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The Endosymbiotic Archaea, Fructose Disease, Chronic Psychiatric Disease and Global Warming

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

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

Global warming can lead to osmotic stress consequent to dehydration. The increase in actinidic archaeal growth leads to cholesterol catabolism and digoxin synthesis. Digoxin produces membrane sodium potassium ATPase inhibition and increase in intracellular calcium producing mitochondrial dysfunction. This results in oxidative stress. The oxidative stress and osmotic stress can induce the enzyme aldose reductase which converts glucose to fructose. Fructose has got a low km value for ketokinase as compared to glucose. Therefore fructose gets phosphorylated more to fructose phosphate and the cell is depleted of ATP. The cell depletion of ATP leads to oxidative stress and chronic inflammation consequent to induction of NFKB. 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 psychiatric 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 civilisation - metabolic syndrome, schizophrenia, autism, cancer, autoimmunity and degenerations. The gut microbiota drives human evolution. The humans don't host the gut microbiota but the gut microbiota host us. The human system forms an elaborate culture laboratory for the propagation and survival of the microbiota. The human system is induced by the microbiota for their survival and growth. The human system exists for the microbiota and not the other way round. The same mechanism holds good in plant systems. Plant started the colonized earth as they started symbiosing with bacteria in the roots systems which can derive nutrients from the soil. Human beings form a mobile culture laboratory for the more effective propagation and survival of the microbiota. The microbiota induces the formation of specialized immune cells called innate lymphoid cells. The innate lymphoid cells will direct the lymphocytes not to attack the beneficial bacteria. Thus the endosymbiotic archaea and the gut archaea induce human, primate and animal evolution to generate structures for them to survive and propagate. The source of endosymbiotic archaea, the third element of life is the colonic archaea that leaks into the tissue spaces and blood systems due to breach in the gut blood barrier. The increase in colonic archaea is due to the starvation of the gut microbiota consequent to a low fibre diet. This

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

The 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 adipogeneis. Fructose induces ChREBP and SREBP elements. This results in increased hepatic lipogenesis by the induction of the enzyme fatty acid synthase, acetyl CoA carboxylase and 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
Schizo	31.14	4.446	22.19	2.634	11.63	3.081	21.50	1.714
Autism	28.66	5.089	24.09	2.146	12.30	1.621	22.60	3.054
AD	33.13	2.754	19.87	1.646	11.37	1.406	22.97	3.662
PD	30.24	4.551	22.72	1.955	11.93	2.999	20.13	1.507
Bipolar	29.88	5.150	22.29	1.641	10.87	1.895	23.47	2.878
F value	17.373		13.973		13.903		21.081	
p value	< 0.01		< 0.01		< 0.01		< 0.01	

Table 2

	Total TG		Serum ATP levels		Uric acid		Anti-aldolase	
	Mean	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**
Normal	124.00	3.688	2.50	0.405	5.70	0.369	7.50	1.704
Schizo	244.00	31.383	0.72	0.102	8.65	0.701	1.35	0.319
Autism	284.30	19.743	0.87	0.072	8.14	0.538	1.35	0.218
AD	244.70	22.106	0.82	0.121	8.74	0.687	1.70	0.361
PD	284.30	19.945	0.83	0.090	8.90	0.579	2.03	0.232
Bipolar	289.89	23.406	0.74	0.115	9.59	0.783	1.80	0.402
F value	16.378		59.169		14.166		55.173	
p value	< 0.01		< 0.01		< 0.01		< 0.01	

Table 3

	Anti-enolase		Anti-pyruvatekinase		Anti-GAPDH	
	Mean	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**
Normal	1.50	0.358	50.40	5.960	5.20	0.363
Schizo	0.40	0.142	22.02	11.954	1.31	0.235
Autism	0.20	0.060	19.27	2.201	1.20	0.205
AD	0.38	0.205	18.87	3.899	1.37	0.305
PD	0.42	0.208	20.11	3.220	1.44	0.342
Bipolar	0.39	0.124	18.93	6.447	1.78	0.355
F value	14.091		21.073		58.769	
p value	< 0.01		< 0.01		< 0.01	

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2

Archaeal Digoxin Mediated Model for Schizophrenia

Introduction

Changes involving the isoprenoid pathway have been described in schizophrenia and bipolar mood disorder. 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. Decreased ubiquinone levels have been reported in the erythrocyte in schizophrenia. Involvement of the endogenous dioxin like factor (EDLF) has been reported in the brain in bipolar mood disorder. Altered levels of dolichol in the brain and altered glycoproteins in the serum and brain have been reported in schizophrenia.

Archaeal EDLF may play an important role in the pathophysiology of bipolar mood disorder. It was proposed that a hypothalamic-pituitary-adrenal dysregulation frequently documented in major mood disorders may underlie a pathological increase in the production of EDLF which suppress Na^+-K^+ ATPase activity. It was also observed that in human bipolar patients, mania and depression are both characterised by decreased membrane Na^+-K^+ ATPase activity. It is well known that schizophrenia and bipolar mood disorder can occur in the same families suggesting a common genetic origin for both the disorders.

Archaeal digoxin can regulate the transport of neutral amino acids, tyrosine and tryptophan. L-tryptophan is a precursor for the biosynthesis of a number of neuroactive substances. The amino acid apart from being a precursor for serotonin biosynthesis is also the precursor for the biosynthesis of kynurenines. There is a decrease in RBC L-tryptophan uptake in schizophrenic patients and the alteration in RBC L-tryptophan uptake is associated with loss of impulse control in schizophrenic patients. The depressive syndromes were characterized by a decrease of facilitated diffusion of tyrosine, an increase of facilitated

diffusion of tryptophan and a decrease in the index of diffusion of tyrosine/tryptophan. It has been reported that appearance of a transient neurologic and psychiatric syndrome occurs in patients receiving tryptophan in doses ranging from 2 to 10 g. Neuronal membrane changes have also been described in schizophrenia (Brown, 1994). As mentioned above the isoprenoid pathway produces four metabolites important in neuronal membrane structure and function cholesterol, digoxin, ubiquinone (membrane antioxidant) and dolichol.

Archaeal digoxin by altering intracellular calcium / magnesium ratios and changes in ubiquinone levels can contribute to mitochondrial dysfunction and free radical generation. There is evidence of free radical pathology in schizophrenia as evidenced by abnormal activities of critical antioxidant enzymes and other indices of lipid peroxidation in the plasma.

Hypomagnesemia consequent to membrane Na^+-K^+ ATPase inhibition and dolichol can alter glycoconjugate metabolism. Altered dolichol and glycoproteins can also contribute to functional disorders like schizophrenia. Disordered synaptic connectivity has been described in this disorder. Increased expression of the neuronal cell adhesion molecule (N-CAM) has been described in schizophrenia.

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 psychiatric 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. A hypothesis implicating 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 schizophrenia. The concentration of serum ubiquinone, the activity of erythrocyte membrane Na^{+}-K^{+} ATPase and serum magnesium war decreased.

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

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

(4) The concentration of total glycosaminoglycans (GAG) increased in the serum of schizophrenia patients. The concentration of heparan sulphate (HS) heparin (H) dermatan sulphate (DS), chondroitin sulphates (ChS) and hyaluronic acid (HA) was increased. 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, cerebrosides and sulphatides showed significant increase in the serum in these patients.

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

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

(7) Concentration of total serum cholesterol and LDL cholesterol increased significantly in schizophrenia while HDL cholesterol was unaltered. Serum triglycerides increased in these patients while free fatty acids levels were unaltered.

(8) The activity of superoxide dismutase (SOD), catalase, glutathione reductase and glutathione peroxidase in the erythrocytes decreased significantly in schizophrenia. The concentration of malon dialdehyde (MDA), hydroperoxides, conjugated dienes and nitric oxide (NO) increased significantly. The concentration of reduced glutathione

decreased in schizophrenia. Alpha-tocopherol was unaltered. Serum ceruloplasmin, iron binding capacity and albumin decreased significantly in these patients.

