GLOBAL WARMING

Archaea and Viroid Induced Symbiotic Human Evolution – The Tridosha Theory of Three Biological Humours and Cerebral Dominance

Ravikumar Kurup
Parameswara Achutha Kurup

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Chapter 1

A Cholesterol and Actinide Dependent Shadow Biosphere of Archaea and Viroids

Introduction

Endomyocardial fibrosis along with the root wilt disease of coconut is endemic to Kerala with its radioactive actinide beach sands. Actinides like rutile, endogenous digoxin as well as organisms like phytoplasmas and viroids have been implicated in the etiology of these diseases.[1-4] Endogenous digoxin has been related to the pathogenesis of schizophrenia, malignancy, metabolic syndrome X, autoimmune disease and neuronal degeneration.[4] The possibility of endogenous digoxin synthesis by actinide based primitive organism like archaea with a mevalonate pathway and cholesterol catabolism was considered.[5-8] An actinide dependent shadow biosphere of archaea and viroids in the above mentioned disease states is described.[7, 9] Metal actinides in beach sands have been postulated to play a role in abiogenesis.[7] A hypothesis of cholesterol as the primal prebiotic molecule synthesized on actinide surfaces with all other biomolecules arising from it and a self replicating cholesterol lipid organism as the initial life form is presented.

Endosymbiotic archaeal digoxin, hemispheric dominance and the three biological humours in Ayurveda are interrelated. The three states of biological humours described in Ayurveda have a correlation with hemispheric chemical dominance. The Kapha state represents the right hemispheric dominant hyperdigoxinemic state. The Pitta state represents the left hemispheric dominant hypodigoxinemic state. The Vata state represents the bihemispheric dominant or fluctuating dominant normodigoxinemic state. The three states of hemispheric dominance'em - Vata, Pitta and Kapha can differentially regulate neuro-immuno-endocrine / cellular integration. It can thus regulate the predisposition to various systemic and neuropsychiatric diseases.

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 neandethal metabolonomics and phenotype inducing the evolution of homo neanderthalis. Transfer of colonic microflora predominantly archaea and modulation of endosymbiotic archaea by a paleo diet and antibiotics from higher plants can lead to interconversion of human species between homo neanderthalis and homo sapiens. The hologenome especially the microbial flora endosymbiotic/gut drives human and animal evolution and can be experimentally induced. Symbiotic microflora drives evolution. Every animal, every human species, different communities, different races and different caste

have their signature endosymbiotic and gut microflora which can be transmitted vertically and horizontally. Thus symbiosis drives human and animal evolution.

This can be interpreted on the basis of Villarreal hypothesis of group identity and cooperativity of RNA collectives. Archaeal symbiosis in the gut and in the tissue spaces determines speciation of human beings as homo sapiens and homo neanderthalis. The endosymbiotic archaea can secrete RNA viroids and viruses and there is a viroid-archaeal host relationship between the two. A dynamic state of virus lysis and persistence can occur in archaea suggesting that viral addiction can occur in archaea. The RNA viroids in the archaea coordinate their behavior by information exchange, modulation and innovation generating new sequence based content. This occurs due to a phenomenon of symbiosis in contrast to the concept of survival of the fittest. The generation of new RNA viroidal sequences is a result of practical competence of living agents to generate new sequences by symbiosis and sharing. This represents highly productive RNA viroidal quasi-species consortia for the evolution, conservation and plasticity of genomic environments. The behavioural motives of the RNA are single stem loop structures. They have self folding and group building capabilities depending upon functional needs. The evolution process depends upon what Villareal calls RNA stem loop consortia. The whole entity can function only if participatory groups of RNA viroids can get their function coordinated. There is competent denovo generation of new sequences by cooperative action and not by competition. These RNA viroidal group consortia can contribute to the host identity, group identity and group immunity. The term used for this is RNA viroidal sociological behavior. The RNA viroids can build groups that invade the archaea and compete as a group for limited resources such host genomes. A key behavioural motif is able to integrate a persistent life style into the archaeal colony with the addiction module forming competing viroidal groups that are counter balancing each other together with the

archaeal/host immune system. This leads to creation of an identity for the archaeal colony and the homo neanderthalis host. Viroids can kill their host and also colonize their host without disease and protect the host from similar viruses and viroids. Together with lysis and protection we see a viroid colonized host that is both symbiotic and innovative acquiring new competent codes. Thus the viroid-host relationship is a pervasive, ancient force in the origin and evolution of life. Cumulative evolution at the level of RNA viroids is like a ratchet effect used for transmission of cultural memes. This learning accumulates so that every new generation must not repeat all innovative thoughts and techniques. Quasi-species of RNA viroids are cooperative and exclusive of other quasi-species. They have group recognition differentiating self-groups and non-self-groups allowing for quasi-species to promote the emergence of group identity. With group identity via counter related addiction modules two opposing components must be present and work coherently and define the group as a whole. Biological identity is constituted by dynamic interaction of cooperative groups. Virus addiction module is an essential strategy for existence of life in the virosphere. Viruses are transmissible and can persist in specific host population leading to a form of group immunity / identity since identical but uncolonized host population remains susceptible to a killing action of lytic viruses. In this way we see that viruses are necessary providing opposing functions for addiction (persistence/protection and lytic/killing). Viroids can function as consortia, an essential interacting group and provide a mechanism from which consortial function could emerge in the origin of protobiotic life. Genetic parasites can act as a group (qs-c). But for this group to be coherent they must attain group identity and this is typically via an addiction strategy. Antiviral and proviral system in the archaea will themselves emerge in the host from virus derived information. The archaeal viruses themselves provide the critical function required for antiviral defence. The opposing functions are the

basis of addiction modules. Thus the emergence of group identity becomes an essential and early event in the emergence of life. This is coherent to the basically group behavior of RNA viroids in archaea. This group selection and group identity are needed to create information coherence and network formation and to establish a system of communication - code competent interactions. This identity serves as information also for the ones that do not share this identity. This is the beginning of self/non-self differentiating capability. In this way viroids promote the emergence of group identity in archaeal colonies and host humans. The archaeal colony identity depends upon the colonizing set of RNA viroids producing a coherent network that is inclusive opposing functions and favours the persistence of parasite derived new information. On the basis of population-based functions of RNA DNA can be considered as a habitat for consortia RNA. Thus RNA viroids of the archaea are involved in complex multicellular identity. This is called as the Gangen hypothesis by Villarreal. The Gangen describes the emergence of commonly shared code use, group membership and collective living function of RNA viroids. Communication is a code depended interaction and transmission of infectious code defines the origin of the virosphere. This issue refers to the idea of collective of RNA viroids with inherent toxic and antitoxic features should be able to transmit or communicate these agents and their features to a nearby competing population. It strongly favours the survival of RNA viroidal population with compatible addiction modules that will inhibit agent toxicity and allow persistence of new agents. This is thus the survival of the persistently colonized set which is an inherently symbiotic and consortial process. It also promotes increasing complexity and identity/immunity of the host collective via a new agent colonization, and stable addition. Thus the transmission of RNA agents attains both communication and recognition of group membership. In this way the emergence of the virosphere must had been an early event in the

origin of life and group identity. Viruses and viroids are genetic parasites and the most abundant living entities on earth. The virosphere is a network of infectious genetic agents. Evolution, conservation and plasticity of genetic identities are the result of cooperative consortia of RNA viroids that are competent to communicate. Thus the archaeal viroidal consortia can symbiotically share and communicate producing new sequences and give an identity to the archaeal colony. The low fibre diet and extreme temperatures of the Eurasian steppes leads to archaeal multiplication and induction of the homo neanderthalis species. The archaeal colony's characteristics are determined by the cooperative consortia of RNA viroids in the archaea and the archaeal colony identity determines the homo neanderthalis identity. Thus the archaeal colonies with their quasi-species consortia of RNA viroids determine the homo neanderthalis identity. The new sequence generation by the RNA viroidal consortia's symbiotic sharing character contributes to the diversity in the behavior and creativity of the homo neanderthalis population. The archaeal RNA viruses and viroids and the archaeal colonies themselves protect the homo neanderthalis population from retroviral infections. Thus the homo neanderthalis population is retroviral resistant and the quasi-species consortia of archaea and archaeal viroids gives them a group identity as retroviral resistant. Thus the quasi-species consortia of archaea and RNA viroids give homo neanderthalis colonies their identity and idea of self. The homo neanderthalis is resistant to retroviral infection like the Australian aboriginals and the endogenous retroviral sequences in the Neanderthal genome are limited. This leads to lack of plasticity and dynamicity of the human genome and the cerebral cortex in ill-developed with a dominant impulsive cerebellar cortex in the homo neanderthalis population. This produces the impulsive creative surrealistic spiritual neanderthalic brain. As the extreme of temperature goes off and the ice age ends the archaeal population density also comes down. This also can result

from the consumption of a high fibre diet in the African continent. The high fibre diet digested by clostridial clusters in the colon promotes butyrate synthesis and butyrate will induce HDAC inhibition and expression of retroviral sequences in the primate genome. This leads to increase in endogenous retroviral sequences in the human genome, increasing genomic dynamicity and the evolution of complicated cerebral cortex dominant brain with its complex synaptic connectivity in the homo sapiens. This leads onto a logical, commonsensical, pragmatic and practical homo sapien brain. The homo sapiens due to lack of archaea and the RNA viroids are susceptible retroviral infection. Thus the archaeal colonies and RNA viroidal quasi-species consortia determine the evolution of the human species and the brain networks. Thus extremes of temperature, fibre intake, archaeal colony density, RNA viroidal quasi-species, group identity and retroviral resistance decides on the evolution of homo sapiens and homo neanderthalis as well as the brain networks. The present extremes of temperature and low fibre intake in civilized society can lead to increase in archaeal population densities and quasi-species RNA viroidal networks generating a new homo neanderthalis in a new neanderthalic anthropocene age as opposed to the present homo sapien anthropocene age. The archaeal population densities and quasi-species RNA viroidal networks determine homo sapien / homo neanderthalis species, racial, caste, community, national, sexual, metabolic, phenotypic, immune, neuronal, psychiatric, psychological, genotypic and individual identity. The archaea secretes the trephone digoxin which can edit the RNA viroids and generate new sequences. Archaeal dipolar magnetite and porphyrins in the setting of digoxin induced membrane sodium potassium ATPas inhibition can produce a pumped phonon system mediated quantal perceptive state and quantal communication in the RNA viroidal symbiotic system generating new sequences by steroidal digoxin enzymatic editing action. This gives rise to archaeal RNA viroidal quasi-species

symbiotic diversity and identity to species, race, caste, sex, culture, individual and national identity.

The roots of Western civilisational disease can be related to the starvation of the colonic microflora. The colonic microflora depends upon complex carbohydrates derived from dietary fibre. The processed food of high protein, fat and sugars is digested and absorbed in the stomach and small intestine. A very little of it reaches the colon and widespread use of antibiotics in medicine has produced mass extinction of the colonic microflora. The colonic microflora is extremely diverse and the diversity is lost. There are 100 trillion bacteria in the colon belonging to 1200 species. They regulate the immune system by inducing the T-regulatory cells. A high fibre diet contributes to colonic microbiota diversity. Interaction with farm animals like cows and dogs also contributes to the colonic microflora diversity. The typical Western diet of high fat, high protein and sugars decreases the colonic microbiota diversity and increase colonic/endosymbiotic archaea producing methanogenesis. The colonic archaea feed upon the mucous lining of the colon and produces leakage of archaea into the blood and tissue system producing endosymbiotic archaea. This results in a chronic inflammatory state. The high fibre diet of Africans, South Americans and Indians produces increased colonic microbiota diversity and increase in clostridial clusters generating SCFA in the gut. High fibre diet is protective against metabolic syndrome and diabetes mellitus. Metabolic syndrome is related to degeneration, cancer, neuropsychiatric illness and autoimmune disease. A high fibre diet of upto 40 g/day can be called as a gut diet. The colonic microflora especially the clostridial cluster digests the fibre generating short chain fatty acids which regulates immunity and metabolism. High fibre diet increases the colonic mucus secretion and the thickness of the mucus lining. A high fibre diet produces increase in clostridial clusters and mucous secretion. This produces a strong gut blood barrier and prevents

metabolic endotoxemia which produces a chronic inflammatory response. High dietary fibre intake and the diversity of the colonic microflora with prominent SCFA producing clostridial clusters are interrelated. The clostridial clusters metabolise the complex carbohydrate in dietary fibre to short chain fatty acids butyrate, propionate and acetate. They increase the T-regulatory function. A high fibre diet increases the bacteroides and reduces the firmecutes of the colonic microflora. A high fibre diet is associated with a low body-mass index. A low fibre diet produces increase in colonic archaeal growth as well as endosymbiotic tissue and blood archaea. This produces more of methanogenesis rather than short chain fatty acid synthesis contributing to immune activation. A low fibre diet is associated a high body-mass index and chronic systemic inflammation. Germ-free mice show cardiac, pulmonary and liver atrophy. Gut microflora is required for the generation of organ systems. The gut microflora is also required for generation of T-regulatory cells. High fibre intake produces more colonic microbiota diversity and increase in clostridial clusters and fermentation by products like butyrate which suppresses inflammation and increases T-regulatory cells. A low fibre diet produces increase in archaeal growth, methanogenesis, destruction of the mucus lining and leakage of the colonic archaea producing endosymbiotic tissue and blood archaea. This produces an immune hyperreactivity contributing to the modern plagues of civilization - metabolic syndrome, schizophrenia, autism, cancer, autoimmunity and degenerations. The gut microbiota drives human evolution. The humans don’t host the gut microbiota but the gut microbiota host us. The human system forms an elaborate culture laboratory for the propagation and survival of the microbiota. The human system is induced by the microbiota for their survival and growth. The human system exists for the microbiota and not the other way round. The same mechanism holds good in plant systems. Plant started the colonized earth as they started symbiosing with bacteria in the roots systems

which can derive nutrients from the soil. Human beings form a mobile culture laboratory for the more effective propagation and survival of the microbiota. The microbiota induces the formation of specialized immune cells called innate lymphoid cells. The innate lymphoid cells will direct the lymphocytes not to attack the beneficial bacteria. Thus the endosymbiotic archaea and the gut archaea induce human, primate and animal evolution to generate structures for them to survive and propagate. The source of endosymbiotic archaea, the third element of life is the colonic archaea that leaks into the tissue spaces and blood systems due to breach in the gut blood barrier. The increase in colonic archaea is due to the starvation of the gut microbiota consequent to a low fibre diet. This results in increase in colonic archaeal growth and destruction of clostridial clusters and bacteroides. The increase colonic archaeal growth in the presence of gut starvation due to low fibre diet eats up the mucus lining and produces breakages in the gut blood barrier. The colonic archaea enters the blood stream and produces endosymbiosis generating endosymbiotic archaea and various new organelle - fructosoids, steroidelle, vitaminocyte, viroidelle, neurotransminoid, porphyrinoids and glycosaminoglycoids.

