion and increase in the level of its metabolites kynurenine and quinolinic acid. Cachexia related to cancer has also been related to indoleamine 2,3-digoxygenase induction and depletion of tryptophan by enhancing its catabolism. The kynurenine pathway can also contribute to oncogenesis. Neurotransmitters could contribute to the regulation of the immune response. Elevated serotonin and reduced dopamine levels have been related immune activation and immunoproliferation. Tryptophan and tyrosine catabolism could be important in this respect with regard to immunoproliferative neoplasms like multiple myeloma.

Global warming can lead to osmotic stress consequent to dehydration. The increase in actinidic archaeal growth leads to cholesterol catabolism and digoxin synthesis. Digoxin produces membrane sodium potassium ATPase inhibition and increase in intracellular calcium producing mitochondrial dysfunction. This results in oxidative stress. The oxidative stress and osmotic stress can induce the

enzyme aldose reductase which converts glucose to fructose. Fructose has got a low km value for ketokinase as compared to glucose. Therefore fructose gets phosphorylated more to fructose phosphate and the cell is depleted of ATP. The cell depletion of ATP leads to oxidative stress and chronic inflammation consequent to induction of NFKB. The fructose phosphate can enter the pentose phosphate pathway synthesizing ribose and nucleic acid. The depletion of cellular ATP results in generation of AMP and ADP which are acted upon by deaminases causing hyperuricemia. Uric acid can also produce mitochondrial dysfunction. The fructose phosphate can enter the glucosamine pathway synthesizing GAG and producing mucopolysaccharide accumulation. Fructose can fructosylate proteins making them antigenic and producing an autoimmune response. This can lead to global warming related cancer.

This study was undertaken to assess the following parameters in freshly diagnosed cases of multiple myeloma: (1) The isoprenoid pathway, (2) The tryptophan/tyrosine catabolic patterns, (3) Glycoconjugate metabolism, and (4) RBC membrane changes as a reflection of neoplastic cell membrane change (the isoprenoid pathway produces four metabolites which can regulate membrane function and structure - dolichol, digoxin. cholesterol and ubiquinone. A hypothesis implicating membrane Na^+-K^+ ATPase inhibition as pivotal to all these changes in multiple myeloma is also presented. Since digoxin can regulate multiple neurotransmitter systems it could possibly play a role in the genesis of cerebral dominance. The isoprenoid pathway and digoxin status was studied in individuals of differing hemispheric dominance in order to elucidate the role of cerebral dominance in the pathogenesis of multiple myeloma and neoplasms.

Materials and Methods

Fifteen freshly diagnosed cases of multiple myeloma were chosen randomly for the study from the orthopaedics and hematology wards of Medical College, Trivandrum and the Regional Cancer Centre, Trivandrum over a three year period. The age of the patients ranged from 50-60 years. All fifteen patients with multiple myeloma were right handed / left hemispheric dominant by the dichotic listening test. Informed consent was obtained from all the patients. The permission of the Ethics committee of the institute was also obtained. None of the subjects studied was under medication at the time of removal of blood. Samples were drawn before treatment was initiated. All the patients included in the study were non-smokers (active and passive). They were free of systemic diseases like hypertension and diabetes. Each patient had an age and sex matched healthy normal control.

Fifteen normal male healthy individuals (50-60 years of age) each of left handed / right hemispheric dominant, right handed / left hemispheric dominant and amphidextrous / bihemispheric dominant individuals diagnosed by the dichotic listening test were chosen for the study. This group was chosen at random from the general population of Trivandrum city. These individuals were not on any drugs like digoxin and were free from any systemic disease. All individuals in this group also were non-smokers (passive or active).

Fasting blood was removed from each of the patients for various estimations. RBCs were separated within 1 hour of collection of blood for the estimation of membrane Na^+-K^+ ATPase. Serum was used for the estimation of HMG CoA reductase activity. Plasma/serum was used for the estimation of the other parameters. All biochemicals used in this study were obtained from M/s Sigma Chemicals, USA. Activity of HMG CoA reductase of the plasma was determined using the method of Rao and Ramakrishnan by determining the ratio of HMG CoA to mevalonate. For the determination of Na^+-K^+ ATPase activity

of the erythrocyte membrane, the procedure described by Wallach and Kamat was used. Digoxin in the plasma was determined by the procedure described by Arun, Ravikumar, Leelamma and Kurup. For estimation of ubiquinone and dolichol in the plasma, the procedure described by Palmer, Maureen and Robert was used. Magnesium in the plasma was estimated by atomic absorption spectrophotometry. Tryptophan was estimated by the method of Bloxam and Warren and tyrosine by the method of Wong, O'Flynn and Innoye. Serotonin was estimated by the method of Curzon and Green and catecholamines by the method of Well-Malherbe. Quinolinic acid content of plasma was estimated by HPLC (C_{18} column micro Bondapak^{TM} 4.6 x 150 mm), solvent system 0.01 M acetate buffer (pH 3.0) and methanol (6:4), flow rate (1.0 ml/min) and detection UV (250 nm). Nicotine, morphine and strychnine were estimated by the method described by Arun, Ravikumar, Leelamma and Kurup. Details of the procedures used for the estimation of total and individual GAG, carbohydrate components of glycoproteins, activity of enzymes involved in the degradation of GAG (beta glucuronidase, beta N-acetyl hexosaminidase, hyaluronidase and cathepsin-D), activity of glycohydrolases (beta galactosidase, beta fucosidase and beta glucosidase) have been described earlier. Serum glycolipids (gangliosides, glycosyl diglycerides, cerebrosides and sulphatides) were estimated as described in methods in enzymology. Cholesterol was estimated by using kits supplied by Sigma Chemicals, USA. SOD was assayed by the method of Kakkar, Das, and Viswanathan. Catalase activity was estimated by the method of Maehly and Chance, glutathione peroxidase by the method of Paglia and Valentine and glutathione reductase by the method of Horn and Burns. MDA was estimated by the method of Wills and conjugated dienes and hydroperoxides by the procedure of Brien. Reduced glutathione was estimated the method of Beutler, Duran and Kelley. Extraction of erythrocytes for vitamin E was out according to the procedure described by Cohn, Rammel, Cunlifee and

