Chapter 2

Hyperdigoxinemic Right Hemispheric Dominant Familial Cluster - Digoxin Excess Syndrome - The Homo Neanderthalis Family

Introduction

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

The 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. The archaeal symbiosis leads to the evolution of a new human neoneanderthal species. This can be called as the neoneanderthal age or Kali yuga.

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 bye-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.

The increase in endogenous EDLF, a potent inhibitor of membrane Na^+-K^+ ATPase, can decrease this enzyme activity. The results showed increased endogenous EDLF synthesis as evidenced by increased HMG CoA reductase activity, which functions as the rate limiting step of the isoprenoid pathway. Studies in our laboratory have demonstrated that EDLF is synthesized by the isoprenoid pathway. The endosymbiotic archaeal sequences in the human genome get expressed by redox stress and osmotic stress of global warming. This results in induction of HIF alpha which will upregulate fructolysis and glycolysis. In the setting of redox stress all glucose gets converted to fructose by the induction of enzymes aldose reductase and sorbitol dehydrogenase. Aldose reductase converts glucose to sorbitol and sorbitol dehydrogenase converts sorbitol to fructose. Since fructose is preferentially phosphorylated by ketohexokinases the cell is depleted of ATP and glucose phosphorylation comes to a halt. Fructose becomes the dominant sugar that is metabolized by fructolysis in expressed archaeal particles in the cell functioning as organelle called fructosoids. The fructose is phosphorylated to fructose 1-phosphate which is acted upon by aldolase B which converts it into glyceraldehyde 3-phosphate and dihydroxy acetone phosphate. Glyceraldehyde 3-phosphate is converted to D1,3-biphosphoglycerate which is then converted to 3-phosphoglycerate. The 3-phosphglycerate is converted to 2-phosphoglycerate. 2-phosphoglycerate is converted to phosphoenol pyruvate by the enzyme enolase. Phosphoenol pyruvate is converted to pyruvate by the enzyme pyruvic kinase. The archaeaon induces HIF alpha which upregulates fructolysis and glycolysis but inhibits pyruvate dehydrogenase. The forward metabolism of pyruvate is stopped. The dephosphorylation of phosphoenol pyruvate is inhibited in the setting of pyruvic kinase inhibition. Phosphoenol pyruvate

enters the shikimic acid pathway where it is converted to chorismate. The shikimic acid is synthesized by a pathway starting from glyceraldhyde 3-phosphate. Glyceraldehyde 3-phosphate combines with the pentose phosphate pathway metabolite sedoheptulose 7-phosphate which is converted to erythrose 4-phosphate. The pentose phosphate pathway is upregulated in the presence of the suppression of glycolytic pathway. Erythrose 4-phosphate combines with phosphoenol pyruvate to generate shikimic acid. Shikimic acid combines with another molecule of phosphoenol pyruvate to generate chorismate. The chorismate is converted to prephenic acid and then to parahydroxy phenyl pyruvic acid. Parahydroxy phenyl pyruvic acid is converted to tyrosine and tryptophan as well as neuroactive alkaloids. The shikimic acid pathway is structured in expressed archaeaon organelle called the neurotransminoid. The fructolytic intermediates glyceraldehydes 3-phosphate and pyruvate are the starting points of the DXP pathway of cholesterol synthesis. Glyceraldehyde 3-phosphate combines with pyruvate to form 1-deoxy D-xylulose phosphate (DOXP) which is then converted to 2-C methyl erythritol phosphate. 2-C methyl erythritol phosphate can be synthesized from erythrose 4-phosphate a metabolite of the shikimic acid pathway. DXP combines with MEP to form isopentenyl pyrophosphate which is converted to cholesterol. Cholesterol is catabolised by archaeal cholesterol oxidases to generate digoxin. The digoxin sugars digitoxose and rhamnose are synthesized by the upregulated pentose phosphate pathway. Glycolytic suppression leads to upregulation of the pentose phosphate pathway. The expressed archaeaon organelle concerned with cholesterol catabolism and digoxin synthesis is called the steroidelle. The suppression of glycolysis and stimulation of fructolysis results in upregulation of the hexosamine pathway. Fructose is converted to fructose 6-phosphate by ketohexokinases. The fructose 6-phosphate is converted to glucosamine 6-phosphate by the action of glutamine fructose 6-phosphate amidotransferase

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

archaeaon particles concerned with the synthesis of vitamin C, vitamin E and ubiquinone which are all antioxidants are called the vitaminocyte.

The isoprenoid pathway produces various metabolites that are essential for diverse cellular functions - cholesterol involved in membrane structure, dolichol involved in protein glycosylation, ubiquinone which participates in mitochondrial electron transport and is a membrane antioxidant and digoxin, an inhibitor of Na^+-K^+ ATPase produced by the hypothalamus. Deficiency of ubiquinone has been documented in Parkinson's disease, epilepsy, schizophrenia and multiple sclerosis. Increased levels of EDLA (endogenous digoxin like activity) have been reported in epilepsy, bipolar mood disorder, vasculitis and syndrome X. Altered levels of dolichol have been observed in Alzheimer's disease.