Materials and Methods

The following groups were included in the study: - endomyocardial fibrosis, Alzheimer's disease, multiple sclerosis, non-Hodgkin's lymphoma, metabolic syndrome X with cerebrovascular thrombosis and coronary artery disease, schizophrenia, autism, seizure disorder, Creutzfeldt Jakob's disease and acquired immunodeficiency syndrome. There were 10 patients in each group and each patient had an age and sex matched healthy control selected randomly from the general population. The blood samples were drawn in the fasting state before treatment was initiated. Plasma from fasting heparinised blood was used and the experimental protocol was as follows (I) Plasma+phosphate buffered

saline, (II) same as I+cholesterol substrate, (III) same as II+rutile 0.1 mg/ml, (IV) same as II+ciprofloxacine and doxycycline each in a concentration of 1 mg/ml. Cholesterol substrate was prepared as described by Richmond.[10] Aliquots were withdrawn at zero time immediately after mixing and after incubation at 37℃ for 1 hour. The following estimations were carried out: - Cytochrome F420, free RNA, free DNA, polycyclic aromatic hydrocarbon, hydrogen peroxide, dopamine, serotonin, pyruvate, ammonia, glutamate, cytochrome C, hexokinase, ATP synthase, HMG CoA reductase, digoxin and bile acids.[11-13] Cytochrome F420 was estimated flourimetrically (excitation wavelength 420 nm and emission wavelength 520 nm). Polycyclic aromatic hydrocarbon was estimated by measuring hydrogen peroxide liberated by using glucose reagent. Informed consent of the subjects and the approval of the ethics committee were obtained for the study. The statistical analysis was done by ANOVA.

Results

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Group	DOPAMINE % (Increase with Rutile)		DOPAMINE % (Decrease with Doxy+Cipro)		5 HT % change (Increase with Rutile)		5 HT % change (Decrease with Doxy+Cipro)	
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
Normal	4.41	0.15	18.63	0.12	4.34	0.15	18.24	0.37
Schizo	21.88	1.19	66.28	3.60	23.02	1.65	67.61	2.77
Seizure	22.29	1.33	65.38	3.62	22.13	2.14	66.26	3.93
AD	23.66	1.67	65.97	3.36	23.09	1.81	65.86	4.27
MS	22.92	2.14	67.54	3.65	21.93	2.29	63.70	5.63
NHL	23.81	1.90	66.95	3.67	23.12	1.71	65.12	5.58
DM	24.10	1.61	65.78	4.43	22.73	2.46	65.87	4.35
AIDS	23.43	1.57	66.30	3.57	22.98	1.50	65.13	4.87
CJD	23.70	1.75	68.06	3.52	23.81	1.49	64.89	6.01
Autism	22.76	2.20	67.63	3.52	22.79	2.20	64.26	6.02
EMF	22.28	1.52	64.05	2.79	22.82	1.56	64.61	4.95
F value	403.394		680.284		348.867		364.999	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Discussion

There was increase in cytochrome F420 indicating archaeal growth. The archaea can synthesize and use cholesterol as a carbon and energy source.[6, 14] The archaeal origin of the enzyme activities was indicated by antibiotic induced suppression. The study indicates the presence of actinide based archaea with an alternate actinide based enzymes or metalloenzymes in the system as indicated by rutile induced increase in enzyme activities.[15] There was also an increase in archaeal HMG CoA reductase activity indicating increased cholesterol synthesis by the archaeal mevalonate pathway. The archaeal beta hydroxyl steroid dehydrogenase activity indicating digoxin synthesis and archaeal cholesterol hydroxylase activity indicating bile acid synthesis were increased.[8] The archaeal cholesterol oxidase activity was increased resulting in generation of pyruvate and hydrogen peroxide.[14] The pyruvate gets converted to glutamate and

ammonia by the GABA shunt pathway. The archaeal aromatization of cholesterol generating PAH, serotonin and dopamine was also detected.[16] The archaeal glycolytic hexokinase activity and archaeal extracellular ATP synthase activity were increased. The archaea can undergo magnetite and calcium carbonate mineralization and can exist as calcified nanoforms.[17] There was an increase in free RNA indicating self replicating RNA viroids and free DNA indicating generation of viroid complementary DNA strands by archaeal reverse transcriptase activity. The actinides modulate RNA folding and catalyse its ribozymal action. Digoxin can cut and paste the viroidal strands by modulating RNA splicing generating RNA viroidal diversity. The viroids are evolutionarily escaped archaeal group I introns which have retrotransposition and self splicing qualities.[18] Archaeal pyruvate can produce histone deacetylase inhibition resulting in endogenous retroviral (HERV) reverse transcriptase and integrase expression. This can integrate the RNA viroidal complementary DNA into the noncoding region of eukaryotic noncoding DNA using HERV integrase as has been described for borna and ebola viruses.[19] The noncoding DNA is lengthened by integrating RNA viroidal complementary DNA with the integration going on as a continuing event. The archaea genome can also get integrated into human genome using integrase as has been described for trypanosomes.[20] The integrated viroids and archaea can undergo vertical transmission and can exist as genomic parasites.[19, 20] This increases the length and alters the grammar of the noncoding region producing memes or memory of acquired characters as well as eukaryotic speciation and individuality.[21] The viroidal complementary DNA can function as jumping genes producing a dynamic genome important in storage of synaptic information, HLA gene expression and developmental gene expression. The RNA viroids can regulate mRNA function by RNA interference.[18] The phenomena of RNA interference can modulate T-cell and B-cell function, insulin signalling lipid metabolism,

cell growth and differentiation, apoptosis, neuronal transmission and euchromatin / heterochromatin expression.

The archaea and viroids can regulate the nervous system including the NMDA / GABA thalamo-cortico-thalamic pathway mediating conscious perception.[4, 22] NMDA / GABA receptors can be modulated by digoxin induced calcium oscillations resulting NMDA / GAD activity induction, PAH increasing NMDA activity and inducing GAD as well as viroid induced RNA interference.[4] The cholesterol ring oxidase generated pyruvate can be converted by the GABA shunt pathway to glutamate and GABA. The dipolar PAH and archaeal magnetite in the setting of digoxin induced sodium potassium ATPase inhibition can produce a pumped phonon system mediated Frohlich model superconducting state [22] inducing quantal perception with nanoarchaeal sensed gravity producing the orchestrated reduction of the quantal possibilities to the macroscopic world.[4, 22] The archaea can regulate limbic lobe transmission with archaeal cholesterol aromatase/ring oxidase generated norepinephrine, dopamine, serotonin and acetyl choline.[16] The higher degree of integration of the archaea into the genome produces increased digoxin synthesis producing right hemispheric dominance and lesser degree producing left hemispheric dominance.[4] The increased integration of archaea into the neuronal genome can produce increased cholesterol oxidase and aromatase mediated monoamine and NMDA transmission producing schizophrenia and autism. Archaea and RNA viroid can bind the TLR receptor induce NFKB producing immune activation and cytokine TNF alpha secretion. The archaeal DXP and mevalonate pathway metabolites can bind γδ TCR and digoxin induced calcium signalling can activate NFKB producing chronic immune activation.[4, 23] The archaea and viroid induced chronic immune activation and generation of superantigens can lead on to autoimmune disease. Archaea, viroids and digoxin can induce the host AKT PI3K, AMPK, HIF alpha and NFKB producing the Warburg

metabolic phenotype.[24] The increased glycolytic hexokinase activity, decrease in blood ATP, leakage of cytochrome C, increase in serum pyruvate and decrease in acetyl CoA indicates the generation of the Warburg phenotype. There is induction of glycolysis, inhibition of PDH activity and mitochondrial dysfunction resulting in inefficient energetics and metabolic syndrome. The archaea and viroid generated cytokines can lead to TNF alpha induced insulin resistance and metabolic syndrome X. The accumulated pyruvate enters the gaba shunt pathway and is converted to citrate which is acted upon by citrate lyase and converted to acetyl CoA, used for cholesterol synthesis.[24] The pyruvate can be converted to glutamate and ammonia which is oxidised by archaea for energy needs. The increased cholesterol substrate leads to increased archaeal growth and digoxin synthesis leading to metabolic channelling to the mevalonate pathway. The archaeal bile acids are steroidal hormones which can bind GPCR and modulate D_2 regulating the conversion of T_4 to T_3 which activates uncoupling proteins, can activate NRF½ inducing NQO1, GST, HOI reducing redox stress, can bind FXR regulating insulin receptor sensitivity and bind PXR inducing the bile acid shunt pathway of cholesterol detoxification.[25] The archaea and viroid induced monocyte activation and Warburg phenotype induced increased cholesterol synthesis leads to atherogenesis. The Warburg phenotype induced increased mitochondrial PT pore hexokinase, archaeal PAH and viroid induced RNA interference can lead on to malignant transformation. The digoxin and PAH induced increased intracellular calcium can lead to PT pore dysfunction, cell death and neuronal degeneration.[4] The archaeal cholesterol catabolism can deplete the cell membranes of cholesterol resulting in organelle dysfunction and degeneration. The RNA viroids can recombine with HERV sequences and get encapsulated in microvesicles contributing to the retroviral state. The prion protein conformation is modulated by RNA viroid binding producing prion disease. The archaeal digoxin and rutile induced

magnesium depletion can lead MPS deposition and produce EMF, CCP, MNG and mucoid angiopathy.[4]

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

Endosymbiotic archaeal digoxin, hemispheric dominance and the three biological humours in ayurveda are interrelated. The three states of biological humours described in Ayurveda have a correlation with hemispheric chemical dominance. The Kapha state represents the right hemispheric dominant hyperdigoxinemic state. The Pitta state represents the left hemispheric dominant hypodigoxinemic state. The Vata state represents the bihemispheric dominant or fluctuating dominant nonnodigoxinemic state. The three states of hemispheric dominance - Vata, Pitta and Kapha can differentially regulate

neuro-immuno-endocrine / cellular integration. It can thus regulate the predisposition to various systemic and neuropsychiatric diseases. This theme will be discussed in subsequent chapters.

References

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

[22] Lockwood, M. (1989). *Mind, Brain and the Quantum*. Oxford: B. Blackwell.

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

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

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

[26] Wächtershäuser, G. (1988). Before enzymes and templates: theory of surface metabolism. *Microbiol Rev*, 52(4), 452-84.

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

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

Chapter 2

The Endosymbiotic Archaea, Fructose Disease and Global Warming - The Tridosha Theory of Three Humours

Endosymbiotic archaeal digoxin, hemispheric dominance and the three biological humours in Ayurveda are interrelated. The three states of biological humours described in Ayurveda have a correlation with hemispheric chemical dominance. The Kapha state represents the right hemispheric dominant hyperdigoxinemic state. The Pitta state represents the left hemispheric dominant hypodigoxinemic state. The Vata state represents the bihemispheric dominant or fluctuating dominant normodigoxinemic state. The three states of hemispheric dominance - Vata, Pitta and Kapha can differentially regulate neuro-immuno-endocrine / cellular integration. It can thus regulate the predisposition to various systemic and neuropsychiatric diseases.

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

organelle called the vitaminocyte as well as the glycosaminoglycan synthetic organelle called glycosaminoglycoid. The archaea can secrete capsulated RNA viroidal particles which can function as blocking RNAs modulating cell metabolism and such archaeaon organelle are called viroidelle. The archaea suppresses pyruvate dehydrogenase and promotes fructolysis resulting in accumulation of pyruvate which enters the GABA shunt pathway producing succinyl CoA and glycine, the substrates for porphyrin synthesis. Porphyrin forms a template for the formation of RNA viroids, DNA viroids, prions and isoprenoids which can symbiose together to form an archaea. Thus endosymbiotic archaea have an abiogenic replication. The archaeaon concerned with GABA shunt pathway and porphyrinogenesis are called porphyrinoids. The archaeaon colony forms a network with different areas showing differential specialization of function - fructosoids, steroidelle, vitaminocyte, viroidelle, neurotransminoid, porphyrinoids and glycosaminoglycoids. This forms a living organized structure within human cells and tissues regulating their function and reducing the human body to zombie working under the directions of the organized archaeal colony. The organized archaeal colony has abiogenetic replication and is eternal.