Keiboom and Vitamin E estimated in the extract by HPLC (Waters HPLC, Nova Pak C_8 column (4.6 x 150 mm), solvent -acetonitrite: methanol: water (63:33:4), flow rate - 2 ml/min, detection (UV 280 nm). For vitamin E, the retention time was 3.5 mm under these conditions. Nitric oxide was estimated in the plasma by the method of Gabor and Allon. Iron binding capacity in plasma was estimated by the method of Wootton and ceruloplasmin by the method of Henry, Chiamori, Jacobs and Segalov. Serum albumin was estimated by the method of Spencer and Price. Free fatty acid was estimated by the method of Falholt, Lund and Fatholt. Statistical analysis was done by 'ANOVA'.

Results

(1) The activity of HMG CoA reductase and the concentration of digoxin and dolichol were increased in multiple myeloma when compared with controls. The concentration of serum ubiquinone, the activity of erythrocyte membrane Na^+-K^+ ATPase and serum magnesium were decreased.

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

(3) Nicotine aid strychnine could be detected n the plasma of patients with multiple myeloma but was not detectable in control serum. Morphine was not detected in the plasma of these patients.

(4) The concentration of total glycosaminoglycans (GAG) increased in the serum of multiple myeloma patients. The concentration of heparan sulphate (HS) heparin (H), chondroitin sulphates (ChS), hyaluronic acid and dermatan sulphate was increased in multiple myeloma. The concentration total hexose, fucose and sialic acid were increased in the glycoproteins of the serum in these patients. The concentration of

gangliosides, glycosyl-diglycerides, cerebroside and sulphatide showed significant increase in the serum of these patients.

(5) The activity of glycosaminoglycan (GAG) degrading enzymes - beta glucuronidase, beta N-acetyl hexoseaminidase, hyaluronidase and cathepsin-D - was increased in multiple myeloma when compared to the controls. The activity of beta galactosidase, beta fucosidase and beta glucosidase increased in multiple myeloma patients.

(6) The concentration of total GAG and hexose and fucose residues of glycoproteins in the RBC membrane decreased significantly in multiple myeloma. The concentration of RBC membrane cholesterol was unaltered in multiple myeloma while that of phospholipid decreased. The ratio of RBC membrane cholesterol phospholipids increased in multiple myeloma.

(7) The activity of superoxide dismutase (SOD), catalase, glutathione reductase and glutathione peroxidase in the erythrocytes decreased significantly in multiple myeloma. The concentration of MDA, hydroperoxides, conjugated dienes and NO increases significantly. The concentration of glutathione was decreased and of alpha tocopherol was unaltered in multiple myeloma. Iron binding capacity and ceruloplasmin decreased significantly in multiple myeloma while albumin was reduced.

(8) The results showed that HMG CoA reductase activity, serum digoxin and dolichol were increased and ubiquinone reduced in left handed / right hemispheric dominant individuals. The results also showed that HMG CoA reductase activity, serum digoxin and dolichol were decreased and ubiquinone increased in right handed / left hemispheric dominant individuals. The results showed that the concentration of tryptophan, quinolinic acid serotonin, strychnine and nicotine was found to be higher in the plasma of left handed / right hemispheric dominant individuals

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

Discussion

Archaeal Digoxin and Membrane Na^+-K^+ ATPase Inhibition in Relation to Multiple Myeloma

The archaeaon steroidelle DXP pathway and the upregulated pentose phosphate pathway contribute to digoxin synthesis. The increase in endogenous digoxin, a potent inhibitor of membrane Na^+-K^+ ATPase, can decrease this enzyme activity. In multiple myeloma there was significant inhibition of the RBC membrane Na^+-K^+ ATPase. The inhibition of Na^+-K^+ ATPase digoxin is known to cause an increase in intracellular calcium resulting from increased Na^+-Ca^{++} exchange, increased entry of calcium via the voltage gated calcium channel and increased release of calcium from intracellular endoplasmic reticulum calcium stores. This increase in intracellular calcium by displacing magnesium from its binding sites causes a decrease in the functional availability of magnesium. The decrease in the availability of magnesium can cause decreased mitochondrial ATP formation which along with low magnesium can cause further inhibition of Na^+-K^+ ATPase since the ATP-magnesium complex is the actual substrate for this reaction. There is thus a progressive inhibition of Na^+-K^+ ATPase activity first triggered by digoxin. Low intracellular magnesium and high intracellular calcium consequent to Na^+-K^+ ATPase inhibition appear to be crucial to the pathophysiology of multiple myeloma. Serum magnesium was assessed in multiple myeloma and was found to be reduced. Increased intracellular calcium activates phospholipase C beta which results in increased

production of diacyglycerol (DAG) with resultant activation of protein kinase C. The protein kinase C (PKC) activates the MAP kinase cascade resulting in cellular proliferation. The decreased intracellular magnesium can produce dysfunction of GTPase activity of the alpha - subunit of G-protein. This results in ras oncogene activation, as more of the ras is bound to GTP rather than GDP. Phosphorylation mechanisms are required for the activation of the tumour suppressor gene P_{53}. The activation of P_{53} is impaired owing to intracellular magnesium deficiency producing a phosphorylation defect. Intracellular magnesium depletion can produce defective phosphorylation of microtubule associated proteins (MAP) resulting in microtubule related spindle fibre dysfunction and chromosoma1 non-dysjunction. This produces the characteristic neoplastic cellular polyploidy and aneuploidy. Upregulation of the isoprenoid pathway can result in increased produclion of farnesyl phosphate which can farnesylate the ras oncogene producing its activation.

