3

Archaeal Digoxin and Parkinson's Disease

Changes involving the isoprenoid pathway have been described in neuronal degeneration. Mitochondrial dysfunction particularly involving ubiquinone has been reported in platelet mitochondria in Parkinson's disease. Altered levels of dolichol in the brain and altered glycoproteins like beta amyloid have been reported in Alzheimer's disease. Dolichol and ubiquinone are both products of the isoprenoid pathway. Sodium potassium ATPase inhibition has been reported to lead to neuronal degeneration. An endogenous inhibitor of sodium potassium ATPase archaeal digoxin is produced by the isoprenoid pathway. It was therefore considered pertinent to study the isoprenoid pathway in neuronal degeneration. Digoxin induced membrane Na^{+}-K^{+} ATPase inhibition can produce Mg^{++} depletion leading on to altered glycoconjugate metabolism. The dolichol pathway can regulate N-glycosylation of glycoproteins. Alteration in glycoconjugate metabolism has also been described in neuronal degeneration. Amyloid and hyperphosphorylated tau protein in Alzheimers disease and alpha synuclein in Parkinson's disease are defectively processed proteins resistant to the action of proteases. Accumulation of heparan sulphate proteoglycan (HS-PG) and its interaction with beta amyloid precursor protein (beta APP) have been suggested as a possible mechanism for amyloid plaque formation in Alzheimer's disease. Glycolipids like ceramide can produce cell death by opening up the mitochondrial PT pore and contribute to neuronal degeneration and aging. Digoxin can alter intracellular Ca^{++}/Mg^{++} ratios in the cell leading on to free radical generation. Alteration in the ubiquinone pathway can also lead to mitochondrial dysfunction and free radical generation. Free radical mechanisms have been implicated in the pathogenesis of the major neurodegenerative disorders like Parkinson's disease, Alzheimer's disease and amyotrophic lateral sclerosis. In Parkinson's disease, free radical generation has been reported to be due to formation of H_2O_2 from dopamine by the action of monoamine oxidase and the subsequent reaction of H_2O_2 with iron to generate the hydroxyl radical

by the Fenton reaction. A critical role for iron in free radical generation has been suggested in neurodegenerations like Parkinson's disease and Alzheimer's disease. An altered free radical defence mechanism like decreased levels of antioxidant enzymes and antioxidants has been suggested for the free radical damage in Parkinson's disease. Increased formation of NO which forms peroxynitrite with superoxide promoting lipid peroxidation has also been reported in neurodegeneration. Digoxin has been reported to regulate the transport of amino acids especially the neutral amino acids. Abnormalities in tryptophan catabolism and the kynurenine pathway have been described in neuronal degeneration. Of the kynurenines, quinolinic acid is most relevant to neurodegenerative disease. Quinolinic acid toxicity in the brain appears to be mediated through its action as an agonist of the NMDA receptor. Neurotoxicity induced by quinolinic acid occurs preferentially in the neocortex, striatum and hippocampus in the brain. The neuro-toxic effects of quinolinic acid are mediated via the magnesium sensitive NMDA receptor. Membrane abnormalities have been described in neurodegenerative disorders like neuroacanthocytosis and motor neuron disease. In motor neuron disease abnormalities in the RBC handling of the glutamate have been reported. In Alzheimer's disease alteration in membrane fluidity especially of the platelet membrane has been reported. The isoprenoid pathway produces four metabolites important in maintaining cell membrane structure and function - digoxin (a membrane Na^+-K^+ ATPase inhibitor), dolichol (involve in N-glycosylation of proteins), ubiquinone (a membrane antioxidant) and cholesterol. This study was undertaken to assess (1) the isoprenoid pathway (2) the tryptophan/tyrosine catabolic patterns (3) glycoconjugate metabolism in PD and (4) RBC membrane changes as a reflection of neuronal membrane change. A hypothesis implicating neuronal membrane sodium potassium ATPase inhibition as pivotal to all these changes is also presented.[1-8]

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 neurological disease.

