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Fructolysis, Archaeal Digoxin, Cerebral Dominance and Pathogenesis of Chronic Pulmonary Disease

Introduction

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

The increase in endogenous EDLF, a potent inhibitor of membrane Na^+-K^+ ATPase, can decrease this enzyme activity. The results showed increased endogenous EDLF synthesis as evidenced by increased HMG CoA reductase activity, which functions as the rate limiting step of the isoprenoid pathway.

Studies in our laboratory have demonstrated that EDLF is synthesized by the isoprenoid pathway. The endosymbiotic archaeal sequences in the human genome get expressed by redox stress and osmotic stress of global warming. This results in induction of HIF alpha which will upregulate fructolysis and glycolysis. In the setting of redox stress all glucose gets converted to fructose by the induction of enzymes aldose reductase and sorbitol dehydrogenase. Aldose reductase converts glucose to sorbitol and sorbitol dehydrogenase converts sorbitol to fructose. Since fructose is preferentially phosphorylated by ketohexokinases the cell is depleted of ATP and glucose phosphorylation comes to a halt. Fructose becomes the dominant sugar that is metabolized by fructolysis in expressed archaeal particles in the cell functioning as organelle called fructosoids. The fructose is phosphorylated to fructose 1-phosphate which is acted upon by aldolase B which converts it into glyceraldehyde 3-phosphate and dihydroxy acetone phosphate. Glyceraldehyde 3-phosphate is converted to D 1,3-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 archaeaon induces HIF alpha which upregulates fructolysis and glycolysis but inhibits pyruvate dehydrogenase. The forward metabolism of pyruvate is stopped. The dephosphorylation of phosphoenol pyruvate is inhibited in the setting of pyruvic kinase inhibition. Phosphoenol pyruvate enters the shikimic acid pathway where it is converted to chorismate. The shikimic acid is synthesized by a pathway starting from 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 archaeaon organelle called the neurotransminoid. The fructolytic intermediates glyceraldehydes 3-phosphate and pyruvate are the starting points of the DXP pathway of cholesterol synthesis. Glyceraldehyde 3-phosphate combines with pyruvate to form 1-deoxy D-xylulose phosphate (DOXP) which is then converted to 2-C methyl erythritol phosphate. 2-C methyl erythritol phosphate can be synthesized from erythrose 4-phosphate a metabolite of the shikimic acid pathway. DXP combines with MEP to form isopentenyl pyrophosphate which is converted to cholesterol. Cholesterol is catabolized by archaeal cholesterol oxidases to generate digoxin. The digoxin sugars digitoxose and rhamnose are synthesized by the upregulated pentose phosphate pathway. Glycolytic suppression leads to upregulation of the pentose phosphate pathway. The expressed archaeaon organelle concerned with cholesterol catabolism and digoxin synthesis is called the steroidelle. The suppression of glycolysis and stimulation of fructolysis results in upregulation of the hexosamine pathway. Fructose is converted to fructose 6-phosphate by ketohexokinases. The fructose 6-phosphate is converted to glucosamine 6-phosphate by the action of glutamine fructose 6-phosphate amidotransferase (GFAT). Glucosamine 6- phosphate is converted to UDP N-acetyl glucosamine which is then converted to N-acetyl glucosamine and various amino sugars. UDP glucose is converted to UDP D-glucuronic acid. UDP D-glucuronic acid is converted to glucuronic acid. This forms the uronic acid synthetic pathway. Uronic acids and hexosamines form repeating units of glycosaminoglycans. In the setting of glycolytic suppression and fructolytic metabolism fructolysis

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

Several theories have been put forward to explain the pathogenesis of lung diseases - bronchial asthma, chronic bronchitis emphysemia, interstitial lung disease and sarcoidosis. A number of causes have been postulated for the increased airway reactivity of asthma. The most popular hypothesis at present is

that of airway inflammation. The cells thought to play important roles are mast cells, eosinophils, macrophages, neutrophils and lymphocytes. The mediators released are - histamine, bradykinin, the leukotrienes - C, D and E, platelet activating factor and prostaglandins (PGs) E_2, F_2 alpha and D_2 producing intense inflammatory reaction involving bronchoconstriction, vascular congestion and oedema formation. T-lymphocytes also appear to be important in the inflammatory response. Interleukin-2 can promote B-cell differentiation and activation of macrophages. Interleukin-4 and 5 can promote eosinophil and basophil proliferation, differentiation and activation.