Archaeal Digoxin and Regulation of Neurotransmitter Synthesis and Function in Relation to Multiple Myeloma

The archaeaon neurotransminoid shikimic acid pathway contributes to tryptophan and tyrosine synthesis and catabolism generating neurotransmitters and neuroactive alkaloids. Digoxin, apart from affecting cation transport is also reported to influence the transport of various metabolites across cellular membranes, including amino acids and various neurotransmitters. Two of the amino acids in this respect are important - tryptophan, a precursor for nicotine and strychnine and tyrosine a precursor for morphine. We have already shown the presence of endogenous nicotine and strychnine in the brain of rats loaded with tryptophan, and morphine in the brain of rats loaded with tyrosine. The results now obtained showed that the concentration of tryptophan, quinolinic acid and serotonin was higher in the plasma of patients with multiple myeloma

while that of tyrosine, dopamine and noradrenaline was lower. Serum of patients with multiple myeloma showed the presence of high amounts of nicotine in their serum. Morphine and strychnine were absent in the serum of these patients. Thus there is increase in tryptophan and its catabolites and a reduction in tyrosine and its catabolites in the patient's serum. This could be due to the fact that digoxin can regulate the neutral amino acid transport system with preferential promotion of tryptophan transport over tyrosine. The decrease in membrane Na^+-K^+ ATPase activity in all the disorders studied could be due to the fact that the hyperpolarising neurotransmitters (dopamine and noradrenaline) are reduced and the depolarising neuroactive compounds (serotonin, nicotine and quinolinic acid) are increased

The neurotransmitter pattern of reduced dopamine and noradrenaline, and increased serotonin can contribute to cancer related psychosis. This neurotransmitter pattern is common to multiple myeloma and schizophrenia. A schizoid state of mind can predispose the patients to the development of neoplasms. Alteration in natural killer cell activity has been reported in psychiatric disorders. Serotonin and acetyl choline promote cell proliferation and dedifferentiation by inhibiting adenyl cyclase or by activating phospholipase-C (PLC). Nicotine by binding to the nicotinic receptor promotes cholinergic transmission. Dopamine and noradrenaline elevate cyclic AMP levels and inhibit cell proliferation and differentiation. Increased quinolinic acid can lead to cancer related cachexia. Serotonin, dopamine and noradrenaline receptors have been demonstrated in the lymphocytes. It has been reported that during immune activation serotonin is increased with the corresponding reduction dopamine and noradrenaline in the brainstem monoaminergic nuclei. Thus elevated serotonin and reduced noradrenaline and dopamine can contribute to the immune activation ad immunoproliferation in multiple myeloma. Decreased morphine levels can

lead to increased metastatic property of tumours as morphine has a suppressing effect on tumour metastasis and tumour growth.

In the presence of hypomagnesemia, the magnesium block on the NMDA receptor is removed leading to NMDA excitotoxicity. The increased presynaptic neuronal calcium can produce cyclic AMP dependent phosphorylation of synapsins resulting in increased neurotransmitter release into the synaptic junction and vesicular recycling. Increased intracellular calcium in the post synaptic neuron can also activate the calcium dependent NMDA signal transduction. The plasma membrane neurotransmitter transporter (on the surface of the glial cell and presynaptic neuron) is coupled to a sodium gradient which is disrupted by the inhibition of Na^+-K^+ ATPase, resulting in decreased clearance of glutamate by presynaptic and glial uptake at the end of synaptic transmission. By these mechanisms, inhibition of Na^+-K^+ ATPase can promote glutamatergic transmission. The elevated levels of quinolinic acid and serotonin can also contribute to NMDA excitotoxicity. Quinolinic acid and serotonin are positive modulators of the NMDA receptor. Glutamate excitotoxicity has been implicated in the pathogenesis of neuronal degeneration. This could explain the increased incidence of paraneoplastic motor neuron disease in multiple myeloma. Increased glutamatergic transmission resulting in excitotoxicity has been implicated in cellular proliferation. Excitatory amino acids like glutamate can act as trophic factors and promote cellular proliferations.

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

The archaeaon glycosaminoglycoid and fructosoid contributes to glycoconjugate synthesis and catabolism by the process of fructolysis. The membrane Na^+-K^+ ATPase related magnesium depletion can affect the metabolism of glycosaminoglycans, glycoproteins and glycolipids. The

elevation in the level of dolichol may suggest its increased availability for N-glycosylation of proteins. Magnesium deficiency can lead to defective metabolism of sphinganine producing its accumulation which may lead to increased cerebroside and ganglioside synthesis. In Magnesium deficiency the glycolysis, citric acid cycle and oxidative phosphorylation are blocked and more glucose 6-phosphate is channelled for the synthesis of glycosaminoglycans (GAG). The results now obtained show an increase in the concentration of serum total GAG, individual GAG fractions, glycolipids and carbohydrate components of glycoproteins in multiple myeloma. The increase in the carbohydrate components - total hexose, fucose and sialic acid in multiple myeloma was not to the same extent suggesting qualitative change in glycoprotein structure. The activity of GAG degrading enzymes and that of glycohydrolases showed significant increase in the serum in multiple myeloma. Intracellular magnesium deficiency also results in defective ubiquitin dependent proteolytic processing of glycoconjugates as it requires magnesium for its function. The increase in the activity of glycohydrolases and GAG degrading enzymes could be due to reduced lysosomal stability and consequent leakage of lysosomal enzymes into the serum. The increase in the concentration of carbohydrate components of glycoproteins and GAG in spite of increased activity of many glycohydrolases may be due to their possible resistance to cleavage by glycohydrolases consequent to qualitative change in their structure. Proteoglycan complexes formed in the presence of altered calcium / magnesiurn ratios intracellularly may be structurally abnormal and resistant to lysosomal enzymes and may accumulate. In multiple myeloma, interaction of tumour and host cells with adhesion and extracellular matrix molecules like heparan sulphate, proteoglycan and syndecan are important. Elevated levels of heparan sulphate reported here may favour an upregulated interaction between tumour and host cells with adhesion and extracellular matrix molecules. This interaction