Results

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

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

(3) Nicotine (1.07 ug/100 ml) and strycimine (9.54 ug/dL) were detected in the plasma of patients with PD but were not detectable in the control serum. Morphine was not detected in the plasma of these patients.

(4) The concentration of total glycosaminoglycans (GAG) increased in the serum of PD patients. The concentration of heparan sulphate (HS) heparin (H) and dermatan sulphate (DS) was increased, while that of chondroitin sulphates (ChS) and hyaluronic acid (HA) was decreased. 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, cerebroside and sulphatide showed significant increase in the serum in these patients.

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

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

(7) Concentration of total serum cholesterol and LDL cholesterol was not significantly altered while HDL cholesterol showed a significant decrease

in the plasma in PD. Serum triglycerides were unaltered while free fatty acids (FFA) increased in PD.

(8) The activity of superoxide dismutase (SOD), catalase, glutathione reductase and glutathione peroxidase in the erythrocytes decreased significantly in Parkinson's disease. In Parkinson's disease concentration of MDA, hydroperoxides, conjugated dienes and NO increased significantly. The concentration of glutathione and of alpha tocopherol decreased in Parkinson's disease. Iron binding capacity, ceruloplasmin and albumin decreased significantly in Parkinson's disease.

Discussion

Archaeal Digoxin and Membrane Na^+-K^+ ATPase Inhibition in Relation to Parkinson's Disease

The archaeaon steroidelle contributes to lipid synthesis and metabolism. The archaeaon steroidelle DXP pathway and the upregulated pentose phosphate pathway contribute to digoxin synthesis. The results showed that HMG CoA reductase activity, serum digoxin and dolichol were increased and serum ubiquinone was reduced in PD. Previous studies in this laboratory have demonstrated incorporation of ^{14}C-acetate into digoxin in the rat brain indicating that acetyl CoA is the precursor for digoxin biosynthesis in mammals also. The elevated HMG CoA reductase activity correlates well with elevated digoxin levels and reduced RBC membrane Na^+-K^+ ATPase activity. The increase in endogenous digoxin, a potent inhibitor of membrane Na^+-K^+ ATPase, can decrease this enzyme activity. The inhibition of Na^+-K^+ ATPase by digoxin is known to cause an increase in intracellular Ca^{++} resulting from increased Na^+-Ca^{++} exchange, increased entry of Ca^{++} via the voltage gated Ca^{++} channel and increased release of Ca^{++} from intracellular endoplasmic reticulum Ca^{++} stores. This increase in intracellular Ca^{++} by displacing Mg^{++} from its binding

sites causes a decrease in the functional availability of Mg^{++}. This decrease in the availability of Mg^{++} can cause decreased mitochondrial ATP formation which along with low Mg^{++} can cause further inhibition of Na^{+}-K^{+} ATPase, since the ATP-Mg^{++} complex is the actual substrate for this reaction. Cytosolic free calcium is normally buffered by two mechanisms, ATP dependent calcium extrusion from the cell and ATP dependent sequestration of calcium within the endoplasmic reticulum. The Mg^{++} related mitochondrial dysfunction results in defective calcium extrusion from the cell. There is thus a progressive inhibition of Na^{+}-K^{+} ATPase activity first triggered by digoxin. Low intracellular Mg^{++} and high intracellular Ca^{++} consequent to Na^{+}-K^{+} ATPase inhibition appear to be crucial to the pathogenesis of PD. Serum Mg^{++} was found to be reduced in PD.[1-8]

Archaeal Digoxin and Regulation of Neurotransmitter Synthesis and Function in Relation to Parkinson's Disease

