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Archaeal Digoxin Mediated Model for Metabolic Syndrome X

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 D1,3-biphosphoglycerate which is then converted to 3-phosphoglycerate. The 3-phosphglycerate 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 glyceraldhyde 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 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 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.

Global warming can lead to osmotic stress consequent to dehydration. The increase in actinidic archaeal growth leads to cholesterol catabolism and digoxin synthesis. Digoxin produces membrane sodium potassium ATPase inhibition and increase in intracellular calcium producing mitochondrial dysfunction. This

results in oxidative stress. The oxidative stress and osmotic stress can induce the enzyme aldose reductase which converts glucose to fructose. Fructose has got a low km value for ketokinase as compared to glucose. Therefore fructose gets phosphorylated more to fructose phosphate and the cell is depleted of ATP. The cell depletion of ATP leads to oxidative stress and chronic inflammation consequent to induction of NFKB. Oxidative stress can open the mitochondrial PT pore producing release of cyto C and activation of the caspase cascade of cell death. The fructose phosphate can enter the pentose phosphate pathway synthesizing ribose and nucleic acid. The depletion of cellular ATP results in generation of AMP and ADP which are acted upon by deaminases causing hyperuricemia. Uric acid can produce endothelial dysfunction and vascular disease. Uric acid can also produce mitochondrial dysfunction. The fructose phosphate can enter the glucosamine pathway synthesizing GAG and producing mucopolysaccharide accumulation. Fructose can fructosylate proteins making them antigenic and producing an autoimmune response. This can lead to global warming related metabolic syndrome X.

The components of syndrome X include: non-insulin dependent diabetes mellitus, hyperinsulinism, insulin resistance, central obesity, dyslipidemia marked by hypertriglyceridemia and low HDL levels, accelerated atherosclerosis leading to coronary artery disease and stroke, hypertension and a positive family history. The isoprenoid pathway produces four crucial metabolites important in cellular function - digoxin, an endogenous inhibitor of membrane Na^{+}-K^{+} ATPase ubiquinone, a component of the mitochondrial electron transport chain, dolichol, important in N-glycosylation of proteins and cholesterol, a component of the cellular membrane. Endosymbiotic archaea can synthesize digoxin by cholesterol catabolism. Elevated levels of digoxin and the related increased Na^{+}-Ca++ exchange in the vascular smooth muscle cell has been reported to cause the hypertension associated with the syndrome. The

inhibition of membrane Na^+-K^+ ATPase by digoxin has been reported to cause hypomagnesemia, a risk factor in syndrome X. Magnesium deficiency has been associated with insulin resistance. Hypomagnesemia can also affect the metabolism of glycosaminoglycans and glycolipids and changes in the dolichol levels can alter N-glycosylation of protein. Changes in basement membrane heparin sulphate have been implicated in the microangiopathy of syndrome X and elevated levels of sialic acid, and acute phase response marker has also been documented in syndrome X. The acute phase response plays a role in the genesis of the vascular disease in syndrome X. Archaeal digoxin induced altered to calcium/magnesium ratios and changes in ubiquinone can affect mitochondrial function and lead to free radical generation. Free radicals can contribute to oxidised LDL important in the pathogenesis of atherosclerosis in syndrome X. Alteration in baroreceptor sensitivity and sympatho-vagal balance has been reported to lead to vasospasm in syndrome X. Archaeal digoxin can alter amino acid and neurotransmitter transport. The products of the isoprenoid pathway - cholesterol, ubiquinone, dolichol and digoxin can affect membrane structure and function, with consequent endothelial dysfunction important in syndrome X.

The study was undertaken to assess, (1) the isoprenoid pathway, (2) The tryptophan/tyrosine catabolic patterns, (3) Glycoconjugate metabolism, (4) RBC membrane changes as a reflection of cell membrane change, and (5) Free radical metabolism. A hypothesis implicating membrane Na^+-K^+ ATPase inhibition consequent to increased digoxin secretion as pivotal to all these changes occurring in syndrome X is also presented.

Results

(1) The activity of HMG CoA reductase and the concentration of digoxin and dolichol were increased in syndrome X with multiple lacunar state. The concentration of serum ubiquinone, the activity of erythrocyte membrane

Na^+-K^+ ATPase and serum magnesium were decreased. The concentration of serum tryptophan, quinolinic acid and serotonin was increased in the plasma of these patients while that of tyrosine, dopamine and noradrenaline was decreased. Nicotine and strychnine were detected in the plasma of syndrome X with multiple lacunar state patients but were not detectable in the control serum. Morphine was not detected in the plasma of these patients.