is important in the pathogenesis of myeloma. Accumulation of structurally abnormal glycoproteins leading to amyloid deposition has been described in myeloma. The abnormal glycoconjugate metabolism and lysosomal instability reported here may be important in amyloid deposition. Abnormal glycoconjugates accumulation can lead on to neuronal degeneration like motor neuron disease described in myeloma.

The protein processing defect can result in defective glycosylation of endogenous tumour antigens and exogenous viral glycoprotein antigens with consequent defective formation of the MHC-antigen complex. The MHC linked peptide transporter, a P-glycoprotein which transports the MHC-antigen complex to the antigen presenting cell surface, has an ATP binding site. There is dysfunction of this in the presence of magnesium deficiency. This results in defective transport of the MHC class-1 glycoprotein antigen complex to the antigen presenting cell surface for recognition by CD_4/CD_8 cell/NK cell. Defective presentation of exogenous viral antigens can produce immune evasion by the virus leading on to herpes viral persistence and oncogenesis in multiple myeloma. Kaposi's sarcoma associated herpes virus (KSHV) was found in the bone marrow dendritic cells of multiple myeloma patients but not in malignant plasma cells or bone marrow dendritic cells from normal individuals or patients with other malignancies. In addition the virus was detected in bone marrow dendritic cells from two out of eight patients with MGUS. Viral interleukin-6, the human homolog of which is a growth factor for myeloma was found to be transcribed in the myeloma bone marrow dendritic cells. KSHV may be required for transformation from MGUS to myeloma and perpetuate the growth of malignant plasma cells. Defective presentation of endogenous tumour antigens can lead to loss of NK cell (natural killer cell) immunosurveillance and oncogenesis. Altered cell surface glycoproteins, glycolipids and GAG can lead to defective contact inhibition and oncogenesis. A number of fucose and sialic acids

containing natural ligands have been implicated in neoplastic transformation and metastasis as also immune activation and lymphocytic proliferation.

Archaeal Digoxin and Alteration in Membrane Structure and Membrane Formation in Relation to Multiple Myeloma

The archaeaon steroidelle, glycosaminoglycoid and fructosoid contribute to cell membrane formation synthesizing cholesterol by the DXP pathway and glycosaminoglycans by fructolysis. The alteration in the isoprenoid pathway specifically, cholesterol as well as changes in glycoproteins and GAG can affect cellular membranes. The upregulation of the isoprenoid pathway can lead to increased cholesterol synthesis and magnesium deficiency can inhibit phospholipid synthesis. Phospholipid degradation is increased owing to increase in intracellular calcium activating phospholipase A_2 and D. The RBC membrane cholesterol was unchanged while the phospholipids were reduced resulting in increased cholesterol: phospholipid ratio. The concentration of total GAG, hexose and fucose residues of glycoprotein decreased in the RBC membrane and increased in the serum suggesting their reduced incorporation into the membrane and defective membrane formation. The glycoproteins, GAG and glycolipids of the cellular membrane are formed in the endoplasmic reticulum, which is then budded off as a vesicle which fuses with the golgi complex. The glycoconjugates are then transported via the golgi channel and the golgi vesicle fuses with the cell membrane. This trafficking depends upon GTPases and lipid kinases which are crucially dependent on magnesium and are defective in magnesium, deficiency. The change in membrane structure produced by alteration in glycoconjugates and cholesterol phospholipid ratio can produce changes in the conformation of Na^+-K^+ ATPase resulting in further membrane Na^+-K^+ ATPase inhibition. Similar changes can affect the structure of the organelle membrane. This results in defective lysosomal stability and leakage of glycohydrolases and GAG degrading

enzymes into the serum. Lysosomal instability can contribute to abnormal glycoconjugate metabolism important in paraneoplastic neuronal degeneration and amylodogenesis. Defective peroxisomal membranes lead to catalase dysfunction which has been documented in multiple myeloma.

Archaeal Digoxin and Mitochondrial Dysfunction in Relation to Multiple Myeloma

The archaeaon vitaminocyte contributes to the synthesis of ubiquinone and mitochondrial electron transport chain function. The mitochondrial function related free radical generation is regulated by the archaeaon vitaminocyte synthesized tocopherol and ascorbic acid. The concentration of ubiquinone decreased significantly in most of the cases which may be the result of low tyrosine levels, reported in multiple myeloma consequent to digoxin's effect in preferentially promoting tryptophan transport over tyrosine. The aromatic ring portion of ubiquinone is derived from the tyrosine. Ubiquinone which is an important component of the mitochondrial electron transport chain is a membrane antioxidant and contributes to free radical scavenging. The increase in intracellular ca1ciun can open the mitochondrial PT pore causing a collapse of the hydrogen gradient across the inner membrane and uncoupling of the respiratory chain. Intracellular magnesium deficiency can lead to a defect in the function of ATP synthase. All this leads to a defect in mitochondrial oxidative phosphorylation, incomplete reduction of oxygen and generation of the superoxide ion which produces lipid peroxidation. Ubiquinone deficiency also leads to reduced free radical scavenging. The increase in intracellular calcium may lead to increased generation of NO by inducing the enzyme nitric oxide synthase which combines with the superoxide radical to form peroxynitrite. Increased calcium also can activate phospholipase A_2 resulting in increased generation of arachidonic acid which can undergo increased lipid peroxidation.