The alveolar epithelium is both the target and initiator of inflammation in chronic bronchitis. It is a consequence of action of interleukin-8 and a variety of other chemotactic and proinflammatory cytokines and of colony stimulating factors released by airway epithelial cells in response to toxic, infectious and inflammatory stimuli. Sputum production is stimulated by increased exocytosis from secretary cells, lipid mediators and inflammatory cell products, especially macrophage mucus secretagogue. Mucin gene expression is amplified by tumour necrosis factor alpha and secretory cell hyperplasia is encouraged by the neutrophil enzymes elastase and cathepsin G. The protease inhibitor alpha 1-antitrypsin (alpha 1 AT) is an acute phase reactant and its serum levels rise in association with many inflammatory reactions. Either deficient or absent serum levels of alpha 1 AT are found in some patients with the early onset of emphysema. Cigarette smoking is a most commonly identified correlate with both chronic bronchitis and emphysema, Experimental studies have shown that prolonged smoking impairs ciliary movement, inhibits function of alveolar macrophages, and leads to hypertrophy and hyperplasia of mucous secreting glands.

Immunopathogenic mechanism is involved in IPF. An increased number of macrophages which are activated phagocytes capable of producing many

cytokines that affect other lung cells, is a hallmark of the alveolitis. These macrophage cytokines or mediators can operate in two directions. First, through the production of chemokines, which include leukotriene B_4, interleukin-8, and tumor necrosis factor alpha, inflammatory cells such as polymorphonuclear cell and eosinophils are attracted to the alveoli. Enzymes such as collagenase, or oxidant radicals from inflammatory cells and histamine may cause local injury or alter the permeability of type-1 cells. Second macrophages are also capable of secreting substance like PDGF-B that stimulate mesenchymal cells. Gamma interferons upregulate PDGF-B gene activation. Gamma interferons also act as a chemoattractant and growth factor for fibroblasts.

All available evidence suggests that active sarcoidosis results from an exaggerated cellular immune response to a variety of antigens or self antigens, in which the process of T-lymphocyte triggering, proliferation, and activation is skewed in the direction of helper - inducer T-lymphocyte processes. This result is an exaggerated helper - inducer T-cell response and thus the accumulation of large number of activated T-cells in the affected organs. Since the activated helper - inducer T-lymphocytes releases mediators that attract and activate mononuclear phagocytes, it is likely that the process of granuloma formation is a secondary phenomenon that is a consequence of the exaggerated helper - inducer T-cell process. The T-helper - inducer lymphocytes accumulate at the sites of disease, at least in part, because they proliferate in these sites at an exaggerated rate. This T-cell proliferation is maintained by the spontaneous release of IL-2, the T-cell growth factor, by activated T-helper - inducer cells in the local milieu.

Geschwind has postulated a relationship between cerebral lateralization and immune function. For example, they observed a higher frequency left handedness in patients with some immune disorders. There are no reports on the role of hemispheric dominance in the pathogenesis of lung diseases.

The isoprenoid pathway is possibly involved in lung diseases because of the fact that it produces three important components of significance in the immune response - digoxin, an endogenous membrane Na^+-K^+ ATPase inhibition which can produce T-cell activation by increasing intracellular calcium, ubiquinone which is an important free radical scavenger and dolichol important in glycoconjugate biosynthesis and generation of endogenous antigens. An increase in oxygen free radicals has been reported in lung diseases and has been related to their pathogenesis. Since digoxin can regulate multiple neurotransmitter systems it could possibly play a role in the genesis of cerebral dominance. It was therefore considered pertinent to study the role of endogenous digoxin and isoprenoid pathway in pulmonary disease. Five sets of patient population, (1) bronchial asthma, (2) chronic bronchitis emphysema, (3) Sarcoidosis, (4) interstitial lung diseases and (5) left hemispheric, right hemispheric and bihemispheric dominant individuals to find out whether hemispheric dominance has any relation to hypothalamic archaeal digoxin secretion and risk for pulmonary disease.[1-13]