(2) The concentration of total glycosaminoglycans (GAG) and different GAG fractions, total hexose, fucose and sialic acid content of serum glycoproteins and the concentration of gangliosides, glycosyl-diglycerides and sulphatides showed significant increase in the serum of syndrome X with multiple lacunar state patients. The activity of glycosaminoglycan (GAG) degrading enzymes and glycohydrolases increased in the serum of syndrome X with multiple lacunar state. The concentration of total GAG and hexose and fucose residues of glycoproteins in the RBC membrane decreased significantly in syndrome X with multiple lacunar state. The concentration of RBC membrane cholesterol increased while that of phospholipids decreased resulting in an increased cholesterol: phospholipid ratio.

(3) The activity of superoxide dismutase (SOD), catalase, glutathione reductase and glutathione peroxidase in the erythrocytes decreased significantly in syndrome X with multiple lacunar state. The concentration of malondialdehyde (MDA), hydroperoxides, conjugated dienes and nitric oxide (NO) increased significantly while the concentration of reduced glutathione decreased.

Discussion

Archaeal Digoxin and Membrane Na^+-K^+ ATPase Inhibition in Relation to Metabolic Syndrome X

The archaeaon steroidelle DXP pathway and the upregulated pentose phosphate pathway contribute to digoxin synthesis. The increase in plasma digoxin and dolichol in syndrome X is a consequence of increased operation of the isoprenoid pathway as is evidenced from the increase in the activity of HMG CoA reductase. Incorporation of ^{14}C-acetate into digoxin in the rat brain has been previously shown by us indicating its synthesis in mammals from acetyl CoA and by the isoprenoid pathway. The observed inhibition of RBC membrane Na^+-K^+ ATPase is a consequence of increased digoxin. The inhibition Na^+-K^+ ATPase by digoxin is known to cause increase in intracellular Ca^{++} and a decrease in intracellular Mg^{++}. Low intracellular Mg^{++} and high intracellular Ca^{++} consequent of Na^+-K^+ ATPase inhibition appear to be crucial to the pathophysiology of syndrome X with multiple lacunar state. The intracellular alteration of Ca^{++} and Mg^{++} can affect diverse cellular processes. A large variety of calcium dependent cellular processes are activated by increase in intracellular calcium and several vital processes which require Mg^{++} are downgraded in the presence of inadequate Mg^{++} levels.

Inhibition of membrane Na^+-K^+ ATPase can also explain the pathogenesis of syndrome X in another way. Magnesium is required as a co-factor for cell membrane glucose transport. Hypomagnesemia consequent to membrane Na^+-K^+ ATPase inhibition can lead to defective cell membrane transport of glucose. Increased intracellular calcium can also lead to the activation of the calcineurin signal transduction pathway resulting in T-cell activation and increased levels of TNF alpha, contributing to insulin resistance. Increased intracellular calcium can activate the G-protein coupled signal transduction of the contrainsulin hormones (growth hormone and glucagon) leading to

hyperglycemia. 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 receptor producing the thrombosis observed in syndrome X with multiple lacunar state. Decreased intracellular magnesium can lead to increased thrombin and ADP/collagen induced platelet aggregation. Decrease in intracellular magnesium can block the phosphorylation reactions involved in protein tyrosine kinase receptor activity leading to insulin resistance. Decrease in intracellular magnesium can lead to inhibition of glycolysis causing defective glucose utilization and hyperglycemia. Increase in intracellular calcium can open the mitochondrial PT pore, disrupt the hydrogen gradient across the inner membrane and block mitochondrial oxidative phosphorylation. Intracellular magnesium deficiency can also lead to an ATP synthase defect. This leads to defective glucose utilisation. Increase in beta cell calcium can contribute to increased insulin release from beta cells and hyperinsulinemia. Hypomagnesemia has been reported to markedly increase glucose stimulated insulin secretion by the perfused pancreas. Na^+-K^+ ATPase inhibition related increased smooth muscle calcium and decreased magnesium can contribute to vasospasm and ischemia observed in stroke and CAD. Na^+-K^+ ATPase inhibition induced hypomagnesemia related altered glycoprotein and glycosaminoglycan synthesis can contribute to the microangiopathy and macroangiopathy observed in syndrome X. Decreased intracellular magnesium can produce an endothelial mitochondrial dysfunction, increased membrane fluidity of endothelium and increased permeability of endothelial cells to lipoproteins. Increased intracellular calcium within the endothelial cell leads to fragmentation of the elastic membrane and calcification. Increased intracellular calcium can produce configuration change in arterial elastin, exposing the elastin's hydrophobic sites resulting in increased cholesterol absorption. Increased calcium within the arterial wall alters elastin synthesis, turnover and

