Chapter 3

Archaeal Digoxin - A Model for Conscious and Subliminal Perception, Cerebral Dominance, Neuro-Immuno-Endocrine Integration and Regulation of Cellular Functions - Relation to Brain Evolution and Systemic Disease / Psychological / Physiological States

Introduction

There is a specialization of function in the right and left hemispheres of the brain as manifested in cognitive dysfunctions noticed in lesions of the same. Typical cerebral lateralization is associated with left cerebral dominance for language, praxis and serial processing, whereas the right cerebral hemisphere is dominant for externally directed attention, visuospatial tasks and gestalt processing. The right hemisphere is also dominant for emotional stimuli, and patients with right cerebral lesions may exhibit hypoarousal and emotional indifference. Geschwind postulated a relationship between cerebral lateralisation and immune function. For example, they observed a higher frequency of left handedness in patients with some immune disorders. Differences in natural killer cell activity have been reported in women as a function of asymmetries in frontal EEG activation. Bardos et al. demonstrated that lesions of the left neocortex in mice depress T-cell immunity, whereas right lesions enhance T-cell immunity. There is no data as of now on neurotransmitter differences between right and left hemispheres though functional differences have been noticed as described above. The hypothalamus produces an endogenous membrane Na^+-K^+ ATPase inhibitor digoxin. Digoxin being a steroidal glycoside is synthesized by the isoprenoid pathway. Studies using ^{14}C labelled acetate has demonstrated the synthesis of digoxin by the isoprenoid pathway. Digoxin can regulate synaptic transmission of multiple neurotransmitter systems. The other products of the isoprenoid pathway are also important in cellular functions. Cholesterol is an important component of cellular membranes. Ubiquinone is a component of the mitochondrial electron transport chain and also functions as a free radical scavenger. Dolichol is important in N-glycosylation of protein and processing of proteins. The present study assessed the changes in the synthesis of an endogenous membrane Na^+-K^+

ATPase inhibitor, digoxin and neurotransmitter changes in right hemispheric dominant and left hemispheric dominant individuals. The pathological and psychological correlates of cerebral dominance in relation to endogenous digoxin synthesis have also been documented in this paper. The metabolic differences in the setting of glycoconjugate metabolism membranogenesis and free radical metabolism between right hemispheric dominant and left hemispheric dominant individuals are documented and its relation to systemic and neuropsychiatric diseases is stressed. A model of conscious and subliminal perception mediated by digoxin and its role in regulating interface between the consciousness and universe is postulated. A hypothesis implicating membrane Na^{+}-K^{+} ATPase inhibition in cellular and brain evolution is also put forward.

Materials and Methods

I. The parameters listed below were assessed in right handed / left hemispheric dominant, left handed / right hemisphere dominant and amphidextrous / bihemispheric dominant individuals chosen by the dichotic listening test. There were 15 normal individuals in each group. The age of the individuals chosen ranged from 20 to 30 yrs. None of the subjects studied were on medication at the time of blood removal. They were all non-smokers (active or passive). (1) The isoprenoid pathway - HMG CoA reductase, serum digoxin, dolichol and ubiquinone, (2) RBC Na^{+}-K^{+} ATPase activity and serum magnesium, (3) Neurotransmitter patterns - tryptophan, serotonin, dopamine, noradrenaline, tyrosine, quinolinic acid, strychnine, nicotine and morphine, (4) Lysosomal enzymes, (5) Total glycosaminoglycans and different GAG fractions, (6) Hexose, fucose and sialic acid content of serum glycoproteins, (7) Free radicals and scavenging enzymes, and (8) RBC membrane composition.

II. Serum digoxin levels and RBC Na^+-K^+ ATPase activity was assessed in different pathological conditions - Parkinson's disease (PD), Huntington's disease, CNS glioma, Multiple sclerosis (MS), schizophrenia, primary generalised epilepsy, idiopathic basal ganglia calcification, migraine, addiction, healthy aging, obsessive compulsive disorder, depression, recurrent respiratory infections, osteoporosis, essential hypertension, syndrome X, low body mass index, anorexia nervosa, bulimia nervosa, osteoarthritis, spondylosis (cervical and lumbar), acute coronary artery disease, idiopathic hypotensive states, subacute sclerosing panencephalitis (SSPE), neurolupus (SLE), rheumatoid arthritis, acquired immunodeficiency syndrome (AIDS), acid peptic disease (APD), irritable bowel syndrome (IBS), gall stones, bronchial asthma, cirrhosis liver, mesenteric artery occlusion, inflammatory bowel disease (IBD), interstitial lung disease (ILD), sarcoidosis, chronic bronchitis emphysema, lone atrial fibrillation with embolic stroke, chronic renal failure (CRF), nephrotic syndrome, and nephrolithiasis. There were 15 patients in each of the disease groups mentioned above. 15 individuals who were bihemispheric dominant served as controls. None of the subjects studied was under medication at the time of removal of blood. They were all non-smokers (active or passive).

III. Serum digoxin levels and RBC Na^+-K^+ ATPase activity was assessed in different psychological conditions - spiritually inclined individuals, creative individuals, addiction, promiscuous individuals, anorexic, gastronomic, insomniac, individuals with increased bonding and affection. They were also assessed in individuals with the opposite psychological tendencies. There were 15 normal individuals in each of the above group. 15 individuals who were bihemispheric dominant served as controls. None of the subjects studied were on medication at the time of blood removal. They were all non-smokers (active or passive).

Fasting blood was removed in citrate tubes from each of the number of patients mentioned above. RBCs were separated within one hour of collection of blood for the estimation of membrane Na^{+}-K^{+} ATPase. Plasma was used for the analysis of various parameters. The methodology used in the study was as follows: All biochemicals used in this study were obtained from M/s Sigma Chemicals, USA. Activity of HMG CoA reductase of the plasma was determined by the method of Rao and Ramakrishnan by determining the ratio of HMG CoA to mevalonate. For the determination of the Na^{+}-K^{+} ATPase activity of the erythrocyte membrane, the procedure described by Wallach and Kamat was used. Digoxin in the plasma was determined by the procedure described by Arun et al. For an estimation of ubiquinone and dolichol in the plasma, the procedure described by Palmer et al was used. Magnesium in the plasma was estimated by atomic absorption spectrophotometry. Tryptophan was estimated by the method of Bloxam and Warren and tyrosine by the method of Wong et al. Serotonin was estimated by the method of Curzon and Green and catecholamines by the method of Well-Malherbe. Quinolinic acid content of plasma were estimated by HPLC (C_{18} column micro Bondapak™ 4.6 x 140 mm), solvent system 0.01 M acetate buffer (pH 3.0) and methanol (6:4), flow rate 1.0 ml/minute and detection UV (250 mm). Morphine, strychnine and nicotine were estimated by the method described by Arun et al. Details of the procedure used for the estimation of total and individual GAG, carbohydrate component of glycoproteins, activity of enzymes involved in the degradation of GAG (beta glucuronidase, beta N-acetyl hexosaminidase, hyaluronidase and cathepsin-D) and activity of glycohydrolases (beta galactosidase, beta fucosidase and beta glucosidase) are described previously. Serum glycolipids (gangliosides, glycosyl diglycerides, cerebrosides and sulphatides) were estimated as described in methods in enzymology. Cholesterol was estimated by using commercial kits supplied by M/s Sigma Chemicals, USA. SOD was assayed by the method of Nishikini et al. as modified by Kakkar et al. Catalase activity was estimated by the method of Maehly and Chance, glutathione peroxidase by the method of Paglia and Valentine as modified by Lawrence and Burk and glutathione reductase by the method of Horn and Bums. MDA was estimated by the method of Wills and conjugated dienes and hydroperoxides by the procedure of Brien. Reduced glutathione was estimated by the method of Beutler et al. Nitric oxide was estimated in the plasma by the method of Gabor and Allon. Statistical analysis was done by the student's 't' test.