Discussion

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

The archaeaon steroidelle DXP pathway and the upregulated pentose phosphate pathway contribute to digoxin synthesis. The increase in the activity of HMG CoA reductase in schizophrenia suggests an upregulation of the isoprenoid pathway. There is marked increase in plasma dioxin mid dolichol and this increase may be a consequence of increased channelling of intermediates of the isoprenoid pathway for their biosynthesis. In this connection, incorporation of ^{14}C-acetate into digoxin in the rat brain has been shown by us indicating that acetyl CoA is the precursor of digoxin biosynthesis in mammals also. The increase in endogenous digoxin, a potent inhibitor of membrane Na^+-K^+ ATPase, can decrease this enzyme activity. In schizophrenia there was significant inhibition of the RBC membrane Na^+-K^+ ATPase. The inhibition of Na^+-K^+ ATPase by digoxin is known to cause an increase in intracellular calcium resulting from increased Na^+-Ca^{++} exchange, increased entry of calcium via the voltage gated calcium channel and increased release of calcium from intracellular endoplasmic reticulum calcium stores. This increase in intracellular calcium by displacing magnesium from its binding sites causes a decrease in the functional availability of magnesium. This decrease in the availability of magnesium can cause decreased mitochondrial ATP formation which along with low magnesium can cause further inhibition of Na^+-K^+ ATPase, since the ATP-magnesium complex is the actual substrate for this reaction. Cytosolic free calcium is normally buffered by two mechanisms, ATP

dependent calcium extrusion from the cell and ATP dependent sequestration of calcium within the endoplasmic reticulum. The magnesium related mitochondrial dysfunction results in defective calcium extrusion from the cell. There is thus progressive inhibition of Na^+-K^+ ATPase activity first triggered by digoxin. Low intracellular magnesium and high intracellular calcium consequent to Na^+-K^+ ATPase inhibition appear to be crucial to the pathophysiology of schizophrenia. The intracellular positive calcium signal and negative magnesium signal can regulate diverse cellular process. Calcium on entry into the cell is used to charge up the internal endoplasmic reticulum stores which then release a burst of signal calcium responsible for activating a large variety of calcium dependent cellular processes. The information processing capability of the calcium signalling system is enhanced by amplitude and frequency modulation. The calcium is released from channels on internal endoplasmic reticulum (ER) individually or in small groups (blip/quark and puffs/sparks). Further diversity of calcium signalling is produced by compartmentalization as cytosolic calcium signal and nuclear calcium signal. Serum magnesium was assessed in schizophrenia and was found to be reduced.

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

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 presence of endogenous morphine in the brain of rats loaded with tvrosine and

endogenous strychnine and nicotine in the brain of rats loaded with tryptophan. The results showed that the concentration of tryptophan, quinolinic acid and serotonin was higher in the plasma of patients with schizophrenia while that of tyrosine, dopamine, and norepinephrine was lower. Morphine was absent in the serum of patients with schizophrenia as well as in control subjects. Serum of patients with schizophrenia, showed the presence of strychnine and nicotine. Thus there is increase in tryptophan and its catabolites and a reduction in tvrosine and its catabolites in the patient's serum. This is in concordance with results of other workers. 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 neutronal tryptophan can upregulate tryptophan catabolism and decreased neuronal tyrosine can downregulate tyrosine catabolism. The decrease in membrane Na^+-K^+ ATPase activity in schizophrenia could be due to the fact that the hyperpolarising neurotransmitters (dopanilne and noradrenaline) are reduced and the depolarising neuroactive compounds (serotonin, strychnine, nicotine and quinolinic acid) are increased.

In schizophrenia the glutamatergic excitotoxic mechanism has been described. In the presence of hypomagnesemia, the magnesium block on the NMDA receptor is removed leading to NMDA excitotoxicity. The increased presynaptic neuronal calcium can produce cyclic AMP dependent phosphorylation of synapsins resulting in increased neurotransmitter release into the synaptic junction and vesicular recycling. Increased intracellular calcium in the post synaptic neuron can also activate the calcium dependent NMDA signal transduction. The plasma membrane neurotransmitter transporter (on the surface of the glial cell and presynaptic neuron) is coupled to a sodium gradient, which is disrupted by the inhibition of Na^+-K^+ ATPase, resulting in decreased clearance of glutamate by presynaptic and glial uptake at the end of synaptic transmission. By these mechanisms, inhibition of Na^+-K^+ ATPase can promote glutamatergic

transmission. The elevated levels of quinolinic acid, strychnine and serotonin can also contribute to NMDA excitotoxicity. Strychnine displaces glycine from its binding sites and inhibits glycinergic inhibitory transmission in the brain. The glycine is free to bind to the strychnine insensitive site of the NMDA receptor and promote excitatory NMDA transmission (lshimaru et al., 1994). Strychnine by blocking glycinergic transmission can contribute to the decreased inhibitory transmission in schizophrenia. Quinolinic acid and serotonin are also positive modulators of the NMDA receptor and could contribute to glutamate excitotoxicity. The dopamine hypothesis of schizophrenia postulates increased dopaminergic activity in the mesolimbic dopaminergic system. However there has been no consistent evidence of increased turn-over of dopamine or its metabolites in the CSF in schizophrenia. Nicotine by interacting with nicotinic receptors can facilitate the release of dopamine, promoting the dopaminergic transmission in the brain. This can explain the increased dopaminergic transmission in the presence of decreased dopamine levels. The noradrenaline hypothesis of schizophrenia suggests damage to the noradrenergic fibers originating in the locus coeruleus resulting from defect in the activity of dopamine. The low levels of noradrenaline reported in our study agrees with a defect in noradrenergic transmission but dopamine levels are also reduced suggesting that the defect does not lie at the level of dopamine beta hydroxylase (DBH). The excess serotonin level documented in the serum of patients of schizophrenia is significant and is in agreement with the serotoninergic transmission reported in this disorder previously.

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

The archaeaon glycosaminoglycoid and fructosoid contributes to glycoconjugate synthesis and catabolism by the process of fructolysis. The

membrane Na^+-K^+ ATPase inhibition related magnesium depletion can affect the metabolism of glycosaminoglycans, glycoproteins and glycolipids. The elevation of 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 magnesium as glycolysis, the 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 diglyceride, cerebrosides and sulphatides) and carbohydrate components of glycoproteins (hexose, fucose and sialic acid) in schizophrenia. The increase in the carbohydrate components - total hexose, fucose and sialic acid-in schizophrenia was not to the same suggesting qualitative change in glycoprotein structure. The individual GAG fractions in the serum-heparan sulphate (HS), chondroitin sulphates (ChS), heparin (H), hyaluronic acid and dermatan sulphate increased in schizophrenia. The activity of GAG degrading enzymes (beta glucuronidase, beta N-acetyl hexosaminidase, hyaluronidase and cathepsin-D) showed significant increase in the serum in schizophrenia. The activity of serum beta fucosidase and beta galactosidase increased while that of beta glucosidase was unaltered. 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 and GAG degrading enzymes may be due to their possible resistance to cleavage 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.

Alteration in the sulphated proteoglycan matrix of the synaptic vesicles can alter neurotransmitter release into the synapse and produce a functional disorder like schizophrenia. Altered glycoproteins, glycolipids and GAG of the neuronal membrane can also contribute to schizophrenia by producing disordered synaptic connectivity. Disordered synaptic connectivity in the limbic allocortex caused by abnormal migration of neurons along the radial glial cells has been described in schizophrenia. 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 MHC-antigen complex to the antigen presenting cell surface, has an ATP binding site. The peptide transporter is dysfunctional in the presence of magnesium deficiency. This results in defective transport of the MHC class-1 glycoprotein antigen complex to the antigen presenting cell surface for recognition by the CD4 or CD8 cell. Defective presentation of the endogenous neuronal glycoprotein antigen can explain the immune dysregulation in schizophrenia. An autoimmune hypothesis for schizophrenia has been postulated by certain groups of workers. Anti-brain antibodies have been described in schizophrenia contributing to its pathogenesis. A number of fucose and sialic acid containing natural ligands are involved in trafficking of leukocytes and similar breaches in the blood brain barrier and adhesion of the lymphocyte producing leukocyte trafficking and extravasation into the perivascular space can contribute to the autoimmune phenomena in schizophrenia. Defective presentation of exogenous viral antigens can produce immune evasion by the virus and viral persistence. A virogene hypothesis for schizophrenia has also been described. Borna virus and influenza virus has been implicated in the pathogenesis of schizophrenia. 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 (Tumour necrosis factor alpha). This can also explain the immune activation in schizophrenia contributing to the autoimmunity. Membrane Na^+-K^+ ATPase inhibition can produce immune activation and is reported to increase CD_4/CD_8 ratios as exemplified by the action of lithium, a Na^+-K^+ ATPase inhibitor. 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, which can contribute to defective synaptogenesis and synaptic connectivity in schizophrenia. Defective apoptosis has been related to the developmental abnormality in the limbic system, frontal cortex and basal ganglia in schizophrenia.

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

The archaeaon steroidelle, glycosaminoglycoid and fructosoid contributes 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 concentration of cholesterol increased in the RBC membrane and serum in schizophrenia while the concentration of phospholipids decreased in the RBC membrane. The cholesterol: phospholipid ratio of the RBC membrane was increased in schizophrenia. The concentration of total GAG, hexose and fucose content of glycoproteins 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 the 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. The defective peroxisomal membrane leads to catalase dysfunction, which has been documented in schizophrenia.

