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Fructolysis, Archaeal Digoxin and Chronic Renal Disease

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 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 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 aldoketo reductases. 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.

The isoprenoid pathway is a key regulatory pathway within the cell. It produces several key metabolites important in cellular regulation. Digoxin, an endogenous membrane Na^{+}-K^{+} ATPase inhibitor is synthesized by the isoprenoid pathway. Membrane Na^{+}-K^{+} ATPase inhibition can alter the ionic fluxes across cellular membrane. Digoxin also functions as immune modulating

agent and membrane Na^+-K^+ ATPase inhibition can lead to increase in CD_4/CD_8 ratios. Digoxin, consequent to the intracellular hypomagnesemia it produces can lead to alterations in glycosaminoglycan and glycoprotein metabolism. Dolichol, another product of the isoprenoid pathway is important in N-glycosylation of proteins. Alteration in the sulphated glycosaminoglycan of the basement membrane can produce changes in the glomerular filtration barrier. Ubiquinone, another important product of the pathway, is a component of the mitochondrial electron transport chain and is a free radical scavenger.

Actinidic archaea has been related to global warming and human diseases. The growth of endosymbiotic actinidic archaea in relation to climate change and global warming leads to neanderthalisation of the humans. Neanderthal metabolonomics include the Warburg phenotype and cholesterol catabolism resulting in hyperdigoxinemia. Digoxin produced by archaeal cholesterol catabolism produces neanderthalisation. The neanderthalisation of the human brain due to endosymbiotic archaeal overgrowth results in prefrontal cortical atrophy and cerebellar hyperplasia. This leads on to dysautonomia with sympathetic hyperactivity and parasympathetic neuropathy in these disorders. This can lead onto a chronic renal failure of unknown origin. 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 is exemplified by MEN - the Mesoamerican nephropathy syndrome. The patient develops a chronic renal failure of unknown origin. There is tubular dysfunction and tubular atrophy with fibrosis. There is secondary glomerulosclerosis and mild proteinuria. There is hypokalemia and hyponatraemia. There is also hyperuricemia. Hypertension and edema is absent. MEN syndrome has been attributed to global warming related osmotic stress and induction of the enzyme aldose reductase and fructokinase. Fructose can produce renal injury. CKD of unknown origin in the absence of diabetes and hypertension has been described in the Kerala population. This could be the basis of global warming related kidney disease.

This study was undertaken to assess the changes in the isoprenoid pathway in renal disease - chronic renal failure, nephrotic syndrome and nephrolithiasis. As endosymbiotic archaeal digoxin can modulate synaptic transmission of multiple neurotransmitter systems, the isoprenoid pathway was also assessed in individuals with differing hemispheric dominance to find out the role of hemispheric dominance in the pathogenesis of renal disease. The central role of the isoprenoid pathway in regulating renal function is discussed and its relation to hemispheric dominance elucidated.[1-13]

Results

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

(2) The concentration of serum tryptophan, quinolinic acid and serotonin were increased in the plasma while that of tyrosine, dopamine and noradrenaline were decreased in CRF, nephrotic syndrome and nephrolithiasis.

(3) Nicotine and strychnine were detected in the plasma of patients with CRF, nephrotic syndrome and nephrolithiasis and were undetectable in the control serum. Morphine was not detected in the plasma of CRF, nephrotic syndrome and nephrolithiasis.

(4) The activity of superoxide dismutase (SOD), catalase, glutathione reductase and glutathione peroxidise in the erythrocytes decreased significantly in CRF, nephrotic syndrome and nephrolithiasis. In CRF, nephrotic syndrome and nephrolithiasis the concentration of MDA, hydroperoxides, conjugated dienes and NO increased significantly. The concentration of reduced glutathione decreased in CRF, nephrotic syndrome and nephrolithiasis.

(5) The concentration of total (GAG) increased in the serum of CRF, nephrotic syndrome and nephrolithiasis patients. The concentration of hyaluronic acid (HA), heparin sulphate (HS), heparin (H), dermatan sulphate (DS) and chondroitin sulphates (ChS) were increased in CRF, nephrotic syndrome and nephrolithiasis. The concentration total hexose, fucose and sialic acid were increased in the glycoproteins of the serum in CRF, nephritic syndrome and nephrolithiasis.

(6) The activity of GAG degrading enzymes beta glucuronidase, beta N-acetyl hexosaminidase, hyaluronidase and cathepsin - D were increased in CRF, nephrotic syndrome and nephrolithiasis when compared to the controls. The activity of beta galactosidase, beta fucosidase and beta glucosidase increased in CRF, nephrotic syndrome and nephrolithiasis.

