

3

Archaeal Digoxin and the Aging Process

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

The increase in endogenous EDLF, a potent inhibitor of membrane $\text{Na}^+\text{-K}^+$ ATPase, can decrease this enzyme activity. The results showed increased endogenous EDLF synthesis as evidenced by increased HMG CoA reductase activity, which functions as the rate limiting step of the isoprenoid pathway. Studies in our laboratory have demonstrated that EDLF is synthesized by the isoprenoid pathway. The endosymbiotic archaeal sequences in the human

genome get expressed by redox stress and osmotic stress of global warming. This results in induction of HIF alpha which will upregulate fructolysis and glycolysis. In the setting of redox stress all glucose gets converted to fructose by the induction of enzymes aldose reductase and sorbitol dehydrogenase. Aldose reductase converts glucose to sorbitol and sorbitol dehydrogenase converts sorbitol to fructose. Since fructose is preferentially phosphorylated by ketohexokinases the cell is depleted of ATP and glucose phosphorylation comes to a halt. Fructose becomes the dominant sugar that is metabolized by fructolysis in expressed archaeal particles in the cell functioning as organelle called fructosoids. The fructose is phosphorylated to fructose 1-phosphate which is acted upon by aldolase B which converts it into glyceraldehyde 3-phosphate and dihydroxy acetone phosphate. Glyceraldehyde 3-phosphate is converted to D1,3-biphosphoglycerate which is then converted to 3-phosphoglycerate. The 3-phosphoglycerate is converted to 2-phosphoglycerate. 2-phosphoglycerate is converted to phosphoenol pyruvate by the enzyme enolase. Phosphoenol pyruvate is converted to pyruvate by the enzyme pyruvic kinase. The archaeon induces HIF alpha which upregulates fructolysis and glycolysis but inhibits pyruvate dehydrogenase. The forward metabolism of pyruvate is stopped. The dephosphorylation of phosphoenol pyruvate is inhibited in the setting of pyruvic kinase inhibition. Phosphoenol pyruvate enters the shikimic acid pathway where it is converted to chorismate. The shikimic acid is synthesized by a pathway starting from glyceraldehyde 3-phosphate. Glyceraldehyde 3-phosphate combines with the pentose phosphate pathway metabolite sedoheptulose 7-phosphate which is converted to erythrose 4-phosphate. The pentose phosphate pathway is upregulated in the presence of the suppression of glycolytic pathway. Erythrose 4-phosphate combines with phosphoenol pyruvate to generate shikimic acid. Shikimic acid combines with another molecule of phosphoenol pyruvate to generate chorismate. The

chorismate is converted to prephenic acid and then to parahydroxy phenyl pyruvic acid. Parahydroxy phenyl pyruvic acid is converted to tyrosine and tryptophan as well as neuroactive alkaloids. The shikimic acid pathway is structured in expressed archaeon organelle called the neurotransminoid. The fructolytic intermediates glyceraldehydes 3-phosphate and pyruvate are the starting points of the DXP pathway of cholesterol synthesis. Glyceraldehyde 3-phosphate combines with pyruvate to form 1-deoxy D-xylulose phosphate (DOXP) which is then converted to 2C methyl erythritol phosphate. 2C methyl erythritol phosphate can be synthesized from erythrose 4-phosphate a metabolite of the shikimic acid pathway. DXP combines with MEP to form isopentenyl pyrophosphate which is converted to cholesterol. Cholesterol is catabolised by archaeal cholesterol oxidases to generate digoxin. The digoxin sugars digitoxose and rhamnose are synthesized by the upregulated pentose phosphate pathway. Glycolytic suppression leads to upregulation of the pentose phosphate pathway. The expressed archaeon organelle concerned with cholesterol catabolism and digoxin synthesis is called the steroidelle. The suppression of glycolysis and stimulation of fructolysis results in upregulation of the hexosamine pathway. Fructose is converted to fructose 6-phosphate by ketohexokinases. The fructose 6-phosphate is converted to glucosamine 6-phosphate by the action of glutamine fructose 6-phosphate amidotransferase (GFAT). Glucosamine 6-phosphate is converted to UDP N-acetyl glucosamine which is then converted to N-acetyl glucosamine and various amino sugars. UDP glucose is converted to UDP D-glucuronic acid. UDP D-glucuronic acid is converted to glucuronic acid. This forms the uronic acid synthetic pathway. Uronic acids and hexosamines form repeating units of glycosaminoglycans. In the setting of glycolytic suppression and fructolytic metabolism fructolysis leads to increase synthesis of hexosamines and GAG synthesis. The GAG synthesizing archaeon particles are called the glycosaminoglycoids. The