composition. Decreased intracellular magnesium blocks the activity of delta-6-desaturase resulting in increased levels of oleic acid and linoleic acid and decreased levels of arachidonic acid and stearic acid. This contributes to the retinopathy in syndrome X with multiple lacunar state. Decreased intracellular magnesium can produce dysfunction of lipoprotein lipase producing defective catabolism of triglyceride rich lipoproteins and hypertriglyceridemia. In hypomagnesemia, lecithin cholesterol acyl transferase (LCAT) is defective and there is reduced formation of cholesterol esters in HDL. This results in reduced HDL cholesterol described in syndrome X with multiple lacunar state. Magnesium deficiency has been reported to increase LDL cholesterol levels also.

Archaeal Digoxin and Regulation of Neurotransmitter Synthesis and Function in Relation to Metabolic Syndrome X

The archaeaon neurotransminoid shikimic acid pathway contributes to tryptophan and tyrosine synthesis and catabolism generating neurotransmitters and neuroactive alkaloids. Digoxin, apart from affecting cation transport via inhibition of membrane Na^+-K^+ ATPase, is also reported to influence the transport of various metabolites across cellular membranes, which includes amino acids and various neurotransmitters. Two of the amino acids are important in this respect, tryptophan, a precursor for strychnine and nicotine and tyrosine a precursor for morphine. Digoxin is reported to increase tryptophan transport while decreasing tyrosine transport. The increase in tryptophan and its catabolites - quinolinic acid and serotonin and the decrease in tyrosine and its catabolites - dopamine and norepinephrine now observed in patients with syndrome X may be a reflection of this effect of digoxin on the transport of these amino acids. Serum of syndrome X with multiple lacunar state showed the presence of strychnine and nicotine, which in a previous communication by us were reported in the brain of rats fed with tryptophan. Morphine could not be

detected in the serum of these patients. The decrease in membrane Na^+-K^+ ATPase activity in syndrome X with multiple lacunar state could also be due to the fact that the hyperpolarising neurotransmitters (dopamine, morphine and noradrenaline derived from tyrosine) are reduced and the depolarising neuroactive compounds (serotonine, strychnine, nicotine and quinolinic acid derived from tryptophan) are increased. Thus the schizoid neurotransmitter pattern of reduced dopamine, noradrenaline and morphine and increased serotonin, strychnine and nicotine is also observed by us in syndrome X with multiple lacunar state. The increase now observed in quinolinic acid, an NMDA agonist, can contribute to glutamate excitotoxicity, as in the schizoid state. The elevated levels of serotonin and strychnine arc also known to cause an upregulated excitatory NMDA transmission.

Archaeal Digoxin and Regulation of Golgi Body / Lysosomal Function in Relation to Metabolic Syndrome X

The archaeaon glycosaminoglycoid and fructosoid contributes to glycoconjugate synthesis and catabolism by the process of fructolysis. The magnesium depletion can affect the metabolism of glycosaminoglycans, glycoproteins and glycolipids. The elevation in the level of dolichol may suggest its increased availability for N-glycosylation of proteins. Magnesium deficiency can lead 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). The results show an increase in the concentration of serum total GAG and individuals GAG fractions, glycolipids and carbohydrate components of glycoproteins (hexcose, fucose and sialic acid) in syndrome X with multiple lacunar state. The increase in the carbohydrate components total