Archaeal Digoxin and Mitochondrial Dysfunction in Relation to Schizophrenia

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 schizophrenia, 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 tyrosine. Ubiquinone, which is an important component of the mitochondrial electron transport chain, is a membrane antioxidant and contributes to free radical scavenging. The increase in intracellular calcium can open the mitochondrial PT pore causing a collapse of the H^+ 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 an 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 intracellular calcium also can activate phospholipase A_2 resulting in increased generation of arachidonic acid, which n 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 once 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 and reduced glutathione in schizophrenia. The neurotransmitter NO has got a behavioural function in the brain and an aggressive behaviour has been attributed to increased NO in the brain. The activity of enzymes involved in free radical scavenging like superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase is decreased in schizophrenia suggesting reduced free radical scavenging. This agrees with work by previous authors. Alpha-tocopherol was unaltered in schizophrenia. The concentration of ceruloplasmin and iron binding capacity decreased significantly in schizophrenia suggesting increased amounts of free iron and copper, promoting free radical generation. Ceruloplasmin is a 132 KD monomeric copper oxidase, which has been implicated in iron metabolism because of its catalytic oxidation of Fe^{2+} to Fe^{3+} (ferroxidase activity). In the presence of iron in Fe^{2+} form the conversion of H_2O_2 to hydroxyl radical is greatly increased. Low ceruloplasmin results in more of the

iron to be in Fe^{2+} form. It has been shown that ceruloplasmin increases iron uptake by cells increasing the apparent affinity for the substrate by three times. Low ceruloplasmin levels can result in decreased iron uptake and this results in an increased amount of free iron. The intra cellular magnesium deficiency can produce ribosomal dysfunction and inhibition of protein synthesis as noted by decrease in serum albumin in schizophrenia. The low serum ceruloplasmin levels may be a consequence of reduced ceruloplasmin synthesis. The peroxisomal membrane is defective owing to the membrane Na^+-K^+ ATPase inhibition related defect in membrane formation and leads to reduced catalase activity. Glutathione is synthesized by the enzyme glutathione synthetase, which needs magnesium and ATP. The low intracellular magnesium consequent to Na^+-K^+ ATPase inhibition and the resulting low ATP synthesis 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 downregulation of the pentose phosphate pathway with consequent decreased generation of NADPH. Thus glutathione system of free radical scavenging is defective in the presence of membrane 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. Mitochondrial dysfunction related free radical generation has been implicated in the pathogenesis of schizophrenia. Mitochondrial dysfunction can

remove the magnesium block of the NMDA receptor leading to excitotoxicity contributing to the pathogenesis of schizophrenia.

The increased intracellular calcium and ceramide related opening of the mitochondrial PT pore also lead to volume dysregulation of the mitochondria causing hyperosmolality of the matrix and expansion of the matrix space. The outer membrane of the mitochondria ruptures and releases apoptosis inducing factor and cytochrome C into the cytoplasm. This results in activation of caspase-9. Caspase-9 can produce apoptosis of the cell. Apoptosis can produce defective synaptogenesis and synaptic connectivity contributing to functional disorders like schizophrenia. We have been able to demonstrate neuronal degeneration and apoptosis in the digoxin injected rat brain.

Archaeal Digoxin and Consciousness

The increase in serum digoxin levels in schizophrenia is significant. It has been postulated that there is an underlying generalised disorder of consciousness or self awareness that impairs the ability to think with metarepresentations in schizophrenia. Digoxin, a membrane Na^+-K^+ ATPase inhibitor, probably regulates conscious perception. The elements of conscious perception include perceptual binding, focussed attention and short term memory. The evidence of increased hypothalamic archaeal digoxin points to a role for the hypothalamus. The hypothalamus is connected to the thalamus by the mamillothalamic tract and digoxin may play a role in regulating these synapses. There are two-way connections between the cerebral cortex and the thalamic nucleus. There are also two-way connections between the cerebral cortex and hypothalamus and digoxin may possibly regulate these synapses also. The hypothalamus-thalamus-cerebral cortex reverberatory circuit would play a role in mediating conscious perception.

Perceptual binding important in consciousness occurs when all the neurons associated with any one object's perceptual map in layer 5 of the cerebral cortex fire in bursts and in a synchronised pattern but out of synchrony with those representing other objects. When an object is perceived there is a simultaneous activation of the cerebral cortex-hypothalamic two-way connections and liberation of digoxin from the hypothalamus to stimulate the widely dispersed cerebral cortical neurons receiving the incoming perception and their resultant synchronised burst firing. Digoxin by the sodium potassium ATPase inhibition it produces can lead on to a paroxysmal depolarisation shift resulting in sustained synchronised burst firing of cerebral cortical neurons.

Short-term memory important in conscious perception depends on the hypothalamic-thalamic-cerebral cortex reverberatory circuit as well as the phenomena of sustained synchronised burst firing of neurons in layer 5 of the cerebral cortex. Sustained synchronised burst firing produced by digoxin can temporarily strengthen the relevant synapses so that this particular pattern of firing is recalled quickly which is a type of short term memory. Transient synaptic changes of this type are due to alteration in the presynaptic neuronal calcium produced by digoxin. The thalamic-cerebral cortex reverberatory circuit mediating short term memory is glutainatergic and digoxin could amplify the circuit by its inhibitory effect on glial uptake of glutamate and increasing synaptic glutamate content.

All axons that pass either way between the cerebral cortex and thalamic nucleus must go through the thalamic reticular nucleus and all give off collateral excitatory glutamatergic abranches that innervate the reticular nucleus. The reticular nucleus in turn provides an inhibitory GABAergic innervation back to the thalamic nucleus that provides the input. The reticular nucleus is involved in mediating selective attention by intensifying or detaching a particular active thalamic input into the cortex. The amplification or focussing and detachment of

attention occurs by digoxin's effect in promoting glutamatergic transmission in the collaterals to the reticular nucleus by inhibiting the glial uptake of the glutamate and increasing its synaptic content. The back projections from the cerebral cortical perceptual map of the external world to the hypothalamus decides whether hypothalamic archaeal digoxin act on the glutamatergic collaterals to the reticular nucleus and thus focus or detach attention.

In schizophrenia hypersensitivity to perceptual stimulae is noticed as a deficit and patients find it difficult to screen out various stimuli and to focus on one piece of information. The defective stimulus barrier causes difficulty throughout every phase of development. The increased secretion of digoxin produces a hyperconscious state with increased focused attention, perceptual binding and short term memory. The altered glycoconjugates in schizophrenia lead to disordered synaptic connectivity in the hypothalamic-thalamic-cerebral cortical circuit leading to disordered conscious perception. Cortical cytoarchitectural disorganization of the temporolimbic cortex has been reported in schizophrenia.

The perceived element in quantal or subliminal perception which could play a role in schizophrenic symptomatology could be the quanta of light, sound, vibration pressure and matter dependent electric and magnetic fields. The brain functions as a quantum computer with the quantum computer memory elements constituting of superconducting quantum interference devices - the SQUIDS which can exist as superpositions of macroscopic states. Bose condensation, the basis of superconductivity is achievable at room temperature in the Frohlich model in biological systems. The dielectric protein molecules and polar sphingolipids of the neuronal membrane, nucleosomes which are a combination of basic histones and nucleic acid and cytoplasmic magnetite molecules are excellent electric diplole oscillators which exist under a steep neuronal membrane voltage gradient. The individual oscillators are energised with a constant source of pumping energy from the outside, by digoxin binding to

membrane sodium potassium ATPase and producing a paroxysmal depolarisation shift in the neuronal membrane. This prevents the dipole oscillators from ever settling into thermal equilibrium with the cytoplasma and the interstitial fluid which is always kept at constant temperature. There are connections between the hypothalamus and cerebral cortex and digoxin may serve as a neurotransmitter for these synapses. Bose condensed states produced by the digoxin mediated dielectric protein molecular pumped phonon system could be used to store information which might be encoded all within the lowest collective frequency mode - by appropriately adjusting the amplitudes of and phase relations between the dipole oscillators. The external world sensory impressions exist in the cortical dipole oscillators as probabilistic multiple superimposed patterns - the U phase of quantum mechanics. The part of the incoming quantal data maps of the external world built by subliminal perception in logical sequence and corollary to the cerebral cortical external world maps built by conscious perception is chosen. Hypothalamo-cerebral cortical connections mediated by digoxin acting on the neuronal membrane help to magnify the chosen map to I graviton criteria and to the threshold required for the neuronal network to fire and consciousness. It is then integrated in to the cerebral cortical conscious perceptual external world map. The comparison occurs by the quantal non-local quasicrystal tiling effect which mediates the activation and deactivation of synapses through the contraction and growth of dendritic spines.

