Chapter 3

The Hypodigoxinemic Left Hemispheric Dominant Family - Digoxin Deficiency Syndrome - The Homo Sapien 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 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.

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 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.

A family with coexistent hypotension, recurrent respiratory infection owing to immune deficiency, motor tics, obsessive compulsive disorder, major depressive disorder, early onset osteoporosis, low body mass index, bulimia nervosa and healthy aging is described. The family members had the following behavioural patterns - hyposexual, non-spiritual, non-creative, somnolent tendency, increased bonding and affectionate behaviour and non-addictive tendency. All members in the family were right handed left hemispheric dominant. Alteration in the endogenous membrane Na^+-K^+ ATPase inhibitor, digoxin has been documented in depression as well as in essential hypertension. Digoxin is a steroidal glycoside, synthesized in the human hypothalamus by the isoprenoid pathway and is also reported to modulate neuronal transmission. The other isoprenoidal metabolites of significance are ubiquinone (regulate mitochondrial function), cholesterol (component of cellular membranes) and dolichol (regulate N-glycosylation of proteins). Therefore the isoprenoidal pathway, glycoconjugate metabolism, neurotransmitter patterns, free radical metabolism and membrane composition were studied in the indexed family. Since digoxin can regulate synaptic transmission and possibly hemispheric dominance, the isoprenoid pathway was also compared in right hemispheric and left hemispheric dominance to find out whether hemispheric dominance plays a role in the genesis of the disorder.

Materials and Methods

The indexed family was analysed over three generations for motor tics, OCD, major depressive disorder, bulimia nervosa, recurrent respiratory infections, early onset osteoporosis, hypotension and low body-mass index. OCD, major depressive disorder and bulimia nervosa were diagnosed by the DSM-IV criteria.

Recurrent respiratory infections were diagnosed when there were more than three significant respiratory infections in a month that warranted treatment. Low body mass index was defined as a body-mass index less than 18.5 kg/m^2. The family members were screened for the behavioural patterns mentioned below - (i) the criteria given in the handbook for the 16 PF - the 16 personality factors questionnaire was chosen after modification for defining spirituality, creativity and bonding / affection, and (ii) the criteria for insomnia and somnolence, sexual behaviour, addiction and eating behaviour were chosen from the DSM IV criteria. All the 15 alive affected members of the indexed family were chosen for the study except one family member - A_1 who died. Each patient also had an age and sex matched right handed / left hemispheric dominant control. In addition 15 normal left handed individuals who were right hemisphere dominant and 15 right handed individual who were left hemisphere dominant, between the age group 20 and 30 years chosen by the dichotic listening test were also chosen for comparison of the same parameters.

Results

Clinical Features of the Indexed Family

The description of the indexed family is given in table 1. Motor tics was seen in 22% of the family members, OCD in 56%, major depressive disorder in 44%, hypotension in 72%, osteoporosis in 17%, low body mass index in 50%, recurrent respiratory infection with immunodeficiency in 44% and bulimia nervosa in 17%. The family members had hyposexual behaviour (80%), less tendency for spirituality and creativity (70%), had no insomnia but a tendency towards increased somnolence (60%), no addictive behaviour (80%) and had more bonding and affectionate behaviour (80%). One member of the family survived to 99 years of age and was healthy throughout his life span. There was

total lack of incidence of vascular thrombosis, neuronal degeneration and systemic malignancies as well as healthy longevity (average life span of 85 years) in three generations of the indexed family. All members in the family were right handed left hemispheric dominant.