Patients and Methods

Informed consent was obtained from all the patients / normal individuals included in the study. The permission of the ethics committee of the institute was also obtained. Six sets of patients population were chosen for the study: (1) 15 cases of bronchial asthma, (2) 15 cases of chronic bronchitis emphysema, (3) 15 cases of sarcoidosis, (4) 15 cases of idiopathic pulmonary fibrosis, (5) 15 cases of age and sex matched bihemispheric dominant controls, and (6) 15 cases each of right hemispheric, left hemispheric and bihemispheric dominant individuals diagnosed by the dichotic listening test. The patient population's age ranged from 40-50 years. None of the subjects studied under medication at the time of removal of blood. All subjects included in the study

were non-smokers (active or passive). Fasting blood was removed in citrate tubes from each of the number of patients mentioned above. RBCs were separated within one hour of collection of blood for the estimation of membrane Na^+-K^+ ATPase. Plasma was used for the analysis of various parameters. The methodology used in the study was as follows: All biochemicals used in this study were obtained from M/s Sigma Chemicals, USA. Activity of HMG CoA reductase of the plasma was determined by the method of Rao and Ramakrishnan by determining the ratio of HMG CoA to mevalonate. For the determination of the RBC Na^+-K^+ ATPase activity of the erythrocyte membrane, the procedure described by Arun et al. For estimation of ubiquinone and dolichol in the plasma, the procedure described by Palmer et al. was used. Magnesium in the plasma was estimated by atomic absorption spectrophotometry. Tryptophan, tyrosine, serotonin and catecholamines were estimated by the procedures described in methods of biochemical analysis. Quinolinic acid content of plasma was estimated by HPLC (C_{18} column micro Bondapak^{TM} 4.6 x 150 mm), solvent system 0.01 M acetate buffer (pH 3.0) and methanol (6:4), flow rate 1.0 ml/minute and detection UV (250 nm). Morphine, strychnine and nicotine were estimated by the methods described by Arun et al. Statistical analysis was done by 'ANOVA'.

Results

(1) The results showed HMG CoA reductase activity, serum digoxin and dolichol were increased in bronchial asthma, idiopathic pulmonary fibrosis, sarcoidosis and chronic bronchitis emphysema indicating upregulation of the isoprenoid pathway but serum ubiquinone, RBC membrane Na^+-K^+ ATPase activity and serum magnesium were reduced.

(2) The results showed that the concentration of tryptophan, quinolinic acid, serotonin, strychnine and nicotine was found to be higher in the plasma of

patients with bronchial asthma, idiopathic pulmonary fibrosis. Sarcoidosis and chronic bronchitis emphysema while that of tyrosine, dopamine, norepinephrine and morphine was lower.

(3) The concentration of total GAG increased in the serum of patients with bronchial asthma, idiopathic pulmonary fibrosis, sarcoidosis and chronic bronchitis emphysema. The concentration of hyaluronic acid (HA), heparan sulphate (HS), heparin (H), dermatan sulphate (DS) and chondroitin sulphates (ChS) were increased in patients with bronchial asthma, idiopathic pulmonary fibrosis, sarcoidosis and chronic bronchitis emphysema. The concentration total hexose, fucose and sialic acid were increased in the glycoproteins of the serum in patients with bronchial asthma, idiopathic pulmonary fibrosis, sarcoidosis and chronic bronchitis emphysema.

(4) The activity of serum GAG degrading enzymes beta glucuronidase, beta N-acetyl hexosaminidase, hyaluronidase, cathepsin-D, were increased in patients with bronchial asthma, idiopathic pulmonary fibrosis, sarcoidosis and chronic bronchitis emphysema when compared to the controls. The activity of beta galactosidase, beta fucosidase and beta glucosidase increased in the serum of patients with bronchial asthma, idiopathic pulmonary fibrosis, sarcoidosis and chronic bronchitis emphysema.

(5) The concentration of total GAG, hexose and fucose in the RBC membrane decreased significantly in patients with bronchial asthma, idiopathic pulmonary fibrosis, sarcoidosis and chronic bronchitis emphysema. The concentration of cholesterol increased and phospholipids decreased in the RBC membrane in systemic sarcoidosis and the cholesterol: phospholipid ratio in the RBC membrane increased significantly in patients with

bronchial asthma, idiopathic pulmonary fibrosis, sarcoidosis and chronic bronchitis emphysema.

(6) The activity of superoxide dismutase (SOD), catalase, glutathione reductase and glutathione peroxidase in the erythrocytes decreased significantly in patients with bronchial asthma, idiopathic pulmonary fibrosis, sarcoidosis and chronic bronchitis emphysema. In patients with bronchial asthma, idiopathic pulmonary fibrosis, sarcoidosis and chronic bronchitis emphysema the concentration of MDA, hydroperoxides, conjugated dienes and NO increased significantly. The concentration of reduced glutathione decreased in patients with bronchial asthma, idiopathic pulmonary fibrosis, sarcoidosis and chronic bronchitis emphysema.