The coexistence of four pathophysiological phenomena - oncogene activation and malignant transformation, neuronal degeneration, psychiatric manifestation and immune activation has been described in motor neuron disease, systemic malignancy, multiple sclerosis and schizophrenia. Autoantibodies have been demonstrated in multiple sclerosis, motor neuron disease, Alzheimer's disease, Down's syndrome, paraneoplastic syndromes and acquired immunodeficiency syndrome. Psychosis has been documented in multiple sclerosis, Alzheimer's disease, Parkinson's disease, neoplasms and AIDS dementia. Lymphoma has been shown to coexist with multiple sclerosis, motor neuron disease, vasculitis and the acquired immunodeficiency syndrome. Viral persistence as an etiological factor has been documented in multiple sclerosis, Parkinson's disease, neoplasms and schizophrenia. Insulin resistance has been reported in Alzheimer's disease. Immune mediated neuropathies and neoplasms are described in syndrome X. This interrelationship between these disorders suggests the possibility that a central dysfunction may exist which could play a

part in the pathophysiology of these disorders. The isoprenoid pathway may be a candidate in this respect in view of many reports on the changes in the concentration of many products of this pathway in many neurological and psychiatric disorders and therefore this pathway was assessed in these disorders. The disorders included in the study are multiple sclerosis, schizophrenia, Parkinson's disease, CNS glioma, syndrome X with multiple lacunar state, Down's syndrome and acquired immunodeficiency syndrome. The isoprenoid pathway was assessed by plasma HMG CoA reductase activity, serum digoxin, ubiquinone and dolichol levels. Digoxin induced membrane Na^{+}-K^{+} ATPase can produce magnesium depletion and therefore serum magnesium was assessed in all these disorders. 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. Ongoing studies in our laboratory have 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. In view of these the level of the following substances was assessed in the serum of the patients of the disorders studied - concentration of tryptophan and its metabolites (serotonin, quinolic acid, strychnine and nicotine) and the concentration of tyrosine and its metabolites (dopamine, norepinephrine and morphine). The Mg^{++} depletion produced by digoxin and membrane Na^{+}-K^{+} ATPase inhibition can affect the metabolism of glycosaminoglycans, glycoproteins and glycolipids. The elevation in the level of dolichol may suggest its increased availability of N-glycosylation of proteins. The concentration of glycosaminoglycans, carbohydrate components of glycoprotein, glycolipids and glycohydrolases was studied in the serum in all these disorders. Alteration in ubiquinone levels and altered intracellular

calcium/magnesium ratios can affect free radical metabolism. The free radical metabolism was studied in all these orders. The isoprenoid metabolites ubiquinone, dolichol and digoxin can affect membrane structure and function. Therefore RBC membrane composition was studied in all these disorders. A family with coexistence of schizophrenia, Parkinson's disease, neoplasms, rheumatoid arthritis, syndrome X and increased incidence of left handedness with hyperdigoxinemia has been described previously. The isoprenoid pathway related biochemical cascade was also assessed in the family members. The isoprenoid pathway was also assessed in left handed and right handed individuals to find out whether cerebral dominance can affect the operation of the isoprenoid pathway. The results are presented in this paper as well as a hypothesis discussing the central role of hypothalamic archaeal digoxin in conscious perception, neuro-immuno-endocrine integration and coordination of cellular functions. The relationship between digoxin status and cerebral dominance is also discussed. The role of these factors in the pathogenesis of these disorders is also highlighted.

Results

(1) The results showed that HMG CoA reductase activity serum digoxin and dolichol were increased in all these disorders and in the family described indicating upregulation of the isoprenoid pathway but serum ubiquinone was reduced in all these disorders and in the indexed family.

(2) The results showed that the concentration of tryptophan, quinolinic acid and serotonin was found to be higher in the plasma of patients with all these disorders and in the family described while that of tyrosine, dopamine and norepinephrine was lower. Serum of patients with multiple sclerosis showed the presence of morphine. Serum of patients with epilepsy, PD, schizophrenia, multiple sclerosis syndrome X with multiple

lacunar state and the indexed family showed the presence of strychnine. Serum of patients with epilepsy, Parkinson's disease, syndrome X, schizophrenia, CNS glioma patients and the indexed family contained detectable amounts of nicotine.

(3) 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 most of the disorders and the indexed family studied. The activity of enzymes involved in free radical scavenging like superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase and catalase is decreased in the above disorders and the indexed family studied suggesting reduced free radical scavenging.