This model of quantal perception gives a mechanism for extrasensory or subliminal perception. Hallucination could be due to subliminal extrasensory perception. Paranoid delusions of persecution and alien control could be due to subliminal perception of thoughts of other persons. Normally quantal subliminal perception plays a minor role being a primitive form of perception and is subservient to conscious perception. Hypothalamic archaeal digoxin induced

altered synaptic glycoproteins can lead to synaptic connectivity defects in the hypothalamic-thalamic-cerebral cortical circuit mediating conscious perception and disrupt the conscious perceptive mechanism in schizophrenia. But increased hypothalamic archaeal digoxin secretion also leads to a hyperfunctional digoxin mediated dielectric protein pumped phonon system and hypersensitive subliminal quantal perception, which is also defectively integrated in to conscious perception and is not regulated by conscious perception in schizophrenia. The R part of quantal subthreshold perception is not deterministic and it introduces a completely random element into the time evolution and in the operation of R there might be a role for free will, an important component of conscious perception. It is consciousness that converts the world of probabilities in to the classical objective real world of matter by the act of making an observation. This process is deranged if the observer or human consciousness is dysfunctional owing to a disordered hypothalamic-thalamic-cerebral cortical circuit. This would lead to defective perception of the external world and delusions such as seeing a rope as a snake. ECT produces loss of consciousness and benefits in schizophrenia by interfering with the system of biological dipole oscillator.

Archaeal Digoxin and Integration of Brain Function

Archaeal digoxin can thus integrate multiple brain functions. Digoxin can regulate neuronal transmission and conscious perception in the brain by its effect on neutral amino acid and neurotransmitter transport. Digoxin can also play a role in endocrine integration. The hypothalamic hormone secretion is regulated by the biogenic amines noradrenaline, dopamine and serotonin. Digoxin by regulating the release and uptake of these neurotransmitters can control hypothalamic hormone secretion. Digoxin, by its lithium like action in modulating G-protein function and by facilitating calcium induced signal

transduction consequent to increased sodium-calcium exchange, can regulate the function of these hormones. Digoxin can act as an immuno-modulator owing to its effect on calcineurin signal transduction in the lymphocyte and subsequent immune activation. Schizophrenia can thus be considered as a syndrome of paroxysmal hypothalamic archaeal digoxin hypersecretion contributing to defective neuro-immuno-endocrine integration consequent to an upregulated isoprenoid pathway.

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3

Archaeal Digoxin Mediated Model for OCD / TIC Syndrome

Introduction

The study focuses on alterations in the isoprenoid pathway in obsessive compulsive disorder (OCD) and la tourette's syndrome (TS). Alteration in the cation pump has been described in several neuropsychiatric disorders and an endogenous inhibitor of membrane Na^+-K^+ ATPase has been described. Digoxin is a steroidal glycoside synthesized by the isoprenoid pathway and is reported to be secreted by the human hypothalamus. Digoxin is also reported to modulate neutral amino acid and neurotransmitter transport. In OCD PET studies have shown abnormalities in the orbitofrontal cortex, striatum and cingulate cortex. A series of discrete, parallel, neuroanatomic circuits connecting the prefrontal cortex, striatum, globus pallidus and thalamus, have been described forming a fronto-striato-pallido-thalamo-cortical loop. It involves both direct and indirect pathways the former being facilitatory and the latter inhibitory. The proposed model of OCD pathophysiology is an imbalance of direct > indirect pathway tone in the fronto-subcortical circuits. Serotoninergic drugs change the relative balance of tone through the indirect versus direct orbitofrontal-subcortical pathways thereby normalising the pathological state seen in OCD. Drugs with selective D_1 blockade which specifically decreases activity in the direct pathway also reduce OCD symptoms. The relative preponderence of serotoninergic versus dopaminergic transmission would play an important role in the genesis of OCD symptoms. There is no agreement regarding the pathophysiology of tourette syndrome (TS). The prevailing view is the so-called dopamine hypothesis, which in essence suggests that the syndrome is caused either by disorders in presynaptic release of dopamine or by a dysfunction of its postsynaptic receptors. Other pathogenetic mechanisms have been proposed such as abnormal serotonin uptake, and a hyperactive endogenous opioid system known to influence the sensitivity of dopamine receptors. Other authors have implicated the noradrenergic system and

Kurlan has suggested that TS may occur following an inhibition of the excitatory amino acid, glutamate that regulates the dopamine uptake in neurons within the basal ganglia. Because of the reports implicating digoxin in regulating neurotransmitter transport, the isoprenoidal pathway and digoxin synthesis were studied in TS and OCD. The other metabolites of the isoprenoid pathway of significance are ubiquinone, cholesterol and dolichol. Membrane Na^+-K^+ ATPase inhibition is reported to be lead to magnesium depletion and intracellular calcium excess. Hypomagnesemia and dolichol can affect glycoconjugate metabolism. Alteration in ubiquinone levels and intracellular calcium\magnesium ratios can affect mitochondrial function and free radical metabolism. Therefore the following parameters were studied in OCD and TS: plasma HMG CoA reductase activity, serum cholesterol, digoxin, dolichol, ubiquinone, magnesium and RBC Na^+-K^+ ATPase activity. The levels of serum tyrosine, tryptophan and their catabolites, glycoconjugate metabolism, free radical metabolism and membrane composition were also assessed. The results are presented in this paper and a hypothesis regarding the role of membrane Na^+-K^+ ATPase activity in the pathogenesis of these disorders is discussed. The parameters were also assessed in right hemispheric, left hemispheric and bihemispheric dominant individuals to find out whether hemispheric dominance has any correlation with these neuropsychiatric syndromes.

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 psychiatric disease.

Results

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

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

(3) Nicotine and strychnine were not detected in the plasma of OCD and la Tourette's syndrome patients. Morphine was detected in the plasma of OCD and TS patients.

(4) The concentration of total glycosaminoglycans (GAG) decreased in the serum of OCD and TS patients. The concentration of heparan sulphate (HS) heparin (H), dermatan sulphate (DS), chondroitin sulphates (ChS)

and hyaluronic acid (HA) was decreased. The concentration total hexose, fucose and sialic acid were decreased in the glycoproteins of the serum of TS and OCD patients. The concentration of gangliosides, glycosyl-diglycerides, cerebrosides and sulphatides showed significant decrease in the serum of OCD and TS patients.

(5) The activity of glycosaminoglycan (GAG) degrading enzymes - beta glucuronidase, beta N-acetyl hexosaminidase, hyaluronidase and cathepsin-D was decreased in the serum of OCD and TS patients when compared to the controls. The activity of beta galactosidase, beta fucosidase and beta glucosidase decreased in the serum of OCD and TS cases.

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

(7) The activity of superoxide dismutase (SOD), catalase, glutathione reductase and glutathione peroxidase in the erythrocytes increased significantly in the serum of OCD and TS cases. The concentration of malon dialdehyde (MDA), hydroperoxides, conjugated dienes and nitric oxide (NO) decreased significantly in the serum of OCD and TS cases. The concentration of reduced glutathione increased in OCD and TS cases. Iron binding capacity and ceruloplasm increased significantly in OCD and TS cases.

(8) The results showed that HMG CoA reductase activity serum digoxin and dolichol were increased and serum ubiquinone, RBC membrane sodium-potassium ATPase activity and serum magnesium were reduced in left handed / right hemispheric dominant individuals. The results showed

that HMG CoA reductase activity serum digoxin and dolichol were decreased and serum ubiquinone, RBC membrane sodium-potassium ATPase activity and serum magnesium 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 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 OCD / la Tourette Syndrome

The archaeaon steroidelle DXP pathway and the upregulated pentose phosphate pathway contribute to digoxin synthesis. The decrease in the activity of HMG CoA reductase in OCD / TS patients suggests a downregulation of the isoprenoid pathway. There is a marked decrease in plasma digoxin and dolichol and this decrease may be a consequence of decreased channelling of intermediates of the isoprenoid pathway for their biosynthesis. In this connection, incorporation of ^{14}C-acetate into digoxin in the rat brain has been shown by us indicating that acetyl CoA is the precursor for digoxin biosynthesis in mammals also. The decrease in endogenous digoxin, a potent inhibitor of membrane Na^+-K^+ ATPase, can increase this enzyme activity in OCD/TS cases where there was significant stimulation of the RBC membrane Na^+-K^+ ATPase. The stimulation of Na^+-K^+ ATPase by digoxin deficiency is known to cause a

decrease in intracellular calcium resulting from decreased Na^{+}-Ca^{++} exchange, decreased entry of calcium via the voltage gated calcium channel and decreased release of calcium from intracellular endoplasmic reticulum calcium stores. This decrease in intracellular calcium causes an increase in the functional availability of magnesium. This increase in the availability of magnesium can cause increased mitochondrial ATP formation which along with increased magnesium can cause further stimulation of Na^{+}-K^{+} ATPase, since the ATP-magnesium complex is the actual substrate for this reaction. Cytosolic free calcium is normally buffered by two mechanisms, ATP dependent calcium extrusion from the cell and ATP dependent sequestration of calcium within the endoplasmic reticulum. The increased intracellular magnesium related mitochondrial ATP synthesis results in increased calcium extrusion from the cell. There is thus a progressive stimulation of Na^{+}-K^{+} ATPase activity. High intracellular magnesium and low intracellular calcium consequent to Na^{+}-K^{+} ATPase stimulation appear to be crucial to the pathophysiology of OCD/TS cases. The intracellular negative calcium signal and positive magnesium signal can regulate diverse cellular process. Serum magnesium was and assessed in OCD/TS cases and was found to be increased.