(7) The concentration of total GAG, hexose and fucose in the RBC membrane decreased significantly in CRF, nephrotic syndrome and nephrolithiasis. The concentration cholesterol increased and phospholipids decreased in the RBC membrane in CRF, nephrotic syndrome and nephrolithiasis and the cholesterol: phospholipid ratio in the RBC membrane increased significantly in CRF, nephrotic syndrome and nephrolithiasis.

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

Discussion

Archaeal Digoxin and Membrane Na^+-K^+ ATPase Inhibition in Relation to Renal 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 in CRF, nephrotic syndrome and nephrolithiasis while serum ubiquinone was reduced. Previous studies in this laboratory have demonstrated incorporation of ^{14}C-acetate in to digoxin in the rat brain indicating that acetyl CoA is the precursor for digoxin biosynthesis in mammals also. The elevated HMG CoA reductase activity correlated 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 calcium resulting from increased Na^+-Ca^{++} exchange, increased entry of calcium via the voltage gated calcium channel and increased release of calcium from intracellular endoplasmic reticulum calcium stores. This increase in intracellular calcium by displacing magnesium from its binding sites causes a decrease in the function availability of magnesium. This decrease in the availability of magnesium can cause decreased mitochondrial ATP formation which along with low magnesium can cause further inhibition of Na^+-K^+ ATPase, since the ATP-magnesium complex is the actual substrate for this reaction. Cytosolic free calcium is normally buffered by two mechanisms, ATP dependent calcium extrusion from the cell and ATP dependent sequestration of calcium within the endoplasmic reticulum. The magnesium related mitochondrial dysfunction results in defective calcium extrusion from the cell. There is thus a progressive inhibition of Na^+-K^+ ATPase activity first triggered by digoxin. Low

intracellular magnesium and high intracellular calcium consequents to Na^+-K^+ ATPase inhibition appear to be crucial to the pathogenesis of CRF, nephrotic syndrome and nephrolithiasis. Serum magnesium was found to be reduced in CRF, nephrotic syndrome and nephrolithiasis.

Excess parathormone has been suggested to be an important uraemic toxin. Increase in intracellular calcium consequent to membrane Na^+-K^+ ATPase inhibition can lead on to increased parathormone activity as the parathormone receptor is a G-protein coupled receptor. The increase in intracellular calcium in the tissues is cytotoxic and contributes to the pathophysiology of chronic renal failure. The increased activity and level of parathormone can lead on to osteitis fibrosa cystica. The active 1,25 dihydroxy cholecalciferol has a intracellular DNA binding site. Digoxin induced intracellular hypomagnesemia can lead on to a defect in the action of 1,25 dihydroxy cholecalciferol contributing to renal osteomalacia. Digoxin by membrane Na^+-K^+ ATPase inhibition that it produces can lead on to inhibition of the outward sodium flux and inhibition of the inward potassium flux as also leading on to an increased inward flux of calcium. This leads on to an abnormally high intracellular sodium concentration and hence to osmotically induced overhydration of the cell whereas the same cells are relatively deficient in potassium.

Archaeal Digoxin and Mitochondrial Dysfunction in Relation to Renal Disease

The archaeaon vitminocyte contributes to the synthesis of ubiquinone and mitochondrial electron transport chain function. The low ubiquinone levels can lead on to a mitochondrial dysfunction as ubiquinone is an important component of the mitochondrial electron transport chain and free radical scavenger. The increase in intracellular calcium can also open up the mitochondrial PT pore resulting in a mitochondrial dysfunction. The free radical production is increased

in chronic renal failure and the scavenging enzymes - super oxide dismutase, glutathione synthetase and glutathione peroxidise activity reduced. The reduction in superoxide dismutase activity is due to opening of the mitochondrial PT pore, disruption of the osmotic equilibrium of the matrix and rupture of the outer membrane which leads on to leakage of mitochondrial superoxide dismutase in to the cytoplasm. Glutathione synthetase and glutathione peroxidase activity are reduced in intracellular magnesium deficiency. A mitochondrial dysfunction can lead on to inhibition of membrane Na^+-K^+ ATPase and accentuation of the abnormalities in calcium, sodium and potassium.

