Ravikumar Kurup & Parameswara Achutha Kurup

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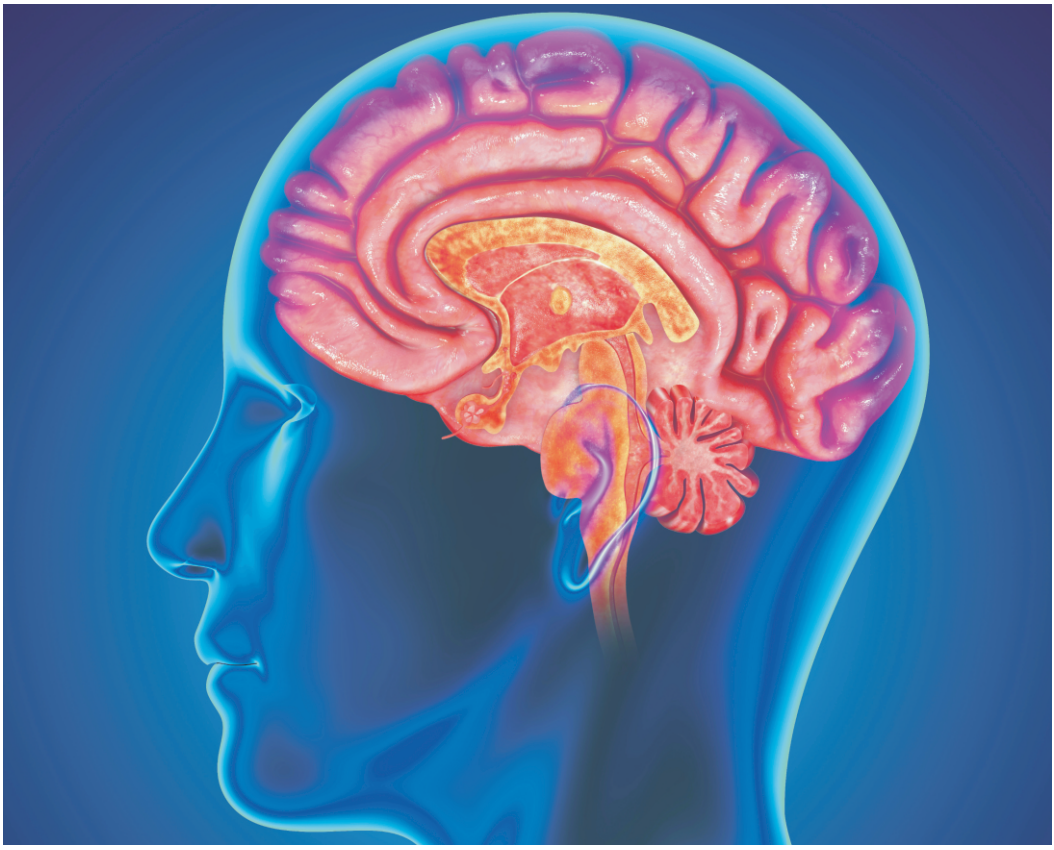

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The Endosymbiotic Archaea, Fructose Disease, Chronic Neurological Disease and Global Warming - Human Genomic Archaeal-Viroidal Sequences and Neurological Disease

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

with GABA shunt pathway and porphyrinogenesis are called porphyrinoids. The archaeaon colony forms a network with different areas showing differential specialization of function - fructosoids, steroidelle, vitaminocyte, viroidelle, neurotransminoid, porphyrinoids and glycosaminoglycoids. This forms a living organized structure within human cells and tissues regulating their function and reducing the human body to zombie working under the directions of the organized archaeal colony. The organized archaeal colony has abiogenetic replication and is eternal.

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

The endosymbiotic actinidic archaea forms the basis of life and can be considered as the third element in the cell. It regulates the cell, the neuro-immune-endocrine system and the conscious / unconscious brain. The endosymbiotic actinidic archaea can be called as the elixir of life. A definite population of endosymbiotic actinidic archaea is required for the existence and survival of life. A higher density of endosymbiotic actinidic archaeal population can lead to human disease. Thus actinidic archaea are important for survival of human life and can be considered as crucial to it. Symbiosis by actinidic archaea is the basis of evolution of humans and primates. The increase in endosymbiotic archaeal growth can lead to the induction of homo neanderthalis. This endosymbiotic archaea induced neanderthalisation of the species leads to human disease like metabolic syndrome X, neurodegenerations, schizophrenia and autism, autoimmune disease and cancer. The reduction in endosymbiotic archaeal growth by a high fibre, high medium chain triglyceride and legume protein ketogenic diet, antibiotics from higher plants like Curcuma longa, Emblica officianalis, Allium sativum, Withania somnifera, Moringa pterygosperma and Zingeber officianalis and transplantation of colonic microflora from normal homo sapien population can lead to deneanderthalisation of species and treatment of the above mentioned diseased states. The colonic microflora of neanderthalised diseased states like metabolic syndrome X, neurodegenerations, schizophrenia and autism, autoimmune disease and cancer when transferred to the normal homo sapien species leads to generation and induction of homo neanderthalis. Thus primate and human evolution is symbiotic event which can be induced the modulating symbiotic archaeal growth. Human populations can be divided into matrilineal Neanderthal population in South Indian Dravidians, Celts, Basques, Jews and Berbers and the Cro-Magnon population seen in Africa and Europe. The symbiotic archaeal colonization decides which species - Neanderthal or

Cro-Magnon to which the society belongs to. It is tempting to postulate symbiotic microflora and archaea determining the family behavior and traits as well as societal and caste behavior and traits. The cell has been postulated by Margulis to be a symbiotic association of bacteria and viruses. Similarly, the family, the caste, the community, nationalities and the species itself is determined by archaeal and other bacterial symbiosis.

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

endosymbiotic archaeal growth determines the racial differences between the matrilineal Harappan / Dravidian societies and the patriarchal Aryan society. The matrilineal Harappan / Dravidian society was neanderthalic and had increased endosymbiotic archaeal growth. Endosymbiotic archaeal growth and neanderthalisation can lead to autoimmune disease, metabolic syndrome X, neurodegeneration, cancer, autism and schizophrenia. The Neanderthal gut flora and endosymbiotic archaea was determined by the non vegetarian ketogenic high fat high protein diet consumed by them in the Eurasian steppes. The homo sapiens including the classical Aryan tribes and African ate a high fibre diet and had lower archaeal growth both endosymbiotic and gut. The dietary fibre intake determines the microbial diversity of the gut. The high fibre intake is associated with increased generation of short chain fatty acids - butyric acid by the gut flora. Butyrate is a HDAC inhibitor and leads to increased generation and incorporation of endogenous retroviral sequences. The high dietary fibre intake related increased HERV sequences leads to increased synaptic connectivity and a dominant frontal cortex as seen in homo sapien species. The neanderthalic species consume a ketogenic non vegetarian high fat high protein low fibre diet. This leads to decreased generation of endogenous HERV sequences and reduced genomic flexibility in neanderthalic species. This produces smaller cerebral cortex and a dominant cerebellar cortex in the neanderthalic brain. The homo neanderthalic species by the low dietary fibre intake starve their microbial self. This leads to increased endosymbiotic and gut archaeal growth. The mucous membrane lining the gut becomes thinned out as the gut bacteria eats up the mucous lining of the gut. This results in leakage of endotoxin and archaea from the gut to the blood breaching the barrier and produces a chronic immunostimulatory inflammatory state which forms the basis of autoimmune disease, metabolic syndrome, neurodegeneration, oncogenic and psychiatric disorders. The Neanderthal species eat a low fibre diet and have a deficiency of

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

experimentally induced. Symbiotic microflora drives evolution. Every animal, every human species, different communities, different races and different caste have their signature endosymbiotic and gut microflora which can be transmitted vertically and horizontally. Thus symbiosis drives human and animal evolution.

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

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

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

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

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

The roots of Western civilisational disease can be related to the starvation of the colonic microflora. The colonic microflora depends upon complex carbohydrates derived from dietary fibre. The processed food of high protein, fat and sugars is digested and absorbed in the stomach and small intestine. A very little of it reaches the colon and widespread use of antibiotics in medicine has produced mass extinction of the colonic microflora. The colonic microflora is extremely diverse and the diversity is lost. There are 100 trillion bacteria in the colon belonging to 1200 species. They regulate the immune system by

inducing the T-regulatory cells. A high fibre diet contributes to colonic microbiota diversity. Interaction with farm animals like cows and dogs also contributes to the colonic microflora diversity. The typical Western diet of high fat, high protein and sugars decreases the colonic microbiota diversity and increase colonic/endosymbiotic archaea producing methanogenesis. The colonic archaea feed upon the mucous lining of the colon and produces leakage of archaea into the blood and tissue system producing endosymbiotic archaea. This results in a chronic inflammatory state. The high fibre diet of Africans, South Americans and Indians produces increased colonic microbiota diversity and increase in clostridial clusters generating SCFA in the gut. High fibre diet is protective against metabolic syndrome and diabetes mellitus. Metabolic syndrome is related to degeneration, cancer, neuropsychiatric illness and autoimmune disease. A high fibre diet of upto 40 g/day can be called as a gut diet. The colonic microflora especially the clostridial cluster digests the fibre generating short chain fatty acids which regulates immunity and metabolism. High fibre diet increases the colonic mucus secretion and the thickness of the mucus lining. A high fibre diet produces increase in clostridial clusters and mucous secretion. This produces a strong gut blood barrier and prevents metabolic endotoxemia which produces a chronic inflammatory response. High dietary fibre intake and the diversity of the colonic microflora with prominent SCFA producing clostridial clusters are interrelated. The clostridial clusters metabolise the complex carbohydrate in dietary fibre to short chain fatty acids butyrate, propionate and acetate. They increase the T-regulatory function. A high fibre diet increases the bacteroides and reduces the firmecutes of the colonic microflora. A high fibre diet is associated with a low body-mass index. A low fibre diet produces increase in colonic archaeal growth as well as endosymbiotic tissue and blood archaea. This produces more of methanogenesis rather than short chain fatty acid synthesis contributing to immune activation. A

low fibre diet is associated a high body-mass index and chronic systemic inflammation. Germ-free mice show cardiac, pulmonary and liver atrophy. Gut microflora is required for the generation of organ systems. The gut microflora is also required for generation of T-regulatory cells. High fibre intake produces more colonic microbiota diversity and increase in clostridial clusters and fermentation by products like butyrate which suppresses inflammation and increases T-regulatory cells. A low fibre diet produces increase in archaeal growth, methanogenesis, destruction of the mucus lining and leakage of the colonic archaea producing endosymbiotic tissue and blood archaea. This produces an immune hyperreactivity contributing to the modern plagues of civilization - metabolic syndrome, schizophrenia, autism, cancer, autoimmunity and degenerations. The gut microbiota drives human evolution. The humans don't host the gut microbiota but the gut microbiota host us. The human system forms an elaborate culture laboratory for the propagation and survival of the microbiota. The human system is induced by the microbiota for their survival and growth. The human system exists for the microbiota and not the other way round. The same mechanism holds good in plant systems. Plant started the colonized earth as they started symbiosing with bacteria in the roots systems which can derive nutrients from the soil. Human beings form a mobile culture laboratory for the more effective propagation and survival of the microbiota. The microbiota induces the formation of specialized immune cells called innate lymphoid cells. The innate lymphoid cells will direct the lymphocytes not to attack the beneficial bacteria. Thus the endosymbiotic archaea and the gut archaea induce human, primate and animal evolution to generate structures for them to survive and propagate. The source of endosymbiotic archaea, the third element of life is the colonic archaea that leaks into the tissue spaces and blood systems due to breach in the gut blood barrier. The increase in colonic archaea is due to the starvation of the gut microbiota consequent to a low fibre diet. This

results in increase in colonic archaeal growth and destruction of clostridial clusters and bacteroides. The increase colonic archaeal growth in the presence of gut starvation due to low fibre diet eats up the mucus lining and produces breakages in the gut blood barrier. The colonic archaea enters the blood stream and produces endosymbiosis generating endosymbiotic archaea and various new organelle - fructosoids, steroidelle, vitaminocyte, viroidelle, neurotransminoid, porphyrinoids and glycosaminoglycoids.

The human brain can be considered as a modified archaeaon colony network. The archaeaon are eternal and can last for billions of years. The human brain is basically an information storage system. The archaeaon has got dipolar magnetite and porphyrins and can function as quantal computer. The archaeal colony with its dipolar magnetite and porphyrin in the setting of archaeal digoxin induced membrane sodium potassium ATPase inhibition can function as a pumped phonon system mediating quantal perception. The archaeaon in the brain is capable of information storage at a point in time and space. The experiences and information stored in the archaeaon is immortal and eternal. The archaeaon can have a wave particle existence and can exist in multiple quantal possible states and can inhabit multiple quantal multiverses. The interaction between information stored in quantal computers in multiple different archaeaon systems all over the universe by the quantal interactions results in eternal existence of information in quantal multiverses. The information in the quantal multiverses can have a particulate existence creating a newer mode by quantal interactions between information stored at multiple points of time. This creates the particulate mythic world of human existence. These are what are called as Samsaras. The mind is uploaded into information in the neuronal archaeal colony network and its quantal computers. The information stored in the archaeal colony network mediated quantal state is eternal and can be considered as a digital version of the brain, a mind

downloading technique or whole brain emulation. The archaeal colony network stores the human experiences in an eternal manner and can contribute to biological reincarnation.