The archaeaon neurotransminoid shikimic acid pathway contributes to tryptophan and tyrosine synthesis and catabolism generating neurotransmitters and neuroactive alkaloids. Digoxin, apart from affecting cation transport is also reported to influence the transport of various metabolites across cellular membranes, including amino acids and various neurotransmitters. Two of the amino acids in this respect are important, tryptophan, a precursor for strychnine and nicotine, and tyrosine, a precursor for morphine. We had already shown the presence of endogenous morphine in the brain of rats loaded with tyrosine and endogenous strychnine and nicotine in the brain of rats loaded with tryptophan. The present study shows that the concentration of tryptophan, quinolinic acid, and serotonin was higher in the plasma of PD patients while that of tyrosine, dopamine and norepinephrine was lower. Serum of patients with PD showed the presence of nicotine and strychnine. Morphine was absent in the serum of these patients. Thus there is an increase in tryptophan and its catabolites (serotonin,

nicotine, strychnine and quinolinic acid) and a reduction in tyrosine and its catabolites (dopamine, norepinephrine and morphine) in the patient's serum. 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 neuronal tryptophan load and reduced neuronal tyrosine load can upregulate tryptophan catabolism and down regulate the catabolism of tyrosine. Reduced dopamine levels can lead on to defects in nigrostriatal dopaminergic transmission, observed in Parkinson's disease. Release of dopamine in to the neostriatum has an inhibitory defect on neostriatal cholinergic neurons and this effect is reduced in the presence of dopamine deficiency. The decreased levels of noradrenaline can contribute to postural and gait disturbance in PD. The decrease in dopamine, and norepinephrine documented by us has also been reported by Eldrup et al. The increase in serotonin levels and decrease in dopamine and noradrenaline could contribute to the psychiatric manifestations and cognitive dysfunction described in PD. Acetyl choline is synthesized and released by small (Golgi type II) neurons in the neostriatum and it has a excitatory effect on these neurons. Nicotine acts as a CNS stimulant and can bind to the central nicotinic receptors contributing to the increase in cholinergic transmission and tremor in PD. The fundamental equilibrium that exists between the excitatory cholinergic and inhibitory dopaminergic mechanism is lost consequent to this alteration in nicotine and dopamine levels. Membrane Na^+-K^+ ATPase inhibition can lead on to increased glutamatergic excitatory transmission in contributing to PD. The decrease in membrane Na^+-K^+ ATPase activity in PD 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 as also to increased digoxin levels. In the presence of hypomagnesemia, consequent to Na^+-K^+ ATPase inhibition the

Mg^{++} block on the NMDA receptor is removed leading to NMDA excitotoxicity. The increased levels of FFA can contribute to epileptogenesis by binding Mg^{++}. This results in the formation of Mg^{++} soaps in the blood and hypomagnesemia. The increased presynaptic neuronal Ca^{++} can produce cyclic AMP dependent phosphorylation of synapsins resulting in increased glutamate release into the synaptic junction and vesicular recycling. Increased intracellular Ca^{++} in the post synaptic neuron can also activate the Ca^{++} dependent NMDA signal transduction. The plasma membrane glutamate transporter (on the surface of the glial cell and presynaptic neuron) is coupled to a Na^{+} gradient which is disrupted by the inhibition of Na^{+}-K^{+} ATPase, resulting in decreased clearance of glutamate by presynaptic and glial uptake at the end of synaptic transmission. By these mechanisms, inhibition of Na^{+}-K^{+} ATPase can promote excitatory glutamatergic transmission. Serotonin and quinolinic acid are NMDA agonist and positive modulators and could contribute to increased NMDA transmission. Strychnine by blocking glycinergic transmission contributes to the decreased inhibitory transmission in the brain. Strychnine displaces glycine from its binding sites and the glycine is free to bind to the strychnine insensitive site of the NMDA receptor and promote excitatory NMDA transmission. Increased NMDA transmission could contribute to increased excitatory transmission in the corticostriatal glutamatergic pathways and also produce derangement of the basal ganglia functional loops. NMDA excitotoxicity contributes to neuronal degeneration in PD by increasing the intracellular Ca^{++} levels.[1-8]

Archaeal Digoxin and Regulation of Golgi Body / Lysosomal Function in Relation to Parkinson's Disease - The Glycosaminoglycoid