Increased generation of free radicals like the superoxide ion, and hydroxyl radical can produce lipid peroxidation and cell membrane damage which can further inactivate Na^{+}-K^{+} ATPase triggering the cycle of free radical generation again. The free radicals and scavenging enzymes were estimated in all these disorders. There was increase in lipid peroxidation as evidenced from the increase in the concentration of MDA, conjugated dienes, hydroperoxides and NO with decreased antioxidant protection as indicated by decrease in ubiquinone and reduced glutathione in multiple myeloma. The activity of enzymes involved in free radical scavenging like superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase and catalase is decreased in multiple myeloma suggesting reduced free radical scavenging. (alpha-tocopherol) values were unchanged in both neoplasms. 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+} form, the conversion of H_2O_2 to hydroxyl radical is greatly increased. Low ceruloplasmin results in more of the iron to be in Fe^{2+} form. It has been shown that ceruloplasmin increases iron uptake by cells increasing the apparent affinity for the substrate by three times. Low ceruloplasmin levels can result in decreased iron uptake and this results in an increased amount of free iron. The intracellular magnesium deficiency can produce ribosomal dysfunction and inhibition of protein synthesis. The low iron binding capacity and low serum ceruloplasmin levels may be a consequence of reduced ferritin and ceruloplasmin synthesis. The peroxisomal membrane is defective owing to a membrane Na^{+}-K^{+} ATPase inhibition related defect in membrane formation and leads to reduced catalase activity. Glutathione is synthesized by the enzyme glutathione synthetase which

needs magnesium and ATP. The low intracellular magnesium 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 OSH 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. Opening of the mitochondrial PT pore produces hyperosmolality and matrix expansion rupturing the outer membrane producing loss of the mitochondrial dismutase and a decrease in its activity. The reduction in catalase, superoxide dismutase (SOD), glutathione peroxidase and glutathione reductase suggests reduced free radical protection. Mitochondrial dysfunction related free radical generation has been implicated in the pathogenesis of the oncogenesis. Free radicals are required for the action of growth factors and promote cellular proliferation. Mitochondrial dysfunction and free radical generation can also contribute to neuronal neuronal degeneration like motor neuron disease described in multiple myeloma.

The increase intracellular calcium and ceramide related opening of the mitochondrial PT also leads to volume dysregulation of the mitochondria causing hyperosmolality of the matrix and expansion of the matrix space. The outer membrane of the mitochondria ruptures and releases cytochrome C into the cytoplasm. This results in activation of caspase-3. Caspase-3 can cleave and

inactivate P_{21} involved in linking DNA duplication to cell division resulting in a polyploidal cell and oncogenesis.

Archaeal Digoxin and Regulation of Cell Division, cell Proliferation and Neoplastic Transformation in Relation to Multiple Myeloma - Relation to Immune Activation

The archaeaon fructosoid contributes to fructolysis and immune activation. Fructose can contribute to induction of NFKB and immune activation. The archaeaon steroidelle synthesized digoxin induces NFKB producing immune activation. Increased intracellular calcium activates the calcium dependent calcineurin signal transduction pathway which can produce T-cell activation and secretion of interleukin-6 and TNF alpha. Interleukin-6 can stimulate the growth of myeloma cells by functioning as an autocrine growth factor. IL-6 was found to induce in vitro of myeloma cells. Myeloma cells spontaneously produced IL-6 and expressed IL-6 receptor. This can explain the immune activation in multiple myeloma and related paraneoplastic syndromes like motor neuron disease. Membrane Na^+-K^+ ATPase inhibition can produce immune activation and is reported to increase CD_4/CD_8 ratios as exemplified by action of lithium. Defective presentation of glycoprotein neuronal antigens to the CD_4 and CD_8 cell can explain the immune dysregulation and autoimmunity describe in paraneoplastic syndromes.

Archaeal Digoxin and Hemispheric Dominance in Relation to Multiple Myeloma

The archaeaon related organelle - steroidelle, neurotransminoid and vitaminocyte contribute to hemispheric dominance. Thus the defective isoprenoid pathway can promote oncogenesis and multiple myeloma by several mechanisms. (i). Altered calcium / magnesium ratios promoting ras oncogene activation and defective function of the P_{53} tumour suppressor gene, (ii) Protein

processing defect and defective presentation of tumour antigens and defective immunosurveillance. This can also lead to defective contact inhibition. Defective processing of viral glycoprotein antigens and their presentation can lead to viral persistance and oncogenesis, (iii) Mitochondrial defect and free radical generation. This also leads to caspase-3 activation and cleaving of P_{21} protein which couples cell division to DNA duplication, (iv) Intracellular magnesium depletion can produce defective phosphorylation of MAP (microtubule associated proteins) resulting in microtubule related spindle fibre dysfunction and cellular polyploidy and aneuploidy, (v) Digoxin related tryptophan / tyrosine transport defect leading to increase in neurotransmitters that promote cell proliferation (nicotine and serotonin) and decrease in neurotransmitters that inhibits cell proliferation (dopamine and noradrenaline). This also leads to quinolinic acid related cachexia and immunoproliferation, (vi) Increased production of farnesyl phosphate leading to farnesylation of ras oncogene and its activation.

