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Archaeal Digoxin Mediated Model for Schizophrenia

Introduction

Changes involving the isoprenoid pathway have been described in schizophrenia and bipolar mood disorder. The isoprenoid pathway produces four key metabolites - ubiquinone (membrane antioxidant and component of the mitochondrial electron transport chain), dolichol (involved in N-glycosylation of proteins), digoxin, (an endogenous inhibitor of membrane Na^+-K^+ ATPase) and cholesterol. Decreased ubiquinone levels have been reported in the erythrocyte in schizophrenia. Involvement of the endogenous dioxin like factor (EDLF) has been reported in the brain in bipolar mood disorder. Altered levels of dolichol in the brain and altered glycoproteins in the serum and brain have been reported in schizophrenia.

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

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

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

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

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

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

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

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

Results

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

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

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

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

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

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

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

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

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

Discussion

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

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

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

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

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

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

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

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

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

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

membrane Na^+-K^+ ATPase inhibition related magnesium depletion can affect the metabolism of glycosaminoglycans, glycoproteins and glycolipids. The elevation of the level of dolichol may suggest its increased availability for N-glycosylation of proteins. Magnesium deficiency can lead on to defective metabolism of sphinganine producing its accumulation which may lead to increased cerebroside and ganglioside synthesis. In magnesium as glycolysis, the citric acid cycle and oxidative phosphorylation are blocked and more glucose 6-phosphate is channelled for the synthesis of glycosaminoglycans (GAG). The results show an increase in the concentration of serum total GAG, glycolipids (ganglioside diglyceride, cerebrosides and sulphatides) and carbohydrate components of glycoproteins (hexose, fucose and sialic acid) in schizophrenia. The increase in the carbohydrate components - total hexose, fucose and sialic acid-in schizophrenia was not to the same suggesting qualitative change in glycoprotein structure. The individual GAG fractions in the serum-heparan sulphate (HS), chondroitin sulphates (ChS), heparin (H), hyaluronic acid and dermatan sulphate increased in schizophrenia. The activity of GAG degrading enzymes (beta glucuronidase, beta N-acetyl hexosaminidase, hyaluronidase and cathepsin-D) showed significant increase in the serum in schizophrenia. The activity of serum beta fucosidase and beta galactosidase increased while that of beta glucosidase was unaltered. Intracellular magnesium deficiency also results in defective ubiquitin dependent proteolytic processing of glycoconjugates as it requires magnesium for its function. The increase in the activity of glycohydrolases and GAG degrading enzymes could be due to reduced lysosomal stability and consequent leakage of lysosomal enzymes into the serum. The increase in the concentration of carbohydrate components of glycoproteins and GAG in spite of increased activity of many glycohydrolases and GAG degrading enzymes may be due to their possible resistance to cleavage consequent to qualitative change in their structure. Proteoglycan complexes formed in the

presence of altered calcium/magnesium ratios intracellularly may be structurally abnormal and resistant to lysosomal enzymes and may accumulate.

Alteration in the sulphated proteoglycan matrix of the synaptic vesicles can alter neurotransmitter release into the synapse and produce a functional disorder like schizophrenia. Altered glycoproteins, glycolipids and GAG of the neuronal membrane can also contribute to schizophrenia by producing disordered synaptic connectivity. Disordered synaptic connectivity in the limbic allocortex caused by abnormal migration of neurons along the radial glial cells has been described in schizophrenia. The protein processing defect can result in defective glycosylation of endogenous neuronal glycoprotein antigens and exogenous viral glycoproteins antigens with consequent defective formation of the MHC antigen complex. The MHC linked peptide transporter, a P-glycoprotein which transports MHC-antigen complex to the antigen presenting cell surface, has an ATP binding site. The peptide transporter is dysfunctional in the presence of magnesium deficiency. This results in defective transport of the MHC class-1 glycoprotein antigen complex to the antigen presenting cell surface for recognition by the CD4 or CD8 cell. Defective presentation of the endogenous neuronal glycoprotein antigen can explain the immune dysregulation in schizophrenia. An autoimmune hypothesis for schizophrenia has been postulated by certain groups of workers. Anti-brain antibodies have been described in schizophrenia contributing to its pathogenesis. A number of fucose and sialic acid containing natural ligands are involved in trafficking of leukocytes and similar breaches in the blood brain barrier and adhesion of the lymphocyte producing leukocyte trafficking and extravasation into the perivascular space can contribute to the autoimmune phenomena in schizophrenia. Defective presentation of exogenous viral antigens can produce immune evasion by the virus and viral persistence. A virogene hypothesis for schizophrenia has also been described. Borna virus and influenza virus has been implicated in the pathogenesis of schizophrenia. Increased intracellular calcium