(4) The results show an increase in the concentration of serum total GAG, glycolipids (ganglioside, glycosyl-diglyceride, cerebrosides and sulphatides) and carbohydrate components of glycoproteins (hexose, fucose and sialic acid) in all the disorders and in the indexed family studied. The increase in the carbohydrate components'em-total hexose, fucose and sialic acid - in the disorders studied was not to the same extent in all cases suggesting qualitative change in glycoprotein structure. For example in epilepsy, the percentage change in total hexose, fucose and sialic acid when compared to the control is 54.3%, 20% and 33% respectively. The pattern of change in individual GAG in the serum was different, however heparan sulphate (HS) and chondroitin sulphates (ChS) increased in most of the disorders and in the indexed family studied. The activity of GAG degrading enzymes (beta glucuronidase, beta N-acetyl hexosaminidase, hyaluronidase and cathepsin-D) and that of glycohydrolases (beta galactosidase, beta

fucosidase and beta glucosidase) showed significant increase in the serum in most cases and in the indexed family.

(5) The cholesterol: phospholipid ratio of the RBC membrane was increased in glioma, the indexed family and schizophrenia decreased in MS and PD and was not significantly altered in epilepsy. The concentration of total GAG, hexose and fucose of glycoproteiri decreased in the RBC membrane and increased in the serum suggesting their reduced incorporation into the membrane and defective membrane formation in these disorders and in the indexed family.

(6) The left handed individuals as compared to right handed individuals had elevated HMG CoA reductase activity, with increased serum digoxin and dolichol levels. The serum ubiquinone, serum magnesium and RBC Na^{+}-K^{+} ATPase activity were reduced in left handed individuals. The left handed individuals compared to right handed individuals had elevated levels of serum tryptophan, quinolinic acid, serotonin, nicotine and strychnine in the serum. The levels, of tyrosine, dopamine, noradrenaline and morphine were lower in the left handed individuals.

(7) The pattern of incidence of diseases and behavioural patterns in the indexed family showed a high prevalence of Parkinson's disease (8%), schizophrenia (23%), neoplasms (20%), syndrome X (33%), rheumatoid arthritis (16%) and epilepsy (6.6%). The psychological behavioural patterns of the family were as follows - creativity and high IQ (60%), hypersexual behaviour (60%), reduced appetite and eating behaviour (60%), insomnia and reduced sleep patterns (60%), increased tendency for spirituality (80%), increased tendency for addiction (50%) and less of bonding and affectionate behaviour (75%). 30% of the family members were left handed.

Discussion

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

The increase in endogenous digoxin, a potent inhibitor or membrane Na^+-K^+ ATPase, can decrease this enzyme activity. In all the disorders studied there was significant inhibition of the RBC membrane Na^+-K^+ ATPase and this inhibition appears to be a common feature for neuropsychiatric disorders. 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 Ca^{++} via the voltage gated Calcium channel and increased release of Ca^{++} from intracellular endoplasmic reticulum Ca^{++} stores. This increase in intracellular Ca^{++} by displacing Mg^{++} from its binding sites causes a decrease in the functional availability of Mg^{++}. This decrease in the availability of Mg^{++} can cause decreased mitochondrial ATP formation which along with low Mg^{++} can cause further inhibition of Na^+-K^+ ATPase, since the ATP-Mg^{++} complex is the actual substrate for this reaction. Cytosolic free calcium is normally buffered by two mechanisms, ATP dependent calcium extrusion from the cell and ATP dependent sequestration of calcium within the endoplasmic reticulum. The Mg^{++} related mitochondrial dysfunction results in defective calcium extrusion from the cell. There is thus a progressive inhibition of Na^+-K^+ ATPase activity first triggered by digoxin. Low intracellular Mg^{++} and high intracellular Ca^{++} consequent to Na^+-K^+ ATPase inhibition appear to be crucial to the pathophysiology of these disorders. The intracellular positive Ca^{++} signal and negative Mg^{++} signal can regulate a diverse cellular process. Ca^{++} 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 Ca^{++} is released from channels on internal ER individually or in small groups (blip/quark and puffs/sparks). Further diversity of calcium signalling is produced by compartmentalization as the cytosolic calcium signal and nuclear calcium signal. Serum Mg^{++} was assessed in all these disorders and was found to be reduced. Increased intracellular calcium can lead on to basal ganglia calcification noticed in the family members.

Archaeal Digoxin and Regulation of Neurotransmitter Synthesis and Function

There is an increase in tryptophan and its catabolites and a reduction in tyrosine and its catabolites in the serum of patients with all these disorders. This could be due to the fact that digoxin can regulate the neutral amino acid transport system with preferential promotion of tryptophan transport over tyrosine. The decrease in membrane Na^{+}-K^{+} ATPase activity in all the disorders studied could be due to the fact that the hyperpolarising neurotransmitters (dopamine, morphine and noradrenaline) are reduced and the depolarising neuroactive compounds (serotonin, strychnine, nicotine and quinolinic acid) are increased.