The gut bacteria can regulate learning, memory and emotional behavior. The gut bacteria regulate neuronal development, brain chemistry, stress systems and pain perception. 95% of the brain serotonin is derived from the gut. Fecal transplantation from anxious mice to bold adventurous mice alters the behavior of mice from anxious to bold. The gut microbial transfer can produce behavioral alterations. Camylobacter jejuni is associated with anxiety behavior. Lactobacilous rhamnosus increases GABA receptor density in the brain and is associated with depression. Vagotomy abolishes this gut bacteria mediated responses. In germ-free mice there is increase in the stress hormones corticosterone and ACTH. Short chain fatty acids derived from fibre degradation by gut bacteria abolishes its response. Gut bacteria has been implicated in the etiology of schizophrenia, autism, depression, anxiety and neuronal degeneration. The gut immune cells mediated cytokine response in relation to gut bacteria also modulates the central nervous system. The gut bacteria generated butyrate can strengthen the blood brain barrier. The gut clostridia increases serotonin production and microbial metabolites can increase serotonin production from the colonic cells. Thus the gut bacteria can regulate neurogenesis, the blood brain barrier and microglyl activation. Germ-free mice grow more neurons in specific brain areas. Germ-free mice are resistant to EAE. The vaginal microflora of the mother can regulate the stress response in the baby. Thus the gut microflora and endosymbiotic archaea can regulate all aspects of brain function. A high fibre diet decreases colonic archaea and increases the clostridial clusters generating butyrate. This produces the homo sapien brain with its dominant cerebral cortex. The butyrate generated produces HDAC inhibition and HERV expression. HERV acts as jumping genes and

provides the genomic basis for the complex connectivity of the cerebral cortex. A high fibre diet decreased archaeal colonic and endosymbiotic density results in decreased formation of digoxin and decreased neuronal membrane sodium potassium ATPase inhibition contributing to the sapien brain. A low fibre diet increases colonic and endosymbiotic archaeal density contributing to reduced butyrate generation, HDAC inhibition and reduced generation of HERV sequences. This decreases the cerebral cortical size and produces a neanderthalised brain with a dominant cerebellar cortex. The low fibre diet with reduced archaeal growth results in decreased digoxin synthesis and a neanderthalised brain. A low fibre diet removes the butyrate mediated protection of the gut blood and brain blood barrier contributing to increased entry of endosymbiotic archaea into the tissue spaces, brain and blood. This leads onto the genesis of the neanderthalised brain.

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

called fructosoids. The fructose is phosphorylated to fructose 1-phosphate which is acted upon by aldolase B which converts it into glyceraldehyde 3-phosphate and dihydroxy acetone phosphate. Glyceraldehyde 3-phosphate is converted to D1,3-biphosphoglycerate which is then converted to 3-phosphoglycerate. The 3-phosphglycerate is converted to 2-phosphoglycerate. 2-phosphoglycerate is converted to phosphoenol pyruvate by the enzyme enolase. Phosphoenol pyruvate is converted to pyruvate by the enzyme pyruvic kinase. The archaeaon induces HIF alpha which upregulates fructolysis and glycolysis but inhibits pyruvate dehydrogenase. The forward metabolism of pyruvate is stopped. The dephosphorylation of phosphoenol pyruvate is inhibited in the setting of pyruvic kinase inhibition. Phosphoenol pyruvate enters the shikimic acid pathway where it is converted to chorismate. The shikimic acid is synthesized by a pathway starting from glyceraldehyde 3-phosphate. Glyceraldehyde 3-phosphate combines with the pentose phosphate pathway metabolite sedoheptulose 7-phosphate which is converted to erythrose 4-phosphate. The pentose phosphate pathway is upregulated in the presence of the suppression of glycolytic pathway. Erythrose 4-phosphate combines with phosphoenol pyruvate to generate shikimic acid. Shikimic acid combines with another molecule of phosphoenol pyruvate to generate chorismate. The chorismate is converted to prephenic acid and then to parahydroxy phenyl pyruvic acid. Parahydroxy phenyl pyruvic acid is converted to tyrosine and tryptophan as well as neuroactive alkaloids. The shikimic acid pathway is structured in expressed archaeaon organelle called the neurotransminoid. The fructolytic intermediates glyceraldehydes 3-phosphate and pyruvate are the starting points of the DXP pathway of cholesterol synthesis. Glyceraldehyde 3-phosphate combines with pyruvate to form 1-deoxy D-xylulose phosphate (DOXP) which is then converted to 2C methyl erythritol phosphate. 2C methyl erythritol phosphate can be synthesized from erythrose 4-phosphate a

metabolite of the shikimic acid pathway. DXP combines with MEP to form isopentenyl pyrophosphate which is converted to cholesterol. Cholesterol is 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, ribonuceloproteins, islet associated amyloid polypeptide and tumour suppressor protein can lead to an epidemic of Alzheimer's disease due to beta amyloid accumulation, alpha synuclein accumulation producing Parkinson's disease, prion like ribonucleoproteins producing motor neuron disease, metabolic syndrome X due to defective insulin secretion as a result of IAPP and abnormal prion like tumour suppressor protein producing tumours. These prion diseases induced by archaeal RNA viroids are also transmissible. Thus global warming related fructolysis leads to archaeal induced RNA viroidal mediated prion disease and amyloidosis. This raises the spectacle of a Cassandra syndrome of human extinction.

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

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

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

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

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

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

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

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

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

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

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

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

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

Table 1

	Serum fructose		Serum fructokinase		Aldolase B		Total GAG	
	Mean	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**
Normal	2.50	0.195	8.50	0.405	3.50	1.304	3.50	0.707
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
Epilepsy	32.24	5.864	20.46	2.864	9.82	1.135	21.42	2.662
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
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
Epilepsy	262.70	30.324	0.83	0.091	8.04	0.667	1.55	0.493
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
AD	0.38abc	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
Epilepsy	0.47	0.151	17.59	2.469	1.44	0.270
F value	14.091		21.073		58.769	
p value	< 0.01		< 0.01		< 0.01	

References

[1] Kurup RK, Kurup PA. *Global Warming, Archaea and Viroid Induced Symbiotic Human Evolution and the Fructosoid Organelle*. New York: Open Science, 2016.

2

Archaeal Digoxin and Alzheimer's Disease

Introduction

Changes involving the isoprenoid pathway have been described in neuronal degeneration. Mitochondrial dysfunction particularly involving ubiquinone has been reported in platelet mitochondria in Alzheimer's disease (AD). Altered levels of dolichol in the brain and altered glycoproteins like beta amyloid have been reported in Alzheimer's disease. Dolichol and ubiquinone are both products of the isoprenoid pathway. Sodium potassium ATPase inhibition has been reported to lead to neuronal degeneration. An endogenous inhibitor of Na^{+}-K^{+} ATPase archaeal digoxin is produced by the isoprenoid pathway. It was therefore considered pertinent to study the isoprenoid pathway in Alzheimer's disease.

Archaeal digoxin induced membrane Na^{+}-K^{+} ATPase inhibition can produce Mg^{++} depletion leading on to altered glycoconjugate metabolism. The dolichol pathway can regulate N-glycosylation of glycoproteins. Alteration in glycoconjugate metabolism has also been described in neuronal degeneration. Amyloid and hyperphosphorylated tau protein in Alzheimer's disease are defectively processed proteins resistant to the action of proteases. Accumulation of heparan sulphate proteoglycan (HS-PG) and its interaction with beta amyloid precursor protein (beta APP) have been suggested as a possible mechanism for amyloid plaque formation in Alzheimer's disease. Glycolipids like ceramide can produce cell death by opening up the mitochondrial PT pore and contribute to neuronal degeneration and aging.

Archaeal digoxin can alter intracellular Ca^{++}/Mg^{++} ratios in the cell leading on to free radical generation. Alteration in the ubiquinone pathway can also lead to mitochondrial dysfunction and free radical generation. Free radical mechanisms have been implicated in the pathogenesis of the major neurodegenerative disorders like Alzheimer's disease. An altered free radical defence mechanism like decreased levels of antioxidant enzymes and

antioxidants has been suggested for the free radical damage in Alzheimer's disease. Increased formation of NO which forms peroxynitrite with superoxide promoting lipid peroxidation has also been reported in neurodegeneration.

Archaeal digoxin has been reported to regulate the transport of amino acids especially the neutral amino acids. Abnormalities in tryptophan catabolism and the kynurenine pathway have been described in neuronal degeneration. Of the kynurenines, quinolinic acid is most relevant to neurodegenerative disease. Quinolinic acid toxicity in the brain appears to be mediated through its action as an agonist of the NMDA receptor. Neurotoxicity induced by quinolinic acid occurs preferentially in the neocortex, striatum and hippocampus in the brain. The neurotoxic effects of quinolinic acid are mediated via the magnesium sensitive NMDA receptor.

Membrane abnormalities have been described in neurodegenerative disorders. In Alzheimer's disease alteration in membrane fluidity especially of the platelet membrane has been reported. The isoprenoid pathway produces four metabolites important in maintaining cell membrane structure and function - digoxin (a membrane Na^+-K^+ ATPase inhibitor), dolichol (involve in N-glycosylation of proteins), ubiquinone (a membrane antioxidant) and cholesterol.

Global warming can lead to osmotic stress consequent to dehydration. The increase in actinidic archaeal growth leads to cholesterol catabolism and digoxin synthesis. Digoxin produces membrane sodium potassium ATPase inhibition and increase in intracellular calcium producing mitochondrial dysfunction. This results in oxidative stress. The oxidative stress and osmotic stress can induce the enzyme aldose reductase which converts glucose to fructose. Fructose has got a low km value for ketokinase as compared to glucose. Therefore fructose gets phosphorylated more to fructose phosphate and the cell is depleted of ATP. The

cell depletion of ATP leads to oxidative stress and chronic inflammation consequent to induction of NFKB. Oxidative stress can open the mitochondrial PT pore producing release of cyto C and activation of the caspase cascade of cell death. The fructose phosphate can enter the pentose phosphate pathway synthesizing ribose and nucleic acid. The depletion of cellular ATP results in generation of AMP and ADP which are acted upon by deaminases causing hyperuricemia. Uric acid can produce endothelial dysfunction and vascular disease. Uric acid can also produce mitochondrial dysfunction. The fructose phosphate can enter the glucosamine pathway synthesizing GAG and producing mucopolysaccharide accumulation. Fructose can fructosylate proteins making them antigenic and producing an autoimmune response. This can lead to global warming related neurological disease.

This study was undertaken to assess (1) the isoprenoid pathway, (2) the tryptophan/tyrosine catabolic patterns, (3) glycoconjugate metabolism, and (4) RBC membrane changes as a reflection of neuronal membrane change in Alzheimer's disease. A hypothesis implicating neuronal membrane Na^+-K^+ ATPase inhibition as pivotal to all these changes in Alzheimer's disease is also presented. Since digoxin can regulate multiple neurotransmitter systems it could possibly play a role in the genesis of cerebral dominance. The isoprenoid pathway and digoxin status was studied in individuals of differing hemispheric dominance in order to elucidate the role of cerebral dominance in the pathogenesis of Alzheimer's disease.[1-8]

Methods

Fifteen cases of Alzheimer's disease were chosen randomly for the study from the medicine and neurology wards of Medical College, Trivandrum. The lCD-10 criterion was chosen for the purpose of the study. The age of the patients ranged from 50 to 70 years. None of the subjects studied was under

medication at the time of removal of blood. All the patients included in the study were non-smokers (passive and active). They were free from other systemic diseases like hypertension, diabetes, renal and hepatic disease. An equal number of age and sex matched healthy subjects served as controls.

15 normal male healthy individuals (50-70 years of age) each of the left handed/right hemispheric dominant, right handed/left hemispheric dominant and amphidextrous / bihemispheric dominant individuals diagnosed by the dichotic listening test were chosen for the study. This group was chosen at random from the general population of Trivandrum city. These individuals were not on any drugs like digoxin and were free from any systemic disease. All individuals in this group also were non-smokers (passive or active).