Results

I. *The isoprenoid pathway and related biochemical cascade in relation to cerebral dominance*

(1) The results showed that HMG CoA reductase activity serum digoxin and dolichol were increased and ubiquinone reduced in left handed / right hemispheric dominant individuals. The results also showed that HMG CoA reductase activity, serum digoxin and dolichol were decreased and ubiquinone increased in right handed / left hemispheric dominant individuals.

(2) The results showed that the concentration of tryptophan, quinolinic acid serotonin, strychnine and nicotine was found to be higher in the plasma of left handed / right hemispheric dominant individuals while that of tyrosine, dopamine, morphine and norepinephrine was lower. The results also showed that the concentration of tryptophan, quinolinic acid serotonin, strychnine and nicotine was found to be lower in the plasma of right

handed / left hemispheric dominant individuals while that of tyrosine, dopamine, morphine and norepinephrine was higher.

(3) There was an 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 a decrease in ubiquinone and reduced glutathione in left handed / right hemispheric dominant individuals. The activity of enzymes involved in free radical scavenging like superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase and catalase is decreased in left handed / right hemispheric dominant individuals. There was decrease in lipid peroxidation as evidenced from the decreased a concentration of MDA, conjugated dienes, hydroperoxides and NO with increased antioxidant protection as indicated by an increase in ubiquinone and reduced glutathione in right handed / left hemispheric dominant individuals. The activity of enzymes involved in free radical scavenging like superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase and catalase is increased in right handed / left hemispheric dominant individuals.

(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 left handed / right hemispheric dominant individuals. The increase in the carbohydrate components - total hexose, fucose and sialic acid-in the disorders studied was not to the same extent in all cases suggesting a qualitative change in glycoprotein structure. The individual GAG fractions - heparan sulphate, hyaluronic acid, heparin, chondroitin sulphates and dermatan sulphate, increased in left handed / right hemispheric dominant individuals. 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 a significant increase in the serum in left handed / right hemispheric dominant individuals. The results show a decrease in the concentration of serum total GAG, glycolipids (ganglioside, glycosyl diglyceride, cerebrosides and sulphatides) and carbohydrate components of glycoproteins (hexose, fucose and sialic acid) in right handed / left hemispheric dominant individuals. The decrease in the carbohydrate components - 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. The individual GAG fractions heparin, dermatan sulphate, heparan sulphate (HS), hyaluronic acid and chondroitin sulphates (ChS) decreased in right handed / left hemispheric dominant individuals. 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 a significant decrease in the serum in right handed / left hemispheric dominant individuals.

(5) The cholesterol: phospholipid ratio of the RBC membrane was increased in left handed / right hemispheric dominant individuals. The concentration of total GAG, hexose and fucose of glycoprotein decreased in the RBC membrane and increased in the serum suggesting their reduced incorporation into the membrane and defective membrane formation in left handed / right hemispheric dominant individuals. The cholesterol: phospholipid ratio of the RBC membrane was decreased in right handed / left hemispheric dominant individuals. The concentration of total GAG, hexose and fucose of glycoprotein increased in the RBC membrane and

decreased in the serum suggesting their increased incorporation into the membrane and defective membrane formation in right handed / left hemispheric dominant individuals.

II. Serum digoxin levels and RBC Na^+-K^+ ATPase activity was assessed in different pathological conditions

(1) In Parkinson's disease, Huntington's disease, idiopathic basal ganglia calcification, CNS glioma, multiple sclerosis, schizophrenia, primary generalized epilepsy, syndrome X, migraine, addiction, anorexia nervosa, osteoarthritis, spondylosis, acute coronary artery disease / acute cerebral thrombosis, essential hypertension, SSPE, acquired immunodeficiency syndrome, bronchial asthma, neurolupus, acid peptic disease, irritable bowel syndrome, gall stones, cirrhosis liver, inflammatory bowel disease, sarcoidosis, chronic bronchitis emphysema, interstitial lung disease, chronic renal failure, nephrotic syndrome, nephrolithiasis, lone atrial fibrillation and Fahr syndrome - serum digoxin levels were elevated, RBC membrane Na^+-K^+ ATPase activity reduced and serum magnesium decreased.

(2) In healthy aging, obsessive compulsive disorder, depression, recurrent respiratory infections, osteoporosis, familial hypotension, low body mass index and bulimia nervosa - serum digoxin levels were reduced, RBC membrane Na^+-K^+ ATPase activity increased and serum magnesium increased.

III. Serum digoxin levels and RBC Na^+-K^+ ATPase activity was assessed in different psychological conditions.

(1) In spiritually inclined individuals, creative individuals, addiction, promiscuous individuals, homosexuals, anorexic, insomniac, individuals with reduced bonding and affection and detached behaviour - serum

digoxin levels were elevated, RBC Na^+-K^+ ATPase activity reduced and serum magnesium reduced.

(2) In spiritually non-inclined individuals, non-creative individuals, individuals without addictive behaviour, non-promiscous individuals, individuals with gastronomic tendency, somnolent individuals and individuals with increased bonding and affection - serum digoxin levels were reduced, RBC Na^+-K^+ ATPase activity increased and serum magnesium increased.