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

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

fructolytic intermediates glyceraldehydes 3-phosphate and pyruvate are the starting points of the DXP pathway of cholesterol synthesis. Glyceraldehyde 3-phosphate combines with pyruvate to form 1-deoxy D-xylulose phosphate (DOXP) which is then converted to 2-C methyl erythritol phosphate. 2-C methyl erythritol phosphate can be synthesized from erythrose 4-phosphate a metabolite of the shikimic acid pathway. DXP combines with MEP to form isopentenyl pyrophosphate which is converted to cholesterol. Cholesterol is catabolized by archaeal cholesterol oxidases to generate digoxin. The digoxin sugars digitoxose and rhamnose are synthesized by the upregulated pentose phosphate pathway. Glycolytic suppression leads to upregulation of the pentose phosphate pathway. The expressed archaeaon organelle concerned with cholesterol catabolism and digoxin synthesis is called the steroidelle. The suppression of glycolysis and stimulation of fructolysis results in upregulation of the hexosamine pathway. Fructose is converted to fructose 6-phosphate by ketohexokinases. The fructose 6-phosphate is converted to glucosamine 6-phosphate by the action of glutamine fructose 6-phosphate amidotransferase (GFAT). Glucosamine 6-phosphate is converted to UDP N-acetyl glucosamine which is then converted to N-acetyl glucosamine and various amino sugars. UDP glucose is converted to UDP D-glucuronic acid. UDP D-glucuronic acid is converted to glucuronic acid. This forms the uronic acid synthetic pathway. Uronic acids and hexosamines form repeating units of glycosaminoglycans. In the setting of glycolytic suppression and fructolytic metabolism fructolysis leads to increase synthesis of hexosamines and GAG synthesis. The GAG synthesizing archaeaon particles are called the glycosaminoglycoids. The expressed archaeaon particles are capable of synthesizing antioxidant vitamin C and E. The UDP D-glucose is converted to UDP D-glucuronic acid. UDP D-glucuronic acid is converted to D-glucuronic acid. D-glucuronic acid is converted to L-gulonate by enzyme aldoketoreductases. L-gulonate is converted

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

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, ribonucleoproteins, 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 derives its energy from the above mentioned mechanism. The glycolytic enzymes and the mitochondrial PT pore hexokinase are fructosylated making them dysfunction. The fructosylated glycolytic enzymes lead to generation of antiglycolytic enzyme antibodies and disease states. The human body's principal method of energetics tissue glycolysis and oxidative phosphorylation comes to a grinding halt. The human body is taken over by the overgrowth of endosymbiotic archaea and assumes hibernatory state with accumulation of glycogen, lipids, mucopolysaccharides and nucleic acids. The catabolic pathways for energy generation related to glucose, glycolysis and oxphos scheme stops. The human body can depend upon ketogenesis from fat and proteins. The upregulated fructolytic pathway generates phosphoglycerate which converted to phosphoserine and glycine. They can be converted to other amino acids and used for ketogenesis. The body assumes a high BMI index and obesity with visceral fat storage and adiposity akin to the Neanderthal metabolic phenotype. Digoxin induced membrane sodium potassium ATPase inhibition results in cortical dysfunction. The brain porphyrins can form a quantal pumped

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

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

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

Table 1

	Serum fructose		**Serum fructokinase**		**Aldolase B**		**Total GAG**	
	Mean	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**
Normal	2.50	0.195	8.5	0.405	3.50	1.304	3.50	0.707
Sy X	21.20	5.201	18.91	2.942	8.01	1.244	18.46	4.623
CAD	31.40	3.212	21.18	2.267	9.02	0.667	21.41	1.653
CVA	29.98	4.002	24.96	3.829	11.72	1.397	21.65	2.755
DCM/EMF	32.04	4.955	21.37	2.050	10.89	1.344	20.12	2.855
Tumour	27.94	3.732	22.29	1.237	9.46	1.386	20.89	1.651
Schizo	31.14	4.446	22.19	2.634	11.63	3.081	21.50	1.714
Autism	28.66	5.089	24.09	2.146	12.30	1.621	22.60	3.054
AD	33.13	2.754	19.87	1.646	11.37	1.406	22.97	3.662
PD	30.24	4.551	22.72	1.955	11.93	2.999	20.13	1.507
MS	29.88	5.150	22.29	1.641	10.87	1.895	23.47	2.878
Lupus	33.11	4.509	20.24	1.639	11.59	0.767	20.62	3.504
CRF	30.24	3.209	22.52	3.196	11.76	1.596	20.55	2.164
ILD	32.04	5.295	22.37	1.585	11.84	0.963	21.49	1.544
COPD	26.68	4.266	21.78	2.253	10.62	1.703	22.84	2.965
BA	33.59	3.938	22.45	2.472	11.30	0.783	23.50	3.225
Cirrhosis	32.53	6.737	23.00	1.722	10.49	1.373	20.57	1.878
IBD	31.75	5.236	21.89	2.292	11.63	1.304	22.46	4.030
MAO	31.53	4.507	22.07	2.324	11.32	1.343	23.89	2.936
IBS	29.90	4.299	22.52	1.995	10.93	1.498	22.09	2.797
PUD	32.49	6.487	21.89	3.431	10.85	1.606	25.27	3.693
EMF	30.79	4.740	21.47	3.056	11.65	1.427	20.54	2.192
CCP	31.16	3.635	22.42	3.126	10.49	1.476	17.94	2.276
MNG	32.24	5.864	20.46	2.864	9.82	1.135	21.42	2.662
Muc ANG	30.40	6.405	23.30	4.089	11.08	1.360	22.16	3.543
DBJD	33.06	5.970	22.42	3.714	11.21	1.660	17.76	3.556
Spondylosis	32.70	4.430	21.92	1.840	14.10	2.423	26.80	3.679
F value	17.373		13.973		13.903		21.081	
p value	< 0.01		< 0.01		< 0.01		< 0.01	

Table 2

	Total TG		**Serum ATP levels**		**Uric acid**		**Anti-aldolase**	
	Mean	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**
Normal	124.00	3.688	2.50	0.405	5.70	0.369	7.50	1.704
Sy X	262.40	32.790	0.82	0.143	6.21	0.452	2.20	0.583
CAD	252.44	35.388	0.85	0.085	9.00	0.485	2.23	0.567
CVA	297.64	36.410	0.79	0.081	9.34	1.641	2.02	0.303
DCM/EMF	302.00	25.166	0.77	0.151	9.26	1.048	1.41	0.310
Tumour	277.60	34.613	0.80	0.136	7.88	0.847	1.45	0.415
Schizo	244.00	31.383	0.72	0.102	8.65	0.701	1.35	0.319
Autism	284.30	19.743	0.87	0.072	8.14	0.538	1.35	0.218
AD	244.70	22.106	0.82	0.121	8.74	0.687	1.70	0.361
PD	284.30	19.945	0.83	0.090	8.90	0.579	2.03	0.232
MS	289.89	23.406	0.74	0.115	9.59	0.783	1.80	0.402
Lupus	294.00	39.903	0.78	0.161	8.34	0.712	1.81	0.691
CRF	272.10	31.057	0.86	0.101	7.76	0.798	1.67	0.363
ILD	292.10	26.337	0.78	0.135	8.40	0.442	1.72	0.360
COPD	306.40	24.419	0.74	0.136	9.62	0.952	1.63	0.440
BA	293.80	31.555	0.72	0.134	9.51	1.059	2.10	0.572
Cirrhosis	271.80	37.818	0.79	0.150	8.12	0.747	1.67	0.377
IBD	287.50	20.414	0.77	0.102	9.44	0.924	1.30	0.223
MAO	316.20	31.283	0.76	0.103	9.32	0.864	1.41	0.307
IBS	279.10	27.606	0.77	0.095	9.68	1.060	1.44	0.350
PUD	285.70	22.628	0.76	0.126	9.77	0.957	1.14	0.134
EMF	270.10	28.792	0.81	0.079	8.76	0.881	1.31	0.329
CCP	293.00	28.111	0.78	0.145	8.30	0.966	1.31	0.265
MNG	262.70	30.324	0.83	0.091	8.04	0.667	1.55	0.493
Muc ANG	275.40	30.351	0.77	0.138	8.83	0.633	1.47	0.466
DBJD	282.60	27.573	0.79	0.136	8.28	0.978	1.89	0.315
Spondylosis	295.30	16.600	0.72	0.108	10.21	1.310	1.54	0.377
F value	16.378		59.169		14.166		55.173	
p value	< 0.01		< 0.01		< 0.01		< 0.01	

Table 3

	Anti-enolase		**Anti-pyruvatekinase**		**Anti-GAPDH**	
	Mean	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**
Normal	1.50	0.358	50.40	5.960	5.20	0.363
Sy X	0.51	0.185	17.04	3.556	1.73	0.371
CAD	0.55	0.154	16.06	6.811	1.78	0.349
CVA	0.66	0.182	21.79	4.567	1.50	0.307
DCM/EMF	0.49	0.197	18.68	4.585	1.54	0.471
Tumour	0.42	0.182	19.93	2.421	1.39	0.253
Schizo	0.40	0.142	22.02	11.954	1.31	0.235
Autism	0.20	0.060	19.27	2.201	1.20	0.205
AD	0.38	0.205	18.87	3.899	1.37	0.305
PD	0.42	0.208	20.11	3.220	1.44	0.342
MS	0.39	0.124	18.93	6.447	1.78	0.355
Lupus	0.42	0.116	18.59	3.721	1.48	0.258
CRF	0.55	0.220	17.06	3.449	1.32	0.358
ILD	0.52	0.202	18.80	3.221	1.41	0.355
COPD	0.59	0.159	18.14	3.500	1.71	0.509
BA	0.36	0.177	15.33	3.212	1.72	0.277
Cirrhosis	0.48	0.273	18.60	2.915	1.52	0.287
IBD	0.43	0.163	17.06	4.366	1.40	0.298
MAO	0.44	0.230	19.08	3.396	1.48	0.220
IBS	0.57	0.242	19.99	2.637	1.39	0.289
PUD	0.51	0.221	20.63	5.116	1.42	0.329
EMF	0.42	0.182	14.55	3.133	1.24	0.239
CCP	0.50	0.149	17.82	2.889	1.44	0.234
MNG	0.47	0.151	17.59	2.469	1.44	0.270
Muc ANG	0.36	0.114	18.63	3.147	1.48	0.271
DBJD	0.54	0.211	22.48	4.638	1.33	0.302
Spondylosis	0.40	0.134	19.91	5.099	1.49	0.282
F value	14.091		21.073		58.769	
p value	< 0.01		< 0.01		< 0.01	

Chapter 3

Endosymbiotic Actinidic Archaea/Viroids, Hemispheric Dominance and the Tridosha Theory

Introduction

The human brain synthesizes an endogenous membrane sodium potassium ATPase inhibitor digoxin which plays a role in neuro-immuno-endocrine integration and pathogenesis of several neuropsychiatric and systemic diseases. Endomyocardial fibrosis (EMF) along with the root wilt disease of coconut is endemic to Kerala with its radioactive actinide beach sands. Actinides like rutile producing intracellular magnesium deficiency due to rutile-magnesium exchange sites in the cell membrane have been implicated in the etiology of EMF.[1] Endogenous digoxin, a steroidal glycoside which functions as a membrane sodium-potassium ATPase inhibitor has also been related to its etiology due to the intracellular magnesium deficiency it produces.[2] Organisms like phytoplasmas and viroids have also been demonstrated to play a role in the etiology of these diseases.[3, 4] Endogenous digoxin has been related to hemispheric dominance.[2] Right hemispheric dominant individuals were hyperdigoxinemic, left hemispheric dominant individuals were hypodigoxinemic and bihemispheric dominant individuals were normodigoxinemic. The possibility of endogenous digoxin synthesis by actinide based primitive organism like archaea with a mevalonate pathway and cholesterol catabolism was considered.[5-7] An actinide dependent shadow biosphere of archaea and viroids in the above mentioned disease states is described.[6] The intracellular endosymbionts archaea and their intron derived viroids constitute the third element regulating the human body.

Ayurveda, the traditional Indian System of Medicine, deals with the theory of the three tridosha states (both physical and psychological): Vata, Pitta and Kapha. They are the three major human constitutional types that both depend on psychological and physical characteristics. The Pitta state is described as a critical, discriminative, and rational psychological state of mind while the

Kapha state is described as being dominant for emotional stimuli. The Vata state is an intermediate unstable shifting state. The Pitta types are of average height and built with well developed musculature. The Vata types are thin individuals with low body mass index. The Kapha types are short stocky individuals that tend toward obesity, and who are sedentary. Previous work in our laboratory had correlated the tridosha states of Kapha, Pitta and Vata with hemispheric dominance and endogenous digoxin status. The Kapha state has been demonstrated as equivalent to right hemispheric dominant hyperdigoxinemic state. The Pitta state has been demonstrated as equivalent to the left hemispheric dominant hypodigoxinemic state. The Vata state has been demonstrated as equivalent to the bihemispheric dominant normodigoxinemic state.[8] The study assessed actinidic archaea and viroids in the tridosha states of Ayurveda. The results are presented in this paper.

Methods

Informed consent of the subjects and the approval of the ethics committee were obtained for the study. The following groups were included in the study: - (I) right handed left hemispheric dominant - pitta group, (II) left handed right hemispheric dominant - kapha group and (III) amphidextrous-bihemispheric dominant - vata group of individuals. Hemispheric dominance was assessed by methods described in previous reports.[2] There were 10 healthy normal individuals in the age range between 20 and 30 years in each group. They were selected randomly from the general population. The blood samples were drawn in the fasting state. Plasma from fasting heparinised blood was used and the experimental protocol was as follows (I) Plasma+phosphate buffered saline, (II) same as I+cholesterol substrate, (III) same as II+rutile 0.1 mg/ml, (IV) same as II+ciprofloxacine and doxycycline each in a concentration of 1 mg/ml. Cholesterol substrate was prepared as described by Richmond.[9] Aliquots were

withdrawn at zero time immediately after mixing and after incubation at 37 ℃ for 1 hour. The following estimations were carried out: - Cytochrome F420, free RNA, free DNA, muramic acid, polycyclic aromatic hydrocarbon, hydrogen peroxide, dopamine, pyruvate, ammonia, glutamate, cytochrome C, hexokinase, ATP synthase, HMG CoA reductase, digoxin and bile acids.[10-13] Cytochrome F420 was estimated flourimetrically (excitation wavelength 420 nm and emission wavelength 520 nm). Polycyclic aromatic hydrocarbon was estimated by measuring hydrogen peroxide liberated by using glucose reagent. The statistical analysis was done by ANOVA.