Fasting blood was removed from each of the patients/individuals for various estimations. RBCs were separated within 1 hour of collection of blood for the estimation of membrane Na^{+}-K^{+} ATPase. Serum was used for the estimation of HMG CoA reductase activity. Plasma/serum was used for the estimation of the other parameters. All biochemicals used in this study were obtained from M/s Sigma Chemicals, USA. Activity of HMG CoA reductase of the plasma was determined using the method of Rao and Ramakrishnan by determining the ratio of HMG CoA to mevalonate. For the determination of the Na^{+}-K^{+} ATPase activity of the erythrocyte membrane, the procedure described by Wallach and Kamat was used. Digoxin in the plasma was determined by the procedure described by Arun et al. For estimation of ubiquinone and dolichol in the plasma, the procedure described by Palmer et al. was used. Mg^{++} in the plasma was estimated by atomic absorption spectrophotometry. Tryptophan was estimated by the method of Bloxam and Warren and tyrosine by the method of Wong et al. Serotonin was estimated by the method of Curzon et al. and catecholamines by the method of Well-Malherbe et al. Quinolinic acid content of plasma was estimated by HPLC (C_{18} column micro Bondapak™

4.6 x 150 mm), solvent system 0.01 M acetate buffer (pH 3.0) and methanol (6:4), flow rate 1.0 ml/minute and detection UV 250 nm). Morphine, strychnine and nicotine were estimated by the method described by Arun et al. Details of the procedures used for the estimation of total and individual GAG, carbohydrate components of glycoproteins, activity of enzymes involved in the degradation of GAG (beta glucuronidase, beta N-acetyl hexosaminadase, hyaluronidase and cathepsin-D) and activity of glycohydrolases (beta galactosidase, beta fucosidase and beta lucosidase) have been described before by Kurup et al. Serum glycolipids (gangliosides, glycosyl diglycerides, cerebrosides and sulphatides) were estimated as described in methods in enzymology. Cholesterol was estimated by using commercial kits supplied by Sigma chemicals, USA. SOD was assayed by the method of Nishikimi et al. as modified by Kakkar et al. Catalase activity was estimated by the method of Maehly and Chance, glutathione peroxidase by the method of Paglia and Valentine as modified by Lawrence and Burk and glutathione reductase by the method of Horn and Burns. MDA was estimated by the method of Wills et al. and conjugated dienes and hydroperoxides by the procedure of Brien et al. Reduced glutathione was estimated by the method of Beutler et al. Extraction of erythrocytes for vitamin E was carried out according to the procedure described by Cohn et al. and vitamin E estimated in the extract by HPLC (Waters HPLC, Nova-Pak C_8 column 4.6 x 150 mm). Solvent-acetonitrile: methanol: water (63:33:4), flow rate - 2 ml/min, detection UV (280 nm). For vitamin E, retention time was 3.5 mm under these conditions. Nitric oxide was estimated in the plasma by the method of Gabor and Allon. Iron binding capacity in the plasma was estimated by the method of Wootton and ceruloplasmin by the method of Henry et al. Free fatty acid were estimated by the method of Falholt et al. Statistical analysis was done by ANOVA'.

Results

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

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

(3) Nicotine and strychnine were detected in the plasma of patients with AD but were not detectable in control serum. Morphine was not detected in the plasma of these patients.

(4) The concentration of total glycosaminoglycans (GAG) and different GAG fractions increased in the serum of AD patients. The concentration total hexose, fucose and sialic acid were increased in the glycoproteins of the serum in these patients. The concentration of gangliosides, glycosyl-diglycerides, cerebroside and sulphatide showed significant increase in the serum in these patients.

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

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

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

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

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

Discussion

Archaeal Digoxin and Membrane Na^+-K^+ ATPase Inhibition in Relation to Alzheimer's Disease

The archaeaon steroidelle contributes to lipid synthesis and metabolism. The archaeaon steroidelle DXP pathway and the upregulated pentose phosphate pathway contribute to digoxin synthesis. The results showed that HMG CoA reductase activity, serum digoxin and dolichol were increased and serum ubiquinone was reduced in AD. Previous studies in this laboratory have demonstrated incorporation of ^{14}C-acetate into digoxin in the rat brain indicating that acetyl CoA is the precursor for digoxin biosynthesis in mammals also. The elevated HMG CoA reductase activity correlates well with elevated digoxin levels and reduced RBC membrane Na^+-K^+ ATPase activity. The increase in endogenous digoxin, a potent inhibitor of membrane Na^+-K^+ ATPase, can decrease this enzyme activity. The inhibition of Na^+-K^+ ATPase by digoxin is known to cause an increase in intracellular Ca^{++} resulting from increased Na^+-Ca^{++} exchange, increased entry of Ca^{++} via the voltage gated Ca^{++} channel and increased release of Ca^{++} from intracellular endoplasmic reticulum Ca^{++} stores. This increase in intracellular Ca^{++} by displacing Mg^{++} from its binding sites causes a decrease in the functional availability of Mg^{++}. This decrease in the availability of Mg^{++} can cause decreased mitochondrial ATP formation which along with low Mg^{++} can cause further inhibition of Na^+-K^+ ATPase, since the ATP-Mg^{++} 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 Mg^{++} related mitochondrial dysfunction results in defective calcium extrusion from the cell. There is thus a progressive inhibition of Na^+-K^+ ATPase activity first triggered by digoxin. Low intracellular Mg^{++} and

high intracellular Ca^{++} consequent to Na^{+}-K^{+} ATPase inhibition appear to be crucial to the pathogenesis of AD. Serum Mg^{++} was found to be reduced in AD.[1-8]

Archaeal Digoxin and Regulation of Neurotransmitter Synthesis and Function in Relation to Alzheimer's Disease

The archaeaon neurotransminoid shikimic acid pathway contributes to tryptophan and tyrosine synthesis and catabolism generating neurotransmitters and neuroactive alkaloids. Digoxin, apart from affecting cation transport is also reported to influence the transport of various metabolites across cellular membranes, including amino acids and various neurotransmitters. Two of the amino acids in this respect are important, tryptophan, a precursor for strychnine and nicotine, and tyrosine, a precursor for morphine. We had already shown the presence of endogenous morphine in the brain of rats loaded with tyrosine and endogenous strychnine and nicotine in the brain of rats loaded with tryptophan. The present study shows that the concentration of tryptophan, quinolinic acid, and serotonin was higher in the plasma of AD patients while that of tyrosine, dopamine and norepinephrine was lower. Serum of the patients with AD showed the presence of nicotine and strychnine. Morphine was absent in the serum of these patients. Thus there is an increase in tryptophan and its catabolites (serotonin, nicotine, strychnine and quinolinic acid) and a reduction in tyrosine and its catabolites (dopamine, norepinephrine and morphine) in the patient's serum. This could be due to the fact that digoxin can regulate the neutral amino acid transport system with preferential promotion of tryptophan transport over tyrosine. Increased neuronal tryptophan load and reduced neuronal tyrosine load can upregulate tryptophan catabolism and down regulate the catabolism of tyrosine. The increase in serotonin levels and decrease in dopamine and noradrenaline could contribute to the psychiatric manifestations and cognitive dysfunction described in AD. Nicotine acts as a CNS stimulant

and can bind to the central nicotinic receptors producing a biphasic effect with initial stimulation followed by inhibition. Prolonged nicotinic action may produce degeneration of the nicotinic cholinergic receptors in a phenomenon similar to glutamate excitotoxicity. Membrane Na^{+}-K^{+} ATPase inhibition can lead on to increased glutamatergic excitatory transmission important in the pathogenesis of AD. The decrease in membrane Na^{+}-K^{+} ATPase activity in AD could be due to the fact that the hyperpolarising neurotransmitters (dopamine, morphine and noradrenaline) are reduced and the depolarising neuroactive compounds (serotonin, strychnine, nicotine and quinolinic acid) are increased as also to increased digoxin levels. In the presence of hypomagnesemia, consequent to Na^{+}-K^{+} ATPase inhibition, the Mg^{++} block on the NMDA receptor is removed leading to NMDA excitotoxicity. The increased levels of FFA can contribute to NMDA excitotoxicity by binding Mg^{++}. This results in the formation of Mg^{++} soaps in the blood and hypomagnesemia. The increased presynaptic neuronal Ca^{++} can produce cyclic AMP dependent phosphorylation of synapsins resulting in increased glutamate release into the synaptic junction and vesicular recycling. Increased intracellular Ca^{++} in the post synaptic neuron can also activate the Ca^{++} dependent NMDA signal transduction. The plasma membrane glutamate transporter (on the surface of the glial cell and presynaptic neuron) is coupled to a Na^{+} gradient which is disrupted by the inhibition of Na^{+}-K^{+} ATPase, resulting in decreased clearance of glutamate by presynaptic and glial uptake at the end of synaptic transmission. By these mechanisms, inhibition of Na^{+}-K^{+} ATPase can promote excitatory glutamatergic transmission. Serotonin and quinolinic acid are NMDA agonist and positive modulators and could contribute to increased NMDA transmission. Strychnine by blocking glycinergic transmission contributes to the decreased inhibitory transmission in the brain. Strychnine displaces glycine from its binding sites and the glycine is free to bind to the strychnine insensitive site of the NMDA receptor and

promote excitatory NMDA transmission. NMDA excitotoxicity contributes to neuronal degeneration in AD by increasing the intracellular Ca^{++} levels.[1-8]

Archaeal Digoxin and Regulation of Golgi Body / Lysosomal Function in Relation to Alzheimer's Disease - The Glycosaminoglycoid

The archaeaon glycosaminoglycoid and fructosoid contributes to glycoconjugate synthesis and catabolism by the process of fructolysis. The membrane Na^{+}-K^{+} ATPase inhibition related Mg^{++} depletion and elevated dolichol levels can affect the metabolism of glycosaminoglycans, glycoproteins and glycolipids. The elevation in the level of dolichol may suggest its increased availability for N-glycosylation of proteins. Magnesium deficiency can lead on to defective metabolism of sphinganine producing its accumulation, which may lead to increased cerebroside and ganglioside synthesis. In Mg^{++} deficiency the glycolysis, citric acid cycle and oxidative phosphorylation are blocked and more glucose 6-phosphate is channelled for the synthesis of glycosaminoglycans (GAG). The results show an increase in the concentration of serum total GAG, glycolipids and carbohydrate components of glycoproteins in AD. The increase in the carbohydrate components - total hexose, fucose and sialic acid - in AD was not to the same extent suggesting qualitative change in glycoprotein structure. The activity of GAG degrading enzymes and glycohydrolases was increased in AD when compared to the controls. Intracellular Mg^{++} deficiency also results in defective ubiquitin dependent proteolytic processing of glycoconjugates as it requires Mg^{++} for its function. Defective ubiquitin dependent proteolytic processing of proteins has been described in AD. The increase in the activity of glycohydrolases and GAG degrading enzymes could be due to reduced lysosomal stability and consequent leakage of lysosomal enzymes into the serum. The increase in the concentration of carbohydrate components of glycoproteins and GAG in spite of increased activity of many glycohydrolases may be due to their

possible resistance to cleavage by glycohydrolases consequent to qualitative change in their structure. Proteoglycan complexes formed in the presence of altered Ca^{++}/Mg^{++} ratios intracellularly may be structurally abnormal and resistant to lysosomal enzymes and may accumulate.

Previous reports of alteration in glycoproteins in this connection include the beta amyloid in AD. 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 and tau protein and reduced proteolytic digestion of these complexes can lead on to their accumulation in the neurons. Alteration in the sulphated proteoglycan matrix of the synaptic vescicles can alter acetyl choline release into the synapse and contribute to the pathogenesis of AD. Altered glycoproteins, glycolipids and GAG of the neuronal membrane can also contribute to AD by producing disordered synaptic connectivity in the central cholinergic pathways. The protein processing defect can result in defective glycosylation of endogenous neuronal glycoprotein antigens and exogenous viral glycoproteins antigens with consequent defective formation of the MHC antigen complex. The MHC linked peptide transporter, a P-glycoprotein which transports the MHC-antigen complex to the antigen presenting cell surface, has an ATP binding site which is dysfunctional in the presence of Mg^{++} deficiency. This results in defective transport of 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 neuronal glycoprotein antigen can explain the immune dysregulation and autoimmunity described in neuronal degenerations like Alzheimer's disease. Defective presentation of exogenous viral antigens can produce immune evasion by the virus as in viral persistence leading on to neuronal degenerations like AD. A number of fucose and sialic acid containing natural ligands are involved in trafficking of

leukocytes and the inflammatory cell process and could contribute to similar phenomena described in neuronal degeneration.[1-8]

Archaeal Digoxin and Alteration in Membrane Structure and Membrane Formation in Relation to Alzheimer's Disease

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

GAG degrading enzymes into the serum. Defective peroxisomal membranes lead to catalase dysfunction which has been documented in AD.[1-8]

Archaeal Digoxin and Mitochondrial Dysfunction in Relation to Alzheimer's Disease - The Vitaminocyte

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 AD which may be the result of low tyrosine levels, consequent to digoxins effect in preferentially promoting tryptophan transport over tyrosine. The aromatic ring portion of ubiquinone is derived from the tyrosine. Ubiquinone, which is an important component of the mitochondrial electron transport chain, is a membrane antioxidant and contributes to free radical scavenging. The increase in intracellular Ca^{++} can open the mitochondrial PT pore causing a collapse of the H^{+} gradient across the inner membrane and uncoupling of the respiratory chain. Intracellular Mg^{++} deficiency can lead to a defect in the function of ATP synthase. All this leads to a defect in mitochondrial oxidative phosphorylation, incomplete reduction of oxygen and generation of the superoxide ion which produces lipid peroxidation. Ubiquinone deficiency also leads to reduced free radical scavenging. The increase in intracellular calcium may lead to increased generation of NO by inducing the enzyme nitric oxide synthase which combines with the superoxide radical to form peroxynitrite. Increased calcium also can activate phospholipase A_2 resulting in increased generation of arachidonic acid which can undergo increased lipid peroxidation. Increased generation of free radicals like the superoxide ion and hydroxyl radical can produce lipid peroxidation and cell membrane damage which can further inactivate Na^{+}-K^{+} ATPase triggering the cycle of free radical generation again.