Discussion

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

The increase in endogenous digoxin, a potent inhibitor or membrane Na^+-K^+ ATPase, can decrease this enzyme activity in left handed / right hemispheric dominant individuals and in Parkinson's disease, CNS glioma, multiple sclerosis, acquired immunodeficiency syndrome, schizophrenia, primary generalised epilepsy, syndrome X, migraine, addiction, anorexia nervosa, osteoarthritis, spondylosis, acute coronary artery disease, hypertension, SSPE, neurolupus, acid peptic disease, irritable bowel syndrome, cirrhosis liver, inflammatory bowel disease, chronic bronchitis emphysema, interstitial lung disease, sarcoidosis, bronchial asthma, chronic renal failure, nephrotic syndrome, nephrolithiasis, lone atrial fibrillation, gall stones and Fahr syndrome. In all the disorders studied, there was significant inhibition of the RBC membrane Na^+-K^+ ATPase and this inhibition appears to be a common feature for these neuropsychiatric and systemic disorders. In creative individuals, addiction, promiscuous individuals, homosexuals, anorexic, insomniac and individuals with reduced bonding / affection and detached behaviour also serum digoxin levels are increased and RBC membrane Na^+-K^+ ATPase activity reduced decreased. In all these pathological and psychological states there is chemical right hemispheric dominance. The inhibition of Na^+-K^+ ATPase by digoxin is known to cause an increase in intracellular calcium resulting from increased Na^+-Ca^{++} exchange, increased entry of calcium via the voltage gated calcium channel and an increased release of calcium from intracellular endoplasmic reticulum calcium stores. This increase in intracellular calcium by displacing magnesium from its binding sites causes a decrease in the functional availability of magnesium. This decrease in the availability of magnesium can cause decreased mitochondrial ATP formation, which along with low magnesium can cause further inhibition of Na^+-K^+ ATPase, since ATP-magnesium complex is the actual substrate for this reaction. Cytosolic free calcium is normally buffered by two mechanisms, ATP dependent calcium extrusion from cell and ATP dependent sequestration of calcium within the endoplasmic reticulum. The magnesium related mitochondrial dysfunction results in defective calcium extrusion from the cell and is a progressive inhibition of Na^+-K^+ ATPase activity first triggered by digoxin. Low intracellular magnesium and high intracellular calcium consequent to Na^+-K^+ ATPase inhibition appear to be crucial to the pathophysiology of these disorders. The intracellular positive calcium signal and negative magnesium signal can regulate diverse cellular process. Calcium on entry into the cell is used to charge up the internal endoplasmic reticulum stores, which then release a burst of signal calcium responsible for activating a large variety of calcium dependent cellular processes. The information processing capability of the calcium signalling system is enhanced by the amplitude and frequency modulation. The calcium is released from channels on internal ER individually or in small groups (bip/quark and puffs/sparks). Further diversity of calcium signalling is produced by compartmentalization such as a cytosolic calcium signal and nuclear calcium signal. There is evidence for increased digoxin synthesis in these groups of diseases from the increase in HMG CoA reductase activity that is noticed. HMG CoA reductase is the rate limiting enzyme of the isoprenoid pathway. In this connection, incorporation of ^{14}C-acetate into digoxin in rat brains has been shown by us indicating that acetyl CoA is the precursor for digoxin biosynthesis in mammals. Serum magnesium was assessed in left handed / right hemispheric dominant individuals and in Parkinson's disease, CNC glioma, multiple sclerosis, schizophrenia, primary generalised epilepsy, syndrome X, migraine, addiction, idiopathic basal ganglia calcification, anorexia nervosa, osteoarthritis, spondylosis, acute coronary artery disease, essential hypertension, SSPE, neurolupus, acquired immunodeficiency syndrome, acid peptic disease, irritable bowel syndrome, gall stones, cirrhosis liver, inflammatory bowel disease, chronic bronchitis emphysema, interstitial lung disease, chronic renal failure, lone atrial fibrillation and bronchial asthma and was found to be reduced. In all these pathological and psychological states there is chemical right hemispheric dominance. Increases intracellular calcium can bring about basal ganglia calcification. Increased in intracellular calcium can lead on to increased calcium load in the bone and degenerative bone disease like cervical spondylosis. Increased digoxin can also contribute to the pathophysiology of CRF (chronic renal failure). Digoxin by the membrane Na^+-K^+ ATPase inhibition that it produces can lead to inhibition of the outward sodium flux, and inhibition of the inward potassium flux, and also an increased inward flux of calcium. This abnormally high intracellular sodium concentration and hence to osmotically induced overhydration of the cell, whereas the same cells are relatively deficient in potassium. Digoxin can alter the conduction of the cardiac SA node and AV node as well as the conducting tissue contributing to lone atrial fibrillation. Increases in bronchial smooth muscle calcium can contribute to bronchospasm in bronchial asthma. Similarly an increase in intestinal smooth muscle cell calcium can lead to irritable bowel syndrome by producing intestinal smooth muscle contraction. Increased intracellular parietal cell calcium and reduced intracellular magnesium can lead on to increased gastric acid secretion. Increased intracellular calcium can also activate the G-protein coupled receptor - histamine, which can cause increased gastric acid secretion. An upregulated isoprenoid pathway and increased cholesterol synthesis can lead on to the formation of gallstones. Hypomagnesemia can lead to inhibition of gall bladder contraction and decreased water content of the bile contributing to the formation of gall bladder sludge. Increased renal tubular cell calcium and accumulation of shed renal tubular cell in the renal pelvis and ureter can bring about the formation of renal stones.

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

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

Archaeal Digoxin and Regulation of Neurotransmitter Synthesis and Function - Cerebral Dominance

There is an increase in tryptophan and its catabolites and a reduction in tyrosine and its catabolites in the serum of left handed / right hemispheric dominant individuals. This could be due to the fact that digoxin can regulate a neutral amino acid transport system with preferential promotion of tryptophan transport over tyrosine. The decrease in membrane Na^{+}-K^{+} ATPase activity in all the above psychological and pathological states could be due to the fact that the hyperpolarising neurotransmitters (dopamine, morphine and noradrenaline) are reduced and the depolarising neuroactive compounds (serotonin, strychnine, nicotine and quinolinic acid) are increased. The schizoid neurotransmitter pattern of reduced dopamine, noradrenaline and morphine and increased serotonin, strychnine and nicotine is common to left handed / right hemispheric dominant individuals and to all these pathological and psychological states and could predispose to their development. Quinolinic acid, a NMDA agonist can contribute to NMDA excitotoxicity reported in schizophrenia. Strychnine, by blocking glycinergic transmission can contribute to the decreased inhibitory transmission in schizophrenia. Recent data suggest, the initial abnormality in schizophrenia involves a hypodopaminergic state and the low dopamine levels now observed agrees with this. Nicotine by interacting with nicotinic receptors can facilitate the release of dopamine, promoting the dopaminergic transmission in the brain. This can explain the increased dopaminergic transmission in the presence of decreased dopamine levels.

The increased serotoninergic activity and reduced noradrenergic outflow from locus coeruleus reported earlier in schizophrenia agrees with our finding of elevated seratonin and reduced noradrenaline levels. A schizophreniform type of psychosis is important in the genesis of irritable bowel syndrome, inflammatory bowel disease, bronchial asthma, acid peptic disease and immune mediated disorders like multiple sclerosis and SLE. In the presence of hypomagnesemia, the magnesium block on the NMDA receptor is removed leading to NMDA excitotoxicity. The increased presynaptic neuronal calcium can produce cyclic AMP dependent phosphorylation of synapsins resulting in an increased neurotransmitter release into the synaptic junction and vesicular recycling. Increased intracellular calcium in the post synaptic neuron can also activate the calcium dependent NMDA signal transduction. The plasma membrane neurotransmitter transporter (on the surface of the glial cell and presynaptic neuron) is coupled to a sodium gradient which is disrupted by the inhibition of Na^+-K^+ ATPase, resulting in a 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 paroxysomal depolarization shift resulting in epileptogenesis. Increased nicotine synthesis can contribute to the pathophysiology of chronic bronchitis emphysema. Elevated levels of serotonin and nitric oxide production could contribute to increased incidence of migraine in right hemisphere dominant left handed individuals. Increased intracellular calcium can activate the gastrin and acetyl choline related gastric acid secretion. Increased intracellular calcium in the presynaptic neuron can promote cholinergic transmission. The increased presynaptic neuronal Ca^{++} can produce cyclic AMP dependent phosphorylation of synapsins resulting in increased neurotransmitter release into the synaptic junction and vesicular recycling. This promotes cholinergic vagal transmission promoting acid secretion and peptic ulcer formation. These neurotransmitter patterns can also lead to irritable bowel syndrome. The increase in serotonin can contribute to altered bowel motility in IBS. Serotonin blockers are useful in the treatment of IBS. Reduced morphine and dopamine levels can contribute to the pathogenesis of IBS. Studies have shown that there is endogenous synthesis of morphine from tyrosine and dopamine. Kappa and opioid agonist are useful in the treatment of bowel motility disorders. The particular neurotransmitter patterns can inhibit gall bladder contractility contributing to the formation of gallstones. Therefore in the right hemisphere dominant hyperdigoxinemic state there is upregulated serotoninergic, cholinergic and glutamatergic transmission and downregulated dopaminergic, glycinergic and noradrenergic transmission. These neurotransmitter patterns could also be correlated with psychological states. There was an increased tendency for spirituality in hyperdigoxinemic individuals. Temporal lobe epileptic phenomenon has been described in spiritual individuals. Increased glutamatergic transmission is associated with memory and intelligence. This can contribute to increased creativity and tendency towards reduced appetite and eating behaviour. Increased serotoninergic transmission can lead to reduced appetite. There was also hypersexual behaviour, homosexuality and promiscuity in hyperdigoxinemic individuals. This could be related to the increased production of nitric oxide in hyperdigoxinemic individuals consequent to the induction of nitric oxide synthase by increased intracellular calcium. Nitric oxide has been related to erectile function. There was an increased tendency to addictive behaviour in hyperdigoxinemic individuals. Endogenous morphine deficiency has been related to addiction. Morphine synthesis is low because of low tyrosine levels. There was tendency to insomnia and reduced sleep. This could be related to reduced levels of morphine. There was less of bonding and affectionate behaviour. Bonding and affectionate behaviour has been related to dopamine and morphine. Dopamine and morphine deficiency in hyperdigoxinemic individuals could contribute to less of bonding and affectionate behaviour.