The schizoid neurotransmitter pattern of reduced dopamine, noradrenaline and morphine and increased serotonin, strychnine and nicotine is common to all the disorders studied and could predispose to their development. Quinolinic acid, an NMDA agonist can contribute to the NMDA excitotoxicity reported in schizophrenia. Strychnine by blocking glycinergic transmission can contribute to the decreased inhibitory transmission in schizophrenia. Recent data suggest that the initial abnormality in schizophrenia involves a hypodopaminergic state and the low dopamine levels now observed agrees with this. 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. The increase in serotoninergic activity and reduced noradrenergic outflow from the locus coeruleus reported earlier in schizophrenia agrees with our finding of elevated serotonin and reduced noradrenaline levels.

In the presence of hypomagnesmia, the Mg^{++} block on the NMDA receptor is removed leading to NMDA exeitotoxicty. The increased presynaptic neuronal Ca^{++} can produce cyclic AMP dependent phosphorylation of synapsins resulting in increased neurotransmitter release into the synaptic junction and vesicular recycling. Increased intracellular Ca^{++} in the post synaptic neuron can also activate the Ca^{++} dependent NMDA signal transduction. The plasma membrane neurotransmitter transporter (On the surface of the glial cell and presynaptic neuron) is coupled to a Na^{+} gradient which is disrupted by the inhibition of Na^{+}-K^{+} ATPase. resulting in decreased clearance of glutamate by presynaptic and glial uptake at the end of synaptic transmission. By these mechanisms, inhibition Na^{+}-K^{+} ATPase can promote glutamatergic transmission. The elevated levels of quinolinic acid, strychnine and serotonin can also contribute to NMDA excitotoxicity. Strychnine displaces glycine from its binding sites and inhibits glycinergic inhibitory transmission in the brain. The glycine is free to bind to the strychnine insensitive site of the NMDA receptor and promote excitatory NMDA transmission. Quinolinic acid and serotonin are also positive modulators of the NMDA receptor. Increased glutamatergic transmission resulting in excitotoxicity has been implicated in neuronal degeneration observed in Parkinson's disease, primary generalised epilepsy, schizophrenia and AIDS dementia. Inhibition of Na^{+}-K^{+} ATPase can also result in defective neuronal membrane repolarisation and a paroxysmal depolarization shift resulting in epileptogenesis.

Thus in the right hemisphere dominant hyperdigoxinemic state there is upregulated serotoninergic, cholinergic and glutamatergic transmission and downregulated dopaminergic, glycinergic and noradrenergic transmission.

Endosymbiotic Archaeal Induced Hyperdigoxinemic State and Hemispheric Dominance

In left handed individuals there was a derangement of the isoprenoid pathway. They had upregulated HMG CoA reductase activity with increased digoxin and dolichol levels and reduced ubiquinone levels. The RBC membrane Na^+-K^+ ATPase activity was reduced and serum magnesium depleted. The isoprenoid pathway metabolites - digoxin, dolichol and ubiquinone, membrane Na^+-K^+ ATPase and serum magnesium levels were normal in right handed individuals. The left handed individuals had increased levels of tryptophan, serotonin, quinolinic acid, strychnine and nicotine while the levels of tyrosine, dopamine, noradrenaline and morphine were lower. Thus an upregulated isoprenoid pathway, increased level of tryptophan and its catabolites and hyperdigoxinemia is suggestive of right hemispheric dominance. Altered right hemispheric function has been described in several of these disorders. In infantile schizophrenia or autism right hemispheric dysfunction is noticed. In the Lewy body variant of Parkinson's disease right hemispheric dysfunction is documented. In immune mediated disorders also increased left handedness and right hemispheric dominance has been described. Epileptic individuals have a heightened sense of creativity and dominant right hemispheric function. The disorders described - schizophrenia, neoplasms, degeneration, epilepsy, multiple sclerosis, acquired immunodeficiency syndrome and syndrome X may have right hemispheric chemical dominance contributing to their pathogenesis. The hyperdigoxinemic state is seen in normal left handed individuals and may indicate right hemisphermic dominance. We had earlier reported a family with

hyperdigoxinemia and coexistence of schizophrenia, epilepsy, Parkinson's disease, rheumatoid arthritis, syndrome X, neoplasms and left handedness. The analysis of the members of the family also showed the following behavioural pattern. There was an increased tendency for spirituality in 75% of the family members. Temporal lobe epileptic phenomenon has been described in spiritual individuals. There was an increase in creativity and intelligence and the family members had a very high IQ. Increased glutamatergic transmission is associated with memory and intelligence. They had a tendency towards reduced appetite and eating behaviour. Increased serotoninergic transmission can lead on to reduced appetite. There was also hypersexual behaviour in the majority of the family members. This could be related to increased production of nitric oxide in hyperdigoxinemic individuals. Nitric oxide has been related to erectile function. There was an increased tendency to addictive behaviour in family members. Endogenous morphine deficiency has been related to addiction. Morphine synthesis is low in members of the indexed family because of low lyrosine levels. There was a tendency of insomnia and reduced sleep. This could be related to reduced levels of morphine. There was less of bonding and affectionate behaviour. Bonding and affectionate behaviour has been related to doparnine. Dopamine deficiency in hyperdigoxinemic individuals could contribute to less bonding and affectionate behaviour.