There was increase in lipid peroxidation as evidenced from the increase in the concentration of MDA, conjugated dienes, hydroperoxides and NO with decreased antioxidant protection as indicated by decrease in ubiquinone, reduced glutathione and alpha tocopherol in AD. The activity of enzymes involved in free radical scavenging like superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase and catalase is decreased in AD suggesting reduced free radical scavenging. In our study the iron binding capacity and serum ceruloplasmin are reduced suggesting increased amounts of free iron and copper, promoting free radical generation. Ceruloplasmin is a 132 KD monomeric copper oxidase which has been implicated in iron metabolism because of its catalytic oxidation of Fe^{2+} to Fe^{3+} (ferroxidase activity). In the presence of iron in Fe^{2+} form the conversion of H_2O_2 to hydroxyl radical is greatly increased. Low ceruloplasmin results in more of the iron to be in Fe^{2+} form. It has been shown that ceruloplasmin increases iron uptake by cells increasing the apparent affinity for the substrate by three times. Low ceruloplasmin levels can result in decreased iron uptake and this results in increased amount of free iron. The intracellular magnesium deficiency can produce ribosomal dysfunction and inhibition of protein synthesis as noted by decrease in serum albumin in these cases. The low iron binding capacity and low serum ceruloplasmin levels may be a consequence of reduced ferritin and ceruloplasmin synthesis. The peroxisomal membrane is defective owing to the membrane Na^{+}-K^{+} ATPase inhibition related defect in membrane formation and leads to reduced catalase activity. Glutathione is synthesized by the enzyme glutathione synthetase which needs magnesium and ATP. The low intracellular Mg^{++} consequent to Na^{+}-K^{+} ATPase inhibition and the resulting low ATP can result in decreased synthesis of glutathione. Glutathione peroxidase, a selenium containing enzyme oxidises reduced glutathione (GSH) to oxidised glutathione (GSSG) which is then rapidly reduced to GSH by glutathione reductase. There is also a concomitant conversion of H_2O_2 to H_2O.

The activity of glutathione reductase needs NADPH for the regeneration of GSH. This NADPH comes mostly from the pentose phosphate pathway. Intracellular magnesium deficiency due to membrane Na^{+}-K^{+} ATPase inhibition leads to decreased formation of glucose 6-phosphate and down regulation of the pentose phosphate pathway with consequent decreased generation of NADPH. Thus the glutathione system of free radical scavenging is defective in the presence of membrane sodium potassium ATPase inhibition. Superoxide dismutase exists in a mitochondrial and cytoplasmic form. The opening of the mitochondrial PT pore produces hyperosmolality and matrix expansion rupturing the outer membrane producing loss of the mitochondrial dismutase and decrease in its activity. The reduction in catalase, superoxide dismutase (SOD), glutathione peroxidase and glutathione reductase suggests reduced free radical protection. Mitochondrial dysfunction related free radical generation has been implicated in the pathogenesis of the neuronal degeneration like AD. Mitochondrial dysfunction can remove the Mg^{++} block of the NMDA receptor leading on to excitotoxicity and neuronal degeneration.[1-8]

Archaeal Digoxin and Immunoregulation in Relation to Alzheimer's Disease - The Fructosoid, Steroidelle and Viroidelle

The archaeaon fructosoid contributes to fructolysis and immune activation. Fructose can contribute to induction of NFKB and immune activation. The archaeaon steroidelle synthesized digoxin induces NFKB producing immune activation. Increased intracellular Ca^{++} activates the Ca^{++} dependent calcineurin signal transduction pathway which can produce T-cell activation and secretion of interleukin - 3, 4, 5, 6 and TNF alpha (Tumour necrosis factor alpha). This can also explain the immune activation in some neuronal degenerations like Alzheimer's disease. TNF alpha can also bring about apoptosis of the cell. It binds to its receptor and activates caspase-9 an ICE protease which converts

IL-1 beta precursor to IL-1 beta. IL-1 beta produces apoptosis of the neurons in neuronal degenerations. 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.

Cell death is also mediated by increased intracellular Ca^{++} and ceramide related opening of the mitochondrial PT pore causing a collapse of the H^{+} gradient across the inner membrane and uncoupling of the respiratory chain. This also leads to volume dysregulation of mitochondria causing hyperosmolality of matrix and expansion of matrix space. The outer membrane of the mitochondria ruptures and releases AIF (apoptosis inducing factor) and cyto C. This results in procaspase-9 activation to caspase-9 which produces cell death. Caspase-9 activates CAD (caspase activated deoxyribonuclease) which cleaves the nuclear membrane lamins and several proteins involved in cytoskeletal regulation like elsolin which cleaves actin. Apoptosis has also been implicated in neuronal aging and neuronal death in neuronal degeneration. We have been able to demonstrate neuronal degeneration and apoptosis in the digoxin injected rat brain.

Intracellular Mg^{++} depletion can produce defective phosphorylation of MAP (microtubule sociated proteins). This results in defective microtubule polymerization / depolymerisation and axonal transport contributing to neuronal degeneration.[1-8]

Archaeal Digoxin and Lipid Metabolism - in Relation to Alzheimer's Disease

The archaeaon steroidelle contributes to lipid synthesis and metabolism. Low HDL cholesterol is another feature observed in AD. Low HDL cholesterol and increased triglycerides is suggestive of insulin resistance. Insulin resistance has been described in Alzheimer's disease. A low HDL cholesterol level indicates

reduced reverse cholesterol transport to the liver for degradation. HDL cholesterol has been related to neuronal regeneration and has a neurotrophic effect. Altered reverse transport of cholesterol and abnormal redistribution of HDL particles have been reported in neuronal degeneration. This may relate low HDL cholesterol to AD. Serum free fatty acids are significantly increased in AD. This may indicate increased lipolysis or decreased mitochondrial fatty acid oxidation or both. Magnesium deficiency can lead to activation of lipoprotein lipase and lipolysis. Increased intracellular calcium by opening up the mitochondrial PT pore can produce mitochondrial dysfunction. The mitochondrial dysfunction can cause reduced beta oxidation of fatty acid leading to an increase in the free fatty acid level. Free fatty acids themselves can produce Na^{+}-K^{+} ATPase inhibition. There was no alteration in serum cholesterol despite elevated HMG CoA reductase activity probably because most of HMG CoA was channelized for the synthesis of other isoprenoid metabolites like dolichol or digoxin. The RBC membrane cholesterol was reduced despite no alteration in the serum suggesting reduced uptake into the RBC membrane.[1-8]

Archaeal Digoxin and Hemispheric Dominance in Relation to Alzheimer's Disease

The archaeaon related organelle-steroidelle, neurotransminoid and vitaminocyte contribute to hemispheric dominance. Thus Alzheimer's disease and neuronal degeneration can happen due to a defect in the isoprenoid pathway. The following mechanisms are involved, (i) NMDA excitotoxicity consequent to hypomagnesemia, digoxin related membrane Na^{+}-K^{+} ATPase inhibition, ubiquinone deficiency and mitochondrial dysfunction removing the Mg^{++} block and elevated levels of positive modulators of the NMDA receptor (quinolinic acid, serotonin and strychnine), (ii) Dolichol related and Mg^{++} depletion related

altered glycoproteins and proteoglycan and possibly complexes formed between them which resist lysosomal digestion, (iii) defective membrane formation and structure contributing to Na^{+}-K^{+} ATPase inhibition, lysosomal instability and peroxisomal dysfunction, (iv) mitochondrial dysfunction due to low ubiquinone levels, altered Ca^{++}/Mg^{++} ratios intracellularly and ceramide leading to free radical generation, and (v) membrane Na^{+}-K^{+} ATPase inhibition related immune activation, apoptosis and defective presentation of neuronal antigens.

Alzheimer's disease can thus be considered as being due to hypothalamic archaeal digoxin hypersecretion consequent to an upregulated isoprenoid pathway. The biochemical patterns obtained in Alzheimer's disease correlated with those obtained in right hemispheric chemical dominance. In left handed / right hemispheric dominant individuals there was a derangement of the isoprenoid pathway. They had an upregulated HMG CoA reductase activity with increased digoxin and dolichol levels and reduced ubiquinone levels. The RBC membrane Na^{+}-K^{+} ATPase activity was reduced and serum magnesium depleted. The left handed/right hemispheric dominant individuals had increased levels of tryptophan, serotonin, quinolinic acid, strychnine and nicotine while the levels of tyrosine, dopamine, noradrenailne and morphine were lower. Thus an upregulated isoprenoid pathway, increased level of tryptophan and its catabolites, decreased levels of tyrosine and its catabolites and hyperdigoxinemia is suggestive of right hemispheric dominance. In right handed/left hemispheric dominant individuals the biochemical patterns were reversed. Alzheimer's disease occurs in right hemispheric chemically dominant individuals and could be a reflection of altered brain function.[1-8]

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3

Archaeal Digoxin and Parkinson's Disease

Changes involving the isoprenoid pathway have been described in neuronal degeneration. Mitochondrial dysfunction particularly involving ubiquinone has been reported in platelet mitochondria in Parkinson's disease. Altered levels of dolichol in the brain and altered glycoproteins like beta amyloid have been reported in Alzheimer's disease. Dolichol and ubiquinone are both products of the isoprenoid pathway. Sodium potassium ATPase inhibition has been reported to lead to neuronal degeneration. An endogenous inhibitor of sodium potassium ATPase archaeal digoxin is produced by the isoprenoid pathway. It was therefore considered pertinent to study the isoprenoid pathway in neuronal degeneration. Digoxin induced membrane Na^{+}-K^{+} ATPase inhibition can produce Mg^{++} depletion leading on to altered glycoconjugate metabolism. The dolichol pathway can regulate N-glycosylation of glycoproteins. Alteration in glycoconjugate metabolism has also been described in neuronal degeneration. Amyloid and hyperphosphorylated tau protein in Alzheimers disease and alpha synuclein in Parkinson's disease are defectively processed proteins resistant to the action of proteases. Accumulation of heparan sulphate proteoglycan (HS-PG) and its interaction with beta amyloid precursor protein (beta APP) have been suggested as a possible mechanism for amyloid plaque formation in Alzheimer's disease. Glycolipids like ceramide can produce cell death by opening up the mitochondrial PT pore and contribute to neuronal degeneration and aging. Digoxin can alter intracellular Ca^{++}/Mg^{++} ratios in the cell leading on to free radical generation. Alteration in the ubiquinone pathway can also lead to mitochondrial dysfunction and free radical generation. Free radical mechanisms have been implicated in the pathogenesis of the major neurodegenerative disorders like Parkinson's disease, Alzheimer's disease and amyotrophic lateral sclerosis. In Parkinson's disease, free radical generation has been reported to be due to formation of H_2O_2 from dopamine by the action of monoamine oxidase and the subsequent reaction of H_2O_2 with iron to generate the hydroxyl radical

by the Fenton reaction. A critical role for iron in free radical generation has been suggested in neurodegenerations like Parkinson's disease and Alzheimer's disease. An altered free radical defence mechanism like decreased levels of antioxidant enzymes and antioxidants has been suggested for the free radical damage in Parkinson's disease. Increased formation of NO which forms peroxynitrite with superoxide promoting lipid peroxidation has also been reported in neurodegeneration. Digoxin has been reported to regulate the transport of amino acids especially the neutral amino acids. Abnormalities in tryptophan catabolism and the kynurenine pathway have been described in neuronal degeneration. Of the kynurenines, quinolinic acid is most relevant to neurodegenerative disease. Quinolinic acid toxicity in the brain appears to be mediated through its action as an agonist of the NMDA receptor. Neurotoxicity induced by quinolinic acid occurs preferentially in the neocortex, striatum and hippocampus in the brain. The neuro-toxic effects of quinolinic acid are mediated via the magnesium sensitive NMDA receptor. Membrane abnormalities have been described in neurodegenerative disorders like neuroacanthocytosis and motor neuron disease. In motor neuron disease abnormalities in the RBC handling of the glutamate have been reported. In Alzheimer's disease alteration in membrane fluidity especially of the platelet membrane has been reported. The isoprenoid pathway produces four metabolites important in maintaining cell membrane structure and function - digoxin (a membrane Na^+-K^+ ATPase inhibitor), dolichol (involve in N-glycosylation of proteins), ubiquinone (a membrane antioxidant) and cholesterol. This study was undertaken to assess (1) the isoprenoid pathway (2) the tryptophan/tyrosine catabolic patterns (3) glycoconjugate metabolism in PD and (4) RBC membrane changes as a reflection of neuronal membrane change. A hypothesis implicating neuronal membrane sodium potassium ATPase inhibition as pivotal to all these changes is also presented.[1-8]

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

Results

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

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

(3) Nicotine (1.07 ug/100 ml) and strycimine (9.54 ug/dL) were detected in the plasma of patients with PD but were not detectable in the control serum. Morphine was not detected in the plasma of these patients.