activates the calcium dependent calcineurin signal transduction pathway which can produce T-cell activation and Secretion of interleukin - 3, 4, 5, 6 and TNF alpha (Tumour necrosis factor alpha). This can also explain the immune activation in schizophrenia contributing to the autoimmunity. Membrane Na^+-K^+ ATPase inhibition can produce immune activation and is reported to increase CD_4/CD_8 ratios as exemplified by the action of lithium, a Na^+-K^+ ATPase inhibitor. TNF alpha can also bring about apoptosis of the cell. It binds to its receptor and activates caspase-9, an ICE protease which converts IL-1 beta precursor to IL-1 beta. IL-1 beta produces apoptosis of the neurons, which can contribute to defective synaptogenesis and synaptic connectivity in schizophrenia. Defective apoptosis has been related to the developmental abnormality in the limbic system, frontal cortex and basal ganglia in schizophrenia.

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

The archaeaon steroidelle, glycosaminoglycoid and fructosoid contributes to cell membrane formation synthesizing cholesterol by the DXP pathway and glycosaminoglycans by fructolysis. The alteration in the isoprenoid pathway specifically, cholesterol as well as changes in glycoproteins and GAG can affect cellular membranes. The upregulation of the isoprenoid pathway can lead to increased cholesterol synthesis and magnesium deficiency can inhibit phospholipid synthesis. Phospholipid degradation is increased owing to increase in intracellular calcium activating phospholipase A_2 and D. The concentration of cholesterol increased in the RBC membrane and serum in schizophrenia while the concentration of phospholipids decreased in the RBC membrane. The cholesterol: phospholipid ratio of the RBC membrane was increased in schizophrenia. The concentration of total GAG, hexose and fucose content of glycoproteins decreased in the RBC membrane and increased in the serum

suggesting their reduced incorporation into the membrane and defective membrane formation. The glycoproteins, GAG and glycolipids of the cellular membrane are formed in the endoplasmic reticulum, which is then budded off as a vesicle, which fuses with the golgi complex. The glycoconjugates are then transported via the golgi channel and the golgi vesicle fuses with the cell membrane. This trafficking depends upon GTPases and lipid kinases, which are crucially dependent on magnesium and are defective in magnesium deficiency. The change in membrane structure produced by alteration in glycoconjugates and the cholesterol: phospholipid ratio can produce changes in the conformation of Na^+-K^+ ATPase resulting in further membrane Na^+-K^+ ATPase inhibition. The same changes can affect the structure of the organelle membrane. This results in defective lysosomal stability and leakage of glycohydrolases and GAG degrading enzymes into the serum. The defective peroxisomal membrane leads to catalase dysfunction, which has been documented in schizophrenia.

Archaeal Digoxin and Mitochondrial Dysfunction in Relation to Schizophrenia

The archaeaon vitaminocyte contributes to the synthesis of ubiquinone and mitochondrial electron transport chain function. The mitochondrial function related free radical generation is regulated by the archaeaon vitaminocyte synthesized tocopherol and ascorbic acid. The concentration of ubiquinone decreased significantly in schizophrenia, which may be the result of low tyrosine levels consequent to digoxin's effect in preferentially promoting tryptophan transport over tyrosine. The aromatic ring portion of ubiquinone is derived from tyrosine. Ubiquinone, which is an important component of the mitochondrial electron transport chain, is a membrane antioxidant and contributes to free radical scavenging. The increase in intracellular calcium can open the mitochondrial PT pore causing a collapse of the H^+ gradient across the inner membrane and