(7) The results showed that HMG CoA reductase activity, serum digoxin and dolichol were increased and ubiquinone reduced in left handed / right hemispheric dominant individuals. The results showed that HMG CoA reductase activity, serum digoxin and dolichol were decreased and ubiquinone increased in right handed / left hemispheric dominant individuals. The results showed that the concentration of tryptophan, quinolinic acid, serotonin, strychnine and nicotine was found to be higher in the plasma of left handed / right hemispheric dominant individuals while that of tyrosine, dopamine, morphine and norepinephrine was lower. The results showed that the concentration of tryptophan, quinolinic acid serotonin, strychnine and nicotine was found to be lower in the plasma of right handed / left hemispheric dominant individuals while that of tyrosine, dopamine, morphine and norepinephrine was higher.

Discussion

Archaeal Digoxin and Membrane Na^+-K^+ ATPase Inhibition in Relation to Lung 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 increase in endogenous digoxin, a potent inhibitor of membrane Na^+-K^+ ATPase, can decrease this enzyme activity. There was increased digoxin synthesis as indicated by elevated HMG CoA reductase activity, which is the rate limiting enzyme of the isoprenoid pathway. Studies in our laboratory have demonstrated that digoxin is synthesized by the isoprenoid pathway. In bronchial asthma, idiopathic pulmonary fibrosis, sarcoidosis and chronic bronchitis emphysema 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 Ca^+ via the voltage gated calcium 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 ATP-Mg^{++} 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 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

pathophysiology of bronchial asthma, idiopathic pulmonary fibrosis, sarcoidosis and chronic bronchitis emphysema. The intracellular positive Ca^{++} signal and negative Mg^{++} signal can regulate diverse cellular process. Ca^{++} 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 Ca^{++} is released from channels on internal ER individually or in small group (blip/quark and puffs/sparks). Further diversity of calcium signalling is produced by compartmentalization as cytosolic calcium signal and nuclear calcium signal. Serum Mg^{++} was assessed in bronchial asthma, idiopathic pulmonary fibrosis, sarcoidosis and chronic bronchitis emphysema and was found to be reduced. Increased intracellular bronchial smooth muscle calcium and reduced intracellular magnesium can lead to bronchoconstriction. Increased intracellular calcium can also activate the G-protein coupled receptors - histamine, serotonin interleukins and platelet derived growth factor all of which can lead to bronchospasm. Although chronic bronchitis and emphysema are usually a combined process one may dominate over the other to the extent that inflammatory airway disease, secretions, and bronchospasms are present.[1-13]

Archaeal Digoxin and Regulation of Neurotransmitter Synthesis and Function in Relation to Lung Disease

The archaeaon 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 patients with bronchial asthma, chronic bronchitis emphysema, sarcoidosis and IPF. 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 Na^+-K^+ ATPase activity in bronchial asthma could be due to the fact that the hyperpolarising neurotransmitter (dopamine, morphine and noradrenaline) are reduced and the depolarising neuroactive compounds (serotonin, strychnine, nicotine and quinolinic acid) are increased. Increased serotonin can contribute to bronchoconstriction as has been described in carcinoid syndrome. Reduced levels of noradrenaline and adrenaline consequent to reduced tyrosine levels can also lead to bronchoconstriction. Adrenaline is a bronchodilator. Increased levels of endogenous nicotine can also lead to bronchospasm.

Nicotine is important in the pathogenesis of chronic bronchitis emphysema. Experimental studies have shown that prolonged smoking and nicotine impairs ciliary movement, inhibits function of alveolar macrophages and leads to hypertrophy and hyperplasia of mucous secreting glands. Smoke also inhibits antiprotease and cause polymorphonuclear leukocytes to release proteolytic enzymes acutely. Nicotine can stimulate vagally mediated smooth-muscle constriction and lead to bronchospasm. The absence of morphine in patients with chronic bronchitis emphysema is also significant. Morphine can inhibit the neutrophilic inflammatory response and the absence of morphine could contribute to an exaggeration of this response.