Endosymbiotic Archaeal Digoxin and Conscious Perception

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 of think with meta-representations in schizophrenia. Digoxin, a membrane Na^+-K^+ ATPase inhibitor may probably regulate 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 the 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 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 - 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 glutamatergic and digoxin could amplify the circuit by its inhibitory effect on glial uptake of glutamate and by increasing the synaptic glutamate content.

All axons that pass either way between the cerebral cortex and thalamic nuclei must go through the thalamic reticular nucleus and all give off collateral excitatory glutamatergic branches 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 due to 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 should act on the glutamatergic collaterals to 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 focussed attention, perceptual binding and short term memory. The altered glycoconjugates in schizophrenia lead to disordered synaptic connectivity in the hypothalamo-thalamo-cerebral cortical circuit leading to disordered conscious perception. Cortical cytoarchitectural disorganization of the temporolimbic cortex has been reported in schizophrenia. Elevated levels of serum digoxin and schizoid neurochemical pathology are common to all the disorders studied and could predispose to their development (In the hyperdigoxinemic right hemisphere over dominant state conscious perceptive mechanism are disrupted leading on to a schizoid state).

Endosymbiotic Archaeal Digoxin and Regulation of Golgi Body / Lysosomal Function

The elevation in the level of dolichol may suggest its increased availability of N-glycosylation of proteins. Magnesium deficiency can lead on to defective metabolism of sphinganine producing its accumulation which may lead to increased cerebroside and ganglioside synthesis. In Mg^{++} deficiency the glycolysis, citric acid cycle and oxidative phosphorylation are blocked and more glucose 6-phosphate is channelled for the synthesis of glycosaminoglycans (GAG). Intracellular Mg^{++} deficiency also results in defective ubiquitin dependent proteolytic processing of glycoconjugates as it requires Mg^{++} for its function. The increase in the activity of glycohydrolases and GAG degrading enzymes could be due to reduced lysosomal stability and consequent leakage of lysosomal enzymes into the serum. The increase in the concentration of carbohydrate components of glycoproteins and GAG in spite of increased activity of many glycohydrolases may be due to their possible resistance to cleavage by glycohydrolases consequent to qualitative change in their structure. Proteoglycan complexes formed in the presence of altered Ca^{++}/Mg^{++} ratios intracellularly may be structurally abnormal and resistant to lysosomal enzymes and may accumulate.

Previous reports of alteration in glycoproteins in this connection include alteration in alpha acid glycoprotein (AAG) and beta amyloid precursor protein in epilepsy and Alzheimer's disease and alpha synuclein in Parkinson's disease. Structurally abnormal glycoproteins resist catabolism by lysosomal enzymes and accumulate in neuronal degeneration. Interaction between HS-proteoglycan and ChS-proteoglycan with proteins like beta amyloid, tau protein, parkin and alpha synuclein and reduced proteolytic digestion of these complexes leading on to their accumulation in the neurons have been reported in neurodegenerative diseases like Alzheimer's disease and Parkinson's disease. Alteration in the

sulphated proteoglycan matrix of the synaptic vesicles can alter neurotransmitter release into the synapse and produce a functional disorder like schizophrenia and epilepsy. Membrane Na^{+}-K^{+} ATPase inhibition can lead to defective notch signalling. Notch is a transmembrane protein that acts as a signal receptor and is important in neurogenesis. Neuronal growth by extending neurites and forming connections is regulated by the notch signalling pathway. The notch signalling inhibits extension of neurites and keeps them stable in the mature brain. A notch ligand known as delta regulates neurogenesis by binding to notch in membranes of embryonal cells and prevents them from developing along the neuronal pathway. Notch activation by the ligand causes notch to be cleaved releasing the notch intracellular domain. This then passes into the nucleus and activates transcription as part of the DNA binding complex with CSL protein. Intracellular cleavage of the notch is regulated by presenilin and also depends upon the lysosomal protease. In the presence of a lysosomal instability consequent to defective lysosomal membranes notch cleavage by protease is defective leading on to functional disorders consequent to defective synaptic connectivity. The defective notch signalling pathway can lead on to neuronal degeneration. Altered glycoproteins, glycolipids and GAG of the neuronal membrane can also contribute to schizophrenia and epilepsy by producing disordered synaptic connectivity.