expressed archaeon particles are capable of synthesizing antioxidant vitamin C and E. The UDP D-glucose is converted to UDP D-glucuronic acid. UDP D-glucuronic acid is converted to D-glucuronic acid. D-glucuronic acid is converted to L-gulonate by enzyme aldoketoreductases. L-gulonate is converted to L-gulonolactone by lactonase. L-gulonolactone is converted to ascorbic acid by the action of archaeal L-gulo oxidase. The vitamin E is synthesized from shikimate which is converted to tyrosine and then to parahydroxy phenyl pyruvic acid. Parahydroxy phenyl pyruvic acid is converted to homogentisate. Homogentisate is converted to 2-methyl 6-phytyl benzoquinone which is converted to alpha tocopherol. 2-methyl 6-phytyl benzoquinone is converted to 2,3-methyl 6-phytyl benzoquinone and gamma tocopherol. Vitamin E can also be synthesized by the DXP pathway. Glyceraldehyde 3-phosphate and pyruvate combined to form 1-deoxy D-xylulose 5-phosphate which is converted to 3-isopentenyl pyrophosphate. 3-isopentenyl pyrophosphate and dimethyl allyl pyrophosphate combined to form 2-methyl 6-phytyl benzoquinone which is converted to tocopherols. The ubiquinone another important membrane antioxidant and part of the mitochondrial electron transport chain is synthesized by the shikimic acid pathway and DXP pathway. The isoprenoid moiety of ubiquinone is contributed from the DXP pathway and the rest of it by tyrosine catabolism. The tyrosine is generated by the shikimic acid pathway. The archaeon particles concerned with the synthesis of vitamin C, vitamin E and ubiquinone which are all antioxidants are called the vitaminocyte.

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 NF κ B. 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 geriatric disease.

Several theories regarding the aging process have been postulated by several groups of workers. Free radical mechanisms have been postulated to be involved in the aging process. Mitochondrial dysfunction and apoptosis consequent to mitochondrial DNA mutations which accumulate with aging have also been implicated. Mutations in nuclear DNA and proof reading defects leading to cellular aging, defective lysosomal function and lysosomal catabolism of cellular proteins and altered Golgi body function leading to protein processing defects have also been postulated to lead to the aging process. The immune theory of aging postulates autoimmune mechanisms and autoantibodies as being crucial to the aging process.

The isoprenoid pathway is an important pathway regulating cellular metabolism, Alteration in ubiquinone, dolichol and cholesterol metabolism with aging has been reported before. Ubiquinone, a component of the pathway, is important in mitochondrial electron transport and plays a vital role as a

membrane antioxidant. Dolichol, an isoprenoidal metabolite, is important in N-glycosylation of proteins. Digoxin, another isoprenoidal metabolites, is an endogenous membrane $\text{Na}^+\text{-K}^+$ ATPase inhibitor. Digoxin can regulate amino acid and neurotransmitter transport. It was therefore considered pertinent to study the isoprenoid pathway in relation to cellular aging. The neurotransmitter profile, glycoconjugate metabolism and free radical metabolism were also studied. A hypothalamic archaeal digoxin mediated model for the aging process is postulated in this paper.

Results

- (1) The results showed that 14MG CoA reductase activity, serum digoxin and dolichol were increased in the healthy aged indicating an upregulation of the isoprenoid pathway but serum ubiquinone, RBC membrane sodium-potassium ATPase activity and serum magnesium were reduced when compared to healthy young individuals.
- (2) The results showed that the concentration of tryptophan, quinolinic acid, strychnine, nicotine and serotonin was found to be higher in the plasma of healthy geriatric patients while that of tyrosine, morphine, dopamine and norepinephrine was lower as compared to healthy young individuals.
- (3) The results show an increase in the concentration of serum total GAG, glycolipids (ganglioside, glycosyl-diglyceride, cerebroside and sulphatides) and carbohydrate components of glycoproteins (hexose, fucose and sialic acid) in geriatric healthy aged individuals as compared to healthy young individuals. The increase in the carbohydrate components - total hexose, fucose and sialic acid in the geriatric healthy aged suggests qualitative change in glycoprotein structure. The individual GAG fractions in the serum were also increased in the geriatric healthy aged as compared to normal healthy young 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 significant increase in the serum in the geriatric healthy aged as compared to healthy young individuals.