The biochemical patterns obtained in right hemispheric chemically dominant individuals correlated with those obtained in multiple myeloma. Left handed / right hemispheric chemically dominant individuals had an upregulated HMG CoA reductase activity with increased digoxin and dolichol levels and reduced ubiquinone levels. The RBC membrane Na^+-K^+ ATPase activity was reduced and serum magnesium depleted. The left handed / right hemispheric dominant individuals had increased levels of tryptophan and its catabolites - serotonin, quinolinic acid, strychnine and nicotine while the levels of tyrosine and its catabolites - dopamine, noradrenaline and morphine were lower. The elevated digoxin levels produce increased tryptophan levels over tyrosine by its effect on neutral amino acid transport. The increased levels of depolarising tryptophan catabolites produced membrane Na^+-K^+ ATPase inhibition. The reverse patterns were obtained in right handed: left hemispheric chemically dominant individuals.

They had down regulated HMG CoA reductase activity with decreased di8oxin and dolichol levels and increased ubiquinone levels. The RBC membrane Na^+-K^+ ATPase activity was increased and serum magnesium levels elevated. The right handed / left hemispheric chemically dominant individuals had decreased levels of tryptophan and its catabolites - serotonin, quinolinic acid, strychnine and nicotine while the levels of tyrosine and its catabolites - dopamine, noradrenaline and morphine were increased. The low digoxin levels produce elevated tyrosine levels over tryptophan. The increased levels of hyperpolarising tyrosine catabolites produced membrane Na^+-K^+ ATPase stimulation. Thus chemical right hemispheric chemical dominance may predispose to oncogenesis by the hypothalamic archaeal digoxin hypersecretion occurring in that state. Chemical left hemispheric dominance and the related digoxin hyposecretion may protect against neoplasms and has an inhibitory effect on oncogenesis.

The biochemical patterns obtained in multiple myeloma are similar to those obtained in left handed / right hemispheric chemically dominant individuals diagnosed by the dichotic listening test. But all the patients with multiple myeloma were right handed/left hemispheric dominance by the dichotic listening test. Hemispheric chemical dominance has no correlation with handedness or the dichotic listening test. Multiple myeloma occurs in right hemispheric chemically dominant individuals and is a reflection of altered brain function.

References

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Neanderthal Hybrids: Climate Change Mediated Actinidic Archaeal Endosymbiosis Generates Neanderthal Hybrids and Cancer

Introduction

Actinidic archaea has been related to global warming and human diseases especially neoplasm. The growth of endosymbiotic actinidic archaea in relation to climate change and global warming leads to neanderthalisation of the human mind-body system. Neanderthal anthropometry and metabolonomics has been described in neoplasm. This includes the Warburg phenotype and hyperdigoxinemia. Digoxin produced by archaeal cholesterol catabolism produces Neanderthalisation. Prefrontal cortical atrophy and cerebellar hyperplasia has been related to cancer. This leads on to dysautonomia with sympathetic hyperactivity and parasympathetic neuropathy in these disorders. Actinidic archaeal related cerebellar dominance leads to changes in brain function.[1-16] The data is described in this paper.

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

can fructosylate proteins making them antigenic and producing an autoimmune response. This can lead to global warming related cancer.

Materials and Methods

Fifteen cases, each of neoplasm and internet addicts were selected for the study. Each case had an age and sex matched control. Neanderthal anthropometric and phenotypic measurements which included protruding supra-orbital ridges, dolichocephalic skull, small mandible, prominent mid face and nose, short upper and lower limbs, prominent trunk, low index finger-ring finger ratio and fair complexion were evaluated in the cases study. Autonomic function tests were done to assess the sympathetic and parasympathetic system in each case. CT scan of the head was done to have a volumetric assessment of the prefrontal cortex and cerebellum. Blood cytochrome F420 activity was assessed by spectrophotometric measurement.

Results

All the case groups studied had higher percentage of Neanderthal anthropometric and phenotypic measurements. There was low index finger-ring finger ratio suggestive of high testosterone levels in all the patient population studied. In all the case groups studied, there also was prefrontal cortex atrophy and cerebellar hyperplasia. Similarly in the all the case groups studied, there was dysautonomia with sympathetic overactivity and parasympathetic neuropathy. Cytochrome F420 was detected in the entire case group studied showing endosymbiotic archaeal overgrowth.

Table 1. *Neanderthal phenotype and systemic disease.*

Disease	Cyt F420	Neanderthal phenotype	Low index finger-ring finger ratio
Non-Hodgkin's lymphoma	72%	60%	69%
Multiple myeloma	70%	68%	74%
Internet users	65%	72%	69%

Table 2. *Neanderthal phenotype and brain dysfunction.*

Disease	Dysautonomia	Prefrontal cortex atrophy	Cerebellar hypertrophy
Non-Hodgkin's lymphoma	79%	65%	75%
Multiple myeloma	69%	72%	80%
Internet users	74%	84%	82%

Discussion

Neanderthal metabolonomics contribute to the pathogenesis of these disorders. There were Neanderthal phenotypic features in all the case groups studied as well as low index finger-ring finger ratios suggestive of increased testosterone levels. Neanderthalisation of the mind-body system occurs due to increased growth of actinidic archaea as a consequence of global warming. Neanderthalisation of the mind leads to cerebellar dominance and prefrontal cortex atrophy. This leads to dysautonomia with parasympathetic neuropathy and sympathetic hyperactivity. This is the basis of oncogenesis.