Results

The parameters checked as indicated above were: - cytochrome F420, free RNA, free DNA, muramic acid, polycyclic aromatic hydrocarbon, hydrogen peroxide, serotonin, pyruvate, ammonia, glutamate, cytochrome C, hexokinase, ATP synthase, HMG CoA reductase, digoxin and bile acids. The plasma of the bihemispheric dominant group showed detectable levels of the above mentioned parameters after incubation for 1 hour and addition of cholesterol substrate resulted in still further increase in these parameters. The addition of antibiotics to the bihemispheric dominant vata group caused a decrease in all the parameters while addition of rutile increased their levels. The plasma of right hemispheric dominant kapha group showed a significant increase in the above mentioned parameters as compared to bihemispheric dominant vata group. The addition of antibiotics to the right hemispheric dominant kapha group caused a decrease in all the parameters while addition of rutile increased their levels but the extent of change was more in right hemispheric dominant kapha group as compared to bihemispheric dominant vata group. The plasma of left hemispheric dominant pitta group showed a significant decrease in the above mentioned parameters as compared to the bihemispheric dominant vata group.

The addition of antibiotics to the left hemispheric dominant pitta group caused a decrease in all the parameters while addition of rutile increased their levels but the extent of change was less in left hemispheric dominant pitta group as compared to bihemispheric dominant vata group. The results are expressed in tables 1-7 as percentage change in the parameters after 1 hour incubation as compared to the values at zero time.

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

Group	CYT F420 % change (Increase with Rutile)		CYT F420 % change (Decrease with antibiotics)		Muramic acid % change (Increase with Rutile)		Muramic acid % change (Decrease with antibiotics)	
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
BHD/VATA	4.48	0.15	18.24	0.66	4.34	0.15	18.24	0.37
RHD/KAPHA	11.35	0.64	60.49	6.22	22.68	1.99	63.29	5.93
LHD/PITTA	2.13	0.13	5.37	1.47	2.26	0.25	7.45	0.40
F value	306.749		130.054		348.867		364.999	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

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

Group	DNA % change (Increase with Rutile)		DNA % change (Decrease with antibiotics)		RNA % change (Increase with Rutile)		RNA % change (Decrease with antibiotics)	
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
BHD/VATA	4.37	0.15	18.39	0.38	4.37	0.13	18.38	0.48
RHD/KAPHA	22.99	1.56	65.19	4.10	23.27	1.36	65.66	3.93
LHD/PITTA	2.26	0.25	7.45	0.40	2.30	0.12	7.62	0.30
F value	337.577		356.621		427.828		654.453	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

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

Group	HMG CoA R % change (Increase with Rutile)		HMG CoA R % change (Decrease with antibiotics)		PAH % change (Increase with Rutile)		PAH % change (Decrease with antibiotics)	
	Mean	**±SD**	**Mean**	**±SD**	**Mean**	**±SD**	**Mean**	**±SD**
BHD/VATA	4.30	0.20	18.35	0.35	4.45	0.14	18.25	0.72
RHD/KAPHA	21.06	2.32	63.87	6.22	21.00	2.54	57.42	7.07
LHD/PITTA	2.33	0.17	7.24	0.59	2.25	0.17	7.01	0.65
F value	319.332		199.553		391.318		257.996	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

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

Group	Digoxin (ng/ml) (Increase with Rutile)		Digoxin (ng/ml) (Decrease with antibiotics)		Bile Acids % change (Increase with Rutile)		Bile Acids % change (Decrease with antibiotics)	
	Mean	**±SD**	**Mean**	**±SD**	**Mean**	**±SD**	**Mean**	**±SD**
BHD/VATA	0.11	0.00	0.054	0.003	4.29	0.18	18.15	0.58
RHD/KAPHA	0.55	0.10	0.248	0.058	21.10	2.43	54.82	8.28
LHD/PITTA	0.07	0.01	0.026	0.004	2.25	0.19	7.25	0.66
F value	135.116		71.706		290.441		203.651	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

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

Group	Pyruvate % change (Increase with Rutile)		Pyruvate % change (Decrease with antibiotics)		Hexokinase % change (Increase with Rutile)		Hexokinase % change (Decrease with antibiotics)	
	Mean	**±SD**	**Mean**	**±SD**	**Mean**	**±SD**	**Mean**	**±SD**
BHD/VATA	4.34	0.21	18.43	0.82	4.21	0.16	18.56	0.76
RHD/KAPHA	11.12	0.66	59.68	6.24	23.27	1.68	67.35	3.77
LHD/PITTA	2.16	0.18	5.91	1.38	2.24	0.17	6.29	1.06
F value	321.255		115.242		292.065		317.966	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

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

Group	ATP synthase % change (Increase with Rutile)		ATP synthase % change (Decrease with antibiotics)		H_2O_2 % change (Increase with Rutile)		H_2O_2 % change (Decrease with antibiotics)	
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
BHD/VATA	4.40	0.11	18.78	0.11	4.43	0.19	18.13	0.63
RHD/KAPHA	11.99	0.38	66.34	3.39	17.60	3.53	54.68	5.09
LHD/PITTA	2.30	0.12	7.62	0.30	2.24	0.23	5.36	0.99
F value	449.503		673.081		380.721		171.228	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

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

Group	ALA % (Increase with Rutile)		ALA % (Decrease with antibiotics)		DOPAMINE % change (Increase with Rutile)		DOPAMINE % change (Decrease with antibiotics)	
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
BHD/VATA	4.40	0.10	18.48	0.39	4.41	0.15	18.63	0.12
RHD/KAPHA	22.98	2.06	66.10	4.03	11.36	0.58	65.41	4.83
LHD/PITTA	2.13	0.11	7.62	0.32	2.13	0.11	7.62	0.32
F value	372.716		556.411		403.394		680.284	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Abbreviation

BHD: Bihemispheric dominance/vata

RHD: Right hemispheric dominance/kapha

LHD: Left hemispheric dominance/pitta

Discussion

Ayurveda, the traditional Indian System of Medicine, deals with the theory of the three tridosha states (both physical and psychological): Vata, Pitta and Kapha. They are the three major human constitutional types that both depend on psychological and physical characteristics. The pitta state is described as a critical, discriminative, and rational psychological state of mind, while the kapha state is

described as being dominant for emotional stimuli. The vata state is an intermediate unstable shifting state. The Pitta types are of average height and built with well developed musculature. The vata types are thin individuals with low body mass index. The kapha types are short stocky individuals that tend toward obesity, and who are sedentary. The study assessed the biochemical differences between right hemispheric dominant, bihemispheric dominant, and left hemispheric dominant individuals, and then compared this with the patterns obtained in the vata, pitta, and kapha states. The isoprenoid metabolites (digoxin, dolichol, and ubiquinone), glycoconjugate metabolism, free radical metabolism, and the RBC membrane composition were studied. The hemispheric chemical dominance in various systemic diseases and psychological states was also investigated. The results showed that right hemispheric chemically dominant/kapha state had elevated digoxin levels, increased free radical production and reduced scavenging, increased tryptophan catabolites and reduced tyrosine catabolites, increased glycoconjugate levels and increased cholesterol: phospholipid ratio of RBC membranes. Left hemispheric chemically dominant/pitta states had the opposite biochemical patterns. The patterns were normal or intermediate in the bihemispheric chemically dominant/vata state. This pattern could be correlated with various systemic and neuropsychiatric diseases and personality traits. Right hemispheric chemical dominance/kapha state represents a hyperdigoxinemic state with membrane sodium-potassium ATPase inhibition. Left hemispheric chemical dominance/pitta state represents the reverse pattern with hypodigoxinemia and membrane sodium-potassium ATPase stimulation. The vata state is the intermediate bihemispheric chemical dominant state. Ninety-five percent of the patients/individuals in the tridosha, pathological, and psychological groups were right-handed/left hemispheric dominant, however, their biochemical patterns were different-either left hemispheric chemical dominant or right hemispheric chemical dominant. Hemispheric chemical

dominance/tridosha states had no correlation with cerebral dominance detected by handedness/dichotic listening test.[8]

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

in endogenous retroviral (HERV) reverse transcriptase and integrase expression. This can integrate the RNA viroidal complementary DNA into the noncoding region of eukaryotic noncoding DNA using HERV integrase as has been described for borna and ebola viruses.[20] The noncoding DNA is lengthened by integrating RNA viroidal complementary DNA with the integration going on as a continuing event. The archaea genome can also get integrated into human genome using integrase as has been described for trypanosomes.[21] The integrated viroids and archaea can undergo vertical transmission and can exist as genomic parasites.[20, 21] This increases the length and alters the grammar of the noncoding region producing memes or memory of acquired characters.[22] The viroidal complementary DNA can function as jumping genes producing a dynamic genome important in storage of synaptic information, HLA gene expression and neurodevelopmental gene expression. The alteration in DNA sequences produced by viroidal complementary DNA jumping genes can lead onto schizophrenia and primary seizure disorder. The RNA viroids can regulate mRNA function by RNA interference.[19] The phenomena of RNA interference can modulate T-cell and B-cell function, neuronal transmission and euchromatin / heterochromatin expression. The RNA viroid induced mRNA interference can modulate dopaminergic, glutamatergic and serotoninergic synaptic transmission. The archaea and viroidal density is high in right hemispheric dominant kapha group, intermediate in bihemispheric dominant vata group and low in left hemispheric dominant pitta group.

The presence of muramic acid, HMG CoA reductase and cholesterol oxidase activity inhibited by antibiotics indicates the presence of bacteria with mevalonate pathway. The density of the mevalonate pathway bacterial is high in right hemispheric dominant kapha state, low in left hemispheric dominant pitta state and intermediate in bihemispheric dominant vata state. The bacterial with mevalonate pathway include streptococcus, staphylococcus, actinomycetes,

listeria, coxiella and borrelia.[23] The bacteria and archaea with mevalonate pathway and cholesterol catabolism had a evolutionarily advantage and constitutes the isoprenoidal clade organism with the archaea evolving into mevalonate pathway gram positive and gram negative organism through horizontal gene transfer of viroidal and virus genes.[24] The isoprenoidal clade prokaryotes develop into other groups of prokaryotes via viroidal/virus as well as eukaryotic horizontal gene transfer producing bacterial speciation.[25] The RNA viroids and its complementary DNA developed into cholesterol enveloped RNA and DNA viruses like herpes, retrovirus, influenza virus, borna virus, cytomegalo virus and ebstein barr virus by recombining with eukaryotic and human genes resulting in viral speciation. Bacterial and viral species are ill defined and fuzzy with all of them forming one common genetic pool with frequent horizontal gene transfer and recombination. Thus the multi and unicellular eukaryote with its genes serves the purpose of prokaryotic and viral speciation. The multicellular eukaryote developed so that their endosymbiotic archaeal colonies could survive and forage better. The multicellular eukaryotes are like bacterial biofilms. The archaea and bacteria with a mevalonate pathway uses the extracellular RNA viroids and DNA viroids for quorum sensing and in the generation of symbiotic biofilm like structures which develop into multicellular eukaryotes.[26, 27] The endosymbiotic archaea and bacteria with mevalonate pathway still uses the RNA viroids and DNA viroids for the regulation of multicellular eukaryote. Pollution is induced by the primitive nanoarchaea and mevalonate pathway bacteria synthesized PAH and methane leading on to redox stress. Redox stress leads to sodium potassium ATPase inhibition, inward movement of plasma membrane cholesterol, defective SREBP sensing, increased cholesterol synthesis and nanoarchaeal / mevalonate pathway bacterial growth.[28] Redox stress leads on to viroidal and archaeal multiplication. Redox stress can also lead to HERV reverse transcriptase and

integrase expression. The noncoding DNA is formed of integrating RNA viroidal complementary DNA and archaea with the integration going on as a continuing event. The archaeal pox like dsDNA virus forms evolutionarily the nucleus. The integrated viroidal, archaeal and mevalonate pathway bacterial sequences can undergo vertical transmission and can exist as genomic parasites. The genomic integrated archaea, mevalonate pathway bacteria and viroids form a genomic reserve of bacteria and viruses which can recombine with human and eukaryotic genes producing bacterial and viral speciation. Bacteria and viruses can contribute to the regulation of hemispheric dominance and tridoshas as exemplified by schizophrenia, a disorder of consciousness. Borrelia, toxoplasma, chlamydia, mycoplasma, retroviruses, herpes virus, influenza virus and borna virus contribute to the neuropathogenesis of schizophrenia.[29-31] The change in the length and grammar of the noncoding region produces eukaryotic speciation and individuality.[32] Changes in the length of noncoding region can lead onto modulation of hemispheric dominance / tridoshas and conscious perception as exemplified in schizophrenia.[33] The human endogenous retroviruses and change in the length and grammar of the noncoding region has been described in schizophrenia. The integration of nanoarchaea, mevalonate pathway prokaryotes and viroids in to the eukaryotic and human genome produces a chimera which can multiply producing biofilm like multicellular structures having a mixed archaeal, viroidal, prokaryotic and eukaryotic characters which is a regression from the multicellular eukaryotic tissue. This results in a new neuronal, metabolic, immune and tissue phenotype producing microchimeras. Microchimeras can also generate tissue and neuronal polyploidy. The higher degree of integration of archaea, mevalonate pathway bacteria and viroids into the genome produces right hemispheric dominant kapha group, intermediate degree of integration produces bihemispheric dominant vata group and lower degree of integration left hemispheric dominant pitta group.