Archaeal Digoxin and Regulation of Neurotransmitter Synthesis and Function in Relation to OCD / la Tourette Syndrome

The archaeaon neurotransminoid shikimic acid pathway contributes to tryptophan and tyrosine synthesis and catabolism generating neurotransmitters and neuroactive alkaloids. Digoxin, apart from affecting cation transport is also reported to influence the transport of various metabolites across cellular membranes, including amino acids and various neurotransmitters. Two of the amino acids in this respect are important, tryptophan, a precursor for strychnine and nicotine, and tyrosine a precursor for morphine. We had already shown

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 result showed that the concentration of tryptophan, quinolinic acid and serotonin was found to be lower in the plasma of patients with OCD/TS cases while that of tyrosine, dopamine and norepinephrine was higher. Serum of OCD/TS cases showed the absence of strychnine and nicotine. Morphine could be detected in the serum of OCD/TS patients. Thus there is a decrease in tryptophan and its catabolites and increase in tyrosine and its catabolites in the serum of OCD/TS cases. This could be due to the fact that digoxin can regulate neutral amino acid transport system with preferential promotion of tryptophan transport over tyrosine and that digoxin levels are low in OCD/TS cases. The increase in membrane Na^{+}-K^{+} ATPase activity in OCD/TS cases could be due to the fact that hyperpolarising neurotransmitters (dopamine, morphine and noradrenaline) are increased and the depolarising neuroactive compounds (serotonin, strychnine, nicotine and quinolinic acid) are decreased.

TS has been postulated to be due to an hyperactive dopaminergic system, the reasons for which are manifold. There is an increased level of dopamine and morphine in TS, due to increased synthesis from tyrosine in our study. Morphine can increase the sensitivity of dopamine receptors. A hyperactive noradrenergic system has also been postulated. Our study shows increased noradrenaline synthesis from tyrosine in TS. Thus most of the neurotransmitter changes producing TS can be attributed to digoxin induced upregulation of tyrosine transport and increased tyrosine catabolism.

In OCD there is an abnormality in the striato-pallido-thalamo-cortical loop especially involving the balance between the facilitatory direct and indirect inhibitory pathway. There is a hyperactive facilitatory direct pathway due to decreased serotoninergic transmission and increased dopaminergic transmission via the D_1 receptor. Our studies show reduced tryptophan levels and consequently

reduced serotonin synthesis in OCD. On the other hand the tyrosine levels and the synthesis of dopamine and morphine from tyrosine is upregulated. Thus there is reduced serotoninergic and increased dopaminergic transmission in OCD owing to low digoxin levels leading on to a hyperactive facilitatory direct pathway.

The low level of quinolinic acid, serotonin and strychnine can contribute to reduced excitatory glutamatergic transmission as they are all positive modulators of the NMDA receptor. In the presence of hypermagnesemia, the magnesium block on the NMDA receptor is strengthened leading on to reduced NMDA transmission. The decreased presynpatic neuronal calcium can produce reduced cyclic AMP dependent phosphorylation of synapsins resulting in decreased glutamate release into the synaptic junction and vesicular recycling. Decreased intracellular calcium in the post synaptic neuron can also inhibit the calcium dependent NMDA signal transduction. The plasma membrane glutamate transporter (on the surface of the glial cell and presynaptic neuron) is coupled to a sodium gradient which is activated by the stimulation of Na^+-K^+ ATPase, resulting in increased clearance of glutamate by presynaptic and glial uptake at the end of synaptic transmission. By these mechanisms, stimulation of Na^+-K^+ ATPase can inhibit glutamatergic transmission. Reduced glutamatergic transmission can lead on to mental subnormality which has been associated with OCD and TS cases, The reduced glutamatergic transmission could also be related to the attention deficit disorder associated with both OCD and TS syndrome.

Archaeal Digoxin and Regulation of Golgi Body / Lysosomal Function in Relation to OCD / la Tourette Syndrome

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

glycoproteins and glycolipids. The decrease in the levels of dolichol may suggest its decreased availability for N-glycosylation of proteins. Magnesium excess can lead on to increased catabolism of sphinganine leading on to decreased cerebroside and ganglioside synthesis. In magnesium excess the glycolysis, citric acid cycle and oxidative phosphorylation are activated and less of glucose 6-phosphate is channelled for the synthesis of glycosaminoglycans (GAG). The results show a decrease in the Concentration of serum total GAG, glycolipids (ganglioside, glycosyl-diglyceride, cerebrosides and sulphatides) and carbohydrate components of glycoproteins (hexose, fucose and sialic acid) in OCD/TS cases. The individual GAG fractions in the serum - heparan sulphate (HS), chondroitin sulphates (ChS), heparin (H), hyaluronic acid (HA) and dermatan sulphate (DS) are decreased in OCD/TS cases. The activity of GAG degrading enzymes (beta glucuronidase, beta N-acetyl hexosaminidase, hyaluronidase and cathepsin-D) and that of glycohydrolases (beta galactosidase, beta fucosidase and beta glucosidase) showed significant decrease in the serum in OCD/TS cases. Intracellular magnesium excess also results in increased ubiquitin dependent proteolytic processing of glycoconjugates as it requires magnesium for its function. The decrease in the activity of glycohydrolases and GAG degrading enzymes could be due to increased lysosomal stability. Increased lysosomal stability would lead to decreased phagocytosis and increased incidence of respiratory infections. A number of fucose and sialic acid containing natural ligands have been implicated in inflammatory responses. The decrease in fucose and sialic acid noted in these cases could inhibit a protective inflammatory response to the virus or bacteria leading on to recurrent respiratory infection. This could account for the linkage between OCD and streptococcal infection. Altered glycoconjugates in OCD play an important role in the pathogenesis of the syndrome. This could lead to altered synaptic

connectivity in the frontostriato-pallido-thalamo cortical loops important in the pathogenesis of OCD.

Archaeal Digoxin and Alteration in Membrane Structure and Membrane Formation in Relation to OCD / la Tourette Syndrome

The archaeaon steroidelle, glycosaminoglycoid and fructosoid contributes 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 downregulation of the isoprenoid pathway can lead to decreased cholesterol synthesis and magnesium excess can stimulate phospholipid synthesis. Phospholipid degradation is decreased owing to decrease in intracellular calcium inhibiting phospholipase A_2 and D. The cholesterol: phospholipid ratio of the RBC membrane was decreased in OCD/TS cases. The concentration of total GAG, hexose and fucose of glycoprotein increased in the RBC membrane and decreased in the serum suggesting their increased incorporation into the membrane and defective membrane formation. The 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 activated in magnesium excess. The change in membrane structure produced by alteration in glycoconjugates and the cholesterol: phospholipid ratio can produce changes in the conformation of Na^+-K^+ ATPase resulting in further membrane Na^+-K^+ ATPase stimulation. This leads to increased intracellular hypermagnesemia. Elevated magnesium levels inhibit HMG CoA reductase activity and reduced digoxin synthesis. This leads

to further membrane Na^+-K^+ ATPase stimulation and the amino acid transport defect gets accentuated. The tyrosine/tryptophan defect in OCD / TS could be due to the neuronal membrane abnormality. Similar membrane abnormalities have been described in choreoacanthocytosis-tic syndrome. The same changes can affect the structure of the organallae membrane. This results in increased lysosomal stability. Altered peroxisomal membranes could lead to catalase hyperactivity which has been documented in OCD/TS cases.