(4) The cholesterol: phospholipid ratio of the RBC membrane was increased in the geriatric healthy aged as compared to healthy young 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 the geriatric healthy aged as compared to healthy young individuals.

(5) 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 geriatric healthy aged individuals as compared to healthy young individuals. The activity of enzymes involved in free radical scavenging like superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase is decreased in the geriatric healthy aged as compared to healthy young individuals suggesting reduced free radical scavenging.

Archaeal Digoxin and Membrane $\text{Na}^+\text{-K}^+$ ATPase Inhibition in Relation to Aging

The archaeon steroidelle DXP pathway and the upregulated pentose phosphate pathway contribute to digoxin synthesis. The increase in endogenous digoxin, a potent inhibitor of membrane $\text{Na}^+\text{-K}^+$ ATPase, can decrease this enzyme activity in geriatric healthy aged individuals. In geriatric healthy aged individuals there was significant inhibition of the RBC membrane $\text{Na}^+\text{-K}^+$ ATPase. There is also increased synthesis of digoxin as evidenced by increased

HMG CoA reductase activity. The inhibition of $\text{Na}^+\text{-K}^+$ ATPase by digoxin is known to cause an increase in intracellular calcium resulting from increased $\text{Na}^+\text{-Ca}^{++}$ 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 $\text{Na}^+\text{-K}^+$ 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 cell and ATP dependent sequestration of calcium within the endoplasmic reticulum. The intracellular magnesium depletion related mitochondrial dysfunction results in defective calcium extrusion from the cell. There is thus a progressive inhibition of $\text{Na}^+\text{-K}^+$ ATPase activity first triggered by digoxin. Low intracellular magnesium and high intracellular calcium consequent to $\text{Na}^+\text{-K}^+$ ATPase inhibition appear to be crucial to the pathophysiology of aging. The intracellular positive calcium signal and negative magnesium signal can regulate a 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 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 geriatric healthy aged individuals and was found to be reduced.

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

The archaeon neurotransminoid shikimic acid pathway contributes to tryptophan and tyrosine synthesis and catabolism generating neurotransmitters and neuroactive alkaloids. There is an increase in tryptophan and its catabolites and a reduction in tyrosine and its catabolites in the serum of geriatric healthy aged patients. This could be due to the fact that digoxin can regulate the neutral amino acid transport system with preferential promotion of tryptophan transport over tyrosine. The decrease in membrane $\text{Na}^+\text{-K}^+$ ATPase activity in geriatric healthy aging 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 geriatric healthy aged individuals and schizophrenia and could predispose to it. Quinolinic acid, an 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 suggests that the initial abnormality in schizophrenia is a hypodopaminergic state and the low dopamine levels now observed agree with this. Nicotine by interacting with the 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 serotonergic activity and reduced noradrenergic outflow from locus coeruleus reported earlier in schizophrenia agrees with our finding of elevated serotonin and reduced noradrenaline levels. 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 $\text{Na}^+\text{-K}^+$ ATPase, resulting in decreased clearance of glutamate by presynaptic and glial uptake at the end of synaptic transmission. By these mechanisms, inhibition $\text{Na}^+\text{-K}^+$ 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 pathological aging contributing to the higher incidence of Alzheimer's disease and Parkinson's disease.

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

The archaeon glycosaminoglycoid and fructosoid contributes to glycoconjugate synthesis and catabolism by the process of fructolysis. The elevation in the level of dolichol may suggest its increased availability for N-glycosylation of proteins. Magnesium deficiency can lead 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 channelled for the synthesis of glycosaminoglycans (GAG). 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 abnormal and resistant to lysosomal enzymes and may accumulate.