The results showed that the concentration of tryptophan, quinolinic acid, strychnine, and serotonin was found to be lower in the plasma of right handed / left hemispheric dominant individuals while that of tyrosine, morphine, dopamine and norepinephrine was higher. Thus there is a decrease in tryptophan and its catabolites and increase in tyrosine and its catabolites in the serum of right handed / left hemispheric dominant individuals and the above described psychological / pathological states. This could be due to the fact digoxin can regulate the neutral amino acid transport system with preferential promotion of tryptophan transport over tyrosine and that digoxin levels are low in right handed / left hemispheric dominant individuals and in the above mentioned pathological / psychological states. The increase in membrane Na^+-K^+ ATPase activity in these cases could be due to the fact that the hyperpolarising neurotransmitters (dopamine, morphine and noradrenaline) are increased and the depolarising neuroactive compounds (serotonin, strychnine, nicotine and quinolinic acid) are decreased. The low level of quinolinic acid, serotonin and strychnine can contribute to reduced excitatory glutamatergic transmission as they are all positive modulators of the NMDA receptor. In the presence of hypermagnesemia, the magnesium block on the NMDA receptor is strengthened leading on to reduced NMDA transmission. The decreased presynaptic neuronal calcium can produce reduced cyclic AMP dependent phosphorylation of synapsins resulting in decrease in glutamate release into the synaptic junction and vesicular recycling. The plasma membrane glutamate transporter (On the surface of the glial cell and presynaptic neuron) is coupled to the sodium gradient, which is activated by the stimulation of Na^+-K^+ ATPase, resulting in increased clearance of glutamate by presynaptic and glial uptake at the end of synaptic transmission. By these mechanisms, stimulation of Na^+-K^+ ATPase can inhibit glutamatergic transmission. Reduced glutamatergic transmission can lead on to healthy aging and protect the brain from neuronal degeneration. The depressive syndrome noted could be due to low serotonin. Decreased serotoninergic transmission has been related to depression. The presence of OCD syndrome could also be related to serotonin depletion. Deficiency of serotonin can lead to increased appetite and eating behaviour resulting in bulimia nervosa. Dopamine and morphine has been related to bonding behaviour. Increased morphine and dopamine could lead to increased bonding and affectionate behaviour. Increased synthesis of morphine can also lead on to lack of addictive behaviour. Morphine deficiency has been related to addiction. The reduced glutamatergic transmission noted could be related to the average to normal IQ and creativity noticed. Dementia has also been related to depression and the phenomenon of pseudomentia has been described. Decreased production of nitric oxide can lead on to hyposexual behaviour. Synthesis of NO has been related to erectile function. These behavioural patterns are suggestive of left hemispheric dominance.

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 to think with metarepresentations 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 a role for the hypothalamus. The hypothalamus is connected to the thalamus by the mamillothalamic tract and digoxin may play a role in regulating these synapses. There are two way connections between the cerebral cortex and the thalamic nucleus. There are also two way connections between the cerebral cortex and hypothalamus and digoxin may possibly regulate these synapses also. The hypothalamus-thalamus-cerebral cortex reverberatory circuit would play a role in mediating conscious perception.

Perceptual binding important in consciousness occurs when all the neurons associated with any one object's perceptual map in layer 5 of 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 amp1if the circuit by its inhibitory effect on glial uptake of glutamate and increasing synaptic glutamate content.

All axons that pass either way between the cerebral cortex and thalamic nucleus must go through the thalamic reticular nucleus and all give off collateral excitatory glutamatergic abranches that innervate the reticular nucleus. The reticular nucleus in turn provides an inhibitory GABAergic innervation back to the thalamic nucleus that provides the input. Reticular nucleus is involved in mediating selective attention by intensifying or detaching a particular active thalamic input into the cortex. The amplification or focussing and detachment of attention occurs by digoxin's effect in promoting glutamatergic transmission in the collaterals to the reticular nucleus by inhibiting the glial uptake of the glutamate and increasing its synaptic content. The back projections from the cerebral cortical perceptual map of the external world to the hypothalamus decides whether hypothalamic archaeal digoxin 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 hypothalamic-thalamic-cerebral cortical circuit leading to disordered conscious perception. Cortical cytoarchitectural disorganization of the temporolimbic cortex has been reported in schizophrenia.

Archaeal Digoxin and Quantal Perception

The perceived element in quantal or subliminal perception which could play a role in schizophrenic symptomatology could be the quanta of light, sound, vibration pressure and matter dependent electric and magnetic fields. The brain functions as a quantum computer with the quantum computer memory elements constituted of superconducting quantum interference devices - the SQUIDS which can exist as superpositions of macroscopic states. Bose condensation, the basis of superconductivity is achievable at room temperature in the Frohlich model in biological systems. The dielectric protein molecules and polar sphingolipids of the neuronal membrane, nucleosomes which are a combination of basic histones and nucleic acid and cytoplasmic magnetite molecules are excellent electric dipole oscillators which exist under a steep neuronal membrane voltage gradient. The individual oscillators are energized with a constant source of pumping energy from outside, by digoxin binding to membrane sodium potassium ATPase and producing a paroxysmal depolarisation shift in the neuronal membrane. This prevents the dipole oscillators from ever settling into thermal equilibrium with the cytoplasm and the interstitial fluid which is always kept at constant temperature. There are connections between the hypothalamus and cerebral cortex and digoxin may serve as a neurotransmitter for these synapses. Bose condensed states produced by the digoxin mediated dielectric protein molecular pumped phonon system could be used to store information which might be encoded - all within the lowest collective frequency mode - by appropriately adjusting the amplitudes of and phase relations between the dipole oscillators. The external world sensory impressions exist in the cortical dipole oscillators as probabilistic multiple superimposed patterns - the U-phase of quantum mechanics. The part of the incoming quantal data maps of the external world built by subliminal perception in logical sequence and corollary to the cerebral cortical external world maps built by conscious perception is chosen. Hypothalamic-cerebral cortical connections mediated by digoxin acting on the neuronal membrane help to magnify the chosen map to I graviton criteria and to the threshold required for the neuronal network to fire and consciousness. It is then integrated into the cerebral cortical conscious perceptual external world map. The comparison occurs by quantal non-local quasicrystal tiling effect which mediates the activation and deactivation of synapses through the contraction and growth of dendritic spines.