The archaea and viroids can regulate the nervous system including the NMDA / GABA thalamo-cortico-thalamic pathway mediating conscious perception.[2, 34] NMDA / GABA receptors can be modulated by digoxin induced calcium oscillations resulting in NMDA / glutamic acid decarboxylase (GAD) activity induction, PAH increasing NMDA activity and inducing GAD as well as viroid induced RNA interference modulating NMDA / GABA receptors.[2] The cholesterol ring oxidase generated pyruvate can be converted by the GABA shunt pathway to glutamate and GABA. Increased NMDA transmission has been described in schizophrenia and primary seizure disorder. The dipolar PAH and archaeal magnetite in the setting of digoxin induced sodium potassium ATPase inhibition can produce a pumped phonon system mediated Frohlich model superconducting state inducing quantal perception with nanoarchaeal sensed gravity producing the orchestrated reduction of the quantal possibilities to the macroscopic world.[2, 34] The archaea can regulate limbic lobe transmission with archaeal cholesterol aromatase/ring oxidase generated norepinephrine, dopamine, serotonin and acetyl choline.[17] Thus the shadow biosphere of archaea and viroids can regulate conscious and quantal perception. The archaea and viriods can also modulate multiple neurotransmitter systems. Schizophrenia is described as a disorder of consciousness and increased integration of archaea and viroids into the genome can contribute to its neuropathogenesis. Increased dopaminergic, serotoninergic and NMDA transmission is important in the pathogenesis of schizophrenia. The higher degree of integration of the archaea into the genome produces increased digoxin synthesis producing right hemispheric dominant kapha group and lesser degree producing left hemispheric dominant pitta group.[2] Bihemispheric dominant vata group is intermediate with normal digoxin synthesis. Right hemispheric dominant kapha group has been described in schizophrenia. The increased integration of archaea into the neuronal genome can produce increased cholesterol oxidase and

aromatase mediated monoamine and NMDA transmission producing schizophrenia. The archaeal bile acids are chemically diverse and structurally different from human bile acids. The archaeal bile acids can bind olfactory GPCR receptors and stimulate the limbic lobe producing a sense of social identity. The dominance of archaeal bile acids over human bile acids in stimulating the olfactory GPCR - limbic lobe pathway leads to loss of social identity leading to schizophrenia and autism.[35]

Archaea and RNA viroid can bind the TLR receptor induce NFKB producing immune activation and cytokine TNF alpha secretion. The archaeal DXP and mevalonate pathway metabolites can bind γδ TCR and digoxin induced calcium signalling can activate NFKB producing chronic immune activation.[2, 36] The archaea and viroid induced chronic immune activation and generation of superantigens can lead on to autoimmune disease. This produces a state of chronic immune activation in right hemispheric dominant kapha group producing increased predisposition to autoimmune diseases. The left hemispheric dominant pitta group is immunosuppressed and the bihemispheric dominant vata group has normal immune function.

Archaea, viroids and digoxin can induce the host AKT PI3K, AMPK, HIF alpha and NFKB producing the Warburg metabolic phenotype.[37] The increased glycolytic hexokinase activity, decrease in blood ATP, leakage of cytochrome C, increase in serum pyruvate and decrease in acetyl CoA indicates the generation of the Warburg phenotype. There is induction of glycolysis, inhibition of PDH activity and mitochondrial dysfunction resulting in inefficient energetics. The immune activation mediated increased levels of TNF alpha can produce insulin resistance acting at the level of insulin receptor. Thus a state similar to metabolic syndrome X exists in right hemispheric dominant kapha group. Left hemispheric dominant pitta group can have a pattern of increased insulin sensitivity and low body mass index producing a reverse metabolic syndrome X.

The bihemispheric dominant vata state will be metabolically intermediate. Cholesterol oxidase activity, increased glycolysis related NADPH oxidase activity and mitochondrial dysfunction generates free radicals. Free radical production and mitochondrial dysfunction can increase NMDA transmission important in conscious perception. The accumulated pyruvate enters the GABA shunt pathway and is converted to citrate which is acted upon by citrate lyase and converted to acetyl CoA, used for cholesterol synthesis.[37] The increased cholesterol substrate leads to increased archaeal growth and digoxin synthesis leading to metabolic channelling to the mevalonate pathway. Hyperdigoxinemia is important in the regulation of hemispheric dominance and the tridoshas.[2] The right hemispheric dominant kapha group is hyperdigoxinemic, left hemispheric dominant pitta group is hypodigoxinemic and bihemispheric dominant vata group is normodigoxinemic. The pyruvate can be converted to glutamate and ammonia which is oxidised by archaea for energy needs. Ammonia can regulate both NMDA and GABA transmission depending on its levels.

The Warburg phenotype can contribute to the hemispheric dominance and tridoshas by augmenting the bacterial shikimic acid pathway. The upregulated glycolysis consequent to the Warburg phenotype produces phosphoenolpyruvate, a basic substrate for the bacterial shikimic acid pathway which can synthesise monoamines and neuroactive alkaloids. The shikimic acid pathway can generate dopamine and serotonin producing increased monoaminergic transmission. The shikimic acid pathway can also synthesize the neuroactive alkaloids strychnine, nicotine, morphine, mescaline and LSD important in regulating neural transmission.[2] The upregulated glycolysis can also contribute to increased NMDA and GABA transmission in the thalamo-cortico-thalamic pathway. The glycolytic pathway produces phosphoglycerate which is converted to phosphoserine and then serine which activates the NMDA receptor. The glycolytic enzyme glyceraldehyde

3-phosphate dehydrogenase is a GABA receptor kinase and activates GABA transmission. Thus the archaea and viroid induced Warburg phenotype can contribute to the modulation of hemispheric dominance and tridoshas by regulating the multiple neurotransmitter systems. The archaeal cholesterol catabolism can deplete the cell membranes of cholesterol resulting in alteration in lipid microdomains and their related neurotransmitter receptor contributing to the regulation of NMDA, serotoninergic and dopaminergic transmission. Thus the archaeal cholesterol catabolism and viroids can regulate brain function and hemispheric dominance/tridoshas. The archaea and viroids have axonal and transynaptic transport functioning as biological neurotransmitters. The brain can be visualized evolutionarily as a modified mevalonate pathway bacteria and archaeal colony functioning by mechanisms of quorum sensing using RNA viroids with its bacterial flagellar system forming axo-axonic and axo-dendritic connections. The third element of archaea and their derived viroids can also regulate the immune, genetic, metabolic and neural systems producing its integration.

The third element formed of intracellular archaea and viroidal symbiosis determines hemispheric dominance and tridoshas. Also archaeal cholesterol synthesis and cholesterol catabolism determines hemispheric dominance and tridoshas.

References

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

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

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

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

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

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

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

[8] Kurup, R. K., Kurup, P. A. (2003). Hypothalamic digoxin, hemispheric chemical dominance, and the tridosha theory. *The International journal of Neuroscience*, 113(5), 657-681.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

[29] Fritzsche M. (2002). Seasonal correlation of sporadic schizophrenia to Ixodes ticks and Lyme borreliosis. *Int J Health Geogr*, 1(1), 2.

[30] Waltrip R. W. 2nd, Buchanan, R. W., Summerfelt, A., Breier, A., Carpenter, W. T. Jr., Bryant, N. L., Rubin, S. A., Carbone, K. M. (1995). Borna disease virus and schizophrenia. *Psych Res*, 56(1), 33-44.

[31] Torrey E. F., Yolken, R. H. (2003). Toxoplasma gondii and schizophrenia. *Emerg Infect Dis*, 9(11), 1375-80.

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

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

[34] Lockwood M. (1989). *Mind, Brain and the Quantum*. Oxford: B. Blackwell.

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

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

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

Chapter 4

Cerebral Dominance and Archaeal Digoxin - Relation to the Tridosha Theory and Pathogenesis of Disease

Introduction

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

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

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

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

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

Discussion

There is a specialisation of function in the right and left hemispheres of the brain as manifested in cognitive dysfunctions noticed in lesions of the same. Typical cerebral lateralization is associated with left cerebral dominance for language, praxis and serial processing, whereas the right cerebral hemisphere is dominant for externally directed attention, visuospatial tasks and gestalt processing. The right hemisphere is also dominant for emotional stimuli, and patients with right cerebral lesions may exhibit hypoarousal and emotional indifference. The pitta state is described as a critical, discriminative and rational psychological state of mind while the kapha state is described as being dominant for emotional stimuli. The vata state in between is an unstable shifting state. Geschwind also postulated a relationship between cerebral lateralization and immune function. For example, they observed a higher frequency of left-handedness in patients with some immune disorders. Difference in natural killer cell activity has been reported in women as a function of asymmetries in frontal EEG activation. Bardos et al. demonstrated that lesions of the left neocortex in mice depress T-cell immunity, whereas right lesions enhance T-cell immunity. There is no data as of now on neurotransmitter differences between right and left hemispheres though functional differences have been noticed as described above. The present study assessed the changes in the synthesis of an endogenous membrane Na^+-K^+ ATPase inhibitor, digoxin and neurotransmitter changes in right and left handed individuals and their relationship to cerebral dominance. The pathological and psychological correlates of cerebral dominance in relation to endogenous digoxin synthesis have also been documented. Also it has been compared with the parameters obtained in vata, pitta and kapha state. The results are presented in this chapter.

Archaeal Digoxin and Membrane Na^+-K^+ ATPase Inhibition - Cerebral Dominance

The archaeaon steroidelle DXP pathway and the upregulated pentose phosphate pathway contribute to digoxin synthesis. The increase in endogenous digoxin, a potent inhibitor or membrane Na^+-K^+ ATPase, can decrease this enzyme activity in left handed / right hemispheric dominant individuals and in Parkinson's disease, CNS glioma, multiple sclerosis, acquired immunodeficiency syndrome, schizophrenia, primary generalised epilepsy, syndrome X, migraine, addiction, anorexia nervosa, osteoarthritis, spondylosis, acute coronary artery disease, hypertension, SSPE, neurolupus, acid peptic disease, irritable bowel syndrome, cirrhosis liver, inflammatory bowel disease, chronic bronchitis emphysema, interstitial lung disease, sarcoidosis, bronchial asthma, chronic renal failure, nephrotic syndrome, nephrolithiasis, lone atrial fibrillation, gall stones and Fahr syndrome. In all the disorders studied, there was significant inhibition of the RBC membrane Na^+-K^+ ATPase and this inhibition appears to be a common feature for these neuropsychiatric and systemic disorders. In creative individuals, addiction, promiscuous individuals, homosexuals, anorexic, insomniac and individuals with reduced bonding / affection and detached behaviour also serum digoxin levels are increased and RBC membrane Na^+-K^+ ATPase activity reduced decreased. In all these pathological and psychological states there is chemical right hemispheric dominance. The inhibition of Na^+-K^+ ATPase by digoxin is known to cause an increase in intracellular calcium resulting from increased Na^+-Ca^{++} exchange, increased entry of calcium via the voltage gated calcium channel and increased release of calcium from intracellular endoplasmic reticulum calcium stores. This increase in intracellular calcium by displacing magnesium from its binding sites causes a decrease in the functional availability of magnesium. This decrease in the availability of magnesium can cause decreased mitochondrial ATP

formation which along with low magnesium can cause further inhibition of Na^+-K^+ ATPase, since the ATP-magnesium complex is the actual substrate for this reaction. Cytosolic free calcium is normally buffered by two mechanisms, ATP dependent calcium extrusion from the cell and ATP dependent sequestration of calcium within the endoplasmic reticulum. The magnesium related mitochondrial dysfunction results in defective calcium extrusion from the cell. There is thus a progressive inhibition of 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 these disorders. The intracellular positive calcium signal and negative magnesium signal can regulate diverse cellular process. Calcium on entry into the cell is used to charge up the internal endoplasmic reticulum stores which then release a burst of signal calcium responsible for activating a large variety of calcium dependent cellular processes. The information processing capability of the calcium signalling system is enhanced by amplitude and frequency modulation. The calcium is released from channels on internal ER individually or in small groups (bip/quark and puffs/sparks). Further diversity of calcium signalling is produced by compartmentalization as cytosolic calcium signal and nuclear calcium signal. There is evidence for increased digoxin synthesis in these groups of diseases from the increase in HMG CoA reductase activity that is noticed. HMG CoA reductase is the rate limiting enzyme of the isoprenoid pathway. In this connection, incorporation of ^{14}C-acetate into digoxin in the rat brain has been shown by us indicating that acetyl CoA is the precursor for digoxin biosynthesis in mammals also. Serum magnesium was assessed in left handed / right hemispheric dominant individuals and in Parkinson's disease, CNS glioma, multiple sclerosis, schizophrenia, primary generalised epilepsy, syndrome X, migraine, addiction, idiopathic basal ganglia calcification, anorexia nervosa, osteoarthritis,

spondylosis, acute coronary artery disease, essential hypertension, SSPE, neurolupus, acquired immunodeficiency syndrome, acid peptic disease, irritable bowel syndrome, gall stones, cirrhosis liver, inflammatory bowel disease, chronic bronchitis emphysema, interstitial lung disease, chronic renal failure, lone atrial fibrillation and bronchial asthma and was found to be reduced. In all these pathological and psychological states there is chemical right hemispheric dominance. Increased intracellular calcium can lead on to basal ganglia calcification. Increase in intracellular calcium can lead on to an increased calcium load in the bone and degenerative bone disease like cervical spondylosis. Increased digoxin can also contribute to the pathophysiology of CRF (chronic renal failure). Digoxin by the membrane Na^{+}-K^{+} ATPase inhibition that it produces can lead on to inhibition of the outward sodium flux and inhibition of the inward potassium flux as also leading on to an increased inward flux of calcium. This leads on to an abnormally high intracellular sodium concentration and hence to osmotically induced overhydration of the cell whereas the same cells are relatively deficient in potassium. Digoxin can alter the conduction of the cardiac SA node and AV node as well as the conducting tissue contributing to lone atrial fibrillation. Increase in bronchial smooth muscle calcium can contribute to bronchospasm in bronchial asthma. Similarly an increase in intestinal smooth muscle cell calcium can lead on to irritable bowel syndrome by producing intestinal smooth muscle contraction. Increased intracellular parietal cell calcium and reduced intracellular magnesium can lead on to increased gastric acid secretion. Increased intracellular calcium can also activate the G-protein coupled receptor histamine, which can lead on to increased gastric acid secretion. An upregulated isoprenoid pathway and increased cholesterol synthesis can lead on to the formation of gallstones. Hypomagnesemia can lead on to inhibition of gall bladder contraction and decreased water content of the bile contributing to the formation

of gall bladder sludge. Increased renal tubular cell calcium and accumulation of the shed renal tubular cell in the renal pelvis and ureter can lead on to the formation of renal stones.