Quinolinic acid has been implicated in immune activation in other immune diseases and could contribute to the same in chronic bronchitis emphysema, bronchial asthma and IPF. Serotonin, dopamine and noradrenaline receptors have been demonstrated in the lymphocytes. It has been reported that during immune activation serotonin is increased with the corresponding reduction in dopamine and noradrenaline in the brainstem monoaminergic nuclei. Thus elevated serotonin and reduced noradrenaline and dopamine can contribute to the immune activation in these lung diseases. The absence of morphine in these

patients is also significant. Morphine can inhibit the neutrophilic inflammatory response and the absence of morphine could contribute to an exaggeration of this response, especially important in IPF.

Gamma interferons released by activated T-cells can activate and recruit mononuclear phagocytes in sarcoidosis. Gamma interferons act by inducing the enzyme indoleamine 2,3-dioxygenase and promoting tryptophan catabolism. The increased levels of tryptophan and its catabolitic products consequent to elevated digoxin levels can promote gamma interferon action.

The Schizoid neurotransmitter pattern of reduced dopamine, noradrenaline and morphine and increased serotonin, strychnine and nicotine is also noticed in bronchial asthma, chronic bronchitis emphysema, sarcoidosis and IPF could predispose to their development. 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 suggest that the initial abnormality in schizophrenia involves a hypodopaminergic state and the low dopamine levels now observed agrees with this. By interacting with nicotine receptors nicotine 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 reported earlier in schizophrenia agrees with our finding of elevated serotonin and reduced noradrenaline levels. A schizoid neurotransmitter pattern can predispose to bronchial asthma, chronic bronchitis emphysema, sarcoidosis and IPF.[1-13]

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

The archaeaon 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. Decrease in intracellular magnesium can produce upregulation of collagen and elastin biosynthesis and produce replacement fibrosis. 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). Intracellular Mg^{++} deficiency also results in defective ubiquitin dependent proteolytic processing of glycoconjugates as it requires Mg^{++} 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 in to 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. Alteration in glycoprotein and proteoglycans can alter the bronchial mucosa making it more susceptible to inflammation. Alteration in the sulphated proteoglycan matrix of the neurotransmitter vesicles in the mast cell and eosinophils can produce breakage of the vesicles due to structural instability and release of histamine and serotonin producing bronchospasm. The upregulated glycoproteins and glycosaminoglycans synthesis can contribute to the formation of intraalveloar hyaline membranes and interstitial fibrosis. Leakness of the alveolar type-1 cell layer and adjacent capillary endothelial surface occurs, due to changes in the GAG and glycoproteins of alveolar basement membranes. Fibrosis in IPF follows from an organisation of inflammatory exudates within

the air spaces in which fibroblast beneath the type-1 epithelium proliferates and increases their production of fibronectin and collagen. The upregulated glycoproteins and glycosaminoglycans synthesis can also contribute to the replacement fibrosis in systemic sarcoidosis.

The protein processing defect can result in defective glycosylation of endogenous bronchial glycoprotein antigens with consequent formation of newer endogenous antigens. There is also defective formation of MHC-bronchial glycoprotein antigen complex. The MHC linked peptide transporter, a P-glycoprotein which transports MHC-bronchial glycoprotein antigen complex to the antigen presenting cell surface, has an ATP binding site. The peptide transporter is dysfunctional in the presence of Mg^{++} deficiency. This results in defective transport of MHC class-1 bronchial glycoprotein antigen complex to the antigen presenting cell surface for recognition by CD_4 or CD_8 cell. Defective presentation of endogenous bronchial / lung glycoprotein antigen can explain the immune dysregulation / autommunity in bronchial asthma, sarcoidosis and IPF. Defective presentation of exogenous viral or bacterial glycoprotein antigens can produce immune evasion by the virus / bacteria and viral / bacterial persistence. Persistent viral inflections have been implicated in the pathogenesis of IPF. Defective exogenous glycoprotein antigen presentation consequent to a defective MHC antigen presenting pathway can contribute to cutaneous anergy in systemic sarcoidosis. A number of fucose and sialic acid containing natural ligands are involved in trafficking of leukocytes and could play a role in the genesis of the inflammatory response in bronchial asthma, IPF, chronic bronchitis emphysema and sarcoidosis.[1-13]

Archaeal Digoxin and Alteration in Membrane Structure and Membrane Formation in Relation to Lung 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 isoprenoid pathway can lead to increased cholesterol synthesis and Mg^{++} deficiency can inhibit phospholipid synthesis. Phospholipid degradation is increased owing to an increase in intracellular calcium activating phospholipase A_2 and D. The cholesterol: phospholipid ratio of the RBC membrane was increased in bronchial asthma. 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 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 GTPase 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 organelle membrane. This results in defective lysosomal stability and leakage of glycohydrolases and GAG degrading enzymes into the serum. Defective lysosomal stability could lead to increased release of lysosomal enzymes which can produce destruction of the bronchial mucosa. Alteration in the bronchial mucous membrane structure can also predispose to inflammation and generation

of free radicals. Defective peroxisomal membranes lead to catalase dysfunction which has been documented in lung disease.