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

In the quantal perceptive state there is no past, present or future. All of them can exist together. This gives an explanation for premonitions and visions of the past. Also in the quantal state action at a distance is possible. This can explain psychokinesis and mind travel. Quantal perceptive modal of the brain function also gives an explanation for hypnosis. In the quantal state depending on the observer function of consciousness matter can be created. The information store in one brain can be quantally transferred to other brains raising the possibility of reincarnative experiences.

Archaeal Digoxin - Golgi Body / Lysosomal Function - Hemispheric Dominance

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

Previous reports of alteration in glycoproteins in this connection include alteration in alpha acid glycoprotein (AAG) and beta amyloid precursor protein in epilepsy and Alzheimer's disease and alpha synuclein in Parkinson's disease. Structurally abnormal glycoproteins resist catabolism by lysosomal enzymes and accumulate in neuronal degeneration. Interaction between HS-proteoglycan and ChS-proteoglycan with proteins like beta amyloid, tau protein, parkin and alpha synuclein and reduced proteolytic digestion of these complexes leading on to their accumulation in the neurons have been reported in neurodegenerative diseases like Alzheimer's disease and Parkinson's disease. Alteration in the sulphated proteoglycan matrix of the synaptic vesicles can alter neurotransmitter release into the synapse and produce a functional disorder like schizophrenia and epilepsy. Membrane Na^+-K^+ ATPase inhibition can lead to defective notch signalling. Notch is a transmembrane protein that acts as a signal receptor and is important in neurogenesis. Neuronal growth by extending neurites and forming connections is regulated by the notch signalling pathway. The notch signalling inhibits extension of neurites and keep them stable in the mature brain. A notch ligand known as delta regulates neurogenesis by binding to notch in membranes of embryonal cells and prevents them from developing along the neuronal pathway. Notch activation by the ligand causes notch to be cleaved releasing the notch intracellular domain. This then passes in to the nucleus and activates transcription as part of the DNA binding complex with CSL protein. Intracellular cleavage of the notch is regulated by presenilin and also depends upon the lysosomal protease. In the presence of a lysosomal instability consequent to defective lysosomal membranes notch cleavage by protease is defective leading on to functional disorders consequent to defective synaptic connectivity. The defective notch signalling pathway can lead to neuronal degeneration. Altered glycoproteins, glycolipids and GAG of the neuronal membrane can also contribute to schizophrenia and epilepsy by producing disordered synaptic connectivity. The protein processing defect can result in defective glycosylation of endogenous myelin glycoprotein antigens and exogenous viral glycoproteins antigens with consequent defective formation of MHC class-1 glycoprotein antigen complex. The MHC linked peptide transporter, a P-glycoprotein which transports MHC class-1 glycoprotein antigen complex to the antigen presenting cell surface, has an ATP binding site. The peptide transporter is dysfunctional in the presence of magnesium deficiency. This results in defective transport 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. This can also explain the immune dysregulation in interstitial lung disease, nephrotic syndrome, inflammatory bowel disease sarcoidosis, rheumatoid arthritis and SLE (systemic lupus erythematosis). Defective presentation of exogenous viral antigens can produce immune evasion by the virus as in AIDS dementia and SSPE. Viral persistence has been implicated in the development of tumours (ebstein barr virus and lymphoma), multiple sclerosis (retro virus), degenerations (Parkinson's disease and corona virus) and schizophrenia (borna virus disease). Altered myelin glycoprotein due to defective glycosylation and alteration in GAG of proteoglycans of myelin can affect the structural integrity of myelin leading onto demyelination. A number of fucose and sialic acid containing natural ligands are involved in trafficking of leukocytes and similar breaches in the blood brain barrier and adhesion of the lymphocyte producing leukocyte trafficking and extravasation in to the perivascular space as has been described in MS. Similar changes can explain the immune infiltration in bronchial asthma, sarcoidosis, interstitial lung disease, inflammatory bowel disease and SLE. A number of fucose and sialic acid containing natural ligands have been implicated in neoplastic transformation and metastasis. Abnormally glycosylated tumour antigens can lead to defective tumour antigen presentation and loss of immunosurveillance by the natural killer cells. Altered cell surface glycoproteins, glycolipids and GAG can lead to defective contact inhibition and oncogenesis. The MHC glycoproteins are involved in formation of synaptic connectivity during neuronal development. Defective formation and presentation of the MHC class-1 neuronal glycoprotein complex can lead on to disordered synaptic connectivity and functional disorders like schizophrenia and epilepsy. Altered glycoproteins can affect the synaptic connectivity in the nerve plexus of the bowel wall contributing to irritable bowel syndrome. Magnesium deficiency can upregulate collagen and elastin synthesis along with glycoconjugates. This can contribute to the pathogenesis of fibrosis in ILD and cirrhosis of the liver. Increased glycoconjugate synthesis can interfere with the structure of the alveolar basement membrane contributing to the increased alveolar leakiness leading on to the formation of the intra-alveolar hyaline membrane in interstitial lung disease. Increased synthesis of sulphated glycosaminoglycans and alteration in the glomerular basement membrane can contribute to the pathogenesis of nephrotic syndrome by interfering with the glomerular filtration barrier. Altered mucoproteins can affect the gastric mucosal barrier leading on to acid peptic disease. Non-mucin glycoproteins are pro-nucleating factors with regard to gallstone formation. Urine glycoproteins on the other hand have an inhibitory effect on renal stone formation. Altered glycoproteins lead to removal of these particular effects either inhibitory or stimulatory contributing to gallstones and renal stone formation. Altered proteoglycans of the articular surface of the joint can lead on to osteoarthritis as well as degenerative spondylosis of the spine. Thus in the hyperdigoxinemic right hemisphere dominant state there is reduced lysosomal stability, defective ubiquitin dependent proteolytic processing of proteins and alteration in glycoconjugate structure leading on to their defective catabolism and accumulation. There is also a defect in the MHC antigen presenting pathway leading on to immunodysregulation and viral persistence.

The decrease in the level of dolichol in right handed / left hemispheric dominant individuals and in healthy aging, obsessive compulsive disorder, depression, recurrent respiratory infections, osteoporosis, familial hypotension, patients with low body mass index and bulimia nervosa may suggest its decreased availability for N-glycosylation of proteins. Magnesium excess can lead on to increased catabolism of sphinganine leading on to decreased cerebroside and ganglioside synthesis. In magnesium excess the glycolysis, citric acid cycle and oxidative phosphorylation are activated and less of glucose 6-phosphate is channelled for the synthesis of glycosaminoglycans (GAG). The results show a decrease in the concentration of serum total GAG, glycolipids (ganglioside, glycosyl diglyceride, cerebrosides and sulphatides) and carbohydrate components of glycoproteins (hexose, fucose and sialic acid). The individual GAG fractions in the serum-heparan sulphate (HS), chondroitin sulphates (ChS), heparin (H), hyaluronic acid (HA) and dermatan sulphate (DS) are decreased in left hemisphere dominant individuals (pathological / psychological). The activity of GAG degrading enzymes (beta glucuronidase, beta N-acetyl hexosaminidase, hyaluronidase and cathepsin-D) and that of glycohydrolases (beta galactosidase, beta fucosidase and beta glucosidase) showed significant decrease in the serum in hypodigoxinemic left hemisphere dominant states. Intracellular magnesium excess also results in increased ubiquitin dependent proteolytic processing of glycoconjugates as it requires magnesium for its function. The decrease in the activity of glycohydrolases and GAG degrading enzymes could be due to increased lysosomal stability. Defective lysosomal stability and defective degradation of glycoprotein - GAG complexes as in the case of tau protein /