Archaeal Digoxin and Mitochondrial Dysfunction in Relation to OCD / la Tourette Syndrome

The archaeaon vitaminocyte contributes to the synthesis of ubiquinone and mitochondrial electron transport chain function. The mitochondrial function related free radical generation is regulated by the archaeaon vitaminocyte synthesized tocopherol and ascorbic acid. The concentration of ubiquinone increased significantly in OCD/TS cases which may be the result of increased tyrosine levels, consequent to digoxin deficiency promoting tyrosine transport over tryptophan. The aromatic ring promotion of ubiquinone is derived from lyrosine. Ubiquinone, which is an important component of the mitochondrial electron transport chain, is a membrane antioxidant arid contributes to free radical scavenging. The decrease in intracellular calcium can stabilise the mitochondrial PT pore and improve mitochondrial function. Intracellular magnesium excess can lead to an increase in the activity of ATP synthase. All this leads to improved efficiency in mitochondrial oxidative phosphorylation and reduced free radical generation. Ubiquinone excess also leads to increased free radical scavenging. The decrease in intracellular calcium may lead to decreased generation of NO by inhibiting enzyme nitric oxide synthase and reduced peroxynitrite formation. Decreased calcium also can inhibit phospholipase A_2 resulting in decreased generation of arachidonic acid and free

radical formation. Decreased generation of free radicals like the superoxide ion and hydroxyl radical can stabilise the cell membrane and stimulate membrane Na^+-K^+ ATPase. There was decrease in lipid peroxidation as evidenced from the decrease in the concentration of MDA, conjugated dienes, hydroperoxides and NO with increased antioxidant protection as indicated by the increase in ubiquinone and increased reduced glutathione in OCD/TS cases. The activity of enzymes involved in free radical scavenging like superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase is increased in OCD/TS cases suggesting increased free radical scavenging. The peroxisomal membrane is stabilised owing to membrane Na^+-K^+ ATPase stimulation related alteration in membrane formation and leads to increased catalase activity. Glutathione is synthesized by the enzyme glutathione synthetase which needs magnesium and ATP. The high intracellular magnesium consequent to Na^+-K^+ ATPase stimulation and the resulting increased ATP synthesis can result in increased 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 excess due to membrane Na^+-K^+ ATPase stimulation leads to increased formation of glucose-6-phosphate and upregulation of the pentose phosphate pathway with consequent increased generation of NADPH. Thus glutathione system of free radical scavenging is activated in the presence of membrane Na^+-K^+ ATPase stimulation. Superoxide dismutase exists in a mitochondrial and cytoplasmic form. The stabilisation of the mitochondrial PT pore consequent to reduced intracellular calcium produces increased efficiency of superoxide dismutase activity. The increase in catalase, superoxide dismutase (SOD), glutathione peroxidase and

glutathione reductase suggests increased free radical protection. Free radicals are required for lymphocyte activation and this leads to a hypoimmune response and increased respiratory infection owing to immunodeficiency.

Archaeal Digoxin and Immune Function in OCD / la Tourette Syndrome

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. Decreased intracellular calcium inactivates the calcium dependent calcineurin signal transduction pathway involved in T-cell inactivation and decreased secretion of interleukin-3, 4, *5,* 6 and TNF alpha. TNF alpha can also bring about apoptosis of the cell and this is inhibited. TNF alpha binds to its receptor TNFR1 and activates the transcription factors NFkB and AP-l leading to induction of proinflammatory and immunomodulatory genes. Low levels of TNF alpha can lead to immunosuppression. This can explain the immunosuppression and increased rate of respiratory infection noted in OCD/TS cases. Morphine has also got an immunosuppressive action. This could also contribute to increased incidence of respiratory infections.

Thus elevated membrane Na^{+}-K^{+} ATPase can lead on to an obsessive compulsive personality and TS syndrome. It can produce a hypoimmune state and recurrent respiratory infections. This could be due to three factors - altered levels of sialo and fucoligands, decreased T-cell activation consequent to inhibition of calcineurin signal transduction system and reduced free radical generation leading on to defective phagocytosis.

Archaeal Digoxin and Hemispheric Dominance in Relation to OCD / la Tourette Syndrome

The archaeaon related organelle - steroidelle, neurotransminoid and vitaminocyte contribute to hemispheric dominance. The biochemical patterns in left hemispheric dominant individuals correlated with OCD and la tourette's syndrome. In left hemispheric dominant individuals there is a downregulated isoprenoid pathway and reduced digoxin synthesis. In right hemispheric dominant individuals there is an upregulated isoprenoid pathway and increased digoxin synthesis. The neurotransmitter patterns are also different in right hemispheric and left hemispheric dominant individuals. In left hemispheric dominant individuals there is upregulated tryptophan catabolism and down regulated tyrosine catabolism. In right hemispheric dominant individuals there is downregulated tryptophan catabolism and upregulated tyrosine catabolism.

References

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4

Digoxin and the Bipolar Mood Disorder

Introduction

The isoprenoid pathway produces an endogenous membrane Na^+-K^+ ATPase inhibitor digoxin, a steroidal glycoside. Digoxin is reported to be secreted by the human hypothalamus. Previous reports have demonstrated alteration in the cation pump in bipolar mood disorder. Bipolar mood disorder and schizophrenia can occur in the same families suggesting that both these disorders are genetically interlinked. Digoxin is also reported to modulate neutral amino acid and neurotransmitter transport. Membrane Na^+-K^+ ATPase inhibition is reported to be lead to magnesium depletion and intracellular calcium excess. Therefore the following parameters were studied in bipolar mood disorder, major depressive disorder and schizophrenia-plasma HMG CoA reductase activity, serum digoxin, serum magnesium and RBC Na^+-K^+ ATPase activity. The levels of serum tyrosine, tryptophan and their catabolites were also assessed. These parameters were studied during the manic phase and depressive phase of the illness. It has been noticed that depression is strongly associated with left anterior frontal lesions. Right hemispheric lesions produce a manic syndrome. In infantile schizophrenia or autism right hemispheric dysfunction has been documented. The neurotransmitter patterns were compared with those in right handed / left hemisphere dominant and left handed / right hemisphere dominant individuals. The results are presented in this chapter.

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 psychiatric disease.

Results

(1) The activity of HMG CoA reductase and the concentration of digoxin were decreased in the depressive phase of bipolar mood disorder, major depressive disorder and right handed / left hemispheric dominant individuals. The activity of erythrocyte membrane Na^+-K^+ ATPase and serum magnesium were increased in the depressive phase of bipolar mood disorder, major depressive disorder and right handed / left hemispheric dominant individuals. The activity of HMG CoA reductase and the concentration of digoxin were increased in the manic phase of bipolar mood disorder, schizophrenia and left handed / right hemispheric dominant individuals. The activity of erythrocyte membrane Na^+-K^+ ATPase and serum magnesium were decreased in the manic phase of bipolar mood disorder, schizophrenia and left handed / right hemispheric dominant individuals.

(2) The concentration of serum tryptophan, quinolinic acid and serotonin was decreased in the plasma of patients in depressive phase of bipolar mood disorder, major depressive disorder and right handed / left hemispheric dominant individuals while that of tyrosine, dopamine and noradrenaline was increased. The concentration of serum tryptophan, quinolinic acid and serotonin was increased in the plasma of patients in manic phase of bipolar mood disorder, schizophrenia and left handed / right hemispheric dominant individuals while that of tyrosine, dopamine and noradrenaline was increased.

(3) Nicotine and strychnine were not detected in the plasma of patients in the depressive phase of bipolar mood disorder; major depressive disorder and right handed / left hemispheric dominant individuals while morphine was detected in the plasma of these patients. Nicotine and strychnine were detected in the plasma of patients in the manic phase of bipolar mood disorder; schizophrenia and left handed / right hemispheric dominant individuals while morphine was not detected in the plasma of these patients.

Discussion

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

The archaeaon steroidelle DXP pathway and the upregulated pentose phosphate pathway contribute to digoxin synthesis. The decrease in the activity of HMG CoA reductase in the depressive phase of bipolar mood disorder major depressive disorder and right handed / left hemispheric dominant individuals suggests a downregulation of the isoprenoid pathway. There is a marked decrease in plasma digoxin and this decrease may be a consequence of decreased channelling of intermediates of the isoprenoid pathway for their biosynthesis. In this connection, incorporation of ^{14}C-acetate into digoxin in rat

brain has been shown by us indicating that acetyl CoA is the precursor for digoxin biosynthesis in mammals also. The decrease in endogenous digoxin, a potent inhibitor of membrane Na^+-K^+ ATPase, can increase this enzyme activity. In the depressive phase of bipolar mood disorder, major depressive disorder and right handed / left hemispheric dominant individuals there was significant stimulation of RBC membrane Na^+-K^+ ATPase. The stimulation of Na^+-K^+ ATPase by digoxin is known cause a decrease in intracellular calcium resulting from decreased Na^+-Ca^{++} exchange, decreased entry of calcium via the voltage gated calcium channel and decreased release of urn from intracellular endoplasmic reticulum calcium stores. This decrease in intracellular calcium by displacing magnesium from its binding sites causes an increase in the functional availability of magnesium. This increase in the availability of magnesium can increase mitochondrial ATP formation which along with increased magnesium can cause further stimulation of Na^+-K^+ ATPase, since ATP magnesium complex is the actual substrate for this reaction. Cytosolic free calcium is normally buffered by two mechanisms, ATP dependent calcium extrusion from cell and ATP dependent sequestration of calcium within the endoplasmic reticulum. The increased intracellular magnesium related mitochondrial ATP synthesis results in increased calcium extrusion from the cell. There is thus a progressive stimulation of Na^+-K^+ ATPase activity. High intracellular magnesium and low intracellular calcium consequent to Na^+-K^+ ATPase stimulation appear to be crucial to the pathophysiology of the depressive phase of bipolar mood disorder and major depressive disorder. The intracellular negative calcium signal and positive magnesium signal can regulate diverse cellular process. Serum magnesium was assessed in depressive phase of bipolar mood disorder, major depressive disorder and right handed / left hemispheric dominant individuals was found to be increased. Hypermagnesemia can lead on to depression. On the other hand the isoprenoid pathway and digoxin synthesis

was upregulated in the manic phase of bipolar mood disorder, schizophrenia and in left handed / right hemispheric dominant individuals leading on to membrane Na^+-K^+ ATPase inhibition and an increase in intracellular calcium and reduction in intracellular magnesium. The depressive phase of bipolar mood disorder and major depressive disorder is suggestive of hypodigoxinemia and left hemispheric chemical dominance and the manic phase of bipolar mood disorder and schizophrenia of right hemispheric chemical dominance and hyperdigoxinemia. Thus in bipolar mood disorder there is phasic variation in hypothalamic archaeal digoxin hypersecretion and fluctuating chemical hemispheric dominance. In major depressive disorderthere is permanent hypodigoxinemia and left hemispheric chemical dominance. In schizophrenia there is permanent hyperdigoxinemia and right hemispheric chemical dominance.