Global warming and the ice age produces increased growth of extremophiles. This leads to increased growth of actinidic archaeal endosymbiosis in humans. There is archaeal proliferation in the gut which enters the cerebellum and brain stem by reverse axonal transport via the vagus. The cerebellum and brain stem can be considered as an archaeal colony. The archaea are cholesterol catabolising and use cholesterol as a carbon and energy source. The actinidic archaea activates the toll receptor HIF alpha inducing the Warburg phenotype resulting in increased glycolysis with generation of glycine as well as pyruvate dehydrogenase suppression. The accumulated pyruvate enters the GABA shunt

generating of succinyl CoA and glycine. The archaeal catabolism of cholesterol produces ring oxidation and generation of pyruvate which also enters the GABA shunt scheme producing glycine and succinyl CoA. This leads to increased synthesis of porphyrins. In the setting of digoxin induced sodium potassium ATPase inhibition the dipolar porphyrins produce a pumped phonon system resulting in the Frohlich model Bose-Einstein condensate and quantal perception of low level EMF. Low level EMF pollution is common with internet usage. Perception of low level of EMF leads to neanderthalisation of the brain with prefrontal cortex atrophy and cerebellar hyperplasia. The archaea which reaches the cerebellum from the gut via the vagus nerve proliferates and makes the cerebellum dominant with resultant suppression and atrophy of the prefrontal cortex. This leads to wide spread autistic and schizophrenic traits in population. The actinidic archaea induces the Warburg phenotype with increased glycolysis, PDH inhibition and mitochondrial suppression. This produces neanderthalisation of the mind-body system. The actinidic archaea secretes RNA viroids which block HERV expression by RNA interference. The HERV suppression contributes to the inhibition of prefrontal cortex development in Neanderthals and cerebellar dominance. Archaeal digoxin produces sodium potassium ATPase inhibition and magnesium depletion causing reverse transcriptase inhibition and decreased generation of HERV. The HERV contributes to the dynamicity of the genome and are required for the development of the prefrontal cortex. The HERV suppression contributes to retroviral resistance in Neanderthals. The actinidic archaea catabolizes cholesterol leading to cholesterol depleted state. Cholesterol depletion also leads to poor synaptic connectivity and decreased development of prefrontal cortex. This is not genetic change but a form of symbiotic change with endosymbiotic actinidic archaeal growth in the body and brain. These changes lead to oncogenesis.

Internet use and low level EMF pollution is common in this century. This results in increased low level EMF perception by the brain by the digoxin-porphyrin mediated pumped phonon system created Bose-Einstein condensates contributing to prefrontal cortex atrophy and cerebellar dominance. Cerebellar dominance leads to cancer. There is an epidemic of cancer in the present day community. The porphyrin mediated extrasensory perception can contribute to communication among Neanderthals. Neanderthals did not have a language and used extrasensory perception as a form of group communication. Because of dominant extrasensory quantal perception, the Neanderthals did not have individual identity but only group identity. Cerebellar dominance results in creativity consequent to quantal perception and group perception. The Neanderthalic traits contribute to innovation and creativity. Cerebellar dominance results in development of a symbolic language. The Neanderthals used dance and music as a form of communication. Painting as a form of communication was also common in Neanderthals. Neanderthal behaviour was robotic. Robotic behaviour is characteristic of cerebellar dominance. Robotic, symbolic and ritualistic behaviour is common with cerebellar dominance. The cerebellar dominance in Neanderthals leads to intuitive intelligence and a hypnotic quality to communication. The increased extrasensory quantal perception leads to more communion with nature and a form of eco-spirituality. The increasing use of dance and music as a form of communication and eco-spirituality is common in the modern century. The cholesterol depletion leads to bile acid deficiency and generation of small social groups in Neanderthals. Bile acid binds to olfactory receptors and contributes to group identity. These features of cerebellar dominance lead to the genesis of cancer.

The modern population is a hybrid of homo sapiens and homo neanderthalis. This contributes to 10 to 20% dominant hybrids who tend to contribute to creativity of civilisation. The Neanderthals tend to be innovative and chaotic.

They tend to be creative in art, literature, dance, spirituality and science. Eighty per cent of less dominant hybrids are stable and contribute to a stabilizing influence leading to growth of civilisation. The homo sapiens were stable and non-creative over a long period of their existence. There was a burst of creativity with generation of music, dance, painting, ornaments, the creation of concept of God and compassionate group behaviour around 10,000 years ago in the homo sapiens community. This correlated with the generation of Neanderthal hybrids when the Eurasian Neanderthal male mated with homo sapiens African females. The extrasensory/quantal perception due to dipolar porphyrins and digoxin induced sodium potassium ATPase inhibition and the generated pumped phonon system mediated quantal perception leads to the globalisation phenomena and feeling of the world being a global village. The archaeal cholesterol catabolism leads to increased synthesis of digoxin. Digoxin promotes tryptophan transport over tyrosine. Tyrosine deficiency leads to dopamine deficiency and morphine deficiency. This leads to a morphine deficiency syndrome in Neanderthals. This contributes to addiction traits and creativity. The increased tryptophan levels produce increased alkaloids like LSD contributing to ecstasy and spirituality of Neanderthal population. The ketogenic diet consumed by the meat eating Neanderthals leads on to increased generation of hydroxy butyric acid which produces ecstasy and a dissociative type of anaesthesia contributing to the Neanderthal psychology. The dopamine deficiency leads to decreased melanin synthesis and fairness of the population. This was responsible for the fair colour of the Neanderthals. These psychedelic features lead to cancer.