The protein processing defect can result in defective glycosylation of endogenous myelln glycoprotein antigens and exogenous viral glycoproteins antigens with consequent defective formation of the MHC-antigen complex. The MHC linked peptide transporter, a Pglycoprotein which transports the MHC-antigen complex to the antigen presenting cell surface has an ATP binding site. The peptide transporter is dysfunctional in the presence of Mg^{++} deficiency. This results in defective transport of the MHC class-1 glycoprotein antigen complex to the antigen presenting cell surface for recognition by the

CD_4 or CD_8 cell. Defective presentation of the endogenous myelin glycoprotein antigen can explain the immune dysregulation in MS. A CD_8 MHC class-1 restricted immune dysregulatory defect has been described in MS. Defective presentation of exogenous viral antigens can produce immune evasion by the virus as in AIDS dementia. Viral persistence has been implicated in the development of tumours (ebstein barr virus and lymphoma), degenerations (Parkinson's disease and corona virus) and schizophrenia (borna virus disease). A number of fucose and sialic acids containing natural ligands are involved in trafficking of leukocytes and similar breaches in the blood brain barrier and adhesion of the lymphocyte producing leukocyte trafficking and extravasation in to the perivascular space have been described in MS. Altered myelin glycoprotein due to defective glycosylation and alteration in GAG of proteoglycans of myelin can affect the structural integrity of myelin leading on to demyelination. Abnormally glycosylated tumour antigens can lead to defective tumour antigen presentation and loss of immunosurveillance by the natural killer cells. Altered cell surface glycoproteins, glycolipids and GAG can lead to defective contact inhibition and oncogenesis. A number of fucose and sialic acids containing natural ligands have been implicated in neoplastic transformation and metastasis. The MHC glycoproteins are involved in formation of synaptic connectivity during neuronal development. Defective formation and presentation of the MHC - neuronal glycoprotein complex can lead on to disordered synaptic connectivity and functional disorders like schizophrenia and epilepsy.

Thus in the hyperdigoxinemic right hemisphere dominant state there is reduced lysosomal stability, defective ubiquitin dependent proteolytic processing of proteins and alteration in the glycoconjugate structure leading on to their defective catabolism and accumulation. There is also a defect in the MHC antigen presenting pathway leading on to immunodysregulation and viral persistence.

Endosymbiotic Archaeal Digoxin and Alteration in Membrane Structure and Membrane Formation

The alteration in the isoprenoid pathway specifically, cholesterol as well as changes in glycoproteins and GAG can affect cellular membranes. The upregulation of isoprenoid pathway can lead to increased cholesterol synthesis and Mg^{++} deficiency can inhibit phospholipid synthesis. Phospholipid degradation is increased owing to increase in intracellular calcium activating phospholipase A_2 and D. The cholesterol: phospholipid ratio of the RBC membrane was increased in glioma, the indexed family and schizophrenia, decreased in MS and PD and was not significantly altered in epilepsy. The concentration of total GAG, hexose and fucose of glycoprotein decreased in the RBC membrane and increased in the serum suggesting their reduced incorporation into the membrane and defective membrane formation. The glycoproteins, GAG and glycolipids of the cellular membrane are formed in the endoplasmic reticulum, which is then budded of as a vesicle which fuses with the golgi complex. The glycoconjugates are then transported via the golgi channel and the golgi vesicle fuses with the cell membrane. This trafficking depends upon GTPases and lipid kinases which are crucially dependent on magnesium and are defective in Mg^{++} 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. Defective peroxisomal membranes lead to catalase dysfunction which has been documented in these disorders. Thus in the hyperdigoxinemic right hemisphere dominant state there is defective membrane formation, membrane structure and function.

Endosymbiotic Archaeal Digoxin and Mitochondrial Dysfunction

The concentration of ubiquinone decreased significantly in most of the cases which may be the result of low tyrosine levels, reported in most of the disorders, consequent to digoxin's effect in preferentially promoting tryptophan transport over tyrosine. The aromatic ring portion of ubiquinone is derived from tyrosine. Ubiquinone, which is an important component of the mitochondrial electron transport chain, is a membrane antioxidant and coniributes to free radical scavenging. The increase in intracellular Ca^{++} can open the mitoehondrial PT pore causing a collapse of the H^{+} gradient across the inner membrane and uncoupling of the respiratory chain. Intracellular Mg^{++} deficiency can lead to a defect in the function of ATP synthase. All this leads to defects in mitochondrial oxidative phosphorylation, incomplete reduction of oxygen and generation of the superoxide ion which produces lipid peroxidation. Ubiquinone deficiency also leads to reduced free radical scavenging. The increase in intracellular calcium may lead to increased generation of NO by inducing the enzyme nitric oxide synthase which combines with the superoxide radical to form peroxynitrite. Increased calcium also can activate phospholipase A_2 resulting in increased generation of arachidonic acid which can undergo increased lipid peroxidation. Increased generation of free radicals like the superoxide ion, and hydroxyl radical can produce lipid peroxidation and cell membrane damage which can further inactivate Na^{+}-K^{+} ATPase, triggering the cycle of free radical generation once again. Mg^{++} deficiency can affect glutathione synthetase and glutathione reductase function. The mitochondrial superoxide dismutase leaks out and becomes dysfunctional with calcium related opening of the mitochondrial PT pore and outer membrane rupture. The peroxisomal membrane is defective owing to the membrane Na^{+}-K^{+} ATPase inhibition related defect in membrane formation and leads to reduced catalase activity. Mitochondrial dysfunction related free radical generation has been