Archaeal Digoxin and Regulation of Neurotransmitter Synthesis and Function in Relation to Mood Disorder

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 results showed that the concentration of tryptophan, quinolinic acid and serotonin was found to be lower in the plasma of patients with depressive phase of bipolar mood disorder, major depressive disorder and right handed / left hemispheric dominant individuals while that of tyrosine, dopamine and

norepinephrine was higher. Serum of patients in depressive phase of bipolar mood disorder, major depressive disorder and right handed / left hemispheric dominant individuals showed the absence of strychnine and nicotine while morphine could be detected in the serum of these patients. Thus there is a decrease in tryptophan and its catabolites and increase in tyrosine and its catabolites in the serum of patients in the depressive phase of bipolar mood disorder, major depressive disorder and right handed / left hemispheric dominant individuals. This could be due to the fact digoxin can regulate neutral amino acid transport with preferential upregulation of tryptophan transport over tyrosine and that digoxin levels are low in depressive phase of bipolar mood disorder, major depressive disorder and right handed / left hemispheric dominant individuals. The increase in membrane Na^+-K^+ ATPase activity in depressive phase of bipolar mood disorder, major depressive disorder and right handed / left hemispheric dominant individuals could be due to the fact that the hyperpolarising neurotransmitters (dopamine, morphine and noradrenaline) are increased and the depolarising neuroactive compounds (serotonin, strychnine, nicotine and quinolinic acid) are decreased. The opposite is noticed in the manic phase of bipolar mood disorder, schizophrenia and left handed / right hemispheric dominant individuals with increase in the tryptophan catabolites - serotonin, quinolinic acid, strychnine and nicotine and a decrease in the tyrosine catabolites - dopamine, morphine and noradrenaline. This could be the result of elevated digoxin levels in left handed / right hemispheric dominant individuals, the manic phase of bipolar mood disorder and schizophrenia.

The low level of quinolinic acid, serotonin and strychnine in the depressive phase of bipolar mood disorder, major depressive disorder and in right handed / left hemispheric dominant individuals can contribute to reduced excitatory glutamatergic transmission as they are all positive modulators of the NMDA receptor. In the presence of hyperinagnesemia, the magnesium block on the

NMDA receptor is strengthened leading on to reduced NMDA transmission. The decreased presynaptic neuronal calcium can produce reduced cyclic AMP dependent phosphorylation of synapsins resulting in decreased glutamate release into the synaptic junction and vesicular recycling. Decreased intracellular calcium in the post synaptic neuron can also inhibit the calcium dependent NMDA signal transduction. The plasma membrane glutamate transporter (on the surface of the glial cell and presynaptic neuron) is coupled to a sodium gradient, which is activated by the stimulation of Na^+-K^+ ATPase, resulting in increased clearance of glutamate by presynaptic and glial uptake at the end of synaptic transmission. By these mechanisms, stimulation of Na^+-K^+ ATPase can inhibit glutamatergic transmission. Reduced excitatory glutamatergic transmission, decrease serotoninergic transmission and upregulated morphinergic transmission can contribute to depression. Reduced glutamatergic transmission can contribute to the pseudodementia associated with depression.

In the manic phase of bipolar mood disorder, schizophrenia as well as in the left handed right hemispheric dominant individuals glutamatergic excitotoxicity could happen due to increased levels of positive modulators of the NMDA receptor - serotonin, quinolinic acid and strychnine. In the presence of hypomagnesemia, the magnesium block on the NMDA receptor is removed leading to NMDA excitotoxicity. The increased presynaptic neuronal calcium can produce cyclic AMP dependent phosphorylation of synapsins resulting in increased neurotransmitter release into the synaptic junction and vesicular recycling. Increased intracellular calcium in the post synaptic neuron can also activate the calcium dependent NMDA signal transduction. The plasma membrane neurotransmitter transporter (on the surface of the glial cell and presynaptic neuron) is coupled to a sodium gradient which is disrupted by the inhibition of Na^+-K^+ ATPase resulting in decreased clearance of glutamate by presynaptic and glial uptake at the end of synaptic transmission. By these

mechanisms, inhibition of Na^+-K^+ ATPase can promote glutamatergic transmission. Glutamatergic excitotoxic mechanisms have been described in the manic phase of bipolar mood disorder and schizophrenia. Strychnine displaces glycine from its binding sites and inhibits glycinergic inhibitory transmission in the brain. The glycine is free to bind to the strychnine insentive site of the NMDA receptor and promote excitatory NMDA transmission. Strychnine by blocking glycinergic transmission can contribute to the decreased inhibitory transmission in the manic phase of bipolar mood disorder and schizophrenia. In the manic phase of bipolar mood disorder and schizophrenia increased dopaminergic activity has been reported. Nicotine by interacting with nicotine receptors can facilitate the release of dopamine, promoting the dopaminergic transmission in the brain. This can explain the increased dopaminergic transmission in the presence of decreased dopamine levels. Low level of noradrenaline has also been related to manic phase of bipolar mood disorder and schizophrenia. The low levels of noradrenaline reported in our study agree with a defect in noradrenergic transmission reported previously in schizophrenia. Excess serotonin level documented in the serum of patients in the manic phase of bipolar mood disorder and schizophrenia is significant and is in agreement with the excess serotoninergic transmission reported in these conditions previously. The pattern of the neurotransmitters and neuroactive alkaloids in the manic phase of bipolar mood disorder and schizophrenia correlates with those obtained in left handed / right hemisphere dominant individuals.

Archaeal Digoxin and Fluctuating Hemispheric Dominance in Relation to Mood Disorder

The archaeaon related organelle-steroidelle, neurotransminoid and vitaminocyte contribute to hemispheric dominance. Thus the bipolar mood disorder represents phasic changes in digoxin secretion and fluctuating

hemispheric chemical dominance. There is a hyperdigoxinemic right hemisphere dominant manic phase and hypodigoxinemic left hemisphere dominant depressive phase. This alternating chemical hemispheric dominance represents phasic changes in digoxin secretion by the hypothalamus. In major depressive disorder there is permanent hypodigoxinemia and left hemispheric chemical dominance. We had previously reported elevated digoxin, tryptophan, serotonin, strychnine and nicotine in schizophrenia with reduced tyrosine, morphine, dopamine and noradrenaline levels. The pattern in schizophrenia correlates with those obtained in the manic phase of bipolar mood disorder and in left handed / right hemispheric dominant individuals. In schizophrenia there is permanent hyperdigoxinemia and right hemispheric chemical dominance. There are two way connections between the hypothalamus and the cerebral cortex. There are also projections from the hypothalamus to the serotoninergic dorsal raphe nucleus, noradrenergic, locus coeruleus, cholinergic nucleus basalis of meynert and dopaminergic nuclei in the brain stem. Thus phasic or permanent upregulation or downregulation of hypothalamic archaeal digoxin Secretion can modulate the function of these structures.