hexose, fucose and sialic acid in syndrome X with multiple lacunar state was not to the same extent, suggesting a qualitative change in glycoprotein structure. The activity of GAG degrading enzymes and that of glycohydrolases showed significant increase in the serum of syndrome X with multiple lacunar slate. 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. Increased levels of sialic acid and ICAM-1 have been reported in syndrome X with multiple lacunar state, suggesting changes in glycoprotein metabolism. Increase in basement membrane heparan sulphate can contribute to the microangiopathy of syndrome X. Alteration in arterial wall glycoprotein and GAG has been described in arteriosclerosis and atherosclerosis. Increased glycosaminoglycans in the arterial wall can lead to increased interaction between GAG and lipoproteins contributing to atherogenesis. Thus the alteration in glycoproteins and GAG can contribute to microangiopathy and macroangiopathy of syndrome X with multiple lacunar state. A number of fucose and sialic acids containing natural ligands are involved in adhesion of the lymphocyte, producing leukocyte trafficking and extravasation in to the perivascular space. This could lead to the acute phase response in syndrome X with multiple lacunar state and immune mediated neuropathies described in syndrome X with multiple lacunar state.

Archaeal Digoxin and Alteration in Membrane Structure and Membrane Formation in Relation to Metabolic Syndrome X

The archaeaon steroidelle, glycosaminoglycoid and fructosoid contribute to cell membrane formation synthesizing cholesterol by the DXP pathway and glycosaminoglycans by fructolysis. The alteration in the isoprenoid pathway specifically cholesterol as well as changes in glycoproteins and GAG can affect cellular membranes. The upregulation of the isoprenoid pathway can lead to increased cholesterol synthesis and magnesium deficiency can inhibit phospholipid synthesis. 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 glycoconjugate are defectively incorporated into the membrane in syndrome X. The change in membrane structure produced by alteration in glycoconjugates and the cholesterol: phospholipid ratio can produce changes in the conformation of Na^+-K^+ ATPase resulting in further membrane Na^+-K^+ ATPase inhibition. The alteration in cell membrane structure can result in defective transport of glucose across cell membranes due to alteration in the configuration of the glucose transporter. The same changes can affect the structure of the organelle membrane. This results in defective lysosomal stability and leakage of glycohydrolases and GAG degrading enzymes into the serum. Defective peroxisomal membranes lead to catalase dysfunction which has been documented in syndrome X with multiple lacunar state. Alteration in the endothelial cell membrane can contribute to the endothelial dysfunction described in the vascular disease in syndrome X.

Archaeal Digoxin and Mitochondrial Dysfunction in Relation to Metabolic Syndrome X

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 syndrome X with multiple lacunar state which may be the result of low tyrosine levels, consequent to digoxin's effect in preferentially promoting tryptophan transport over tyrosine. The aromatic ring portion of ubiquinone is derived from tyrosine. Ubiquinone, which is an important component of the mitochondrial electron transport chain, is a membrane antioxidant and contributes to free radical scavenging. The increase in intracellular calcium can open up 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 these lead 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 reduced free radical scavenging. The increase in intracellular calcium may lead to increased generation of NO by inducing the enzyme nitric oxide synthase which combines with the superoxide radical to form peroxynitrite. Increased calcium also can activate phospholipase A_2 resulting in increased generation of arachidonic acid which can undergo increased lipid peroxidation. Increased generation of free radicals like the superoxide ion and hydroxyl radical can produce lipid peroxidation and cell membrane damage which can further inactivate Na^+-K^+ ATPase, triggering the cycle of free radical generation once again. There was increase in lipid peroxidation with decreased antioxidant protection as indicated by the decrease in ubiquinone and reduced glutathione in

syndrome X with multiple lacunar state. The activity of free radical scavenging enzymes decreased in syndrome X with multiple lacunar state suggesting reduced free radical scavenging. Mitochondrial dysfunction related free radical generation has been implicated in the pathogenesis of syndrome X with multiple lacunar state and the vascular disease described in the syndrome. A defect in mitochondrial genome has been described in certain cases of syndrome X. Increased free radical generation can result in the formation of oxidised LDL which is atherogenic. Oxidised LDL is toxic to vascular endothelium and the macrophage. The proteolytic enzymes released from necrotic macrophages can alter the structural integrity of fibrous plaque and rupture the plaque. In addition as has already been described, the lysosomal stability is reduced in NIDDM consequent to an altered lysosomal membrane. This results in leakage of lysosomal enzymes in to the arterial wall. This endothelial denudation by oxidised LDL triggers coronary and cerebral thrombosis.

References

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