Lysosomal stability is also important in the genesis of chronic bronchitis emphysema. The role of proteolytic enzymes in the induction of emphysema is not restricted to patients with alpha 1 antitrypsin deficiency. Evidence is accumulating that proteolytic enzymes derived from neutrophilic leukocytes and alveolar macrophages can produce emphysema even in subjects with normal circulating level of antiproteases. Secretary cell hyperplasia is encouraged by the neutrophilic lysosomal enzymes elastase and cathepsin-G. There is experimental evidence that the structural integrity of lung elastin depends on antienzymes which protect the lung from proteases released by neutrophilic leukocytes. It is possible that local concentration of proteolytic enzymes may exceed that inhibitory capacity of antiproteases; that some proteases present are not susceptible to the available antiproteases or that some of the proteolytic enzymes may be physically inaccessible to antiprotease activity.

Lysosomal stability is important in the genesis of IPF. Lysosomal enzymes such as collagenase can alter the permeability of type-1 cells leading on to the formation of intraalveolar hyaline membranes. The unstable lysosomes and increased lysosomal enzymes noted in IPF could contribute to leakness of the alveolar type 1 cell layer an adjacent capillary endothelial surface.[1-13]

Archaeal Digoxin and Mitochondrial Dysfunction in Relation to Lung 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 bronchial asthma, chronic bronchitis emphysema,

sarcoidosis and IPF which may be the result of low tyrosine levels, reported in bronchial asthma, 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 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 defects in mitochondrial oxidative phosphorylation, incomplete reduction of oxygen and generation of 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 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. This can lead to increased generation of prostaglandins E_2 and F_2 alpha and leukotrienes-C, D and E involved in genesis of bronchial asthma. 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. Mg^{++} 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 Na^{+}-K^{+} ATPase inhibition related defect in membrane formation and leads to reduced catalase activity. Mitochondrial dysfunction related free radical generation has been implicated in

the pathogenesis of immune mediated disorders. Free radicals can produce immune activation and has been implicated in the pathogenesis of bronchial asthma, chronic bronchitis emphysema, sarcoidosis and idiopathic pulmonary fibrosis. Increased level of lysophophatidyl choline has been reported in bronchial asthma. Phospholipase A_2 releases an unsaturated fatty acid and a lysophospholipid. The activation of phospholipase A_2 is due to increased intracellular calcium produced by digoxin induced membrane Na^+-K^+ ATPase inhibition. Lysophosphatidyl choline is known to inhibit Na^+-K^+ ATPase activity and thus continues the vicious cycle of free radical generation and bronchial mucosal injury.

Mitochondrial dysfunction related free radical generation has been implicated in the pathogenesis of the IPF. Oxidant radicals from inflammatory cells can alter the permeability of type-1 cells leading to the formation of the alveolar hyaline membrane in IPF.[1-13]

Archaeal Digoxin and Immunoregulation in Relation to Lung 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. Increased intracellular calcium activates the calcium dependent calcineurin signal transduction pathway which can produce macrophage and T-cell activation and secretion of interleukin-3, 4, 5, 6 and 8 and TNF alpha (Tumour necrosis factor alpha). 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. Interleukin-2, 4 and 5 can produced growth differentiation and activation of the eosinophils and basophils involved in bronchial asthma. This can also explain the immune activation in chronic

bronchitis emphysema. It is a consequence of the action of interleukin 8 that there is inflammatory neutrophilic exudates filling the mucosal and submucosal area of small airway. Mucin gene expression is amplified by tumour necrosis factor alpha. 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. Macrophages which are activated phagocytes capable of producing many cytokines are the hallmark of alveolitis. The immune activation in IPF is a consequence of the action of interleukin-8 and TNF alpha that there is an inflammatory neutrophilic exudate in the alveoli.