The archaeaon glycosaminoglycoid and fructosoid contributes to glycoconjugate synthesis and catabolism by the process of fructolysis. The membrane Na^{+}-K^{+} ATPase inhibition related Mg^{++} depletion and elevated

dolichol levels can affect the metabolism of glycosaminoglycans, glycoproteins and glycolipids. The elevation in 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 Mg^{++} deficiency the glycolysis, citric acid cycle and oxidative phosphorylation are blocked and more glucose 6 phosphate is channelled for the synthesis of glycosaminoglycans (GAG). 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 PD. The increase in the carbohydrate components-total hexose, fucose and sialic acid-in PD was not to the same extent suggesting qualitative change in glycoprotein structure. In PD the percentage change in total hexose, fucose and sialic acid when compared to the control is 69%, 19% and 64% respectively. The concentration of heparan sulphate (HS) heparin (H) and dermatan sulphate (DS) was increased, while that of chondroitin sulphates (ChS) and hyaluronic acid (HA) was decreased. The activity of GAG degrading enzymes - beta glucuronidase, beta N-acetyl hexoseaminidase, hyaluronidase and cathepsin-D - was increased in PD when compared to the controls. The activity of beta galactosidase increased in PD while that of beta fucosidase and beta glucosidase was unaltered. Intracellular Mg^{++} deficiency also results in defective ubiquitin dependent proteolytic processing of glycoconjugates as it requires Mg^{++} for its function. Defective ubiquitin dependent proteolytic processing of proteins has been described in PD. The increase in the activity of glycohydrolases and GAG degrading enzymes could be due to reduced lysosomal stability and consequent leakage of lysosomal enzymes into the serum. The increase in the concentration of carbohydrate components of glycoproteins and GAG in spite of increased activity of many glycohydrolases may be due to their possible resistance to cleavage by

glycohydrolases consequent to qualitative change in their structure. Proteoglycan complexes formed in the presence of altered Ca^{++}/Mg^{++} ratios intracellularly may be structurally abnormal and resistant to lysosomal enzymes and may accumulate.

Previous reports of alteration in glycoproteins in this connection include alpha synuclein and parkin 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 parkin and alpha synuclein and reduced proteolytic digestion of these complexes can lead on to their accumulation in the neurons. Lewy bodies observed in selective vulnerable neuronal population in PD have got positive anti-ubiquitin staining and accumulation of neurofilament proteins and alpha-synuclein which are defectively processed. Similar interaction between HS proteoglycan and ChS proteoglycan with beta amyloid and tau protein has been described in Alzheimer's disease. Alteration in the sulphated proteoglycan matrix of the synaptic vesicles can alter dopamine release into the synapse and contribute to the pathogenesis of PD. Altered glycoproteins, glycolipids and GAG of the neuronal membrane can also contribute to PD by producing disordered synaptic connectivity in the nigrostriate pathways. 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 the MHC-antigen complex to the antigen presenting cell surface, has an ATP binding site which is dysfunctional in the presence of Mg^{++} deficiency. This results in defective transport of the MHC class-1 glycoprotein antigen complex to the antigen presenting cell surface for recognition by the CD_4 or CD_8 cell. Defective presentation of the endogenous neuronal glycoprotein antigen can explain the immune dysregulation and autoimmunity described in neuronal degenerations like Parkinson's disease,

Alzheimer's disease and motor neuron disease. Defective presentation of exogenous viral antigens can produce immune evasion by the virus as in viral persistence leading on to neuronal degenerations. A number of fucose and sialic acid containing natural ligands are involved in trafficking of leukocytes and the inflammatory cell process and could contribute to similar phenomena described in neuronal degeneration.[1-8]

Archaeal Digoxin and Alteration in Membrane Structure and Membrane Formation in Relation to Parkinson's Disease

The archaeaon steroidelle, glycosaminoglycoid and fructosoid contribute 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 Mg^{++} deficiency can inhibit phospholipid synthesis. Phospholipid degradation is increased owing to increase in intracellular calcium activating phospholipase A_2 and D. The cholesterol: phospholipid ratio of the RBC membrane was decreased in PD. The concentration of total GAG, cholesterol, hexose and fucose of glycoprotein decreased in the RBC membrane and increased (unaltered in the case of cholesterol) 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 Mg^{++} deficiency. The change in membrane structure produced by alteration in

glycoconjugates and cholesterol: phospholipid ratio can produce changes in the conformation of Na^+-K^+ ATPase resulting in further membrane Na^+-K^+ ATPase inhibition. The same changes can affect the structure of the organelle membrane. This results in defective lysosomal stability and leakage of glycohydrolases and GAG degrading enzymes into the serum. Defective peroxisomal membranes lead to catalase dysfunction which has been documented in Parkinson's disease.[1-8]