The decrease in the activity of HMG CoA reductase in right handed individuals / left hemispheric dominant and in healthy aging, obsessive compulsive disorder, depression, recurrent respiratory infections, osteoporosis, familial hypotension, low body-mass index and bulimia nervosa suggests a downregulation of the isoprenoid pathway. In spiritually non-inclined individuals, non-creative individuals, individuals without addictive behaviour, non-promiscuous individuals, individuals with gastronomic tendency, somnolent individuals and individuals with increased bonding and affection also there is a reduction in HMG CoA reductase activity and down regulation of the isoprenoid pathway. In all these psychological states there is chemical left hemispheric dominance. There is a marked decrease in plasma digoxin and dolichol and this decrease may be a consequence of decreased channeling of intermediates of the isoprenoid pathway for their biosynthesis. The decrease in endogenous digoxin, a potent inhibitor of membrane Na^{+}-K^{+} ATPase, can increase this enzyme activity. In all these cases there was significant stimulation of the RBC membrane Na^{+}-K^{+} ATPase. The stimulation of Na^{+}-K^{+} ATPase by decrease in digoxin synthesis is known to cause a decrease in intracellular calcium resulting from decreased Na^{+}-Ca^{++} exchange, decreased entry of calcium via the voltage gated calcium channel and decreased release of calcium from intracellular endoplasmic reticulum calcium stores. The increased intracellular magnesium related mitochondrial ATP synthesis results in increased calcium extrusion from the cell. There is thus a progressive stimulation of Na^{+}-K^{+} ATPase activity. High intracellular magnesium and low intracellular calcium consequent to Na^{+}-K^{+} ATPase stimulation appear to be crucial to the pathophysiology of these diseases. Serum magnesium was

assessed in right handed / left hemispheric dominant individuals and the above mentioned psychological and pathological state and was found to be increased. Decrease in bone calcium load can lead on to osteoporosis.

Thus there are three different neurological states which correlates with various systemic diseases and psychological profiles. There is the hyperdigoxinemic right hemispheric dominant state, hypodigoxinemic left hemispheric dominant state and normodigoxinemic bihemispheric dominant / fluctuating dominant state.

Endosymbiotic Archaeal Digoxin, Hemispheric Dominance and the Three Biological Humours in Ayurveda

The three states of biological humours described in Ayurveda have a correlation with hemispheric chemical dominance. The kapha state represents the right hemispheric dominant hyperdigoxinemic state. The pitta state represents the left hemispheric dominant hypodigoxinemic state. The vata state represents the bihemispheric dominant or fluctuating dominant normodigoxinemic state. The three states of hemispheric dominance - Vata, Pitta and Kapha can differentially regulate neuro-immuno-endocrine / cellular integration. It can thus regulate the predisposition to various systemic and neuropsychiatric diseases.

Endosymbiotic Archaeal Digoxin and Regulation of Neurotransmitter Synthesis and Function - Cerebral Dominance and Three Biological Humours

The archaeaon neurotransminoid shikimic acid pathway contributes to tryptophan and tyrosine synthesis and catabolism generating neurotransmitters and neuroactive alkaloids. There is increase in tryptophan and its catabolites and a reduction in tyrosine and its catabolites in the serum of left handed / right hemispheric dominant individuals. 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 above psychological and pathological states could be due to the fact that the hyperpolarising neurotransmitters (dopamine, morphine and noradrenaline) are reduced and the depolarising neuroactive compounds (serotonin, strychnine, nicotine and quinolinic acid) are increased. The schizoid neurotransmitter pattern of reduced dopamine, noradrenaline and morphine and increased serotonin, strychnine and nicotine is common to left handed / right hemispheric dominant individuals and to all these pathological and psychological states and could predispose to their development. Quinolinic acid, an NMDA agonist can contribute to NMDA excitotoxicity reported in schizophrenia. Strychnine by blocking glycinergic transmission can contribute to the decreased inhibitory transmission in schizophrenia. Recent data suggest that the initial abnormality in schizophrenia involves a hypodopaminergic state and the low dopamine levels now observed agree with this. Nicotine by interacting with nicotinic receptors can facilitate the release of dopamine, promoting the dopaminergic transmission in the brain. This can explain the increased dopaminergic transmission in the presence of decreased dopamine levels. The increased serotoninergic activity and reduced noradrenergic outflow from the locus coeruleus reported earlier in schizophrenia agrees with our finding of elevated serotonin and reduced noradrenaline levels. A schizophreniform type of psychosis is important in the genesis of irritable bowel syndrome, inflammatory bowel disease, bronchial asthma, acid peptic disease and immune mediated disorders like multiple sclerosis and SLE. In the presence of hypotnagnesemia, 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 recylcing.

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 Na^{+}-K^{+} ATPase can promote glutamatergic transmission. The elevated levels of quinolinic acid, strychnine and serotonin can also contribute to NMDA excitotoxicity. Strychnine displaces glycine from its binding sites and inhibits glycinergic inhibitory transmission in the brain. The glycine is free to bind to the strychnine insensitive site of the NMDA receptor and promote excitatory NMDA transmission. Quinolinic acid and serotonin are also positive modulators of the NMDA receptor. Increased glutamatergic transmission resulting in excitotoxicity has been implicated in neuronal degeneration as observed in Parkinson's disease, primary generalised epilepsy, schizophrenia and AIDS dementia. Inhibition of Na^{+}-K^{+} ATPase can also result in defective neuronal membrane repolarisation and a paroxysomal depolarisation shift resulting in epileptogenesis. Increased nicotine synthesis can contribute to the pathophysiology of chronic bronchitis emphysema. Elevated levels of serotonin and nitric oxide production could contribute to increased incidence of migraine in right hemisphere dominant left handed individuals. Increased intracellular calcium can activate the gastrin and acetyl choline related gastric acid secretion. Increased intracellular calcium in the presynaptic neuron can promote cholinergic transmission. The increased presynaptic neuronal Ca^{++} can produce cyclic AMP dependent phosphorylation of synapsins resulting in increased neurotransmitter release into the synaptic junction and vesicular recycling. This promotes cholinergic vagal transmission promoting acid secretion and peptic ulcer formation. These neurotransmitter patterns can lead on to irritable bowel syndrome also. The increase in serotonin can contribute

to altered bowel motility in IBS. Serotonin blockers are useful in the treatment of IBS. Reduced morphine and dopamine levels can contribute to the pathogenesis of IBS. Studies have shown that there is endogenous synthesis of morphine from tyrosine and dopamine. Kappa and the opioid agonist are useful in the treatment of bowel motility disorders. The particular neurotransmitter patterns can inhibit gall bladder contractility contributing to formation of gallstones. Thus in the right hemisphere dominant hyperdigoxinemic state there is upregulated serotoninergic, cholinergic and glutamatergic transmission and downregulated dopaminergic, glycinergic and noradrenergic transmission. This neurotransmitter patterns could also be correlated with psychological states. There was an increased tendency for spirituality in hyperdigoxinemic individuals. Temporal lobe epileptic phenomenon has been described in spiritual individuals. Increased glutamatergic transmission is associated with memory and intelligence. This can contribute to increased creativity. They had a tendency towards reduced appetite and eating behaviour. Increased serotoninergic transmission can lead on to reduced appetite. There was also hypersexual behaviour, homosexuality and promiscuity in hyperdigoxinemic individuals. This could be related to increased production of nitric oxide in hyperdigoxinemic individuals consequent to induction of nitric oxide synthase by increased intracellular calcium. Nitric oxide has been related to erectile function. There was an increased tendency to addictive behaviour in hyperdigoxinemic individuals. Endogenous morphine deficiency has been related to addiction. Morphine synthesis is low because of low tyrosine levels. There was tendency to insomnia and reduced sleep. This could be related to reduced levels of morphine. There was less of bonding and affectionate behaviour. Bonding and affectionate behaviour has been related to dopamine and morphine. Dopamine and morphine deficiency in hyperdigoxinemic individuals could contribute to less of bonding and affectionate behaviour.

The results showed that the concentration of tryptophan, quinolinic acid, strychnine, nicotine and serotonin was found to be tower in the plasma of right handed / left hemispheric dominant individuals while that of tyrosine, morphine, dopamine and norepinephrine was higher. Thus there is a decrease in tryptophan and its catabolites and increase in tyrosine and its catabolites in the serum of right handed / left hemispheric dominant individuals and the above described psychological / pathological states. 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 and that digoxin levels are low in right handed / left hemispheric dominant individuals and in the above mentioned pathological / psychological states. The increase in membrane Na^+-K^+ ATPase activity in these cases could be due to the fact that the hyperpolarising neurotransmitters (dopamine, morphine and noradrenaline) are increased and the depolarising neuroactive compounds (serotonin, strychnine, nicotine and quinolinic acid) are decreased. The low level of quinolinic acid, serotonin and strychnine can contribute to reduced excitatory glutamatergic transmission as they are all positive modulators of the NMDA receptor. In the presence of hypermagnesemia, the magnesium block on the NMDA receptor is strengthened leading on to reduced NMDA transmission. The decreased presynaptic neuronal calcium can produce reduced cyclic AMP dependent phosphorylation of synapsins resulting in decrease in glutamate release into the synaptic junction and vesicular recycling. The plasma membrane glutamate transporter (on the surface of the glial cell and presynaptic neuron) is coupled to the sodium gradient, which is activated by the stimulation of Na^+-K^+ ATPase, resulting in increased clearance of glutamate by presynaptic and glial uptake at the end of synaptic transmission. By these mechanisms, stimulation of Na^+-K^+ ATPase can inhibit glutamatergic transmission. Reduced glutamatergic transmission can lead on to healthy aging and protect the brain from neuronal degeneration. The depressive syndrome noted

could be due to low serotonin. Decreased serotoninergic transmission has been related to depression. The presence of OCD syndrome could also be related to serotonin depletion. Deficiency of serotonin can lead to increased appetite and eating behaviour resulting in bulimia nervosa. Dopamine and morphine has been related to bonding behaviour. Increased morphine and dopamine could lead to increased bonding and affectionate behaviour. Increased synthesis of morphine can also lead on to lack of addictive behaviour. Morphine deficiency has been related to addiction. The reduced glutamatergic transmission noted could be related to the average to normal IQ and creativity noticed. Dementia has also been related to depression and the phenomenon of pseudomentia has been described. Decreased production of nitric oxide can lead on to hyposexual behaviour. Synthesis of NO has been related to erectile function. These behavioural patterns are suggestive of left hemispheric dominance.

Endosymbiotic Archaeal Digoxin - Golgi Body / Lysosomal Function - Hemispheric Dominance

The archaeaon glycosaminoglycoid and fructosoid contributes to glycoconjugate synthesis and catabolism by the process of fructolysis. The elevation in the level of dolichol in right hemispheric dominance may suggest its increased availability for N-glycosylation of proteins. Magnesium deficiency can lead on 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 chanelled for the synthesis of glycosaminoglycans (GAG). The concentration of total GAG, different GAG fractions, carbohydrate component of the glycoproteins and glycolipids are increased in right hemispheric dominant individuals. 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 usually abnormal and resistant to lysosomal enzymes and may accumulate.

Previous reports of alteration in glycoproteins in this connection include alteration in alpha acid glycoprotein (AAG) and beta amyloid precursor protein in epilepsy and Alzheimer's disease and alpha synuclein in Parkinson's disease. Structurally abnormal glycoproteins resist catabolism by lysosomal enzymes and accumulate in neuronal degeneration. Interaction between HS-proteoglycan and ChS-proteoglycan with proteins like beta amyloid, tau protein, parkin and alpha synuclein and reduced proteolytic digestion of these complexes leading On to their accumulation in the neurons have been reported in neurodegenerative diseases like Alzheimer's disease and Parkinson's disease. Alteration in the sulphated proteoglycan matrix of the synaptic vesicles can alter neurotransmitter release into the synapse and produce a functional disorder like schizophrenia and epilepsy. Membrane Na^+-K^+ ATPase inhibition can lead to defective notch signalling. Notch is a transmembrane protein that acts as a signal receptor and is important in neurogenesis. Neuronal growth by extending neurites and forming connections is regulated by the notch signalling pathway. The notch signalling inhibits extension of neurites and keep them stable in the mature brain. A notch ligand known as delta regulates neurogenesis by binding to notch in membranes of embryonal cells and prevents them from developing

along the neuronal pathway. Notch activation by the ligand causes notch to be cleaved releasing the notch intracellular domain. This then passes in to the nucleus and activates transcription as part of the DNA binding complex with CSL protein. Intracellular cleavage of the notch is regulated by presenilin and also depends upon the lysosomal protease. In the presence of a lysosomal instability consequent to defective lysosomal membranes notch cleavage by protease is defective leading on to functional disorders consequent to defective synaptic connectivity. The defective notch signalling pathway can lead to neuronal degeneration. Altered glycoproteins, glycolipids and GAG of the neuronal membrane can also contribute to schizophrenia and epilepsy by producing disordered synaptic connectivity. The protein processing defect can result in defective glycosylation of endogenous myelin glycoprotein antigens and exogenous viral glycoproteins antigens with consequent defective formation of MHC class-1 glycoprotein antigen complex. The MHC linked peptide transporter, a P-glycoprotein which transports the MHC class-1 glycoprotein antigen complex to the antigen presenting cell surface, has an ATP binding site. The peptide transporter is dysfunctional in the presence of magnesium deficiency. This results in defective transport the MHC class-1 glycoprotein antigen complex to the antigen presenting cell surface for recognition by the CD_4 or CD_8 cell. Defective presentation of the endogenous myelin glycoprotein antigen can explain the immune dysregulation in MS. A CD_8 MHC class-1 restricted immune dysregulatory defect has been described in MS. This can also explain the immune dysregulation in interstitial lung disease, nephrotic syndrome, inflammatory bowel disease sarcoidosis, rheumatoid arthritis and SLE (systemic lupus erythematosis). Defective presentation of exogenous viral antigens can produce immune evasion by the virus as in AIDS dementia and SSPE. Viral persistence has been implicated in the development of turnours (ebstein barr virus and lymphoma), multiple sclerosis (retro virus),