Membrane Na^+-K^+ ATPase inhibition can also explain the immune activation in systemic sarcoidosis. Sarcoidosis is characterised by an exaggerated T-helper-inducer response. There is an accumulation of large numbers of activated T-cells in the affected organs. Since the activated helper-inducer T-lymphocytes releases mediators that attract and activate mononuclear phagocytes, it is likely that the process of granuloma formation is a secondary phenomenon that is a consequence of the exaggerated helper-inducer T-cell processes. The T-helper-inducer lymphocytes accumulate at the sites of disease, at least in part, because they proliferate in these sites at an exaggerated rate. This T-cell proliferation is maintained by the spontaneous release IL-2, the T-cell growth factor, by activated T-helper - inducer cells in the local milieu. The increase in intracellular calcium consequent to membrane Na^+-K^+ ATPase inhibition can increase the function of IL-2 whose receptor is a G-protein coupled. In addition to driving other T-helper-inducer cells in the affected organs to proliferate, the T-helper-inducer cells at the sites of disease are activated and release mediators like TNF alpha that both recruit and activate mononuclear phagocytes.[1-13]

Archaeal Digoxin, Oncogene Activation and Lung Disease

The archaeaon secreting RNA viroids is called the viroidelle. The primitive archaeal DNA is integrated along with RNA viroids which are converted to their corresponding DNA by the action of redox stress induced HERV reverse transcriptase into the human genome by the redox stress induced HERV integrase. The archaeal DNA sequences that are integrated into the human genome forms endogenous archaeal human genomic sequences akin to HERV sequences and can function as jumping genes regulating genomic DNA flexibility. The integrated endogenous genomic archaeal sequences can get expressed in the presence of redox stress forming endosymbiotic archaeal particles which can function as a new organelle called the archaeaons. There are several factors that contribute to interstitial fibrosis in IPF and sarcoidosis. For fibroblasts to replicate in the interstitium and in the alveolar walls, they must be primed to enter the G1 phase of a growth cycle to proliferate. Several products from alveolar macrophages can participate in these steps. PDGF-B is a chemoattractant for mesenchymal cells and a stimulus for fibroblasts to change form resting cells to cells entering G1. Although PDGF-B is not produced by normal macrophages, alveolar macrophages obtained from patients with IPF and sarcoidosis make it abundantly. This is correlated with c-sis, a proto-onocogene the codes for the beta chain of PDGF-B which is increased in IPF / sarcoidosis derived macrophages. Gamma interferons upregulate this gene activation. PDGF receptor is a G-protein coupled receptor. The increase in intracellular calcium consequent to membrane Na^+-K^+ ATPase inhibition can upregulate its activity. Increased intracellular calcium activates phospholipase C beta which results in increased production of diacyglycerol (DAG) with resultant activation of protein kinase C. The protein kinase C (PKC) activates MAP kinase cascade resulting in cellular proliferation. This can activate c-sis, the proto-oncogene that codes for the beta chain of PDGF-B. Gamma

interferons act by inducing the enzyme indoleamine 2,3-dioxygenase and promoting tryptophan catabolism. The increased levels of tryptophan and its catabolitic products consequent to elevated digoxin levels can promote gamma interferon action. Thus the synthesis of PDGF-B is also increased and contributes to fibroblast proliferation in sarcoidosis and IPF.[1-13]

Archaeal Induced Hyperdigoxinemic State and Hemispheric Dominance in Relation to Lung Disease

The archaeaon related organelle - steroidelle, neurotransminoid and vitaminocyte contribute to hemispheric dominance. In left handed / right hemispheric dominant individuals there was a derangement of the isoprenoid pathway. They had an upregulated HMG CoA reductase activity with increased digoxin and dolichol levels and reduced ubiquinone levels. The RBC membrane Na^+-K^+ ATPase activity was reduced and serum magnesium depleted. The left handed / right hemispheric dominant individuals had increased levels of tryptophan, serotonin, quinolinic acid, strychnine and nicotine while the levels of tyrosine, dopamine, noradrenaline and morphine were lower. Thus an upregulated isoprenoid pathway, increased level of tryptophan and its catabolites, decreased levels of tyrosine and its catabolites and hyperdigoxinemia is suggestive of right hemispheric dominance. Lung disease occur in right hemisphere dominant individuals and is a reflection of altered brain function and isoprenoid pathway.[1-13]

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