uncoupling of the respiratory chain. Intracellular magnesium deficiency can lead to a defect in the function of ATP synthase. All this leads to defect in mitochondrial oxidative phosphorylation, incomplete reduction of oxygen an generation of the superoxide ion which produces lipid peroxidation. Ubiquinone deficiency also leads to reduced free radical scavenging. The increase in intracellular calcium may lead to increased generation of NO by inducing the enzyme nitric oxide synthase which combines with the superoxide radical to form peroxynitrite. Increased intracellular calcium also can activate phospholipase A_2 resulting in increased generation of arachidonic acid, which n undergo increased lipid peroxidation. Increased generation of free radicals like the superoxide ion and hydroxyl radical can produce lipid peroxidation and cell membrane damage, which can further inactivate Na^+-K^+ ATPase triggering the cycle of free radical generation once again. There was increase in lipid peroxidation as evidenced from the increase in the concentration of MDA, conjugated dienes, hydroperoxides and NO with decreased antioxidant protection as indicated by decrease in ubiquinone and reduced glutathione in schizophrenia. The neurotransmitter NO has got a behavioural function in the brain and an aggressive behaviour has been attributed to increased NO in the brain. The activity of enzymes involved in free radical scavenging like superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase is decreased in schizophrenia suggesting reduced free radical scavenging. This agrees with work by previous authors. Alpha-tocopherol was unaltered in schizophrenia. The concentration of ceruloplasmin and iron binding capacity decreased significantly in schizophrenia suggesting increased amounts of free iron and copper, promoting free radical generation. Ceruloplasmin is a 132 KD monomeric copper oxidase, which has been implicated in iron metabolism because of its catalytic oxidation of Fe^{2+} to Fe^{3+} (ferroxidase activity). In the presence of iron in Fe^{2+} form the conversion of H_2O_2 to hydroxyl radical is greatly increased. Low ceruloplasmin results in more of the

iron to be in Fe^{2+} form. It has been shown that ceruloplasmin increases iron uptake by cells increasing the apparent affinity for the substrate by three times. Low ceruloplasmin levels can result in decreased iron uptake and this results in an increased amount of free iron. The intra cellular magnesium deficiency can produce ribosomal dysfunction and inhibition of protein synthesis as noted by decrease in serum albumin in schizophrenia. The low serum ceruloplasmin levels may be a consequence of reduced ceruloplasmin synthesis. The peroxisomal membrane is defective owing to the membrane Na^+-K^+ ATPase inhibition related defect in membrane formation and leads to reduced catalase activity. Glutathione is synthesized by the enzyme glutathione synthetase, which needs magnesium and ATP. The low intracellular magnesium consequent to Na^+-K^+ ATPase inhibition and the resulting low ATP synthesis can result in decreased synthesis of glutathione. Glutathione peroxidase, a selenium containing enzyme oxidises reduced glutathione (GSH) to oxidised glutathione (GSSG) which is then rapidly reduced to GSH by glutathione reductase. There is also a concomitant conversion of H_2O_2 to H_2O. The activity of glutathione reductase needs NADPH for the regeneration of GSH. This NADPH comes mostly from the pentose phosphate pathway. Intracellular magnesium deficiency due to membrane Na^+-K^+ ATPase inhibition leads to decreased formation of glucose-6-phosphate and downregulation of the pentose phosphate pathway with consequent decreased generation of NADPH. Thus glutathione system of free radical scavenging is defective in the presence of membrane Na^+-K^+ ATPase inhibition. Superoxide dismutase exists in a mitochondrial and cytoplasmic form. The opening of the mitochondrial PT pore produces hyperosmolality and matrix expansion rupturing the outer membrane producing loss of the mitochondrial dismutase and decrease in its activity. Mitochondrial dysfunction related free radical generation has been implicated in the pathogenesis of schizophrenia. Mitochondrial dysfunction can

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

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

Archaeal Digoxin and Consciousness

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

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

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

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

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

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

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

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

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

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

Archaeal Digoxin and Integration of Brain Function

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

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

References

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