Table 1. *Description of the indexed family.*

Diseases	Percentage
Motor tics	22.22
OCD	55.55
Depression	44.44
Hypotension	72.22
Low body mass index	50.00
Eating behaviour (bulimia)	16.66
Osteoporosis	16.66
Recurrent respiratory infection	44.44

Biochemical Changes in the Indexed Family

The activity of HMG CoA reductase and the concentration of digoxin and dolichol were decreased in familial and left hemispheric dominant cases. The concentration of serum ubiquinone, the activity of erythrocyte membrane Na^{+}-K^{+} ATPase and serum magnesium were increased. The opposite patterns were obtained in right hemispheric dominance. The concentration of serum tryptophan, quinolinic acid and serotonin was decreased while that of tyrosine, dopamine and noradrenaline was increased in the plasma of familial and left hemispheric dominant cases. Nicotine and strychnine were not detected in the plasma of familial and left hemispheric dominant cases. Morphine was detected in the plasma of familial cases (9.56 μg/dL) and left hemispheric dominance (6.92 μg/dL). The opposite patterns were obtained in right hemispheric dominance. Right hemispheric dominant individuals had no detectable morphine in the serum but had detected amounts of strychnine (9.52 μg/dL) and

nicotine (2.07 µg/dL). The concentration of total glycosaminoglycans (GAG) and individual GAG fractions, carbohydrate components of glycoproteins and glycolipids decreased in the serum of familial cases. The activity of glycosaminoglycan (GAG) degrading enzymes and glycohydrolases was decreased in familial cases when compared to the controls. The concentration of total GAG and hexose and fucose residues of glycoproteins in the RBC membrane increased significantly in familial cases.

The concentration of RBC membrane cholesterol decreased while that of phospholipid increased resulting in decreased cholesterol: phospholipid ratio.

The activity of free radical scavenging enzymes, the concentration of reduced glutathione and ceruloplasmin and iron binding capacity increased significantly while the concentration of lipid peroxidation products and nitric oxide decreased significantly in familial cases.

Discussion

Archaeal Digoxin and Membrane Na^+-K^+ ATPase Inhibition in Relation to Digoxin Deficiency 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 familial cases 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. The decrease in endogenous digoxin, a potent inhibitor of membrane Na^+-K^+ ATPase, can increase this enzyme activity. The stimulation of Na^+-K^+ ATPase by digoxin is known to cause a decrease in intracellular calcium and an increase in intracellular

magnesium. Serum magnesium was assessed in familial cases and was found to be increased. Decrease in bone calcium load can lead on to osteoporosis.

Archaeal Digoxin and Regulation of Neurotransmitter Synthesis and Function in Relation to Digoxin Deficiency Syndrome

The archaeaon neurotransminoid shikimic acid pathway contributes to tryptophan and tyrosine synthesis and catabolism generating neurotransmitters and neuroactive alkaloids. The results showed that the concentration of tryptophan, quinolinic acid, serotonin, strychnine and nicotine was found to be lower in the plasma of patients with familial cases while that of tyrosine, dopamine, norepinephrine and morphine was higher. Nicotine and strychnine are synthesized from tryptophan and morphine from tyrosine. Thus there is a decrease in tryptophan and its catabolites and increase in tyrosine and its catabolites in the patient's serum. This could be due to the fact that digoxin can regulate the neutral amino acid transport system with a preferential promotion of tryptophan transport over tyrosine and because digoxin levels are low in familial cases. The increase in membrane Na^+-K^+ ATPase activity in familial cases could be due to the fact that the hyperpolarising neurotransmitters (dopamine, morphine and noradrenaline) are increased and the depolarising neuroactive compounds (serotonin, strychnine, nicotine and quinolinic acid) are decreased. The low level of quinolinic acid, serotonin and strychnine can contribute to reduced excitatory glutamatergic transmission as they are all positive modulators of the NMDA receptor. In the presence of hypermagnesemia, the magnesium block on the NMDA receptor is strengthened leading onto reduced NMDA transmission. Reduced glutamatergic transmission can lead on to healthy aging and protect the brain from neuronal degeneration. The depressive syndrome noted in the family could be due to low serotonin. Decreased serotoninergic transmission has been related to depression. The

presence of OCD syndrome in the family could also be related to serotonin depletion. Serotonin depletion has been related to obsessive psychopathology. The presence of motor tics could be related to increased dopaminergic transmission in the brain. Deficiency of serotonin can lead to increased appetite and eating behaviour with bulimia in the family members.