Previous reports of alteration in glycoproteins in this connection include alteration in beta-amyloid in 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 to their accumulation in the neurons have been reported in neurodegenerative diseases like Alzheimer's disease and Parkinson's disease. Membrane $\text{Na}^+\text{-K}^+$ ATPase inhibition can lead to defective notch signalling. Notch is a transmembrane protein that acts as a signal receptor and is important in neurogenesis. Neuronal growth by extending neurites and forming connections is regulated by the notch signalling pathway. The notch signalling inhibits extension of neurites and keeps them stable in the mature brain. A notch ligand known as delta regulates neurogenesis by binding to notch in membranes of embryonal cells and prevents them from developing along the

neuronal pathway. Notch activation by the ligand causes notch to be cleaved releasing the notch intracellular domain. This then passes into the nucleus and activates transcription as part of the DNA binding complex with CSL protein. Intracellular cleavage of the notch is regulated by presenilin and also depends upon the lysosomal protease. The defective notch signalling pathway consequent to reduced lysosomal stability related to membrane sodium-potassium ATPase inhibition can lead to neuronal degeneration.

The protein processing defect can result in defective glycosylation of endogenous neuronal and tissue glycoprotein antigens and exogenous viral glycoprotein 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. The peptide transporter is dysfunctional in the presence of magnesium deficiency. This results in defective transport of the MHC class-I glycoprotein antigen complex to the antigen presenting cell surface for recognition by the CD₄ or CD₈ cell. Defective presentation of the endogenous neuronal and cellular glycoprotein antigen can explain the immune dysregulation and autoimmunity in aging. Defective presentation of exogenous viral antigens can produce immune evasion by the virus and viral persistence. Viral persistence has been implicated in the development of tumours (Ebstein barr virus and lymphoma) and degenerations (Parkinson's disease and corona virus) common in aging (A number of fucose and sialic acids containing natural ligands are involved in trafficking of leukocytes and similar breaches in the blood brain barrier and adhesion of the lymphocyte producing leukocyte trafficking and extravasation into the perivascular space have been described in autoimmunity common in aging). Abnormally glycosylated tumour antigens can lead to defective tumour antigen presentation and loss of immunosurveillance by the natural killer cells. Altered cell surface glycoproteins, glycolipids and

GAG can lead to defective contact inhibition and oncogenesis. A number of fucose and sialic acids containing natural ligands have been implicated in neoplastic transformation and metastasis. There is an increased incidence of neoplasms in aged individuals.

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

The archaeon steroidal, 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 in the isoprenoid pathway can lead to increased cholesterol synthesis and magnesium deficiency can inhibit the phospholipid synthesis. Phospholipid degradation is increased owing to increase in intracellular calcium activating phospholipase A₂ and D. The cholesterol: phospholipid ratio of the RBC membrane was increased in geriatric healthy aged 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 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. 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 geriatric healthy aged individuals.

Archaeal Digoxin and Mitochondrial Dysfunction in Relation to Aging

The archaeon vitaminocyte contributes to the synthesis of ubiquinone and mitochondrial electron transport chain function. The mitochondrial function related free radical generation is regulated by the archaeon vitaminocyte synthesized tocopherol and ascorbic acid. The concentration of ubiquinone decreased significantly in geriatric healthy aged individuals which may be the result of low tyrosine levels, reported in the geriatric group 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 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 A₂ 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 $\text{Na}^+\text{-K}^+$ 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 membrane $\text{Na}^+\text{-K}^+$ 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 autoimmunity common in the geriatric group.

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 and the aging process. Caspase-3 activation can cleave P_{21} which links DNA duplication to cell division. This results in inactivation of P_{21} and produces cellular polyploidy and oncogenic transformation. We have been able to demonstrate neuronal degeneration and apoptosis in the digoxin injected rat brain.

Archaeal Digoxin and Immune Activation - Relation to Aging

The archaeon fructosoid contributes to fructolysis and immune activation. Fructose can contribute to induction of NF κ B and immune activation. The archaeon steroidelle synthesized digoxin induces NF κ B producing immune activation. 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 and autoimmunity in aging. 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 Alzheimer's disease. Membrane Na⁺-K⁺ ATPase inhibition can produce immune activation and is reported to increase CD₄/CD₈ ratios as exemplified by the action of lithium.