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

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

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

(7) Concentration of total serum cholesterol and LDL cholesterol was not significantly altered while HDL cholesterol showed a significant decrease

in the plasma in PD. Serum triglycerides were unaltered while free fatty acids (FFA) increased in PD.

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

Discussion

Archaeal Digoxin and Membrane Na^+-K^+ ATPase Inhibition in Relation to Parkinson's Disease

The archaeaon steroidelle contributes to lipid synthesis and metabolism. The archaeaon steroidelle DXP pathway and the upregulated pentose phosphate pathway contribute to digoxin synthesis. The results showed that HMG CoA reductase activity, serum digoxin and dolichol were increased and serum ubiquinone was reduced in PD. Previous studies in this laboratory have demonstrated incorporation of ^{14}C-acetate into digoxin in the rat brain indicating that acetyl CoA is the precursor for digoxin biosynthesis in mammals also. The elevated HMG CoA reductase activity correlates well with elevated digoxin levels and reduced RBC membrane Na^+-K^+ ATPase activity. The increase in endogenous digoxin, a potent inhibitor of membrane Na^+-K^+ ATPase, can decrease this enzyme activity. The inhibition of Na^+-K^+ ATPase by digoxin is known to cause an increase in intracellular Ca^{++} resulting from increased Na^+-Ca^{++} exchange, increased entry of Ca^{++} via the voltage gated Ca^{++} channel and increased release of Ca^{++} from intracellular endoplasmic reticulum Ca^{++} stores. This increase in intracellular Ca^{++} by displacing Mg^{++} from its binding

sites causes a decrease in the functional availability of Mg^{++}. This decrease in the availability of Mg^{++} can cause decreased mitochondrial ATP formation which along with low Mg^{++} can cause further inhibition of Na^{+}-K^{+} ATPase, since the ATP-Mg^{++} 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 Mg^{++} related mitochondrial dysfunction results in defective calcium extrusion from the cell. There is thus a progressive inhibition of Na^{+}-K^{+} ATPase activity first triggered by digoxin. Low intracellular Mg^{++} and high intracellular Ca^{++} consequent to Na^{+}-K^{+} ATPase inhibition appear to be crucial to the pathogenesis of PD. Serum Mg^{++} was found to be reduced in PD.[1-8]

Archaeal Digoxin and Regulation of Neurotransmitter Synthesis and Function in Relation to Parkinson's Disease

The archaeaon neurotransminoid shikimic acid pathway contributes to tryptophan and tyrosine synthesis and catabolism generating neurotransmitters and neuroactive alkaloids. Digoxin, apart from affecting cation transport is also reported to influence the transport of various metabolites across cellular membranes, including amino acids and various neurotransmitters. Two of the amino acids in this respect are important, tryptophan, a precursor for strychnine and nicotine, and tyrosine, a precursor for morphine. We had already shown the presence of endogenous morphine in the brain of rats loaded with tyrosine and endogenous strychnine and nicotine in the brain of rats loaded with tryptophan. The present study shows that the concentration of tryptophan, quinolinic acid, and serotonin was higher in the plasma of PD patients while that of tyrosine, dopamine and norepinephrine was lower. Serum of patients with PD showed the presence of nicotine and strychnine. Morphine was absent in the serum of these patients. Thus there is an increase in tryptophan and its catabolites (serotonin,

nicotine, strychnine and quinolinic acid) and a reduction in tyrosine and its catabolites (dopamine, norepinephrine and morphine) in the patient's serum. This could be due to the fact that digoxin can regulate the neutral amino acid transport system with preferential promotion of tryptophan transport over tyrosine. Increased neuronal tryptophan load and reduced neuronal tyrosine load can upregulate tryptophan catabolism and down regulate the catabolism of tyrosine. Reduced dopamine levels can lead on to defects in nigrostriatal dopaminergic transmission, observed in Parkinson's disease. Release of dopamine in to the neostriatum has an inhibitory defect on neostriatal cholinergic neurons and this effect is reduced in the presence of dopamine deficiency. The decreased levels of noradrenaline can contribute to postural and gait disturbance in PD. The decrease in dopamine, and norepinephrine documented by us has also been reported by Eldrup et al. The increase in serotonin levels and decrease in dopamine and noradrenaline could contribute to the psychiatric manifestations and cognitive dysfunction described in PD. Acetyl choline is synthesized and released by small (Golgi type II) neurons in the neostriatum and it has a excitatory effect on these neurons. Nicotine acts as a CNS stimulant and can bind to the central nicotinic receptors contributing to the increase in cholinergic transmission and tremor in PD. The fundamental equilibrium that exists between the excitatory cholinergic and inhibitory dopaminergic mechanism is lost consequent to this alteration in nicotine and dopamine levels. Membrane Na^+-K^+ ATPase inhibition can lead on to increased glutamatergic excitatory transmission in contributing to PD. The decrease in membrane Na^+-K^+ ATPase activity in PD could be due to the fact that the hyperpolarising neurotransmitters (dopamine, morphine and noradrenaline) are reduced and the depolarising neuroactive compounds (serotonin, strychnine, nicotine and quinolinic acid) are increased as also to increased digoxin levels. In the presence of hypomagnesemia, consequent to Na^+-K^+ ATPase inhibition the

Mg^{++} block on the NMDA receptor is removed leading to NMDA excitotoxicity. The increased levels of FFA can contribute to epileptogenesis by binding Mg^{++}. This results in the formation of Mg^{++} soaps in the blood and hypomagnesemia. The increased presynaptic neuronal Ca^{++} can produce cyclic AMP dependent phosphorylation of synapsins resulting in increased glutamate release into the synaptic junction and vesicular recycling. Increased intracellular Ca^{++} in the post synaptic neuron can also activate the Ca^{++} dependent NMDA signal transduction. The plasma membrane glutamate transporter (on the surface of the glial cell and presynaptic neuron) is coupled to a Na^{+} gradient which is disrupted by the inhibition of Na^{+}-K^{+} ATPase, resulting in decreased clearance of glutamate by presynaptic and glial uptake at the end of synaptic transmission. By these mechanisms, inhibition of Na^{+}-K^{+} ATPase can promote excitatory glutamatergic transmission. Serotonin and quinolinic acid are NMDA agonist and positive modulators and could contribute to increased NMDA transmission. Strychnine by blocking glycinergic transmission contributes to the decreased inhibitory transmission in the brain. Strychnine displaces glycine from its binding sites and the glycine is free to bind to the strychnine insensitive site of the NMDA receptor and promote excitatory NMDA transmission. Increased NMDA transmission could contribute to increased excitatory transmission in the corticostriatal glutamatergic pathways and also produce derangement of the basal ganglia functional loops. NMDA excitotoxicity contributes to neuronal degeneration in PD by increasing the intracellular Ca^{++} levels.[1-8]

Archaeal Digoxin and Regulation of Golgi Body / Lysosomal Function in Relation to Parkinson's Disease - The Glycosaminoglycoid

The archaeaon glycosaminoglycoid and fructosoid contributes to glycoconjugate synthesis and catabolism by the process of fructolysis. The membrane Na^{+}-K^{+} ATPase inhibition related Mg^{++} depletion and elevated

dolichol levels can affect the metabolism of glycosaminoglycans, glycoproteins and glycolipids. The elevation in the level of dolichol may suggest its increased availability for N-glycosylation of proteins. Magnesium deficiency can lead on to defective metabolism of sphinganine producing its accumulation which may lead to increased cerebroside and ganglioside synthesis. In Mg^{++} deficiency the glycolysis, citric acid cycle and oxidative phosphorylation are blocked and more glucose 6 phosphate is channelled for the synthesis of glycosaminoglycans (GAG). The results show an increase in the concentration of serum total GAG, glycolipids (ganglioside, glycosyl-diglyceride, cerebrosides and sulphatides) and carbohydrate components of glycoproteins (hexose, fucose and sialic acid) in PD. The increase in the carbohydrate components-total hexose, fucose and sialic acid-in PD was not to the same extent suggesting qualitative change in glycoprotein structure. In PD the percentage change in total hexose, fucose and sialic acid when compared to the control is 69%, 19% and 64% respectively. The concentration of heparan sulphate (HS) heparin (H) and dermatan sulphate (DS) was increased, while that of chondroitin sulphates (ChS) and hyaluronic acid (HA) was decreased. The activity of GAG degrading enzymes - beta glucuronidase, beta N-acetyl hexoseaminidase, hyaluronidase and cathepsin-D - was increased in PD when compared to the controls. The activity of beta galactosidase increased in PD while that of beta fucosidase and beta glucosidase was unaltered. Intracellular Mg^{++} deficiency also results in defective ubiquitin dependent proteolytic processing of glycoconjugates as it requires Mg^{++} for its function. Defective ubiquitin dependent proteolytic processing of proteins has been described in PD. The increase in the activity of glycohydrolases and GAG degrading enzymes could be due to reduced lysosomal stability and consequent leakage of lysosomal enzymes into the serum. The increase in the concentration of carbohydrate components of glycoproteins and GAG in spite of increased activity of many glycohydrolases may be due to their possible resistance to cleavage by

glycohydrolases consequent to qualitative change in their structure. Proteoglycan complexes formed in the presence of altered Ca^{++}/Mg^{++} ratios intracellularly may be structurally abnormal and resistant to lysosomal enzymes and may accumulate.

Previous reports of alteration in glycoproteins in this connection include alpha synuclein and parkin 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 parkin and alpha synuclein and reduced proteolytic digestion of these complexes can lead on to their accumulation in the neurons. Lewy bodies observed in selective vulnerable neuronal population in PD have got positive anti-ubiquitin staining and accumulation of neurofilament proteins and alpha-synuclein which are defectively processed. Similar interaction between HS proteoglycan and ChS proteoglycan with beta amyloid and tau protein has been described in Alzheimer's disease. Alteration in the sulphated proteoglycan matrix of the synaptic vesicles can alter dopamine release into the synapse and contribute to the pathogenesis of PD. Altered glycoproteins, glycolipids and GAG of the neuronal membrane can also contribute to PD by producing disordered synaptic connectivity in the nigrostriate pathways. The protein processing defect can result in defective glycosylation of endogenous neuronal glycoprotein antigens and exogenous viral glycoproteins antigens with consequent defective formation of the MHC-antigen complex. The MHC linked peptide transporter, a P-glycoprotein which transports the MHC-antigen complex to the antigen presenting cell surface, has an ATP binding site which is dysfunctional in the presence of Mg^{++} deficiency. This results in defective transport of 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 neuronal glycoprotein antigen can explain the immune dysregulation and autoimmunity described in neuronal degenerations like Parkinson's disease,

Alzheimer's disease and motor neuron disease. Defective presentation of exogenous viral antigens can produce immune evasion by the virus as in viral persistence leading on to neuronal degenerations. A number of fucose and sialic acid containing natural ligands are involved in trafficking of leukocytes and the inflammatory cell process and could contribute to similar phenomena described in neuronal degeneration.[1-8]

Archaeal Digoxin and Alteration in Membrane Structure and Membrane Formation in Relation to Parkinson's Disease

The archaeaon steroidelle, glycosaminoglycoid and fructosoid contribute to cell membrane formation synthesizing cholesterol by the DXP pathway and glycosaminoglycans by fructolysis. The alteration in the isoprenoid pathway specifically, cholesterol as well as changes in glycoproteins and GAG can affect cellular membranes. The upregulation of the isoprenoid pathway can lead to increased cholesterol synthesis and Mg^{++} deficiency can inhibit phospholipid synthesis. Phospholipid degradation is increased owing to increase in intracellular calcium activating phospholipase A_2 and D. The cholesterol: phospholipid ratio of the RBC membrane was decreased in PD. The concentration of total GAG, cholesterol, hexose and fucose of glycoprotein decreased in the RBC membrane and increased (unaltered in the case of cholesterol) serum suggesting their reduced incorporation into the membrane and defective membrane formation. The glycoproteins, GAG and glycolipids of the cellular membrane are formed in the endoplasmic reticulum, which is then budded off as a vesicle which fuses with the golgi complex. The glycoconjugates are then transported via the golgi channel and the golgi vesicle fuses with the cell membrane. This trafficking depends upon GTPases and lipid kinases which are crucially dependent on magnesium and are defective in Mg^{++} deficiency. The change in membrane structure produced by alteration in

glycoconjugates and cholesterol: phospholipid ratio can produce changes in the conformation of Na^+-K^+ ATPase resulting in further membrane Na^+-K^+ ATPase inhibition. The same changes can affect the structure of the organelle membrane. This results in defective lysosomal stability and leakage of glycohydrolases and GAG degrading enzymes into the serum. Defective peroxisomal membranes lead to catalase dysfunction which has been documented in Parkinson's disease.[1-8]

Archaeal Digoxin and Mitochondrial Dysfunction in Relation to Parkinson's Disease - The Vitaminocyte