amyloid - HS proteoglycan complexes in Alzheimer's disease can lead on to brain aging. Membrane Na^+-K^+ ATPase stimulation could protect against neuronal aging. A number of fucose and sialic acid containing natural ligands have been implicated in inflammatory responses and neoplastic transformation. The decrease in fucose and sialic acid noted in these cases could inhibit a protective inflammatory response to the virus or bacteria leading on to recurrent respiratory infection. Decrease in fucose and sialic acid could also protect against malignant transformation. The reduction in glycoconjugate could also result in increased osteoporosis as it affects the structure of the bone matrix. Thus in the hypodigoxinemic left hemisphere dominant state there is increased lysosomal stability, increased ubiquitin dependent proteolytic processing of proteins and alteration in glycoconjugate metabolism leading to decrease in the levels of glycolipids, the carbohydrate component of glycoproteins and glycosaminoglycans. There is no viral persistence but a resulting hypoimmune state contributing to recurrent respiratory infections.

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

The alteration in the isoprenoid pathway specifically, cholesterol as well as changes in glycoproteins and GAG can affect cellular membranes. The upregulation of the isoprenoid pathway in right hemispheric dominant individuals can lead to increased cholesterol synthesis and magnesium deficiency can inhibit phospholipid synthesis. Phospholipid degradation is increased owing to increase in intracellular calcium activating phospholipases A_2 and D. The cholesterol: phospholipid ratio of the RBC membrane was increased in right hemispheric dominance individuals. The concentration of total GAG, hexose and fucose of glycoprotein decreased in the RBC membrane and increased in the serum suggesting their reduced incorporation into the membrane and defective membrane formation. The glycoproteins, GAG and glycolipids of the cellular membrane are formed in the endoplasmic reticulum, which is then budded of as a vesicle, which fuses with the golgi complex. The glycoconjugates are then transported via the golgi channel and the golgi vesicle fuses with the cell membrane. This trafficking depends upon GTPases and lipid kinases, which are crucially dependent on magnesium and are defective in magnesium deficiency. The change in membrane structure produced by alteration in glycoconjugates and the cholesterol: phospholipid ratio can produce changes in the conformation Na^+-K^+ ATPase resulting in further membrane Na^+-K^+ ATPase inhibition. The same changes can affect the structure of the organelle membrane. This results in defective lysosomal stability and leakage of glycohydrolases and GAG degrading enzymes into the serum. Increased release of lysosomal enzymes can contribute to proteolytic destruction in chronic bronchitis and emphysema, osteoarthritis and rheumatoid arthritis. Defective peroxisomal membranes lead to catalase dysfunction which has been documented in these disorders. Alteration in the alveolar basement membrane can contribute to ILD and the glomerular basement membrane and filtration barrier to nephrotic syndrome. Similar changes in the membrane of the cardiac conducting tissue can contribute to lone atrial fibrillation. Changes in the composition of the neuronal membranes can predispose to epilepsy and functional disorders like schizophrenia. Thus in the hyperdigoxinemic right hemisphere dominant state there is defective membrane formation, membrane structure and function.

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

Archaeal Digoxin and Mitochondrial Function - Relation to Cerebral Dominance

The concentration of ubiquinone decreased significantly in left handed / right hemispheric dominant individuals which may be the result of low tyrosine levels, reported in most of the disorders, consequent to digoxin's effect in preferentially promoting tryptophan transport over tyrosine. The aromatic ring portion of ubiquinone is derived from tyrosine. Ubiquinone, which is an important component of the mitochondrial electron transport chain, is a membrane antioxidant and contributes to free radical scavenging. The increase in intracellular calcium can open the mitochondrial PT pore causing a collapse of the hydrogen gradient across the inner membrane and uncoupling of the respiratory chain. Intracellular magnesium deficiency can lead to a defect in the function of ATP synthase. All this leads to defects in mitochondrial oxidative phosphorylation, incomplete reduction of oxygen and generation of the superoxide ion which produces lipid peroxidation. Ubiquinone deficiency also leads to reduced free radical scavenging. The increase in intracellular calcium may lead to increased generation of NO by inducing the enzyme nitric oxide synthase which combines with the superoxide radical to form peroxynitrite. Increased calcium also can activate phospholipase A_2 resulting in increased generation of arachidonic acid which can undergo increased lipid peroxidation. Increased generation of free radicals like the superoxide ion, and hydroxyl radical can produce lipid peroxidation and cell membrane demage which can further inactivate Na^+-K^+ ATPase, triggering the cycle of free radical generation once again. Magnesium deficiency can affect glutathione synthetase and glutathione reductase function. The mitochondrial superoxide dismutase leaks out and becomes dysfunctional with calcium related opening of the mitochondrial PT pore and Outer membrane rupture. The peroxisomal membrane is defective owing to the membrane Na^+-K^+ ATPase inhibition related defect in membrane formation and leads to reduced catalase activity. Mitochondrial dysfunction related free radical generation has been implicated in the pathogenesis of the neuronal degeneration, oncogenesis and immune mediated disorders. Increased free radical generation can lead on to immune activation important in immune mediated diseases like interstitial lung disease, bronchial asthma, sarcoidosis, inflammatory bowel disease, systemic lupus erythematosis, rheumatoid arthritis, nephrotic syndrome and multiple sclerosis. Mitochondrial dysfunction can lead on to Reye’s syndrome. The increased intracellular calcium and ceramide related opening of the mitochondrial PT pore also leads to volume dysregulation of the mitochondria, causing hyperosmolality of the matrix and expansion of the matrix space. The outer membrane of the mitochondria ruptures and releases apoptosis inducing factor and cytochrome C into the cytoplasm. This results in activation of caspase-9 and caspase-3. Caspase-9 can produce apoptosis of the cell. Apoptosis has been implicated in neuronal degeneration. Apoptosis can produce defective synaptogenesis and synaptic connectivity contributing to functional disorders like schizophrenia and epilepsy. Apoptosis of the CD_4 cell can contribute to CD_4 depletion in the acquired immunodeficiency syndrome. Oligodendrocyte (the myelin forming cell) apoptosis is crucial to the pathogenesis of MS. Hepatocyte apoptosis can contribute to cell death in cirrhosis of the liver. Caspase-3 activation can cleave P_{21} involved in linking DNA duplication to cell division resulting in a polyploid cell and oncogenesis. We have been able to demonstrate neuronal degeneration and apoptosis in the digoxin injected rat brain. Thus in the hyperdigoxinemic right hemisphere dominant state there is defect in mitochondrial function and increased free radical generation and reduced scavenging. There is also increased apoptosis.

The concentration of ubiquinone increased significantly in right handed / left hemispheric dominant individuals which may be the result of increased tyrosine levels, consequent to digoxin deficiency promoting tyrosine transport over tryptophan. The decrease in intracellular calcium can stabilize the mitochondrial PT pore and improve mitochondrial function. Intracellular magnesium excess can lead to an increase in the activity of ATP synthase. All this leads to improved efficiency in mitochondrial oxidative phosphorylation and reduced free radical generation. Ubiquinone excess also leads to increased free radical scavenging. The decrease in intracellular calcium may lead to decreased generation of NO by inhibiting the enzyme nitric oxide synthase and reduced peroxynitrite formation. Decreased calcium also can inhibit phospholipase. A_2 resulting in decreased generation of arachidonic acid and free radical formation.