Archaeal Digoxin and Regulation of Cell Division, Cell Proliferation and Neoplastic Transformation in Relation to Aging

Intracellular magnesium depletion can affect the proof reading function of DNA polymerase leading to DNA mutations of both mitochondrial and nuclear DNA contributing to the aging process. Intracellular magnesium depletion can produce ribosomal dysfunction and block protein synthesis. Defective protein synthesis consequent to defective protein transcription and ribosomal dysfunction has been associated with the aging process.

Increased intracellular calcium activates phospholipase C beta which results in increased production of diacylglycerol (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 GOP. Phosphorylation mechanisms are required for the activation of the tumours suppressor gene P₅₃. The activation of P₅₃ 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 proteins is important in the DNA repair mechanism. In the presence of intracellular magnesium deficiency ubiquitin system of protein catabolic processing and DNA repair mechanisms are defective and this could contribute to oncogenesis common in aging.

Archaeal Digoxin and Metabolic / Vascular Regulation - Relation to the Aging Process

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. Hyperinsulinism and insulin resistance have been associated with the aging process. Decrease in intracellular magnesium can lead to inhibition of glycolysis. Decreased intracellular magnesium can lead 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. All this leads to defective glucose utilisation and contributes to aging. 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 aging. $\text{Na}^+ - \text{K}^+$ ATPase inhibition related increased smooth muscle calcium and decreased magnesium can contribute to vasospasm and ischaemia observed in stroke and CAD common in aged individuals. $\text{Na}^+ - \text{K}^+$ ATPase inhibition related altered glycoprotein and GAG can contribute to the microangiopathy and macroangiopathy observed in atherosclerosis and arteriosclerosis common in aging. Digoxin can thus contribute to the metabolic and vascular abnormalities associated with aging.

Archaeal Digoxin and Neuro-Immuno-Endocrine Integration - Relation to Aging

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 noradrenalin, dopamine and serotonin. Digoxin by regulating the release and uptake of these neurotransmitters can control hypothalamic hormone secretion. Digoxin, by its lithium like action in modulating G-protein function and by facilitating calcium induced signal transduction by increasing Na^+ - Ca^{++} exchange, can regulate the function of these hormones. Digoxin can act as an immuno-modulator owing to its effect on calcineurin signal transduction in the lymphocyte and subsequent immune activation. It is the exaggerated digoxin secretion leading to defective neuro-immuno-endocrine integration that leads to the aging process.

Archaeal Digoxin and Integration of Cellular Function - Relation to Aging

Digoxin can regulate multiple cellular functions. Digoxin can regulate plasma membrane transport as well as membrane structure and fluidity. It can also regulate the fluidity of organelle membranes. Digoxin by its effects of calcium mediated opening of the mitochondrial PT pore and ubiquinone synthesis can regulate mitochondrial function. The dolichol pathway can regulate protein glycosylation and golgi body function. Digoxin induced hypomagnesemia can regulate the ubiquitin dependent protein catabolic pathway. Digoxin induced change in intracellular magnesium can regulate nuclear function as DNA polymerase, DNA ligase and ribosomes require magnesium for their function. Digoxin by producing magnesium depletion can regulate GAG metabolism and the structure of the cell matrix. Digoxin can regulate cell death or apoptosis by

opening up the mitochondrial PT pore consequent to a rise in intracellular calcium that it produces Digoxin by Its effect upon ras oncogene can modulate cell proliferation. Digoxin induced hypomagnesemia by producing changes in cell surface glycoproteins and GAG can also regulate contact inhibition and cell proliferation. Digoxin can regulate the function of heat-shock protein which coordinates the trafficking and regulation of diverse signalling proteins, and which also functions as a molecular chaperone involved in protein folding and maturation. The heat-shock protein has an ATP/ADP switch domain that regulates HSP conformation and digoxin induced hypomagnesemia can modulate its function. Intracellular magnesium deficiency can regulate phosphorylation of MAP (Microtubule associated proteins) and regulate cytoskeletal structure/function. It is the exaggerated digoxin secretion and defective integration of cellular organelle function that leads to aging.

References

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