Digoxin can alter neutral amino acid transport resulting in upregulation of tryptophan transport over tyrosine. This leads on to increased tryptophan catabolites - serotonin, nicotine, strychnine and quinolinic acid in CRF. Increased aromatic amino acid tryptophan catabolites can function as uremic toxin. Digoxin by producing intracellular hypomagnesemia can affect the function of the protein tyrosine kinase insulin receptor. This leads on to hyperinsulinism and insulin resistance of chronic renal failure. The glucose intolerance of uremia results largely from peripheral resistance to the action of insulin. The altered state of metabolism in uremia includes a negative nitrogen balance with profound loss of lean body mass and fat deposits. The intracellular hypomagnesemia consequent to membrane Na^+-K^+ ATPase inhibition produced by digoxin can result in defective DNA transcription and ribosomal function. This leads on to inhibition of protein synthesis. Digoxin induced intracellular hypomagnesemia can lead on to inhibition of lipoprotein lipase and decrease in lecithin cholesterol acyl transferase activity. This leads on to hypertriglycerdemia and low HDL cholesterol values noted in CRF. The hypertension of renal failure could be attributed to membrane Na^+-K^+ ATPase inhibition related increase in smooth muscle vascular cell calcium and decrease in magnesium. Decrease in intracellular vascular smooth muscle magnesium

can lead on to vasospasm and hypertension of renal failure. The increase in intracellular calcium can lead on to increased action the G-protein coupled platelet activating factor receptor and thrombin receptor leading on to increased platelet aggregation and hypercoagulability. This can also contribute to the increased incidence of vascular thrombosis in chronic renal failure. The increase in GAG synthesis and glycoprotein synthesis noticed in renal failure is significant. Hypomagnesemia is reported to upregulate GAG synthesis. Increase in dolichol can lead on to increased N-glycosylation of protein. The lysosomal enzymes and glycohydrolases and increased despite an increase in glycosaminoglycan and carbohydrate residues of glycoproteins. This indicates that the proteoglycans and glycoproteins are defectively processed and are hence resistant to lysosomal digestion. This can lead on to fibrosis and shrunken kidneys of renal failure. The increase in glycosaminoglycans and glycoproteins of the vascular wall can lead on to increased arteriosclerosis noticed in renal disease. Thus most of the metabolic abnormalities noticed in chronic renal failure can be attributed to the alterations in the isoprenoid pathway.

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

The isoprenoid pathway dysregulation also plays an important role in the genesis of nephrotic syndrome. The archaeaon glycosaminoglycoid and fructosoid contributes to glycoconjugate synthesis and catabolism by the process of fructolysis. 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 glycoconjugate metabolism in nephrotic syndrome is significant. As already discussed this alteration is due to hypomagnesemia and increased dolichol levels. There was increase in total GAG and individual GAG fractions in the

serum in nephrotic syndrome. The fucose, hexose and sialic acid content of glycoproteins of the serum also showed an increased. This can contribute to renal tubular fibrosis. This is described in meso-American nephropathy related to global warming.

Archaeal Digoxin and Alteration in Membrane Structure and Membrane Formation in Relation to Renal Disease

There was an increase in the cholesterol: phospholipid ratio of the membrane in nephrotic syndrome. Also the membrane glycoconjugate were reduced in the presence of increased glycoconjugates in the serum. This is due to defective membranogenesis consequent to inhibition of lipid kinases and GTPase involved in membrane trafficking from the golgi body to the cell surface in the presence of intracellular magnesium deficiency. It should be stressed that the key component proteinuria, results from altered permeability of the glomerular filtration barrier for proteins namely the glomerular basement membrane, the podocytes and their slit diaphragms. The probable alteration in the composition of the glomerular basement membrane can increase the permeability of the glomerular filtration barrier leading on to proteinuria. The hypoalbuminemia noticed in nephrotic syndrome could also be due to decreased albumin synthesis. Membrane Na^+-K^+ ATPase inhibition related decreased intracellular magnesium can lead on to inhibition of ribosomal function and protein transcription. This leads to an inhibition of protein synthesis and could contribute to the hypoalbuminemia of nephrotic syndrome. The increased intracellular calcium consequent to membrane Na^+-K^+ ATPase inhibition can lead on to increased G-protein related function of the renin and angiotensin receptors. The renin-angiotensin-aldosterone axis is stimulated. This leads on to renal salt and water retention. Low density lipoproteins and cholesterol tend to be elevated in patients with moderate disease. This is due to the upregulation of the isoprenoid

pathway and increased cholesterol synthesis noticed in nephrotic syndrome. Patients with very severe nephrotic syndrome tend to have an increase in triglycerides and very low density lipoproteins. This is due to the digoxin induced hypomagnesemia inhibiting lipoproteins. This is due to the digoxin induced hypomagnesemia inhibiting lipoprotein lipase activity. The hypercoagulability noticed in nephrotic syndrome could also be related to increased digoxin. The increased intracellular calcium consequent to membrane Na^+-K^+ ATPase inhibition can increase the activity of G-protein coupled platelet activating factor and thrombin receptor leading on to increased thrombosis as mentioned before. Hyperparathyroidism and hypothyroidism are also noticed in nephrotic syndrome. The increase in intracellular calcium can lead on to increased G-protein coupled parathormone action. The thyroid hormone receptor also has a DNA binding site. The intracellular hypomagnesemia consequent to membrane Na^+-K^+ ATPase inhibition can lead on to defective thyroid hormone receptor action and hypothyroidism.