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

The archaeaon glycosaminoglycoid and fructosoid contributes to glycoconjugate synthesis and catabolism by the process of fructolysis. Hypermagnesemia and decreased dolichol (required for N-glycosylation) levels can inhibit GAG, glycolipid and glycoprotein biosynthesis. The activity of GAG degrading enzymes and glycohydrolases decreased in the serum suggesting increased lysosomal stability. Intracellular hypermagnesemia also results in increased ubiquitin dependent proteolytic processing of glycoconjugates as it requires magnesium for its function. Defective lysosomal stability and defective degradation of glycoprotein - GAG complexes as in the case of tau protein / amyloid - HS proteoglycan complexes in Alzheimer's disease can lead on to brain aging. Membrane Na^{+}-K^{+} ATPase stimulation could thus protect against neuronal aging and degeneration. A number of fucose and sialic acids containing natural ligands have been implicated in inflammatory responses and neoplastic transformation. The decrease in fucose and sialic acid noted in these cases could lead on to an immunosuppressive state with recurrent respiratory infection and prevent malignant transformation. Decrease in bone structural glycosaminoglycans could contribute to osteoporosis.

Archaeal Digoxin and Alteration in Membrane Structure and Membrane Formation in Relation to Digoxin Deficiency Syndrome

The archaeaon steroidelle, glycosaminoglycoid and fructosoid contribute to cell membrane formation synthesizing cholesterol by the DXP pathway and glycosaminoglycans by fructolysis. The downregulation of the isoprenoid pathway can lead to decreased cholesterol synthesis and magnesium excess can stimulate phospholipid synthesis leading on to decreased membrane cholesterol: phospholipid ratio. The concentration of total GAG and carbohydrate residues of glycoprotein increased in the RBC membrane and decreased in the serum suggesting their increased incorporation into the membrane. Hypermagnesemia can stimulate the activity of membrane trafficking enzymes - GTPases and lipid kinases. The change in membrane structure produced by alteration in glycoconjugates and the cholesterol: phospholipid ratio can produce changes in the conformation of Na^+-K^+ ATPase resulting in further membrane Na^+-K^+ ATPase stimulation. The same changes can affect the lysosomal membrane increasing its stability.

Archaeal Digoxin and Mitochondrial Dysfunction in Relation to Digoxin Deficiency 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 (free radical scavenger and component of the mitochondrial electron transport chain) increased significantly in familial cases which may be the result of increased tyrosine levels, consequent to digoxin deficiency promoting tyrosine transport over tryptophan. The aromatic ring portion of ubiquinone is derived from tyrosine. The decrease in intracellular calcium can stabilise the mitochondrial

PT pore and improve mitochondrial function. Intracellular hypermagnesemia can lead on to increased ATP synthase activity. All this leads to improved efficiency of mitochondrial oxidative phosphorylation and reduced free radical generation. Decreased intracellular calcium also leads to decreased generation of NO by inhibiting the enzyme nitric oxide synthase and reduced peroxynitrite formation. The free radical scavenging enzyme activity, the concentration of antioxidants (ubiquinone, reduced glutathione, ceruloplasmin) and iron binding capacity increased significantly in familial cases suggesting increased free radical scavenging. The peroxisomal membrane is stabilised owing to membrane Na^{+}-K^{+} ATPase stimulation related upregulation in membrane formation and leads to increased catalase activity. Hypermagnesemia leads to increased glutathione synthetase, glutathione peroxidase and glutathione reductase function. The stabilisation of the mitochondrial PT pore consequent to reduced intracellular calcium produces increased efficiency of superoxide dismutase activity. Mitochondrial dysfunction related free radical generation has been implicated in the pathogenesis of neuronal degeneration like PD, oncogenesis and inflammatory diseases. The reduced generation of free radicals leads to decreased incidence of neuronal degeneration and oncogenesis in the index family. Free radicals are required for lymphocyte activation and this leads to a hypoimmune response and increased respiratory infection owing to immunodeficiency. The decreased intracellular calcium and ceramide related stabilisation of the mitochondrial PT pore inhibits cytochrome C release and the caspase cascade. Apoptosis has been implicated in neuronal degeneration and its inhibition protects against neuronal aging.