implicated in the pathogenesis of neuronal degeneration oncogenesis and immune mediated disorders.

The increased intracellular calcium and ceramide related opening of the mitochondrial PT pore also leads to volume dysregulation of the mitochondria causing hyperosmolality of the matrix and expansion of the matrix space. The outer membrane of the mitochondria ruptures and releases apoptosis inducing factor and cytochrome C into the cytoplasm. This results in activation of caspase-9 and caspase-3. Caspase-9 can produce apoptosis of the cell. Apoptosis has been implicated in neuronal degeneration. Apoptosis can produce defective synaptogenesis and synaptic connectivity contributing to functional disorders like schizophrenia and epilepsy. Apoptosis of the CD_4 cell can contribute to CD_4 depletion in the acquired iinmunodeficiency syndrome. Oligodendrocyte (the myelin forming cell) apoptosis is crucial to the pathogenesis of MS. Caspase-3 activation can cleave P_{21} involved in linking DNA duplication to cell division resulting in a polyploid cell and oncogenesis. We have been able to demonstrate neuronal degneration and apoptosis in the digoxin injected rat brain.

Thus in the hyperdigoxinemic right hemisphere dominant state there is a defect in mitochondrial function and increased free radical generation and reduced scavenging. There is also increased apoptosis.

Endosymbiotic Archaeal Digoxin and Immunoregulation

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). TNF alpha binds to its receptor TNFRI and activates the transcription factors HFkB and AP-1 leading to the induction of proinflammatory and immunomodulatory

genes. This can also explain the immune activation in MS. TNF alpha can also bring about apoptosis of the cell. It binds to its receptor and activates caspase-9, an ICE protease which converts IL-1 beta precursor to IL-1 beta. IL-1 beta produces apoptosis of the neurons (in Alzheimer's disease and AIDS dementia), oligodendrocyte-the myelin forming cell in MS and the CD_4 cell in HIV infection. IL-1 beta and TNF alpha induce HIV protein expression by the transcription related mechanism and contributes to the pathogenesis of AIDS dementia. Membrane Na^+-K^+ ATPase inhibition can produce immune activation and is reported to increase CD_4/CD_8 ratios as exemplified by the action of lithium. The hyperdigoxinemic right hemisphere dominant State results in immune activation.

Endosymbiotic Archaeal Digoxin and Regulation of Cell Division, Cell Proliferation and Neoplastic Transformation

Intracellular magnesium depletion can produce defective phosphorylation of MAP (microtubule associated proteins). This results in defective microtubule related spindle fibre dysfunction and chromosomal non-dysjunction probably contributing to trisomy 21.

Increased intracellular calcium activates phospholipase C beta which results in increased production of diacyglycerol (DAG) with resultant activation of protein kinase C. The protein kinase C (PKC) activates the MAP kinase cascade resulting in cellular proliferation. The decreased intracellular magnesium can produce dysfunction of GTPase activity of the alpha - subunit of G-protein. This results in ras oncogene activation, as more of the ras is bound to GTP rather than GDP. Phosphorylation mechanisms are required for the activation of the tumour suppressor gene P_{53}. The activation of P_{53} is impaired owing to intracellular magnesium deficiency producing a phosphorylation defect. Upregulation of isoprenoid pathway can result in increased production of

farnesyl phosphate which can farnesylate the ras oncogene producing its activation. The ubiquitin system of catabolic processing of processing of proteins is important in the DNA repair mechanism. In the presence of intracellular magnesium deficiency ubiquitin protein catabolic processing and DNA repair mechanisms are defective and this could contribute to oncogenesis. In the hyperdigoxinemic right hemisphere dominant State there is oncogene activation and increased cell proliferation.