degenerations (Parkinson's disease and corona virus) and schizophrenia (borna virus disease). Altered myelin glycoprotein due to defective glycosylation and alteration in GAG of proteoglycans of myelin can affect the structural integrity of myelin leading on to demyelination. A number of fucose and sialic acid containing natural ligands are involved in trafficking of leukocytes and similar breaches in the blood brain barrier and adhesion of the lymphocyte producing leukocyte trafficking and extravasation in to the perivascular space as has been described in MS. Similar changes can explain the immune infiltration in bronchial asthma, sarcoidosis, interstitial lung disease, inflammatory bowel disease and SLE. A number of fucose and sialic acid containing natural ligands have been implicated in neoplastic transformation and metastasis. Abnormally glycosylated tumour antigens can lead to defective tumour antigen presentation and loss of immunosurveillance by the natural killer cells. Altered cell surface glycoproteins, glycolipids and GAG can lead to defective contact inhibition and oncogenesis. The MHC glycoproteins are involved in formation of synaptic connectivity during neuronal development. Defective formation and presentation of the MHC class-l neuronal glycoprotein complex can lead on to disordered synaptic connectivity and functional disorders like schizophrenia and epilepsy. Altered glycoproteins can affect the synaptic connectivity in the nerve plexus of the bowel wall contributing to irritable bowel syndrome. Magnesium deficiency can upregulate collagen and elastin synthesis along with glycoconjugates. This can contribute to the pathogenesis of fibrosis in ILD and cirrhosis of the liver. Increased glycoconjugate synthesis can interfere with the structure of the alveolar basement membrane contributing to the increased alveolar leakiness leading on to the formation of the intralveolar hyaline membrane in interstitial lung disease. Increased synthesis of sulphated glycosaminoglycans and alteration in the glomerular basement membrane can contribute to the pathogenesis of nephrotic syndrome by interfering with the

glomerular filtration barrier. Altered mucoproteins can affect the gastric mucosal barrier leading on to acid peptic disease. Non-mucin glycoproteins are pro-nucleating factors with regard to gallstone formation. Urine glycoproteins on the other hand have an inhibitory effect on renal stone formation. Altered glycoproteins lead to removal of these particular effects either inhibitory or stimulatory contributing to gallstones and renal stone formation. Altered proteoglycans of the articular surface of the joint can lead on to osteoarthritis as well as degenerative spondylosis of the spine. Thus in the hyperdigoxinemic right hemisphere dominant state there is reduced lysosomal stability, defective ubiquitin dependent proteolytic processing of proteins and alteration in glycoconjugate structure leading on to their defective catabolism and accumulation. There is also a defect in the MHC antigen presenting pathway leading on to immunodysregulation and viral persistence.

The decrease in the level of dolichol in right handed / left hemispheric dominant individuals and in healthy aging, obsessive compulsive disorder, depression, recurrent respiratory infections, osteoporosis, familial hypotension, patients with low body mass index and bulimia nervosa may suggest its decreased availability for N-glycosylation of proteins. Magnesium excess can lead on to increased catabolism of sphinganine leading on to decreased cerebroside and ganglioside synthesis. In magnesium excess the glycolysis, citric acid cycle and oxidative phosphorylation are activated and less of glucose 6-phosphate is channelled for the synthesis of glycosaminoglycans (GAG). The results show a decrease in the concentration of serum total GAG, glycolipids (ganglioside, glycosyl diglyceride, cerebrosides and sulphatides) and carbohydrate components of glycoproteins (hexose, fucose and sialic acid). The individual GAG fractions in the serum-heparan sulphate (HS), chondroitin sulphates (ChS), heparin (H), hyaluronic acid (HA) and dermatan sulphate (DS) are decreased in left hemisphere dominant individuals

(pathological/psychological). 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 decrease in the serum in hypodigoxinemic left hemisphere dominant states. Intracellular magnesium excess also results in increased ubiquitin dependent proteolytic processing of glycoconjugates as it requires magnesium for its function. The decrease in the activity of glycohydrolases and GAG degrading enzymes could be due to increased lysosomal stability. Defective lysosomal stability and defective degradation of glycoprotein - GAG complexes as in the case of tau protein / amyloid - HS proteoglycan complexes in Alzheimer's disease can lead on to brain aging. Membrane Na^+-K^+ ATPase stimulation could protect against neuronal aging. A number of fucose and sialic acid containing natural ligands have been implicated in inflammatory responses and neoplastic transformation. The decrease in fucose and sialic acid noted in these cases could inhibit a protective inflammatory response to the virus or bacteria leading on to recurrent respiratory infection. Decrease in fucose and sialic acid could also protect against malignant transformation. The reduction in glycoconjugate could also result in increased osteoporosis as it affects the structure of the bone matrix. Thus in the hypodigoxinemic left hemisphere dominant state there is increased lysosomal stability, increased ubiquitin dependent proteolytic processing of proteins and alteration in glycoconjugate metabolism leading to decrease in the levels of glycolipids, the carbohydrate component of glycoproteins and glycosaminoglycans. There is no viral persistence but a resulting hypoimmune state contributing to recurrent respiratory infections.

Endosymbiotic Archaeal Digoxin and Alteration in Membrane Structure and Membrane Formation - Relation to Hemispheric Dominance

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 in right hemispheric dominant individuals can lead to increased cholesterol synthesis and magnesium deficiency can inhibit phospholipid synthesis. Phospholipid degradation is increased owing to increase in intracellular calcium activating phospholipases A_2 and D. The cholesterol: phospholipid ratio of the RBC membrane was increased in right hemispheric dominance individuals. The concentration of total GAG, hexose and fucose 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 of as a vesicle, which fuses with the golgi complex. The glycoconjugates are then transported via the golgi channel and the golgi vesicle fuses with the cell membrane. This trafficking depends upon GTPases and lipid kinases, which are crucially dependent on magnesium and are defective in magnesium deficiency. The change in membrane structure produced by alteration in glycoconjugates and the cholesterol: phospholipid ratio can produce changes in the conformation Na^+-K^+ ATPase resulting in further membrane Na^+-K^+ ATPase inhibition. The same 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. Increased release of lysosomal enzymes can contribute to proteolytic destruction in chronic bronchitis and emphysema,

osteoarthritis and rheumatoid arthritis. Defective peroxisomal membranes lead to catalase dysfunction, which has been documented in these disorders. Alteration in the alveolar basement membrane can contribute to ILD and the glomerular basement membrane and filtration barrier to nephrotic syndrome. Similar changes in the membrane of the cardiac conducting tissue can contribute to lone atrial fibrillation. Changes in the composition of the neuronal membranes can predispose to epilepsy and functional disorders like schizophrenia. Thus in the hyperdigoxinemic right hemisphere dominant state there is defective membrane formation, membrane structure and function.

The downregulation of the isoprenoid pathway in right handed / left hemispheric dominant individuals and in healthy aging, obsessive compulsive disorder, depression, recurrent respiratory infections, osteoporosis, familial hypotension, patients with low body mass index and bulimia nervosa can lead to decreased cholesterol synthesis and magnesium excess can stimulate phospholipid synthesis. Phospholipid degradation is decreased owing to decrease in intracellular calcium inhibiting phospholipase A_2 and ID. The cholesterol: phospholipid ratio of the RBC membrane was decreased in hypodigoxinemia. The concentration of total GAG, hexose and fucose of glycoprotein increased in the RBC membrane and decreased in the serum suggesting their increased incorporation into the membrane and defective membrane formation. The membrane trafficking depends upon GTPases and lipid kinases, which are crucially dependent on magnesium and are activated in magnesium excess. The change in membrane structure produced by alteration in glycoconjugates and the cholesterol: phospholipid ratio can produce changes in the conformation of Na^+-K^+ ATPase resulting in further membrane Na^+-K^+ ATPase stimulation. The same changes can affect the structure of organelle membrane. This results in increased lysosomal stability. Altered peroxisomal membranes could lead to catalase hyperactivity noticed in hypodigoxinemic states. Thus there is increased

membrane formation and increased stability of membrane of the cellular organelle in the left hemisphere dominant hypodigoxinemic state.

Endosymbiotic Archaeal Digoxin and Mitochondrial Function - Relation to Cerebral Dominance

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 left handed / right hemispheric dominant individuals which may be the result of low tyrosine levels, reported in most of the disorders, consequent to digoxin's effect in preferentially promoting tryptophan transport over tyrosine. The aromatic ring portion of ubiquinone is derived from tyrosine. Ubiquinone, which is an important component of the mitochondrial electron transport chain, is a membrane antioxidant and contributes to free radical scavenging. The increase in intracellular 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 defects 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 demage which can further inactivate Na^+-K^+ ATPase, triggering the cycle of free radical generation once again. Magnesium deficiency can affect glutathione synthetase and glutathione reductase function. The mitochondrial superoxide dismutase leaks out and becomes dysfunctional with calcium related opening of the mitochondrial PT pore and outer membrane rupture. The peroxisomal membrane is defective owing to the membrane Na^+-K^+ ATPase inhibition related defect in membrane formation and leads to reduced catalase activity. Mitochondrial dysfunction related free radical generation has been implicated in the pathogenesis of the neuronal degeneration, oncogenesis and immune mediated disorders. Increased free radical generation can lead on to immune activation important in immune mediated diseases like interstitial lung disease, bronchial asthma, sarcoidosis, inflammatory bowel disease, systemic lupus erythematosis, rheumatoid arthritis, nephrotic syndrome and multiple sclerosis. Mitochondrial dysfunction can lead on to Reye's syndrome. The increased intracellular calcium and ceramide related opening of the mitochondrial PT pore also leads to volume dysregulation of the mitochondria, causing hyperosmolality of the matrix and expansion of the matrix space. The outer membrane of the mitochondria ruptures and releases apoptosis inducing factor and cytochrome C into the cytoplasm. This results in activation of caspase-9 and caspase-3. Caspase-9 can produce apoptosis of the cell. Apoptosis has been implicated in neuronal degeneration. Apoptosis can produce defective synaptogenesis and synaptic connectivity contributing to functional disorders like schizophrenia and epilepsy. Apoptosis of the CD_4 cell can contribute to CD_4 depletion in the acquired immunodeficiency syndrome. Oligodendrocyte (the myelin forming cell) apoptosis is crucial to the pathogenesis of MS. Hepatocyte apoptosis can contribute to cell death in cirrhosis of the liver. Caspase-3 activation can cleave P_{21} involved in linking DNA duplication to cell division resulting in a polyploid cell and oncogenesis.

We have been able to demonstrate neuronal degeneration and apoptosis in the digoxin injected rat brain. Thus in the hyperdigoxinemic right hemisphere dominant state there is a defect in mitochondrial function and increased free radical generation and reduced scavenging. There is also increased apoptosis.

The concentration of ubiquinone increased significantly in right handed / left hemispheric dominant individuals which may be the result of increased tyrosine levels, consequent to digoxin deficiency promoting tyrosine transport over tryptophan. The decrease in intracellular calcium can stabilise the mitochondrial PT pore and improve mitochondrial function. Intracellular magnesium excess can lead to an increase in the activity of ATP synthase. All this leads to improved efficiency in mitochondrial oxidative phosphorylation and reduced free radical generation. Ubiquinone excess also leads to increased free radical scavenging. The decrease in intracellular calcium may lead to decreased generation of NO by inhibiting the enzyme nitric oxide synthase and reduced peroxynitrite formation. Decreased calcium also can inhibit phospholipase. A_2 resulting in decreased generation of arachidonic acid and free radical formation. Decreased generation of free radicals like the superoxide ion and hydroxyl radical can stabilise the cell membrane and stimulate membrane Na^+-K^+ ATPase. There was decrease in lipid peroxidation as evidenced from the decrease in the concentration of MDA, conjugated dienes, hydroperoxides and NO with increased antioxidant protection as indicated by increase in ubiquinone and increased reduced glutathione in hypodigoxinemic left hemisphere dominant individuals. The activity of enzymes involved in free radical scavenging like superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase is increased suggesting increased free radical scavenging. The peroxisomal membrane is stabilised owing to membrane Na^+-K^+ ATPase stimulation related alteration in membrane formation and this leads to increased catalase activity. Glutathione is synthesized by the enzyme glutathione synthetase, which needs magnesium and ATP. The

high intracellular magnesium consequent to Na^+-K^+ ATPase stimulation and the resulting increased ATP can result in increased synthesis of glutathione. Glutathione peroxidase, a selenium containing enzyme oxidases reduced glutathione (GSH) to oxidised glutathione (GSSG) which is rapidly reduced to GSH by glutathione reductase. There is also a concomitant conversion of H_2O_2 to H_2O. The activity of glutathione reductase needs NADPH for the regeneration of GSH. This NADPH comes mostly from the pentose phosphate pathway. Intracellular magnesium excess due to membrane Na^+-K^+ ATPase stimulation leads to increased formation of glucose 6-phosphate and upregulation of the pentose phosphate pathway with consequent increased generation of NADPH. Thus glutathione system of free radical scavenging is activated in the presence of membrane Na^+-K^+ ATPase stimulation. Superoxide dismutase exists in a mitochondrial and cytoplasmicform. The stabilisation of the mitochondrial PT pore consequent to reduced intracellular calcium produces increased efficiency of superoxide dismutase activity. The increase in catalase, superoxide dismutase (SOD), glutathione peroxidase and glutathione reductase suggests increased free radical protection. This leads to decreased incidence of neuronal degeneration and oncogenesis in the hypodigoxinemic individuals. Free radicals are required for lymphocyte activation and this leads to a hypoimmune response and increased respiratory infection owing to immunodeficiency. The decreased intracellular calcium and ceramide related stabilisation of the mitochondrial PT pore also leads to down regulation of the apoptotic program and reduced apoptosis. The stabilisation of the mitochondria leads to reduced release of apoptosis inducing factor and cytochrome C into the cytoplasm. This results in inactivation of caspase-9 and caspase-3. Inhibition of apoptosis protects against neuronal aging. Caspase-3 inactivation inhibits P_{21} cleavage and protects against oncogenesis. Thus the hypodigoxinemic left hemisphere dominant state has improved

efficiency of mitochondrial oxidative phosphorylation, reduced generation of free radicals, increased free radical scavenging and reduced apoptosis.