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5

Neanderthal Hybrids: Climate Change Mediated Actinidic Archaeal Endosymbiosis Generates Neanderthal Hybrids and Mind-Body Phenotypic Change - The Origins of Schizophrenia, Autism and Epilepsy

Introduction

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

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

Materials and Methods

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

Results

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

Table 1. *Neanderthal phenotype and systemic disease.*

Disease	Cyt F420	Neanderthal phenotype	Low index finger-ring finger ratio
Schizophrenia	69%	75%	65%
Autism	80%	75%	72%
Epilepsy	80%	75%	75%
Internet users	65%	72%	69%

Table 2. *Neanderthal phenotype and brain dysfunction.*

Disease	Dysautonomia	Prefrontal cortex atrophy	Cerebellar hypertrophy
Schizophrenia	65%	60%	70%
Autism	72%	69%	72%
Epilepsy	69%	74%	76%
Internet users	74%	84%	82%

Discussion

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

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

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

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

The Neanderthal population was predominantly autistic and schizophrenic. The modern population is a hybrid of homo sapiens and homo neanderthalis. This contributes to 10 to 20 per cent dominant hybrids who tend to have schizophrenic and autistic qualities and contributes to creativity of civilisation. The Neanderthals tend to be innovative and chaotic. They tend to be creative in art, literature, dance, spirituality and science. Eighty per cent of less dominant hybrids are stable and contribute to a stabilizing influence leading to growth of civilisation. The homo sapiens were stable and non-creative over a long period of their existence. There was a burst of creativity with generation of music, dance, painting, ornaments, the creation of concept of God and compassionate group behaviour around 10,000 years ago in the homo sapiens community. This correlated with the generation of Neanderthal hybrids when the Eurasian Neanderthal male mated with homo sapiens African females. The extrasensory/quantal perception due to dipolar porphyrins and digoxin induced sodium potassium ATPase inhibition and the generated pumped phonon system mediated quantal perception leads to the globalisation phenomena and feeling of the world being a global village. The archaeal cholesterol catabolism leads to increased synthesis of digoxin. Digoxin promotes tryptophan transport over tyrosine. Tyrosine deficiency leads to dopamine deficiency and morphine deficiency. This leads to a morphine deficiency syndrome in Neanderthals. This contributes to addiction traits and creativity. The increased tryptophan levels produce increased alkaloids like LSD contributing to ecstasy and spirituality of Neanderthal population. Addictive, ADHD and autistic features are related to the morphine deficiency state. The ketogenic diet consumed by the meat eating Neanderthals leads on to increased generation of hydroxy butyric acid which produces ecstasy and a dissociative type of anaesthesia contributing to the Neanderthal psychology. The dopamine deficiency leads to decreased melanin

synthesis and fairness of the population. This was responsible for the fair colour of the Neanderthals.

The Neanderthals were essentially meat eaters taking a ketogenic diet. The acetoacetic acid is converted to acetyl CoA which enters the TCA cycle. When the Neanderthal hybrids consume a glucogenic diet owing to the spread of settled civilisation it produces pyruvate accumulation owing to PDH suppression in Neanderthals. The increased archaeal growth activates the toll receptor and induces HIF alpha resulting in increased glycolysis, PDH suppression and mitochondrial dysfunction - the Warburg phenotype. The pyruvate enters the GABA shunt pathway producing glutamate, ammonia and porphyrins resulting in neuropathology of autism and schizophrenia. Neanderthals consuming a ketogenic diet produces more of GABA an inhibitory neurotransmitter resulting in the docile quiet nature of the Neanderthals. There is less production of glutamate the predominant excitatory neurotransmitter of the prefrontal cortex and consciousness pathways. This leads onto dominance of cerebellar function. The Neanderthal hybrids have cerebellar dominance and less of conscious behaviour. Cerebellum is responsible for intuitive, unconscious behaviour as well as creativity and spirituality. The cerebellum is the site of extrasensory perception, magical acts and hypnosis. The predominant homo sapiens had prefrontal cortex dominance over the cerebellum resulting in more of conscious behaviour. This leads onto the ontogenesis of schizophrenia, autism and epilepsy.

The Neanderthals consuming a glucogenic diet produces increased glycolysis in the setting of PDH inhibition. This produces the Warburg phenotype. There is increased lymphocytic glycolysis producing autoimmune diseases and immune activation. The increased levels of GAPD result in nuclear cell death and neurodegeneration. The predominance of glycolysis and suppression of mitochondrial function results in glycemia and metabolic syndrome X. The

increased mitochondrial PT pore hexokinase leads to cell proliferation and oncogenesis. The glycolytic intermediate 3-phosphoglycerate is converted to glycine resulting in NMDA excitotoxicity contributing to schizophrenia and autism. Cerebellar dominance is reported in schizophrenia, autism and epilepsy.

The cerebellar hyperplasia results in sympathetic hyperactivity and parasympathetic neuropathy. This contributes to oncogene activation. Vagal neuropathy results in immune activation and autoimmunity important in schizophrenia, autism and epilepsy. Vagal neuropathy and sympathetic overactivity can contribute to glycogenolysis and lipolysis resulting in insulin resistance. Insulin resistance leads to schizophrenia, autism and epilepsy. Cerebellar dominance and cerebellar cognitive affective dysfunction can contribute to schizophrenia and autism. The increased porphyrin synthesis resulting from succinyl CoA generated by GABA shunt and glycine generated by glycolysis contributes to increased extrasensory perception important in schizophrenia and autism. Sympathetic overactivity and parasympathetic neuropathy can contribute to schizophrenia, autism and epilepsy.

The archaeal cholesterol catabolism generates digoxin which produces sodium potassium ATPase inhibition and increase in intracellular calcium and decrease in intracellular magnesium. The increase in intracellular calcium produces oncogene activation and NFKB activation resulting in schizophrenia, autism and epilepsy. The increase in intracellular calcium opens the mitochondrial PT pore resulting in cell death of schizophrenia, autism and epilepsy. The increase in intracellular calcium can modulate the neurotransmitter release from presynaptic vesicles. This can modulate neurotransmission. Digoxin induced magnesium depletion can remove the magnesium block on the NMDA receptor resulting in NMDA excitotoxicity. Digoxin can modulate the glutamatergic thalamo-cortico-thalamic pathway and consciousness resulting in schizophrenia, autism and epilepsy. Digoxin induced

magnesium depletion can inhibit reverse transcriptase activity and HERV generation modulating the dynamicity of the genome. HERV expression has been related to schizophrenia, autism and epilepsy. Digoxin induced intracellular calcium accumulation and magnesium depletion can modulate G-protein and protein tyrosine kinase dependent neurotransmitter and endocrine receptors. This can produce digoxin induced neuro-immuno-endocrine integration. The dysfunction of this integrative phenomenon can lead to schizophrenia, autism and epilepsy. Digoxin functions as a Neanderthal master hormone.

The actinidic archaea are cholesterol catabolising and leads to low levels of testosterone and estrogen. This leads on to asexual features and low reproductive rates of the Neanderthal population. The Neanderthals consume a low fibre diet with low lignan content. The actinidic archaea has cholesterol catabolising enzymes generating more of testosterone than estrogens. This contributes to estrogen deficiency and testosterone overactivity. The Neanderthal population is hypermales with concomitant right hemispheric dominance and cerebellar dominance. Testosterone suppresses left hemispheric function. The high testosterone levels in Neanderthals contribute to a bigger brain. The Neanderthals males as well as females had a higher level of testosterone contributing to gender equality and gender neutral states. There was group identity and group motherhood with no differences between roles of both males and females. This also resulted in matrilinearity. The higher testosterone levels in males as well as females led to alternate type of sexuality and aberrant behaviour. The homo sapiens eat a high fibre diet with low cholesterol and high lignan content contributing to estrogen dominance, left hemispheric dominance and cerebellar hypoplasia. Homo sapiens had higher reproductive rates and overtook the Neanderthal population resulting in its extinction. The homo sapien population was conservative with normal sexual mores, family values and patriarchal type of behaviour. The role of females the homo sapien

community was inferior to males. The increasing generation of Neanderthal hybrids due to climate change mediated archaeal overgrowth leads to gender equality and equidominance of male and female in this century. This gender phenomenon can lead onto the ontogenesis of schizophrenia, autism and epilepsy.

The cholesterol catabolism results in cholesterol depletion and bile acid deficiency. Bile acids bind to VDR and are immunomodulatory. Bile acid deficiency leads to immune activation and autoimmunity in schizophrenia, autism and epilepsy. Bile acids bind to FXR, LXR and PXR modulating lipid and carbohydrate metabolism. This leads to insulin resistance in the presence of bile acid deficiency. Bile acid uncouples oxidative phosphorylation and its deficiency leads to insulin resistance. Insulin resistance is important in schizophrenia, autism and epilepsy. Schizophrenia is called as an insulin resistance state of the brain. Bile acids bind to olfactory receptors and are important in group identity. Bile acid deficiency leads to formation of small social groups in Neanderthals and genesis of autism. Cholesterol depletion also leads to vitamin D deficiency. Vitamin D binds to VDR and produces immunomodulation. Vitamin D deficiency leads to immune activation and autoimmunity in schizophrenia, autism and epilepsy. Vitamin D deficiency can also produce rickets and contribute to the phenotypic features of Neanderthals. Vitamin D deficiency can contribute to brain development resulting in macrocephaly. Vitamin D deficiency contributes to insulin resistance and truncal obesity of Neanderthals. Vitamin D deficiency contributes to the fairness of the Neanderthal skin as a phenotypic adaptation. The Neanderthal phenotypic features are due to vitamin D deficiency and insulin resistance. All these lead to schizophrenia, autism and epilepsy.

Thus global warming and increased endosymbiotic actinidic archaeal growth leads to cholesterol catabolism and generation of the Warburg phenotype resulting in increased porphyrin synthesis, extrasensory low EMF perception,

prefrontal cortex atrophy, insulin resistance and cerebellar dominance. This leads on to neanderthalisation of the body and brain. This phenomenon leads to the ontogenesis of schizophrenia, autism and epilepsy.

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