Archaeal Digoxin and Immunoregulation in Relation to Renal Disease

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 viroidelle can secrete RNA viroids modulating immune function by blocking mRNAs. Increased intracellular calcium activates the calcium dependent calcineurin signal transduction pathway which can produce T-cell and macrophage activation with secretion of interleukin 3, 4, 5, 6, 8 and TNF alpha. This can also explain the immune activation in nephrotic syndrome. Membrane Na^+-K^+ ATPase inhibition can produce immune activation and is reported to increase CD_4/CD_8 ratios as exemplified by the action lithium.

The increase in fucoligands and sialoligands can also lead on to immune activation. The protein processing defect can result in defective glycosylation of endogenous renal 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 which is dysfunctional in the presence of magnesium deficiency. This result in defective transport of MHC class 1 renal basement membrane glycoprotein antigen complex to the antigen presenting cell surface for recognition by the CD_4 or CD_8 cell. Defective presentation of the endogenous renal basement membrane glycoprotein antigen can explain the immune dysregulation in nephrotic syndrome. This can contribute towards the autoimmunity in nephrotic syndrome. Relatively cationic antigens tend to permeate the glomerular basement membrane and deposit within the glomerular basement membrane or in the subepithelial space. Anionic antigens are repelled by the glomerular basement membrane which is negatively charged, and tend to be trapped in the subendothelial cell space and mesangium. The probable change in the sulphated glycosaminoglycans of the glomerular basement can contribute to trapping of the antibodies.

Archaeal Digoxin, Shikimic Acid Pathway - Regulation of Neurotransmitter Synthesis and Function in Relation to Renal Disease

The archaeaon neurotransminoid shikimic acid pathway contributes to tryptophan and tyrosine synthesis and catabolism generating neurotransmitters and neuroactive alkaloids. Digoxin induced upregulation of tryptophan transport over tyrosine can result in increased tryptophan catabolites and reduced tyrosine catabolites in the serum. Quinolinic acid has been implicated in immune activation in other immune disease and could contribute to the same in nephrotic syndrome. 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 and dopamine can contribute to the immune activation in nephrotic syndrome. We have 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. Serum of patients with nephrotic syndrome showed the presence of strychnine and nicotine but morphine was absent. The absence of morphine in patients with nephrotic syndrome is also significant as deficiency of morphine can lead on to immune activation.

Archaeal Digoxin, Glycosaminoglycoid and Steroidelle - Relation to Renal Stone

The role of the isoprenoid pathway in nephrolithiasis is also significant. The increased digoxin synthesis noticed can contribute to the genesis of renal stones. Membrane Na^+-K^+ ATPase inhibition can lead on to increase in intracellular calcium and a reduction in intracellular magnesium. The increase in renal tubular epithelial calcium can contribute to increased formation of renal stones consequent to shedding of the calcium loaded tubular epithelial cells. Thus hyperdigoxinemia can also contribute to the pathogenesis of nephrolithiasis. The digoxin induced hypomagnesemia and dolichol related upregulated glycosaminoglycan and glycoprotein synthesis is also significant. There is an increase in the fucose, hexose and sialic acid content of serum glycoprotein in nephrolithiasis. Urine components that appear to be glycoproteins inhibit processes concerned with of stone formation - supersaturation and crystalisation. Altered glycoproteins can lead on to loss of the inhibitory function. The increased total serum glycosaminoglycans and different glycosaminoglycan fractions can lead on to increased glycosaminoglycan excretion in the urine. This GAG can form a matrix on which crystallisation can happen. Thus the

isoprenoid pathway related cascade can contribute to nephrolithiasis by way of two metabolites - digoxin and dolichol.

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

The archaeaon related organelle - steroidelle, viroidelle, 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. In right handed / left hemispheric dominant individuals the biochemical patterns were reversed. CRF, nephrotic syndrome and nephrolithiasis occurs in right hemisphere dominant individuals and is a reflection of altered brain function.[1-13]

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