Archaeal Digoxin and Mitochondrial Dysfunction in Relation to Parkinson's Disease - The Vitaminocyte

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 PD 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 the 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 Ca^{++} can open the mitochondrial PT pore causing a collapse of the H^+ gradient across the inner membrane and uncoupling of the respiratory chain. Intracellular Mg^{++} deficiency can lead to a defect in the function of ATP synthase. All this leads to a defect in mitochondrial oxidative phosphorylation, incomplete reduction of oxygen and generation of the superoxide ion which produces lipid peroxidation. Ubiquinone deficiency also leads to reduced free radical scavenging. The increase in intracellular calcium may lead to increased generation of NO by inducing the enzyme nitric oxide synthase, which combines with the superoxide radical to form peroxynitrite. Increased calcium also can activate phospholipase A_2 resulting in increased

generation of arachidonic acid, which can undergo increased lipid peroxidation. Increased generation of free radicals like the superoxide ion, and hydroxyl radical can produce lipid peroxidation and cell membrane damage, which can further inactivate Na^{+}-K^{+} ATPase triggering the cycle of free radical generation 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, reduced glutathione and alpha tocopherol in PD. The activity of enzymes involved in free radical scavenging like superoxide dismutase, glutathione peroxidase, glutathione reductase and catalase is decreased in PD suggesting reduced free radical scavenging. In our study the iron binding capacity and serum ceruloplasmin are reduced 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 3 times. Low ceruloplasmin levels can result in decreased iron uptake and this results in an increased amount of free iron. The intracellular magnesium deficiency can produce ribosomal dysfunction and inhibition of protein synthesis as noted by the decrease in serum albumin in these cases. The low iron binding capacity and low serum ceruloplasmin levels may be a consequence of reduced ferritin and ceruloplasmin synthesis. Nigral iron accumulation in PD is primarily within neuromelanin granules. Neuromelanin binds to iron and is relatively protective. Neuromelanin is synthesized from tyrosine and the digoxin related tyrosine transport defect may lead to decreased neuromelanin 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 Mg^{++} consequent to Na^{+}-K^{+} ATPase inhibition and the resulting low ATP 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 down regulation of the pentose phosphate pathway with consequent decreased generation of NADPH. Thus the 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. The reduction in catalase, superoxide dismutase (SOD), glutathione peroxidase and glutathione reductase suggests reduced free radical protection. Mitochondrial dysfunction related free radical generation has been implicated in the pathogenesis of the neuronal degeneration like PD. Mitochondrial dysfunction can remove the Mg^{++} block of the NMDA receptor leading on to excitotoxicity and neuronal degeneration.[1-8]

Archaeal Digoxin and Immunoregulation in Relation to Parkinson's Disease - The Fructosoid, Steroidelle and Viroidelle

The archaeaon fructosoid contributes to fructolysis and immune activation. Fructose can contribute to induction of NFKB and immune activation. The

archaeaon steroidelle synthesized digoxin induces NFKB producing immune activation. The archaeaon viroidelle secreted RNA viroids can modulate immune activation by functioning as blockers of mRNA expression. Increased intracellular Ca^{++} activates the Ca^{++} 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 some neuronal degeneration like, in Parkinson's disease, motor neuron disease (MND) and Alzheimer's disease. It has been noted that HLA DR positive reactive microglia as well as increased levels of cytokines such as interleukin-l and tumor necrosis factor alpha in the pars compacta of the substantia nigra is seen even in the late stages of Parkinson's disease. TNF alpha can also bring about apoptosis of the cell. It binds to its receptor and activates caspase-9 an ICE protease which converts the IL-1 beta precursor to IL-1 beta. IL-1 beta produces apoptosis of the neurons in neuronal degenerations. 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.