The Neanderthals were essentially meat eaters taking a ketogenic diet. The acetoacetic acid is converted to acetyl CoA which enters the TCA cycle. When the Neanderthal hybrids consume a glucogenic diet owing to the spread of settled civilisation it produces pyruvate accumulation owing to PDH

suppression in Neanderthals. The increased archaeal growth activates the toll receptor and induces HIF alpha resulting in increased glycolysis, PDH suppression and mitochondrial dysfunction - the Warburg phenotype. The pyruvate enters the GABA shunt pathway producing glutamate, ammonia and porphyrins. Neanderthals consuming a ketogenic diet produces more of GABA an inhibitory neurotransmitter resulting in the docile quiet nature of the Neanderthals. There is less production of glutamate the predominant excitatory neurotransmitter of the prefrontal cortex and consciousness pathways. This leads onto dominance of cerebellar function. The Neanderthal hybrids have cerebellar dominance and less of conscious behaviour. Cerebellum is responsible for intuitive, unconscious behaviour as well as creativity and spirituality. The cerebellum is the site of extrasensory perception, magical acts and hypnosis. The predominant homo sapiens had prefrontal cortex dominance over the cerebellum resulting in more of conscious behaviour. This brain dysfunction can lead to oncogenesis.

The Neanderthals consuming a glucogenic diet produces increased glycolysis in the setting of PDH inhibition. This produces the Warburg phenotype. There is increased lymphocytic glycolysis producing immune activation and lymphoproliferative disorders. The predominance of glycolysis and suppression of mitochondrial function results in glycemia. The increased mitochondrial PT pore hexokinase leads to cell proliferation and oncogenesis. Cerebellar dominance produces cancer.

The cerebellar hyperplasia results in sympathetic hyperactivity and parasympathetic neuropathy. This contributes to cell proliferation and oncogenesis. Vagal neuropathy results in immune activation and lymphoproliferative diseases. Vagal neuropathy and sympathetic overactivity can contribute to glycogenolysis and lipolysis. This increases tumour cell growth. Cerebellar dominance and cerebellar cognitive affective dysfunction

can contribute to cancer. The increased porphyrin synthesis resulting from succinyl CoA generated by GABA shunt and glycine generated by glycolysis contributes to increased extrasensory perception. Low level EMF perception can lead to cancer.

The archaeal cholesterol catabolism generates digoxin which produces sodium potassium ATPase inhibition and increase in intracellular calcium and decrease in intracellular magnesium. The increase in intracellular calcium produces oncogene activation and NFKB activation resulting in malignancies. The increase in intracellular calcium opens the mitochondrial PT pore resulting in oncogenesis. Digoxin induced magnesium depletion can remove the magnesium block on the NMDA receptor resulting in NMDA excitotoxicity. This can increase tumour cell load. Digoxin induced magnesium depletion can inhibit reverse transcriptase activity and HERV generation modulating the dynamicity of the genome. Digoxin induced intracellular calcium accumulation and magnesium depletion can modulate G-protein and protein tyrosine kinase dependent neurotransmitter and endocrine receptors. This can produce digoxin induced neuro-immuno-endocrine integration. Digoxin functions as a Neanderthal master hormone. The interruption of this neuro-immuno-endocrine integration leads to cancer.

The actinidic archaea are cholesterol catabolising and leads to low levels of testosterone and estrogen. This leads on to asexual features and low reproductive rates of the Neanderthal population. The Neanderthals consume a low fibre diet with low lignan content. The actinidic archaea has cholesterol catabolising enzymes generating more of testosterone than estrogens. This contributes to estrogen deficiency and testosterone overactivity. The Neanderthal population is hypermales with concomitant right hemispheric dominance and cerebellar dominance. Testosterone suppresses left hemispheric function. The high testosterone levels in Neanderthals contribute to a bigger brain. The Neanderthals males as well as females had a higher level of

testosterone contributing to gender equality and gender neutral states. There was group identity and group motherhood with no differences between roles of both males and females. This also resulted in matrilinearity. The higher testosterone levels in males as well as females led to alternate type of sexuality and aberrant behaviour. The homo sapiens eat a high fibre diet with low cholesterol and high lignan content contributing to estrogen dominance, left hemispheric dominance and cerebellar hypoplasia. Homo sapiens had higher reproductive rates and overtook the Neanderthal population resulting in its extinction. The homo sapien population was conservative with normal sexual mores, family values and patriarchal type of behaviour. The role of females the homo sapien community was inferior to males. The increasing generation of Neanderthal hybrids due to climate change mediated archaeal overgrowth leads to gender equality and equidominance of male and female in this century. These endocrine and gender alterations can lead to cancer.

The cholesterol catabolism results in cholesterol depletion and bile acid deficiency. Bile acids bind to VDR and are immunomodulatory. Bile acid deficiency leads to immune activation and lymphomas. Bile acids bind to FXR, LXR and PXR modulating lipid and carbohydrate metabolism. This leads to hyperglycemia and hyperlipidemia in the presence of bile acid deficiency. This leads to cancer. Bile acid uncouples oxidative phosphorylation and its deficiency leads to cancer. Cholesterol depletion also leads to vitamin D deficiency. Vitamin D binds to VDR and produces immunomodulation. Vitamin D deficiency leads to immune activation and lymphoma. Vitamin D deficiency can also produce rickets and contribute to the phenotypic features of Neanderthals. Vitamin D deficiency can contribute to brain development resulting in macrocephaly. Vitamin D deficiency contributes to insulin resistance and truncal obesity of Neanderthals. Vitamin D deficiency contributes to the fairness of the Neanderthal skin as a phenotypic adaptation.

The Neanderthal phenotypic features are due to vitamin D deficiency and insulin resistance. This leads to cancer.

Thus global warming and increased endosymbiotic actinidic archaeal growth leads to cholesterol catabolism and generation of the Warburg phenotype resulting in increased porphyrin synthesis, extrasensory low EMF perception, prefrontal cortex atrophy, insulin resistance and cerebellar dominance. This leads on to neanderthalisation of the body and brain and oncogenesis.

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