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 PD which may be the result of low tyrosine levels, consequent to digoxin's effect in preferentially promoting tryptophan transport over tyrosine. The aromatic ring portion of ubiquinone is derived from the tyrosine. Ubiquinone, which is an important component of the mitochondrial electron transport chain, is a membrane antioxidant and contributes to free radical scavenging. The increase in intracellular Ca^{++} can open the mitochondrial PT pore causing a collapse of the H^+ gradient across the inner membrane and uncoupling of the respiratory chain. Intracellular Mg^{++} deficiency can lead to a defect in the function of ATP synthase. All this leads to a defect in mitochondrial oxidative phosphorylation, incomplete reduction of oxygen and generation of the superoxide ion which produces lipid peroxidation. Ubiquinone deficiency also leads to reduced free radical scavenging. The increase in intracellular calcium may lead to increased generation of NO by inducing the enzyme nitric oxide synthase, which combines with the superoxide radical to form peroxynitrite. Increased calcium also can activate phospholipase A_2 resulting in increased

generation of arachidonic acid, which can undergo increased lipid peroxidation. Increased generation of free radicals like the superoxide ion, and hydroxyl radical can produce lipid peroxidation and cell membrane damage, which can further inactivate Na^{+}-K^{+} ATPase triggering the cycle of free radical generation again. There was increase in lipid peroxidation as evidenced from the increase in the concentration of MDA, conjugated dienes, hydroperoxides and NO with decreased antioxidant protection as indicated by decrease in ubiquinone, reduced glutathione and alpha tocopherol in PD. The activity of enzymes involved in free radical scavenging like superoxide dismutase, glutathione peroxidase, glutathione reductase and catalase is decreased in PD suggesting reduced free radical scavenging. In our study the iron binding capacity and serum ceruloplasmin are reduced suggesting increased amounts of free iron and copper, promoting free radical generation. Ceruloplasmin is a 132 KD monomeric copper oxidase, which has been implicated in iron metabolism because of its catalytic oxidation of Fe^{2+} to Fe^{3+} - (ferroxidase activity). In the presence of iron in Fe^{2+} form the conversion of H_2O_2 to hydroxyl radical is greatly increased. Low ceruloplasmin results in more of the iron to be in Fe^{2+} form. It has been shown that ceruloplasmin increases iron uptake by cells increasing the apparent affinity for the substrate by 3 times. Low ceruloplasmin levels can result in decreased iron uptake and this results in an increased amount of free iron. The intracellular magnesium deficiency can produce ribosomal dysfunction and inhibition of protein synthesis as noted by the decrease in serum albumin in these cases. The low iron binding capacity and low serum ceruloplasmin levels may be a consequence of reduced ferritin and ceruloplasmin synthesis. Nigral iron accumulation in PD is primarily within neuromelanin granules. Neuromelanin binds to iron and is relatively protective. Neuromelanin is synthesized from tyrosine and the digoxin related tyrosine transport defect may lead to decreased neuromelanin synthesis. The peroxisomal membrane is defective owing to the membrane Na^{+}-K^{+} ATPase

inhibition related defect in membrane formation and leads to reduced catalase activity. Glutathione is synthesized by the enzyme glutathione synthetase, which needs magnesium and ATP. The low intracellular Mg^{++} consequent to Na^{+}-K^{+} ATPase inhibition and the resulting low ATP can result in decreased synthesis of glutathione. Glutathione peroxidase, a selenium containing enzyme oxidises reduced glutathione (GSH) to oxidised glutathione (GSSG) which is then rapidly reduced to GSH by glutathione reductase. There is also a concomitant conversion of H_2O_2 to H_2O. The activity of glutathione reductase needs NADPH for the regeneration of GSH. This NADPH comes mostly from the pentose phosphate pathway. Intracellular magnesium deficiency due to membrane Na^{+}-K^{+} ATPase inhibition leads to decreased formation of glucose-6-phosphate and down regulation of the pentose phosphate pathway with consequent decreased generation of NADPH. Thus the glutathione system of free radical scavenging is defective in the presence of membrane Na^{+}-K^{+} ATPase inhibition. Superoxide dismutase exists in a mitochondrial and cytoplasmic form. The opening of the mitochondrial PT pore produces hyperosmolality and matrix expansion rupturing the outer membrane producing loss of the mitochondrial dismutase and decrease in its activity. The reduction in catalase, superoxide dismutase (SOD), glutathione peroxidase and glutathione reductase suggests reduced free radical protection. Mitochondrial dysfunction related free radical generation has been implicated in the pathogenesis of the neuronal degeneration like PD. Mitochondrial dysfunction can remove the Mg^{++} block of the NMDA receptor leading on to excitotoxicity and neuronal degeneration.[1-8]

Archaeal Digoxin and Immunoregulation in Relation to Parkinson's Disease - The Fructosoid, Steroidelle and Viroidelle

The archaeaon fructosoid contributes to fructolysis and immune activation. Fructose can contribute to induction of NFKB and immune activation. The

archaeaon steroidelle synthesized digoxin induces NFKB producing immune activation. The archaeaon viroidelle secreted RNA viroids can modulate immune activation by functioning as blockers of mRNA expression. Increased intracellular Ca^{++} activates the Ca^{++} dependent calcineurin signal transduction pathway which can produce T-cell activation and secretion of interleukin - 3, 4, 5, 6 and TNF alpha (Tumour necrosis factor alpha). This can also explain the immune activation in some neuronal degeneration like, in Parkinson's disease, motor neuron disease (MND) and Alzheimer's disease. It has been noted that HLA DR positive reactive microglia as well as increased levels of cytokines such as interleukin-l and tumor necrosis factor alpha in the pars compacta of the substantia nigra is seen even in the late stages of Parkinson's disease. TNF alpha can also bring about apoptosis of the cell. It binds to its receptor and activates caspase-9 an ICE protease which converts the IL-1 beta precursor to IL-1 beta. IL-1 beta produces apoptosis of the neurons in neuronal degenerations. 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.

Cell death is also mediated by increased intracellular Ca^{++} and ceramide related opening of the mitochondrial PT pore causing a collapse of the H^{+} gradient across the inner membrane and uncoupling of the respiratory chain. This also leads to volume dysregulation of mitochondria causing hyperosmolality of matrix and expansion of matrix space. The outer membrane of the mitochondria ruptures and releases AIF (apoptosis inducing factor) and cyto C (cytochrome C). This results in procaspase-9 activation to caspase-9 which produces cell death. Caspase-9 activates CAD (caspase activated deoxyribonuclease) which cleaves the nuclear membrane lamins and several proteins involved in cytoskeletal regulation like gelsolin which cleaves actin. Apoptosis has also been implicated in neuronal aging and neuronal death in

neuronal degeneration. We have been able to demonstrate neuronal degeneration and apoptosis in the digoxin injected rat brain.

Membrane Na^+-K^+ ATPase inhibition can produce intracellular Mg^{++} depletion leading on to defect in the function of DNA polymerase which functions as the proof reading enzymes in the nucleus during DNA replication. Defective function of DNA polymerase could possibly lead to defect in DNA structure and possibly trinucleotide repeats described in neuronal degeneration. This is exemplified by the protein Parkin described in juvenile Parkinson's disease. Intracellular Mg^{++} depletion can produce defective phosphorylation of MAP (microtubule associated proteins). This results in defective microtubule polymerisation / depolymerisation and axonal transport contributing to neuronal degeneration.[1-8]

Archaeal Digoxin and Lipid Metabolism in Relation to Parkinson's Disease

The archaeaon steroidelle contributes to lipid synthesis and metabolism. Low HDL cholesterol is another feature observed in PD. Low HDL cholesterol level indicates reduced reverse cholesterol transport to the liver for degradation. HDL cholesterol has been related to neuronal regeneration and has a neurotrophic effect. Altered reverse transport of cholesterol and abnormal redistribution of HDL particles have been reported in neuronal degeneration. This may relate low HDL cholesterol to PD. Serum free fatty acids are significantly increased in PD. This may indicate increased lipolysis or decreased mitochondrial fatty acid oxidation or both. Magnesium deficiency can lead to activation of lipoprotein lipase and lipolysis. Increased intra cellular calcium by opening up the mitochondrial PT pore can produce mitochondrial dysfunction. The mitochondrial dysfunction can cause reduced beta oxidation of fatty acid leading to an increase in free fatty acid level. Free fatty acids themselves can produce Na^+-K^+ ATPase inhibition. There was no alteration in serum cholesterol despite elevated HMG CoA reductase

activity probably because most of HMG CoA was channelized for the synthesis of other isoprenoid metabolites like dolichol or digoxin. The RBC membrane cholesterol was reduced despite no alteration in the serum suggesting reduced uptake into the RBC membrane.[1-8]

Archaeal Digoxin and Hemispheric Dominance in Relation to Parkinson's Disease

The archaeaon related organelle-steroidelle, neurotransminoid and vitaminocyte contribute to hemispheric dominance. Thus Parkinson's disease and neuronal degeneration can happen due to a defect in the isoprenoid pathway. The following mechanisms are involved, (1) NMDA excitotoxicity consequent to hypomagnesemia, digoxin related membrane Na^{+}-K^{+} ATPase inhibition, ubiquinone deficiency and mitochoridrial dysfunction removing the Mg^{++} block and elevated levels of positive modulators of the NMDA receptor (quinolinic acid, serotonin and strychnine), (2) Dolichol related and Mg^{++} depletion related altered glycoproteins and proteoglycan and possibly complexes formed between them which resist lysosomal digestion, (3) Defective membrane formation and structure contributing to Na^{+}-K^{+} ATPase inhibition, lysosomal instability and peroxisomal dysfunction, (4) mitochondrial dysfunction due to low ubiquinone levels, altered Ca^{++}/Mg^{++} ratios intracellularly and ceramide leading to free radical generation. Membrane Na^{+}-K^{+} ATPase inhibition related immune activation, apoptosis and defective presentation of neuronal antigens. All these features are chemical markers of right hemispheric dominance.[1-8]

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4

Archaeal Digoxin Mediated Model for Multiple Sclerosis

Alteration in the isoprenoid pathway has been described in multiple sclerosis. Decreased ubiquinone levels have been reported in the serum of patients with multiple sclerosis. Increased urinary excretion of some organic acids which are degradation products from isoprenoid compounds have been reported in multiple sclerosis and it has been suggested that there is a defect in the isoprenoid pathway in this disorder. Increased serum endogenous digoxin like factor (EDLF) activity has been reported in some autoimmune syndromes.

Digoxin has been reported to regulate the transport of amino acids especially by neutral amino acids. Tryptophan and kynurenic metabolism has also been implicated immune mediated disorders. Alterations in quinolinic acid metabolism have been implicated in the pathological lesion of AIDS dementia and neurolupus. Saito et al. reported increased activities of kynurenine pathway enzymes in various tissues following systemic immune stimulation, in conjunction with macrophage infiltration of the affected tissue.

Digoxin can alter Ca^{++}/Mg^{++} in the cell leading on to free radical generation. Defective ubiquinone synthesis can also lead to mitochondrial dysfunction and free radical generation. Microglial activation has been reported in multiple sclerosis and free radical generation is important in this context.

Digoxin induced membrane Na^{+}-K^{+} ATPase inhibition can produce Mg^{++} depletion leading on to altered glycoconjugate metabolism. The dolichol pathway can regulate N-glycosylation of glycoproteins. A number of fucose and sialic acid containing natural ligands are common to the inflammatory acute phase response. A large body of research supports a role for small carbohydrate ligands in trafficking of leukocytes. Similar blood brain barrier changes and altered adhesion and trafficking of the lymphocyte have been described in MS. Galactosyl ceramide can be converted into sulfogalactosyl ceramide which is present in high amounts in myelin and is required for myelin integrity.[1-13]

This study was undertaken to assess, (1) the isoprenoid pathway (2) the tryptophan tyrosine catabolic patterns (3) Glycoconjugate metabolism in multiple sclerosis (4) RBC membrane changes as a reflection of neuronal and glial membrane change. A hypothesis implicating neuronal and glial membrane Na^{+}-K^{+} ATPase inhibition as pivotal to all these changes is also presented.

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

Results

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

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

(3) Morphine and strychnine were detected in the plasma of patients with MS and were undetectable in the control serum. Nicotine was not detected in the plasma of MS patients.

(4) The concentration of total GAG increased in the serum of MS patients. The concentration of hyaluronic acid (HA), heparan sulphate (HS) and heparin (H) was increased, while that of dermatan sulphate (DS) and chondroitin sulphates (ChS) was decreased in MS. The concentration total hexose, fucose and sialic acid were increased in the glycoproteins of the serum in MS. The concentration of gangliosides, glycosyl diglycerides, cerebroside and sulphatide showed significant increase in the serum in MS when compared to controls.

(5) The activity of GAG degrading enzymes beta glucuronidase, beta N-acetyl hexosaminidase, hyaluronidase, cathepsin-D, was increased in MS when compared to the controls. The activity of beta galactosidase and beta fucosidase increased in MS while that of beta glucosidase showed a decrease.

(6) The concentration of total GAG, hexose and fucose in the RBC membrane decreased significantly in MS. The concentration cholesterol and phospholipids were not significantly altered in the RBC membrane in MS

but the cholesterol: phospholipid ratio in the RBC membrane decreased significantly in MS.