Cell death is also mediated by increased intracellular Ca^{++} and ceramide related opening of the mitochondrial PT pore causing a collapse of the H^{+} gradient across the inner membrane and uncoupling of the respiratory chain. This also leads to volume dysregulation of mitochondria causing hyperosmolality of matrix and expansion of matrix space. The outer membrane of the mitochondria ruptures and releases AIF (apoptosis inducing factor) and cyto C (cytochrome C). This results in procaspase-9 activation to caspase-9 which produces cell death. Caspase-9 activates CAD (caspase activated deoxyribonuclease) which cleaves the nuclear membrane lamins and several proteins involved in cytoskeletal regulation like gelsolin which cleaves actin. Apoptosis has also been implicated in neuronal aging and neuronal death in

neuronal degeneration. We have been able to demonstrate neuronal degeneration and apoptosis in the digoxin injected rat brain.

Membrane Na^+-K^+ ATPase inhibition can produce intracellular Mg^{++} depletion leading on to defect in the function of DNA polymerase which functions as the proof reading enzymes in the nucleus during DNA replication. Defective function of DNA polymerase could possibly lead to defect in DNA structure and possibly trinucleotide repeats described in neuronal degeneration. This is exemplified by the protein Parkin described in juvenile Parkinson's disease. Intracellular Mg^{++} depletion can produce defective phosphorylation of MAP (microtubule associated proteins). This results in defective microtubule polymerisation / depolymerisation and axonal transport contributing to neuronal degeneration.[1-8]

Archaeal Digoxin and Lipid Metabolism in Relation to Parkinson's Disease

The archaeaon steroidelle contributes to lipid synthesis and metabolism. Low HDL cholesterol is another feature observed in PD. Low HDL cholesterol level indicates reduced reverse cholesterol transport to the liver for degradation. HDL cholesterol has been related to neuronal regeneration and has a neurotrophic effect. Altered reverse transport of cholesterol and abnormal redistribution of HDL particles have been reported in neuronal degeneration. This may relate low HDL cholesterol to PD. Serum free fatty acids are significantly increased in PD. This may indicate increased lipolysis or decreased mitochondrial fatty acid oxidation or both. Magnesium deficiency can lead to activation of lipoprotein lipase and lipolysis. Increased intra cellular calcium by opening up the mitochondrial PT pore can produce mitochondrial dysfunction. The mitochondrial dysfunction can cause reduced beta oxidation of fatty acid leading to an increase in free fatty acid level. Free fatty acids themselves can produce Na^+-K^+ ATPase inhibition. There was no alteration in serum cholesterol despite elevated HMG CoA reductase

activity probably because most of HMG CoA was channelized for the synthesis of other isoprenoid metabolites like dolichol or digoxin. The RBC membrane cholesterol was reduced despite no alteration in the serum suggesting reduced uptake into the RBC membrane.[1-8]

Archaeal Digoxin and Hemispheric Dominance in Relation to Parkinson's Disease

The archaeaon related organelle-steroidelle, neurotransminoid and vitaminocyte contribute to hemispheric dominance. Thus Parkinson's disease and neuronal degeneration can happen due to a defect in the isoprenoid pathway. The following mechanisms are involved, (1) NMDA excitotoxicity consequent to hypomagnesemia, digoxin related membrane Na^{+}-K^{+} ATPase inhibition, ubiquinone deficiency and mitochoridrial dysfunction removing the Mg^{++} block and elevated levels of positive modulators of the NMDA receptor (quinolinic acid, serotonin and strychnine), (2) Dolichol related and Mg^{++} depletion related altered glycoproteins and proteoglycan and possibly complexes formed between them which resist lysosomal digestion, (3) Defective membrane formation and structure contributing to Na^{+}-K^{+} ATPase inhibition, lysosomal instability and peroxisomal dysfunction, (4) mitochondrial dysfunction due to low ubiquinone levels, altered Ca^{++}/Mg^{++} ratios intracellularly and ceramide leading to free radical generation. Membrane Na^{+}-K^{+} ATPase inhibition related immune activation, apoptosis and defective presentation of neuronal antigens. All these features are chemical markers of right hemispheric dominance.[1-8]

References

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