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

The archaeaon fructosoid contributes to fructolysis and immune activation. Fructose can contribute to induction of NFKB and immune activation. The archaeaon steroidelle synthesized digoxin induces NFKB producing immune activation. There is a decreased oncogenic tendency in the indexed family. Decreased intracellular calcium inactivates phospholipase C beta which results in decreased production of diacylglycerol (DAG) with resultant inactivation of protein kinase C and the MAP kinase cascade. The intracellular hypermagnesemia can produce increase in the GTPase activity of the alpha subunit of G-protein resulting in ras oncogene inactivation, as more of the ras is bound to GDP rather than GTP. Tumour suppressor gene, P_{53} activation is increased owing to intracellular hypermagnesemia producing increased phosphorylation. Decreased intracellular calcium inactivates the calcium dependent calcineurin signal transduction pathway involved in T-cell activation and reduces the 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 TNFRI and activates the transcription factors NFkB and AP-1 leading to induction of proinflammatory and immunomodulatory genes. Low levels of TNF alpha can lead to immunosuppression in the family.

Digoxin Deficiency Syndrome and Reverse Metabolic Syndrome X

Hypermagnesemia can upregulate glucose transport as magnesium is required as a cofactor for cell membrane glucose transport. Intracellular hypennagnesemia can activate the phosphorylation reactions involved in protein tyrosine kinase receptor activity leading to increased insulin receptor activity. Intracellular hypermagnesemia can lead on to stimulation of glycolysis.

Decrease in intracellular calcium can stabilise the mitochondrial PT pore and stimulate mitochondrial oxidative phosphorylation. Intracellular hypermagnesemia can also lead to ATP synthase hyperactivity. This leads to increased glucose utilisation. Decrease in beta cell calcium and increase in magnesium can contribute to decreased insulin release from beta cells and hypoinsulinemia. Increased intracellular magnesium can produce hyperactivity of lipoprotein lipase producing increased catabolism of triglycerides rich lipoproteins and hypotriglyceridemia. In hypermagnesemia, Lecithin cholesterol acyl transferase (LCAT) is increased and there is increased formation of cholesterol esters in HDL. This results in increased HDL cholesterol. Magnesium excess has been reported to decrease LDL cholesterol levels also. Low insulin levels and increased triglyceride catabolism can be correlated with low body mass index noted in the family. Decreased in intracellular calcium can inactivate G-protein coupled angiotensin receptor producing hypotension and G-protein coupled thrombin receptor and platelet activating factor producing decreased thrombosis observed in the family. Increased intracellular magnesium can lead to decreased thrombin and ADP / collagen induced platelet aggregation. Na^{+}-K^{+} ATPase stimulation related decreased smooth muscle calcium and increased magnesium can contribute to vasodilatation and protect the family from ischaemia due to stroke and CAD. The family has an endogenous morphine excess syndrome. Morphine has been reported to have an effect on glucose metabolism. Intrathecal administration of morphine in the lumbar region causes a dose-dependent hypoglycemia. Morphine can also regulate insulin release from the beta cells with an inhibitory effect reported in some cases. Morphine has also got an immunosuppressive action. This could contribute to increased incidence of respiratory infections. Morphine excess can lead on to lack of addiction which has been noticed in the family membrane.

Archaeal Digoxin and Hemispheric Dominance in Relation to Digoxin Deficiency Syndrome

The archaeaon related organelle - steroidelle, neurotransminoid and vitaminocyte contribute to hemispheric dominance. The biochemical pattern obtained in the family correlated with the left hemispheric dominant state. In the left hemispheric dominant state there is a downregulated isoprenoid pathway, hypodigoxinemia, membrane Na^{+}-K^{+} ATPase stimulation, decreased dolichol synthesis and elevated ubiquinone synthesis. There is an upregulated morphinergic, dopaminergic and noradrenergic transmission with a downregulated glutamatergic, cholinergic / nicotinic and serotoninergic transmission. There are no previous reports on a hypodigoxinemic syndrome in literature as also studies on biochemical differences between right and left hemispheric dominance.

References

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