Endosymbiotic Archaeal Digoxin and Immunoregulation - Relation to Cerebral Dominance

In left handed / right hemispheric dominant individuals 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. TNF alpha binds to its receptor TNFR1 and activates the transcription factors NFKB and AP-1 leading to the induction of proinflammatory and immunomodulatory genes. This can also explain the immune activation in MS. TNF alpha can also bring about apoptosis of the cell. It binds to its receptor and activates caspase-9, an ICE protease which converts IL-1 beta precursor to IL-1 beta. IL-1 beta produces apoptosis of the neurons (in Alzheimer's disease and AIDS dementia), the oligodendrocyte - the myelin forming cell in MS and the CD_4 cell in HIV infection. IL-1 beta and TNF alpha induce HIV protein expression by transcription related mechanism and contributes to the pathogenesis of AIDS dementia. Similar digoxin mediated immune activation can play a role in migraine, interstitial lung disease, sarcoidosis, bronchial asthma, inflammatory bowel disease, nephrotic syndrome and immune complex diseases like SLE. 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. The hyperdigoxinemic right hemisphere dominant state results in immune activation.

In the hypodigoxinemic left hemisphere dominant state decreased intracellular calcium inactivates the calcium dependent calcineurin signal transduction pathway involved in T-cell activation and resulting in decreased secretion of interleukin - 3, 4, 5, 6 and TNF alpha. TNF alpha can also bring

about apoptosis of the cell and this is inhibited. Low levels of TNF alpha can lead to immunosuppression. This can explain the immunosuppression and increased rate of respiratory infection. In the hypodigoxinemic left hemisphere dominance there is a tendency for immunosuppression.

Endosymbiotic Archaeal Digoxin and Regulation of Cell Division, Genomic Function, Cell Proliferation and Neoplastic Transformation - Relation to Cerebral Dominance

Intracellular magnesium depletion can a produce defective phosphorylation of MAP (microtubule associated proteins). This results in defective microtubule related spindle fibre dysfunction and chromosomal non-disjunction probably contributing to trisomy 21 and polyploidy. Intracellular magnesium depletion can lead on to defect in the proof reading function of DNA polymerase. This leads on to the genesis of trinucleotide repeats in Huntington's disease. In intracellular magnesium deficiency there is also defective protein transcription owing to ribosomal dysfunction. Thus the hyperdigoxinemic state is associated with genomic instability owing to the intracellular hypomagnesemia it produces. The reverse holds good for the hypodigoxinemic left hemisphere dominant state. Because of increase in intracellular magnesium there is genomic stability.

In the hyperdigoxinemic right hemisphere dominant state 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 tumours suppressor gene P_{53}. The activation of P_{53} is impaired owing to intracellular

magnesium deficiency producing a phosphorylation defect. Upregulation of isoprenoid pathway can result in increased production of farnesyl phosphate which can farnesylate the ras oncogene producing its activation. Ubiquitin system of catabolic processing of processing of proteins is important in DNA repair mechanism. In the presence of intracellular magnesium deficiency ubiquitin protein catabolic processing and DNA repair mechanisms are defective and this could contribute to oncogenesis. In the hyperdigoxinemic right hemisphere dominant state there is oncogene activation and increased cell proliferation.

In the hypodigoxinemic left hemisphere dominant state high intracellular magnesium and low intracellular calcium consequent to Na^{+}-K^{+} ATPase stimulation appears to be crucial to protection against oncogenesis. Decreased intracellular calcium inactivates phospholipase C beta which results in decreased production of diacyglycerol with resultant inactivation of protein kinase C. The protein kinase C activation of the MAP kinase cascade is inhibited resulting in blockade of cellular proliferation. The increased intracellular magnesium can produce increase in the GTPase activity of the alpha-subunit of G-protein. This results in ras oncogene inactivation, as more of the ras is bound to GDP rather than GTP. Phosphorylation mechanisms required for the activation of the tumour suppressor gene P_{53} is increased owing to intracellular magnesium excess producing increased phosphorylation. Downregulation of isoprenoid pathway can result in decreased production of farnesyl phosphate, which is required for ras oncogene activation. Therefore the ras oncogene is inactivated. In the hypodigoxinemic left hemisphere dominant state there is a tendency for oncogene inactivation and inhibition of cellular proliferation.

Endosymbiotic Archaeal Digoxin and the Metabolic Regulation - Relation to Cerebral Dominance

In the hyperdigoxinemic right hemisphere dominant state there is inhibition of Na^+-K^+ ATPase, which can explain the pathogenesis of syndrome X. Increased TNF alpha as mentioned above consequent to Na^+-K^+ ATPase inhibition related T-cell activation can contribute to insulin resistance in syndrome X at the receptor level. Decrease in intracellular magnesium can block the phosphorylation reactions involved in protein tyrosine kinase receptor activity leading to insulin resistance. Increase in beta cell calcium can contribute to increased insulin release from beta cells and hyperinsulinemia. Increased intracellular calcium can activate the G-protein coupled signal transduction of the contra insulin hormones (growth hormone and glucagon) leading to hyperglycemia. Decreased intracellular magnesium can lead on to a mitochondrial ATP synthase defect. Increased intracellular calcium can open up the mitochondrial PT pore, disrupt the hydrogen gradient across the inner membrane and block mitochondrial oxidative phosphorylation. Also this leads to defective glucose utilization and hyperglycemia. Increase in intracellular calcium can activate 0-protein coupled angiotensin receptor producing hypertension and G-protein coupled thrombin receptor and platelet activating factor producing thrombosis observed in syndrome X. Na^+-K^+ ATPase inhibition related increased smooth muscle calcium and decreased magnesium can contribute to vasospasm and ischaemia observed in stroke, coronary artery disease and mesenteric artery occlusion. Na^+-K^+ ATPase inhibition related altered glycoprotein and GAG can contribute to the microangiopathy and macroangiopathy observed in syndrome X. Metabolic syndrome X could be visualised as due to hypothalamic archaeal digoxin hypersecretion. In hypomagnesemia there is inhibition of lipoprotein lipase and decrease catabolism of triglyceride rich lipoprotein resulting in hypertriglycerdemia.

Also magnesium deficiency leads to inhibition of lecithin cholesterol acyl transferase (LCAT) producing decreased formation of cholesterol esters in HDL. This leads on to the dyslipidemia of syndrome X with elevated triglyceride and low HDL cholesterol levels. Digoxin induced hyperinsulinemia and hypertriglyceridemia produces the trunkal obesity in syndrome X. In the hyperdigoxinemic right hemisphere dominant state glucose metabolism and utilisation is impaired consequent to insulin resistance as also there is a tendency for vasospasm and thrombosis.

In the hypodigoxinemic left hemisphere dominant state stimulation Na^+-K^+ ATPase can also lead to metabolic abnormalities. Hypermagnesemia consequent to membrane Na^+-K^+ ATPase stimulation can lead on to increased cell membrane transport of glucose. Increase in intracellular magnesium can activate the phosphorylation reactions involved in protein tyrosine kinase receptor activity leading to increased insulin receptor activity. Increase in intracellular magnesium can lead on to stimulation of glycolysis causing increased glucose utilization. Decrease in intracellular calcium can stabilise the mitochondrial PT pore and stimulate mitochondrial oxidative phosphorylation. Intracellular magnesium excess can also lead to a ATPase synthase hyperactivity. This leads to increased glucose utilisation. Decrease in beta cell calcium can contribute to decreased insulin release from beta cells and hypoinsulinemia. Hypermagnesemia has been reported to markedly decreased glucose stimulated insulin Secretion by the perfused pancreas. Increased intracellular magnesium can produce hyperactivity of lipoprotein lipase producing increased catabolism of triglycerides rich lipoproteins and hypotriglyceridemia. In hypermagnesemia lecithin cholesterol acyl transferase is activated and there is increased formation of cholesterol esters in HDL. This results in increased HDL cholesterol. Magnesium excess has been reported to decrease LDL cholesterol levels also. Low insulin levels and increased

triglyceride catabolism can be correlated with low body mass index. Decreased in intracellular calcium can inactivate the G-protein coupled angiotensin receptor producing hypotension and the G-protein coupled thrombin receptor and platelet activating factor producing decreased thrombosis observed in hypodigoxinemic state. Increased intracellular magnesium can lead to decreased thrombin and ADP/collagen induced platelet aggregation. Na^+-K^+ ATPase stimulation related decreased smooth muscle calcium and increased magnesium can contribute to vasodilatation and protect from ischaemia due to stroke and coronary artery disease. This can also lead on to a hypotensive state and familial hypotension. Na^+-K^+ ATPase stimulation induced hypermagnesemia related altered glycoprotein and glycosaminoglycan synthesis can contribute to the decreased atherosclerosis. Thus in the hypodigoxinemic left hemisphere dominant state there is increased efficiency of mitochondrial oxidative phosphorylation, increased glucose utilisation with hypercatabolism of triglyceride rich lipoproteins low body mass index and decreased vascular thrombosis. This leads on healthy aging. In the left hemisphere dominant hypodigoxinemic state there is an endogenous morphine excess syndrome. Morphine has been reported to have an effect on glucose metabolism. In mice, subcutaneous administration of morphine has been shown to produce a dose-dependent hyperglycemia, while intrathecal administration of much lower concentration in the lumbar region caused a dose dependent hypoglycemia. These effects are thought to be due to an insulin independent mechanism mediated through spinal opiate and central alpha-adrenergic receptor stimulation. The effect of morphine on pancreatic glucagon release has been hypothesized to result from suppression of somatostatin and concurrent release of the alpha cell from tonic inhibition leading to an increase in glucagon secretion. Glucagon is the most potent mediator of morphine induced hyperglycemia. Morphine can regulate insulin release from the beta cells with

both an inhibitory effect and stimulatory effect being reported. Morphine induced hyperglycemia would involve activation of pituitary adrenal axis, endocrine pancreas and endogenous opioid peptides. Morphine can also act as a vasodilator contributing to hypotension. Morphine has also got an immunosuppressive action. This could contribute to increased incidence of respiratory infections in the left hemispheric dominant state.

Endosymbiotic Archaeal Digoxin and Regulation of the Immune Response to Viral Infection - Relation to Cerebral Dominance

The same biochemical Na^+-K^+ ATPase related cascade described above could contribute to the acquired immunodeficiency syndrome in hyperdigoxinemic right hemisphere dominant state. There is increased incidence of neoplasms like non-Hodgkin's lymphomas and vasculitis in the acquired immunodeficiency syndrome. Neuronal degenerations like AIDS dementia has been related to glutamate excitotoxicity. An AIDS related schizophreniform psychosis has been described. Polyclonal beta-cell proliferation and lymphadenopathy have been described in AIDS. Digoxin induced calcineurin signal transduction mediated T-cell activation and polyclonal B-cell proliferation can contribute to HIV-l replication. Digoxin induced T-cell activation can lead on to a secretion of TNF-alpha which induces the immunomodulatory transcription factor NFKB. Chief among the inducible cellular proteins that promote the growth of HIV-l is transcription factor NFKB. HIV-l has incorporated two such NFKB binding-enhancer elements into its own genome, which allows the triggering of HIV-l transcription in the presence of nuclear NFKB. Digoxin induced protein glycosylation defects can also lead to defective glycosylation of HIV glycoprotein antigens leading on to defective formation of HIV glycoprotein antigen-MHC complex for presentation to CD_4 cell. This results in immune evasion by the virus and could also contribute to the persistence of herpes virus

and ebstein barr virus producing Kaposi's sarcoma and non-Hodgkin's lymphoma respectively. In hyperdigoxinemia the intracellular magnesium excess results in Z to B transition of DNA and defective methylation of DNA bases leading on to retroviral transposon expression. Hypothalamic structural abnormalities have been described in homosexuals predisposed to the development of acquired immunodeficiency syndrome. In the hyperdigoxinemic right hemisphere dominant state there is a tendency for viral persistence consequent to defective processing of viral proteins and defective immune response to the virus.

Modulation of the hypo - and hyperdigoxinemic state Treatment of hyperdigoxinemic state:

(1) Digoxin antibodies

(2) HMG CoA reductase inhibitors

(3) Polyphenolic compounds

(4) Free radical scavengers (Vitamin F, Co-enzyme Q, selenium, Vitamin C)

(5) Magnesium supplementation

(6) Taurine and tyrosine supplementation

(7) Vanadium supplementation

(8) Yoga and Reiki healing

(9) Visualisation therapy

(10) High fibre high medium chain triglyceride diet

(11) Use of pulse magnetic fields TMF: the pulse magnetic fields used is of the order 400-800 nT which is only a small fraction of the earth's magnetic fields which is about 100000 nT. This leads on to membrane

Na^+-K^+ ATPase stimulation and increase in intracellular magnesium and a reduction.

(12) Addition ofphospholipid

(13) Electro convulsive therapy

(14) Pranayama - Left nasal breathing

Treatment of the hypodigoxinemic state:

(1) Digoxin therapy

(2) Lithium therapy

(3) Addition of drugs to increase cholesterol synthesis - saturated fats

(4) Addition of cholesterol

(5) Cryo therapy

(6) Pranayama - right nasal breathing

References

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

GLOBAL WARMING

and Symbiotic Evolution of Species

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