(7) Concentration of total serum cholesterol in LDL cholesterol increased significantly while HDL cholesterol was reduced in the plasma in MS. Serum triglycerides and free fatty acids were unaltered in MS.

Discussion

Archaeal Digoxin and Lipid Metabolism - Membrane Na^+-K^+ ATPase Inhibition in Relation to Multiple Sclerosis

The archaeaon steroidelle contributes to lipid synthesis and metabolism. The archaeaon steroidelle DXP pathway and the upregulated pentose phosphate pathway contribute to digoxin synthesis. The results showed that HMG CoA reductase activity, serum digoxin and dolichol were increased in MS while serum ubiquinone was reduced. Previous studied in this laboratory has demonstrated incorporation of ^{14}C-acetate into digoxin in the rat brain indicating that acetyl CoA is the precursor for digoxin biosynthesis in mammals also. The elevated HMG CoA reductase activity correlates well with elevated digoxin levels and reduced RBC membrane Na^+-K^+ ATPase activity. The increase in endogenous digoxin, a potent inhibitor of membrane Na^+-K^+ ATPase, can decrease this enzyme activity. The inhibition of Na^+-K^+ ATPase by digoxin is known to cause an increase in intracellular 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 cell and ATP dependent sequestration of calcium within the endoplasmic reticulum. The magnesium related mitochondrial dysfunction results in defective calcium extrusion from the cell. There is thus a progressive inhibition of Na^+-K^+ ATPase activity first triggered by digoxin. Low intracellular magnesium and high intracellular calcium consequent to Na^+-K^+ ATPase inhibition appear to be crucial to the pathogenesis of MS. Serum magnesium was found to be reduced in MS.[1-13]

Archaeal Digoxin and Immunoregulation in Relation to Multiple Sclerosis - The Fructosoid, Steroidelle and Viroidelle

The archaeaon fructosoid contributes to fructolysis and immune activation. Fructose can contribute to induction of NFKB and immune activation. The archaeaon steroidelle synthesized digoxin induces NFKB producing immune activation. The archaeaon viroidelle secreted RNA viroids can produce immune activation by blocking mRNA function. Increased intracellular calcium activates the calcium dependent calcineurin signal transduction pathway which can produce T-cell activation and secretion of interleukin - 3,4, 5, 6 and TNF alpha. This can 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 oligodendrocyte, the myelin forming cell in MS. 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.[1-13]

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

The archaeaon neurotransminoid shikimic acid pathway contributes to tryptophan and tyrosine synthesis and catabolism generating neurotransmitters

and neuroactive alkaloids. Digoxin, apart from affecting cation transport is also reported to influence the transport of various metabolites across cellular membranes, including amino acids and various neurotransmitters. The results showed that the concentration of tryptophan, quinolinic acid and serotonin were found to be higher in the plasma of patients with MS while that of tyrosine, dopamine and norepinephrine were lower. Thus there is increase in tryptophan and its catabolites and a reduction in tyrosine and its catabolites in the serum of MS patients. This could be due to the fact that digoxin can regulate neutral amino acid transport system with preferential promotion of tryptophan transport over tyrosine. The decrease in membrane Na^+-K^+ ATPase activity in MS could be due to the fact that the hyperpolarising neurotransmitters (dopamine and noradrenaline) are reduced and the depolarising neuroactive compounds (serotonin and quinolinic acid) are increased. The increased levels of quinolinic acid acts as a NMDA agonist producing glutamate excitotoxicity and increasing the intraneuronal calcium load. Quinolinic acid has been implicated in immune activation in other autoimmune diseases like SLE and could contribute to the same in MS. Serotonin, dopamine and noradrenaline receptors have been demonstrated in the lymphocytes. It has been reported that during immune activation serotonin is increased with a corresponding reduction in dopamine and noradrenaline in the brainstem monoaminergic nuclei. Thus elevated serotonin and reduced noradrenaline and dopamine can contribute to the immune activation in MS. The neurotransmitter pattern of reduced dopamine and noradrenaline, and increased serotonin can contribute to the psychosis described in multiple sclerosis.

We had already shown the presence of endogenous morphine in the brain of rats loaded with tyrosine and endogenous strychnine and nicotine in the brain of rats loaded with tryptophan. Serum of patients with multiple sclerosis showed the presence of morphine and strychnine but nicotine was absent. The detection

of increased levels of morphine in multiple sclerosis despite low tyrosine levels may indicate its synthesis from other sources. Morphine has got an immunoregulatory function in the brain. It produces alteration in T-cell deficit in heroin addicts which was shown to consist of their inability to form rosettes on sheep erythrocytes. It has been found to inhibit the expression of antigenic markers for both T-helper and T-suppressor cells. In multiple sclerosis a CD_8 MHC class-1 restricted immune dysregulatory effect has been described. Morphine may contribute to this CD_8 MHC class-1 restricted T-cell defect in multiple sclerosis. Strychnine by blocking glycinergic transmission can contribute to the decreased inhibitory transmission in MS. Serum of patients with MS showed strychnine which can produce increase in intraneuronal calcium load leading to oligodendrocyte apoptosis and immune activation. No nicotine could be detected in MS.[1-13]

Archaeal Digoxin and Regulation of Golgi Body / Lysosomal Function in Relation to Multiple Sclerosis - The Glycosaminoglycoid

The archaeaon glycosaminoglycoid and fructosoid contributes to glycoconjugate synthesis and catabolism by the process of fructolysis. The low magnesium levels consequent to membrane Na^+-K^+ ATPase inhibition can affect the metabolism of glycosaminoglycans, glycoproteins and glycolipids. The elevation in the level of dolichol consequent to its increased synthesis may suggest its increased availability of N-glycosylation of proteins. Magnesium deficiency can lead on to defective metabolism of sponganine 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 glycose 6-phosphate is channelled for the synthesis of glycosaminoglycans (GAG). The results showed an increase in the concentration of serum total GAG, glycolipids (ganglioside,

glycosyl-diglyceride, cerebrosides and sulphatides) and carbohydrate components of glycoproteins (hexose, fucose and sialic acid) in MS. The increase in the carbohydrate components of serum glycoproteins - total hexose, fucose and sialic acid was not to the same extent in MS suggesting qualitative change in glycoprotein structure. In MS the percentage change in total hexose, fucose and sialic acid when compared to the control is 54.3%, 20% and 33% respectively. The pattern of change in individual GAG in the serum was different. The concentration of hyaluronic acid, heparan sulphate and heparin was increased while that of dermatan sulphate and chondroitin sulphates was reduced in the serum of MS patients. The activity of GAG degrading enzymes (beta glucuronidase, beta N-acetyl hexosaminidase, hyaluronidase and cathepsin-D) was increased in the serum of MS patients. The activity of glycohydrolases - beta galactosidase and beta fucosidase was increased while that of beta glucosidase was decreased in the serum of MS patients. Intracellular magnesium deficiency also results in defective ubiquitin dependent proteolytic processing of glycoconjugates as it requires magnesium for its function. The increase in the activity of glycohydrolases and GAG degrading enzymes could be due to reduced lysosomal stability and consequent leakage of lysosomal enzymes into the serum. The increase in the concentration of carbohydrate components of glycoproteins and GAG in spite of increased activity of many glycohydrolases may be due to their possible resistance to cleavage by glycohydrolases consequent to qualitative change in their structure. Proteoglycan complexes formed in the presence of altered calcium / magnesium ratios intracellularly may be structurally abnormal and resistant to lysosomal enzymes and may accumulate.

The protein processing defect can result in defective glycosylation of endogenous myelin glycoprotein antigens and exogenous viral glycoprotein antigens with consequent defective formation of the MHC-antigen complex.

The MHC linked peptide transporter, a P-glycoprotein which transports the MHC-antigen complex to the antigen presenting cell surface, has an ATP binding site which is dysfunctional in the presence of magnesium deficiency. This results in defective transport of the MHC class-1 myelin 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. Defective presentation of the exogenous viral or bacterial glycoprotein antigens can produce immune evasion by the virus / bacteria and viral / bacterial persistence as in the case of retrovirus, herpes virus and chlamydia induced demyelination. A number of fucose and sialic acids containing natural ligands that 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 have been described in MS. Alteration in ganglioside, glycosyl-diglycerides, cerebrosides and sulphatides can affect the structural integrity of myelin. Defectively N-glycosylated myelin glycoproteins and alteration in GAG / proteoglycans of myelin can also affect the structural integrity of myelin leading on to demyelination.[1-13]

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

The archaeaon steroidelle, glycosaminoglycoid and fructosoid contribute to cell membrane formation synthesizing cholesterol by the DXP pathway and glycosaminoglycans by fructolysis. The alteration in the isoprenoid pathway specifically, cholesterol as well as changes in glycoproteins and GAG can affect cellular membranes. The upregulation of the isoprenoid pathway can lead to increased cholesterol synthesis and magnesium deficiency can inhibit

phospholipid synthesis. Phospholipid degradation is increased owing to increase in intracellular calcium activating phospholipase A_2 and D. The total cholesterol and LDL cholesterol were increased and HDL cholesterol was reduced in the serum of MS patients. HDL cholesterol is important in neuronal regeneration. The membrane composition was assessed by RBC membrane cholesterol: phospholipid ratio, carbohydrate residues of glycoproteins and total glycosaminoglycans. The cholesterol: phospholipid ratio of the RBC membrane was decreased in MS. The concentration of total GAG, hexose and fucose of glycoprotein and cholesterol decreased in the RBC membrane and increased in the serum suggesting their reduced incorporation into the membrane and defective membrane formation. The glycoproteins, GAG and glycolipids of the cellular membrane are formed in the endoplasmic reticulum, which is then budded off as a vesicle which fuses with the golgi complex. The glycoconjugates are then transported via the golgi channel and the golgi vesicle fuses with the cell membrane. This trafficking depends upon GTPases and lipid kinases which are crucially dependent on magnesium and are defective in magnesium deficiency. The change in membrane structure produced by alteration in glycoconjugates and cholesterol phospholipid ratio can produce changes in the conformation of Na^+-K^+ ATPase resulting in further membrane Na^+-K^+ ATPase inhibition. 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. Oligodendrocyte, the myelin forming cell in the central nervous system ensheaths several axons during the process of myelination. Alteration in the structure of the oligodendrocyte membrane can affect myelination. Remyelination following demyelination also depends upon heat-shock protein. Digoxin can regulate the function of heat-shock protein which coordinates protein folding and maturation. The heat-shock protein has an ATP/ADP switch domain that regulates its

conformation. Intracellular magnesium deficiency can produce dysfunction of the ATP/ADP switch domain.[1-13]

Archaeal Digoxin and Mitochondrial Dysfunction in Relation to Multiple Sclerosis - The Vitaminocyte

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 MS which may be the result of low tyrosine levels, consequent to digoxin's effect in preferentially promoting tryptophan transport over tyrosine. The aromatic ring portion of ubiquinone is derived from the tyrosine. Ubiquinone, which is an important component of the mitochondrial electron transport chain, is a membrane antioxidant and contributes to free radical scavenging. The increase in intracellular calcium and ceramide 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 defect in mitochondrial oxidative phosphorylation, incomplete reduction of oxygen and generation of the superoxide ion. 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. Lipid peroxidation of myelin lipids can contribute to demyelination. Microglial activation and free radical generation has been implicated in the pathogenesis of immune mediated disorders like MS.