Decreased generation of free radicals like the superoxide ion and hydroxyl radical can stabilise the cell membrane and stimulate membrane Na^+-K^+ ATPase. There was decrease in lipid peroxidation as evidenced from the decrease in the concentration of MDA, conjugated dienes, hydroperoxides and NO with increased antioxidant protection as indicated by the increase in ubiquinone and increased reduced glutathione in hypodigoxinemic left hemisphere dominant individuals The activity of enzymes involved in free radical scavenging like superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase is increased suggesting increased free radical scavenging. The peroxisomal membrane is stabilised owing to membrane Na^+-K^+ ATPase stimulation related alteration in membrane formation and this leads to increased catalase activity. Glutathione is synthesized by the enzyme glutathione synthetase which needs magnesium and ATP. The high intracellular magnesium consequent to Na^+-K^+ ATPase stimulation and the resulting increased ATP can result in increased synthesis of glutathione. Glutathione peroxidase, selenium containing enzyme oxidases reduced glutathione (GSH) to oxidised glutathione (GSSG) which is rapidly reduced to GSH by glutathione reductase. There is also a concomitant conversion of H_2O_2 to H_2O. The activity of glutathione reductase needs NADPH for the regeneration of GSH. This NADPH comes mostly from the pentose phosphate pathway. Intracellular magnesium excess due to membrane Na^+-K^+ ATPase stimulation leads to increased formation of glucose 6-phosphate and upregulation of the pentose phosphate pathway with consequent increased generation of NADPH. Thus glutathione system of free radical scavenging is activated in the presence of membrane Na^+-K^+ ATPase stimulation. Superoxide dismutase exists in a mitochondrial and cytoplasmic form. The stabilization of the mitochondrial PT pore consequent to reduced intracellular calcium produces increased efficiency of superoxide dismutase activity. The increase in catalase, superoxide dismutase (SOD), glutathione peroxidase and glutathione reductase suggests increased free radical protection. This leads to decreased incidence of neuronal degeneration and oncogenesis in the hypodigoxinemic individuals. Free radicals are required for lymphocyte activation and this leads to a hypoimmune response and increased respiratory infection owing to immunodeficiency. The decreased intracellular calcium and ceramide related stabilisation of the mitochondrial PT pore also leads to down regulation of the apoptotic program and reduced apoptosis. The stabilisation of the mitochondria leads to reduced release of apoptosis inducing factor and cytochrome C into the cytoplasm. This results in inactivation of caspase-9 and caspase-3. Inhibition of apoptosis protects against neuronal aging. Caspase-3 inactivation inhibits P_{21} cleavage and protects against oncogenesis. Thus the hypodigoxinemic left hemisphere dominant state has improved efficiency of mitochondrial oxidative phosphorylation, reduced generation of free radicals, increased free radical scavenging and reduced apoptosis.

Archaeal Digoxin and Immunoregulation - Relation to Hemispheric Dominance

In left handed / right hemispheric dominant individuals increased intracellular calcium activates the calcium dependent calcineurin signal transduction pathway which can produce T-cell activation and secretion of interleukin - 3, 4, 5, 6 and TNF alpha. TNF alpha binds to its receptor TNFR1 and activates the transcription factors NFKB and AP-1 leading to the induction of proinflammatory and immunomodulatory genes. This can also explain the immune activation in MS. TNF alpha can also bring about apoptosis of the cell. It binds to its receptor and activates caspase-9, an ICE protease which converts IL-1 beta precursor to IL-1 beta. IL-1 beta produces apoptosis of the neurons (in Alzheimer's disease and AIDS dementia), the oligodendrocyte - the myelin forming cell in MS and the CD_4 cell in HIV infection. IL-1 beta and TNF alpha induce HIV protein expression by the transcription related mechanism and contribute to the pathogenesis of AIDS dementia. Similar digoxin mediated immune activation can play a role in migraine, interstitial lung disease, sarcoidosis, bronchial asthma, inflammatory bowel disease, nephrotic syndrome and immune complex diseases like SLE. Membrane Na^+-K^+ ATPase inhibition can produce immune activation and is reported to increase CD_4/CD_8 ratios as exemplified by the action of lithium. The hyperdigoxinemic right hemisphere dominant state results in immune activation.

In the hypodigoxinemic left hemisphere dominant state decreased intracellular calcium inactivates the calcium dependent calcineurin signal transduction pathway involved in T-cell activation and resulting in decreased secretion of interleukin - 3, 4, 5, 6 and TNF alpha. TNF alpha can also bring about apoptosis of the cell and this is inhibited. Low levels of TNF alpha can lead to immunosuppression. This can explain the immunosuppression and increased rate of respiratory infection. In the hypodigoxinemic left hemisphere dominance there is a tendency for immunosuppression.

Archaeal Digoxin and Regulation of Cell Division, Genomic Function, Cell proliferation and Neoplastic Transformation - Relation to Hemispheric Dominance

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

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

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

Archaeal Digoxin and the Metabolic Regulation - Relation to Hemispheric Dominance

In the hyperdigoxinemic right hemisphere dominant state there is inhibition of Na^+-K^+ ATPase which can explain the pathogenesis of syndrome X. Increased TNF alpha as mentioned above consequent to Na^+-K^+ ATPase inhibition related T-cell activation can contribute to insulin resistance in syndrome X at the receptor level. Decrease in intracellular magnesium can block the phosphorylation reactions involved in protein tyrosine kinase receptor activity leading to insulin resistance. Increase in beta cell calcium can contribute to increased insulin release from beta cells and hyperinsulinemia. Increased intracellular calcium can activate the G-protein coupled signal transduction of the contra insulin hormones (growth hormone and glucagon) leading to hyperglycemia. Decreased intracellular magnesium can lead on to a mitochondrial ATP synthase defect. Increased intracellular calcium can open up the mitochondrial PT pore, disrupt the hydrogen gradient across the inner membrane and block mitochondrial oxidative phosphorylation. Also this leads to defective glucose utilisation and hyperglycemia. Increase in intracellular calcium can activate the G-protein 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, coronary artery disease and mesenteric artery occlusion. Na^+-K^+ ATPase inhibition related altered glycoprotein and GAG can contribute to the microangiopathy and macroangiopathy observed in syndrome X. Metabolic syndrome X could be visualised as being due to hypothalamic archaeal digoxin hypersecretion. In hypomagnesemia there is inhibition of lipoprotein lipase and decrease in catabolism of triglyceride rich lipoprotein resulting in hypertriglyceridemia. Also magnesium deficiency leads to inhibition of lecithin cholesterol acyl transferase (LCAT) producing decreased formation of cholesterol esters in HDL. This leads on to the dyslipidemia of syndrome X with elevated triglyceride and low HDL cholesterol levels. Digoxin induced hyperinsulinemia and hypertriglyceridemia produces the trunkal obesity in syndrome X. In the hyperdigoxinemic right hemisphere dominant state glucose metabolism and utilisation is impaired consequent to insulin resistance as there is also a tendency for vasospasm and thrombosis.