Endosymbiotic Archaeal Digoxin and the Metabolic Regulation

Inhibition of Na^+-K^+ ATPase can also explain the pathogenesis of syndrome X. Increased TNF alpha as mentioned above consequent to Na^+-K^+ ATPase inhibition related T-cell activation can contribute to insulin resistance in syndrome X at the receptor level. Decrease in intracellular magnesium can block the phosphorylation reactions involved in protein tyrosine kinase receptor activity leading to insulin resistance. Increase in beta cell calcium can contribute to increased insulin release from beta cells and hyperinsulinemia. Increased intracellular calcium can activate the G-protein coupled signal transduction of the contra insulin hormones (growth hormone and glucagon) leading to hyperglycemia. Decrease in intracellular magnesium can lead on to inhibition of glycolysis. Decreased intracellular magnesium can lead on to a mitochondrial ATP synthase defect. Increased intracellular calcium can open up the mitochondrial PT pore, disrupt the H^+ gradient across the inner membrane and block mitochondrial oxidative phosphorylation. All this leads to defective glucose utilisation and hyperglycemia. Increase in intracellular calcium can activate the Gprotein coupled angiotensin receptor producing hypertension and the G-protein coupled thrombin receptor and platelet activating factor producing thrombosis observed in syndrome X. Na^+-K^+ ATPase inhibition related increased smooth muscle calcium and decreased magnesium can contribute to

vasospasm and ischaemia observed in stroke and CAD. Na^+-K^+ ATPase inhibition related altered glycoprotein can contribute to the microangiopathy and macroangiopathy observed in syndrome X. Metabolic syndrome X could be visualised as being due to hypothalamic archaeal digoxin hypersecretion. In the hyperdigoxinemic right hemisphere dominant state glucose metabolism and utilisation is impaired consequent to insulin resistance as also a tendency for vasospasm and thrombosis.

Endosymbiotic Archaeal Digoxin and Regulation of the Immune Response to Viral Infection

The same biochemical Na^+-K^+ ATPase related cascade described above could contribute to the acquired immunodeficiency syndrome. There is increased incidence of neoplasms like non-Hodgkin's lymphomas and vasculitis in the acquired immunodeficiency syndrome. Neuronal degenerations like AIDS dementia have been related to glutamate excitotoxicity. An AIDS related schizophreniform psychosis has been described. Polyclonal B-cell proliferation and lymphadenopathy have been described in AIDS. Digoxin induced calcineurin signal transduction mediated T-cell activation and polyclonal B-cell proliferation can contribute to HIV-1 replication. This is because chief among the inducible cellular proteins that promote the growth of HIV-l is transcription factor NFkB. HIV-l has incorporated two such NFkB binding-enhancer elements into its own genome, which allows the triggering of HIV-1 transcription in the presence of nuclear NFkB. Digoxin induced protein glycosylation defects can also lead to defective glycosylation of HIV glycoprotein antigens leading on to defective formation of HIV glycoprotein antigen - MHC complex for presentation to the CD_4 cell. This results in immune evasion by the virus and could also contribute to the persistence of the herpes virus and Epstein Barr virus producing Kaposi's sarcoma and non-Hodgkin's

lymphoma respectively. Hypothalamic structural abnormalities have been described in homosexuals predisposed to the development of acquired immunodeficiency syndrome. In the hyperdigoxinemic right hemisphere dominant state there is a tendency for viral persistence consequent to defective processing of viral proteins and defective immune response to the virus.

Endosymbiotic Archaeal Digoxin and Neuro-immuno-endocrine Integration

Hypothalamic 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 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 by increasing Na^{+}-Ca^{++} 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.

Endosymbiotic Archaeal Digoxin and Integration of Cellular Function

Digoxin can regulate multiple cellular functions. Digoxin can regulate plasma membrane transport as well as membrane structure and fluidity. It can also regulate the fluidity of organelle membranes. Digoxin by its effects of calcium mediated opening of the mitochondrial PT pore and ubiquinone synthesis can regulate mitochondrial function. The dolichol pathway can regulate protein

glycosylation and golgi body function. Digoxin induced hypomagnesemia can regulate the ubiquitin dependent protein catabolic pathway. Digoxin induced change in intracellular magnesium can regulate nuclear function as DNA polymerase, DNA ligase and ribosomes require magnesium for their function. Digoxin by producing magnesium depletion can regulate GAG metabolism and the structure of the cell matrix. Digoxin can regulate cell death or apoptosis by opening up the mitochondrial PT pore consequent to a rise in intracellular calcium it produces. Digoxin by its effect upon ras oncogene can modulate cell proliferation. Digoxin induced hypomagnesemia by producing changes in cell surface glycoproteins and GAG can regulate contact inhibition and cell proliferation. Digoxin can regulate the function of heat-shock protein which coordinates the trafficking and regulation of diverse signalling proteins, and which also functions as a molecular chaperone involved in protein folding and maturation. The heat-shock protein has an ATP/ADP switch domain that regulates hsp conformation and digoxin induced hypomagnesemia can modulate its function. Intracellular magnesium deficiency can regulate phosphorylation of MAP (microtubule associated proteins) and regulate cytoskeletal structure/function.

Digoxin can thus produce conscious perception, neuro-immuno-endocrine integration and integrate the function of multiple cellular organelles. The hyper digoxinemic state is a right hemisphere dominant state.

References

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