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. Caspase-9 can produce apoptosis of oligodendrocyte, the myelin forming cell in MS leading on to demyelination.[1-13]

Archaeal Digoxin and Hemispheric Dominance in Relation to Multiple Sclerosis

The archaeaon related organelle-steroidelle, neurotransminoid and vitaminocyte contribute to hemispheric dominance. Thus the isoprenoid pathway dysfunction is important in the pathogenesis of MS. This can operate at several levels, (1) Membrane Na^+-K^+ ATPase inhibition and immune activation, (2) Digoxin related tryptophan/tyrosine catabolic patterns and neurotransmitters chanes, (3) Alter glycoconjugate metabolism and changes in myelin structure and myelin glycoprotein antigen presentation, (4) Altered membrane formation and oligodendrocyte mediated myelination, (5) Mitochondrial dysfunction leading on to free radical generation and microglial activation / oligodendrocyte apoptosis. It may reflect a defective neuro-immune integration of the brain due to an upregulated isoprenoid pathway and paroxysmal hypothalamic archaeal digoxin hypersecretion. All these chemical features are suggestive of right hemispheric chemical dominance which can lead to multiple sclerosis.[1-13]

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5

Archaeal Digoxin Mediated Model for Epilepsy

Changes involving the isoprenoid pathway have been described in primary generalised epilepsy. The isoprenoid pathway produces four key metabolites - ubiquinone (membrane antioxidant and component of the mitochondrial electron transport chain), dolichol (involved in N-glycosylation of proteins), digoxin, (an endogenous inhibitor of membrane Na^+-K^+ ATPase) and cholesterol, (1) Involvement of endogenous digoxin like activity (EDLA) has been reported in the epileptic cortex and injection of digoxin into the spinal lymphaticus sac in frog with an epileptogenic focus resulted in sharp increase in epileptiform discharges, (2) Rapport et al. measured Na^+-K^+ ATPase activity in four human epileptic cortices and found a 60% reduction suggesting a role for endogenous digoxin, (3) Digoxin can regulate the transport of neutral amino acids tyrosine and tryptophan, (4) The tryptophan metabolite, quinolinic acid has recently been implicated in the etiology of temporal lobe epilepsy. Altered dolichol and glycoproteins can also contribute to functional disorders like epilepsy. Disordered synaptic connectivity has been described in these disorders. Increased beta amyloid precursor protein expression and increased levels of alpha acid glycoprotein in the serum have been described in epilepsy. RBC membrane changes have also been described in primary generalised epilepsy. There is increased osmotic fragility of the RBC in epilepsy and the RBC membrane glycoproteins have been reported to be abnormal. Similar changes have been postulated to occur in the neuronal membrane.[1-9]

Global warming can lead to osmotic stress consequent to dehydration. The increase in actinidic archaeal growth leads to cholesterol catabolism and digoxin synthesis. Digoxin produces membrane sodium potassium ATPase inhibition and increase in intracellular calcium producing mitochondrial dysfunction. This results in oxidative stress. The oxidative stress and osmotic stress can induce the enzyme aldose reductase which converts glucose to fructose. Fructose has got a low km value for ketokinase as compared to glucose. Therefore fructose gets

phosphorylated more to fructose phosphate and the cell is depleted of ATP. The cell depletion of ATP leads to oxidative stress and chronic inflammation consequent to induction of NFKB. Oxidative stress can open the mitochondrial PT pore producing release of cyto C and activation of the caspase cascade of cell death. The fructose phosphate can enter the pentose phosphate pathway synthesizing ribose and nucleic acid. The depletion of cellular ATP results in generation of AMP and ADP which are acted upon by deaminases causing hyperuricemia. Uric acid can produce endothelial dysfunction and vascular disease. Uric acid can also produce mitochondrial dysfunction. The fructose phosphate can enter the glucosamine pathway synthesizing GAG and producing mucopolysaccharide accumulation. Fructose can fructosylate proteins making them antigenic and producing an autoimmune response. This can lead to global warming related neurological disease.

This study was undertaken to assess, (1) the isoprenoid pathway, (2) the tryptophan / tyrosine catabolic pattern, (3) Glycoconjugate metabolism, and (4) RBC membrane changes as a reflection of neuronal and glial membrane change. A hypothesis implicating neuronal and glial membrane Na^+-K^+ ATPase inhibition as pivotal to all these changes is presented.

Results

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

(2) The concentration of serum tryptophan, quinolinic acid and serotonin was increased in the plasma while that of tyrosine, dopamine and noradrenaline was decreased in primary generalised epilepsy. Nicotine and strychnine were detected in the plasma of patients with primary

generalised epilepsy but were not detectable in control serum. Morphine was not detected in the plasma of these patients.

(3) The concentration of total GAG increased in the serum of primary generalized epilepsy patients. The concentration of hyaluronic acid (HA), heparan sulphate (HS) heparin (H) and chondroitin sulphates (ChS) was increased, while that of dermatan sulphate (DS) was decreased. The carbohydrate residues of glycoprotein and glycolipids showed significant increase in the serum of these patients.

(4) The activity of GAG degrading enzymes was increased in primary generalised epilepsy when compared to the controls. The activity of beta galactosidase, beta fucosidase and beta glucosidase was also increased.

(5) The concentration of total GAG in the RBC membrane was not significantly altered in epilepsy. The concentration of hexose and fucose in the RBC membrane decreased significantly. The concentration cholesterol and phospholipids was significantly decreased in the RBC membrane but the cholesterol: phospholipid ratio in the RBC membrane was not significantly altered.

(6) Concentration of total serum cholesterol and LDL cholesterol increased significantly while HDL cholesterol showed no significant alteration in the plasma in primary generalised epilepsy. Serum triglycerides were unaltered while free fatty acids (FFA) increased.

Discussion

Archaeal Digoxin and Lipid Metabolism - Membrane Na^+-K^+ ATPase Inhibition in Relation to Epileptogenesis

The archaeaon steroidelle contributes to lipid synthesis and metabolism. The archaeaon steroidelle DXP pathway and the upregulated pentose phosphate pathway contribute to digoxin synthesis. The results showed that HMG reductase activity, serum digoxin and dolichol were increased and serum ubiquinone was reduced in primary generalised epilepsy. Previous studies in this laboratory have demonstrated incorporation of ^{14}C-acetate into digoxin in the rat brain indicating that acetyl CoA is the precursor for digoxin biosynthesis in mammals also. The elevated HMG CoA reductase activity correlates well with elevated digoxin levels and reduced RBC membrane Na^+-K^+ ATPase activity. The increase in endogenous digoxin, a potent inhibitor of membrane Na^+-K^+ ATPase, can decrease this enzyme activity. The inhibition of Na^+-K^+ ATPase by digoxin is known to cause an increase in intracellular calcium and a reduction in intracellular magnesium. Serum magnesium was found to be reduced in primary generalised epilepsy. Membrane Na^+-K^+ ATPase inhibition can produce defective neuronal membrane repolarisation and a paroxysmal depolarisation shift resulting in epileptogenesis.[1-9]

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

The archaeaon neurotransminoid shikimic acid pathway contributes to tryptophan and tyrosine synthesis and catabolism generating neurotransmitters and neuroactive alkaloids. The present study showed that the concentration of tryptophan, quinolinic acid, serotonin, strychnine and nicotine was higher in the plasma of epilepsy patients while that of tyrosine, dopamine, morphine, norepinephrine was lower. Thus there is an increase in tryptophan and its

catabolites and a reduction in tyrosine and its catabolites in the patient's serum. Endogenous nicotine and strychnine are synthesized from tryptophan and endogenous morphine from tyrosine. This could be due to the fact that digoxin can regulate neutral amino acid transport system, with a preferential promotion of tryptophan transport over tyrosine. The decrease in membrane Na^+-K^+ ATPase activity in primary generalised epilepsy 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. Dopamine deficiency in primary generalised epilepsy and dopamine receptor blockade producing epileptogenesis have been documented in literature. Low dopamine levels can contribute to the hyperpolactinemia described in epilepsy. The increase in serotonin levels documented here is also significant, as serotonin is a positive modulator of the excitotoxic NMDA receptor. The decrease in noradrenaline observed can also contribute to epileptogenesis, since this catacholamine has been reported to have an antiepileptic action due to its hyperpolarising effect on the neuronal membrane. The neurotransmitter pattern of reduced dopamine, noradrenaline and morphine and increased serotonin, strychnine and nicotine could contribute to epilepsy related psychosis. Quinolinic acid, an NMDA agonist can contribute to NMDA excitotoxicity reported in epilepsy. Strychnine by blocking glycinergic transmission contributes to the decreased inhibitory transmission important in epileptogenesis. Strychnine displaces glycine from its binding sites and the glycine is free to bind to the strychnine insensitive site of the NMDA receptor and promote excitatory NMDA transmission. Nicotine acts as a CNS stimulant and has been reported to promote epileptogenesis.

In the presence of hypomagnesemia, the magnesium block on the NMDA receptor is removed leading to NMDA excitotoxicity. The increased levels of FFA can contribute to epileptogenesis by binding magnesium. This results in

the formation of magnesium soaps in the blood and hypomagnesemia. The increased presynaptic neuronal calcium can produce cyclic AMP dependent phosphorylation of synapsins resulting in increased glutamate release into the synaptic junction and vesicular recycling. Increased intracellular calcium in the post synaptic neuron can also activate the NMDA signal transduction in the postsynaptic neuron. The membrane glutamate transporter (on the surface of the glial cell and presynaptic neuron) is coupled to a sodium gradient which is disrupted by the inhibition of Na^{+}-K^{+} ATPase, resulting in decreased clearance of glutamate by presynaptic and glial uptake at the end of synaptic transmission. By these mechanisms, inhibition of Na^{+}-K^{+} ATPase can promote glutamatergic transmission and excitotoxicity contributing to epileptogenesis.[1-9]

Archaeal Digoxin and Regulation of Golgi Body / Lysosomal Function in Relation to Epileptogenesis - The Glycosaminoglycoid

The archaeaon glycosaminoglycoid and fructosoid contributes to glycoconjugate synthesis and catabolism by the process of fructolysis. The increased availability of dolichol for N-glycosylation of proteins and intracellular Mg^{++} deficiency can upregulate the synthesis of glycosaminoglycans, glycolproteins and glycolipids. The increase in the carbohydrate components-total hexose, fucose and sialic acid was not to the same extent suggesting a qualitative change in glycoprotein structure. Proteoglycan complexes formed in the presence of altered intracellular calcium/magnesium ratios may be structurally abnormal and resistant to lysosomal enzymes and may accumulate. The activity of GAG degrading enzymes and that of glycohydrolases showed significant increase in the serum consequent to reduced lysosomal stability resulting from an alteration in lysosomal membranes. Altered glycoconjugates of the neuronal membrane can lead to disordered synaptic connectivity and the altered sulphated proteoglycan

matrix of synaptic vesicles can modulate neurotransmission leading on to epileptogenesis.[1-9]

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

The archaeaon steroidelle, glycosaminoglycoid and fructosoid contribute to cell membrane formation synthesizing cholesterol by the DXP pathway and glycosaminoglycans by fructolysis. The upregulation of the isoprenoid pathway can lead to increased cholesterol synthesis and magnesium deficiency can inhibit phospholipid synthesis. The concentration of cholesterol and phospholipids as well as carbohydrate residues of glycoproteins decreased in the RBC membrane in epilepsy suggesting that their incorporation into the RBC membrane is defective consequent to inhibition of membrane trafficking enzymes - lipid kinases and GTPases in the presence of magnesium deficiency. Altered membrane structure can contribute to membrane Na^+-K^+ ATPase inhibition and also defective lysosomal stability. This can contribute to epileptogenesis.[1-9]

Archaeal Digoxin and Mitochondrial Dysfunction in Relation to Epileptogenesis - The Vitaminocyte

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. In primary generalised epilepsy there is a mitochondrial dysfunction and increased generation of free radicals consequent to, (i) Digoxin induced decreased tyrosine availability which leads to inhibition of ubiquinone synthesis, (ii) Increased intracellular calcium opening up the mitochondrial PT pore and reduced intracellular magnesium inhibiting ATP synthase, and (iii) Increased intracellular calcium inducing NO synthase and liberating NO. There is reduced free radical scavenging owing to ubiquinone

deficiency. A mitochondrial dysfunction can remove the magnesium block of the NMDA receptor contributing to glutamate excitotoxicity and epileptogenesis. The opening of the mitochondrial PT pore leads to rupture of the outer membrane, and release of cytochrome C with consequent activation of caspase-9 and the apoptotic cascade. Disordered apoptosis can produce defective synaptogenesis and synaptic connectivity contributing to epileptogenesis.[1-9]

Archaeal Digoxin and Immunoregulation in Relation to Epileptogenesis - The Fructosoid, Steroidelle and Viroidelle

The archaeaon fructosoid contributes to fructolysis and immune activation. Fructose can contribute to induction of NFKB and immune activation. The archaeaon steroidelle synthesized digoxin induces NFKB producing immune activation. The archaeaon viroidelle secreted RNA viroids can produce immune activation by blocking mRNA function. In primary generalised epilepsy increased intracellular calcium activates the calcium dependent calcineurin signal transduction pathway which can produce T-cell activation and secretion of interleukin-1 and TNF alpha (Tumour necrosis factor alpha). TNF alpha can bind to its receptor TNFR1 and activates the transcription factors NFkB and AP-l leading to the induction of proinflammatory and immunomodulatory genes. This leads to immune activation documented in primary generalised epilepsy.[1-9]

Archaeal Digoxin, Oncogene Activation and Epileptogenesis

The archaeaon secreting RNA viroids is called the viroidelle. 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. In primary generalised epilepsy there is an oncogenic tendency owing to, (i) increased intracellular calcium activating phospholipase C beta which results in increased production of diacyglycerol (DAG) with consequent activation of protein kinase C and the MAP kinase cascade, (ii) The decreased intracellular magnesium can produce dysfunction of GTPase activity of the alpha-subunit of G-protein and ras oncogene activation, as more of the ras is bound to GTP rather than GDP, (iii) The activation of P_{53} is impaired owing to intracellular magnesium deficiency producing a phosphorylation defect. This can lead on to development of benign neural tumours described in histopathological sections of surgically resected temporal lobe tissues in epilepsy.[1-9]

Archaeal Digoxin and Hemispheric Dominance in Relation to Epileptogenesis

The archaeaon related organelle - steroidelle, neurotransminoid and vitaminocyte contribute to hemispheric dominance. Primary generalised epilepsy could thus be considered as a syndrome of paroxysmal digoxin hypersecretion consequent to an upregulated isoprenoid pathway. The upregulated isoprenoid pathway and hyperdigoxinemia is suggestive of right hemispheric dominance. Right hemispheric dominance can contribute to epileptogenesis.[1-9]

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