In the hypodigoxinemic left hemisphere dominant state stimulation Na^+-K^+ ATPase can also lead to metabolic abnormalities. Hypermagnesemia consequent to membrane Na^+-K^+ ATPase stimulation can lead on to increased cell membrane transport of glucose. Increase in intracellular magnesium can activate the phosphorylation reactions involved in protein tyrosine kinase receptor activity leading to increased insulin receptor activity. Increase in intracellular magnesium can lead on to stimulation of glycolysis causing increased glucose utilization. Decrease in intracellular calcium can stabilise the mitochondrial PT pore and stimulate mitochondrial oxidative phosphorylation. Intracellular magnesium excess can also lead to ATPase synthase hyperactivity. This leads to increased glucose utilisation. Decrease in beta cell calcium can contribute to decreased insulin release from beta cells and hypoinsulinemia. Hypermagnesemia has been reported to markedly decreased glucose stimulated insulin secretion by the perfused pancreas. Increased intracellular magnesium can produce hyperactivity of lipoprotein lipase producing increased catabolism of triglycerides rich lipoproteins and hypotriglyceridemia. In hypermagnesemia lecithin cholesterol acyl transferase is activated and there is increased formation of cholesterol esters in HDL. This results in increased HDL cholesterol. Magnesium excess has been reported to decrease LDL cholesterol levels also. Low insulin levels and increased triglyceride catabolism can be correlated with low body mass index. Decrease in intracellular calcium can inactivate the G-protein coupled angiotensin receptor producing hypotension and the G-protein coupled thrombin receptor and platelet activating factor producing decreased thrombosis observed in the hypodigoxinemic state. Increased intracellular magnesium can lead to decreased thrombin and ADP / collagen induced platelet aggregation. Na^+-K^+ ATPase stimulation related decreased smooth muscle calcium and increased magnesium can contribute to vasodilatation and protect from ischaemia due to stroke and coronary artery disease. This can also lead on to a hypotensive state and familial hypotension. Na^+-K^+ ATPase stimulation induced hypermagnesemia related altered glycoprotein and glycosaminoglycan synthesis can contribute to the decreased atherosclerosis. Thus in the hypodigoxinemic left hemisphere dominant state there is increased efficiency of mitochondrial oxidative phosphorylation, increased glucose utilisation with hypercatabolism of triglyceride rich lipoproteins, low body mass index and decreased vascular thrombosis. This leads on to healthy aging. In the left hemisphere dominant hypodigoxinemic state there is an endogenous morphine excess syndrome. Morphine has been reported to have an effect on glucose metabolism. In mice, subcutaneous administration of morphine has been shown to produce a dose dependent hyperglycemia, while intrathecal administration of a much lower concentration in the lumbar region caused a dose dependent hypoglycemia. These effects are thought to be due to an insulin independent mechanism mediated through spinal opiate and central alpha-adrenergic receptor stimulation. The effect of morphine on pancreatic glucagon release has been hypothesized to result from suppression of somatostatin and concurrent release of the alpha cell from tonic inhibition leading to an increase in glucagon secretion. Glucagon is the most potent mediator of morphine induced hyperglycemia. Morphine can regulate insulin release from the beta cells with both an inhibitory effect and stimulatory effect being reported. Morphine induced hyperglycemia would involve activation of the pituitary adrenal axis, endocrine pancreas and endogenous opioid peptides. Morphine can also act as a vasodilator contributing to hypotension. Morphine also has an immunosuppressive action. This could contribute to increased incidence of respiratory infections in the left hemispheric dominant state.

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 in the hyperdigoxinemic right hemisphere dominant state. There is increased incidence of neoplasms like non-Hodgkin’s lymphomas and vasculitis in the acquired immunodeficiency syndrome. Neuronal degenerations like AIDS dementia has been related to glutamate excitotoxicity. An AIDS related schizophreniform psychosis has been described. Polyclonal beta-cell proliferation and lymphadenopathy have been described in AIDS. Digoxin induced calcineurin signal transduction mediated

T-cell activation and polyclonal B-cell proliferation can contribute to HIV-l replication. Digoxin induced T-cell activation can lead on to a secretion of TNF-alpha which induces the immunomodulatory transcription factor NFKB. Chief among the inducible cellular proteins that promote the growth of HIV-1 is transcription factor NFKB. HIV-1 has incorporated two such NFKB binding-enhancer elements into its own genome, which allows the triggering of HIV-l transcription in the presence of nuclear NFKB. Digoxin induced protein glycosylation defects can also lead to defective glycosylation of HIV glycoprotein antigens leading on to defective formation of the 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. In hyperdigoxinemia the intracellular magnesium excess results in Z to B transition of DNA and defective methylation of DNA bases leading on to retroviral transposon expression. Hypothalamic structural abnormalities have been described in homosexuals predisposed to the development of acquired immunodeficiency syndrome. In the hyperdigoxinemic right hemisphere dominant state there is a tendency for viral persistence consequent to defective processing of viral proteins and defective immune response to the virus.

The Isoprenoid Organism and Evolution

In the hypothalamic archaeal digoxin induced neuronal quantal state individual dielectric molecules like proteins, nucleic acid, mucopolysaccharides and lipids can store information and undergo self-replication on a preexisting template. The cellular organelle can be considered as symbiotic conglomeration of these macromolecules. The cell can be considered as a symbiotic collection of these organelle. Each organelle may evolutionally represent an organism-like mitochondria and nucleic acids. The brain with its axonal and dendritic connections can be visualised as a colony of such organisms with its interlinking connections. In this theoretical model there is no evolution but only different conglomeration of the initially existing macromolecules - anevolution. The isoprenoid macromolecule could have been the initial self-replicating organism at the beginning of evolution. Information could have been stored in the isoprenoid-repeating units. It would be tempting to speculate on a role for self-replicating macromolecules like proteins, nucleic acid, mucopolysaccharide and isoprenoid in human diseases. Prions are self-replicating proteins and have been implicated in neurodegenerative disorders.

Archaeal Digoxin and Integration of Brain and Cellular Function

Hypothalamic archaeal digoxin can thus integrate multiple brain and cellular functions. It can integrate the function of multiple cellular organelle - golgi body, lysosome, nucleus and genomic function, mitochondria and cell membrane. It can regulate cell death, cell differentiation and cell proliferation. Digoxin can regulate neuronal transmission and conscious perception in the brain by its effect on neutral amino acid and neurotransmitter transport. Digoxin can also play a role in endocrine integration. The hypothalamic hormone secretion is regulated by the biogenic amines noradrenaline, dopamine and serotonin. Digoxin by regulating the release and uptake of these neurotransmitters can control hypothalamic hormone secretion. Digoxin, by its lithium like action in modulating G-protein function and by facilitating calcium induced signal transduction consequent to increased sodium-calcium exchange, can regulate the function of these hormones. Digoxin can act as an immunomodulator owing to its effect on calcineurin signal transduction in the lymphocyte and subsequent immune activation. Digoxin can thus produce neuro-immuno-endocrine integration in the brain.

The Mind-Body Universe

Digoxin by modulating conscious perception contributes to the observer function of human consciousness. Human consciousness depends on the information perceived from the external world by conscious or subliminal perception and is momentary. It is consciousness that converts the quantal world of probabilities in to the classical objective real world of matter by the act of making an observation. Thus human consciousness and the external world have an interrelated existence. Hypothalamic archaeal digoxin can produce integration and coordination of cellular organelle function. It can also function as the principal conductor of the neuro-immuno-endocrine orchestra.

References

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