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Archaeal Digoxin, Cerebral Dominance and Regulation of Cardiovascular Function

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.

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 cardiac and vascular disease.

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 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 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.

The human hypothalamus and the vascular endothelial cell synthesize a steroidal glycoside, digoxin which functions as an endogenous membrane Na^+-K^+ ATPase inhibitor. Studies in our laboratory by feeding ^{14}C labelled acetate have demonstrated the synthesis of digoxin from the isoprenoid pathway. Membrane Na^+-K^+ ATPase inhibition results in increase in intracellular calcium and a reduction in intracellular magnesium. Calcium also has been implicated in the pathogenesis of essential hypertension. Calcium entry blockers are effective antihypertensive agents. Previous reports have demonstrated increased levels of digoxin in essential hypertension suggesting a role for endogenous digoxin in its pathogenesis. Abnormalities of transport of sodium across the cell membrane have been documented in hypertension. It has been assumed that this abnormality in sodium transport reflects a undefined alteration in the cell

membrane and this defect occurs also in the vascular smooth muscle cell. The defect leads to an abnormal accumulation of calcium in vascular smooth muscle resulting in heightened vascular responsiveness to vasoconstrictor agents. This defect has been proposed to be present in 35-50% of essential hypertensive patients on the basis of studies using red cells. Insulin resistance or hyperinsulinism has been suggested as being responsible for the increased arterial pressure in some patients with hypertension. While it is clear that a substantial fraction of the hypertensive population has insulin resistance and hyperinsulinemia, it is less certain that it is more than an association. All target tissues are not resistant to the action of insulin especially those involved in the hypertensive process. Hyperinsulinemia can increase arterial pressure by several mechanisms. Hyperinsulinemia produces renal sodium retention and increases sympathetic activity. Another mechanism is vascular smooth muscle hypertrophy secondary to the mitogenic action of insulin. Finally insulin also modifies ion transport across the cell membrane, thereby potentially increasing the cytosolic calcium levels of insulin sensitive vascular or renal tissues. Hypertension is a risk factor for coronary artery disease and thrombotic stroke. The factors that predispose to hypertension could also predispose to vascular occlusion. We have been able to detect patients who were persistently hypotensive with the systolic blood pressure below 80-90 mm. It was therefore considered crucial to assess the factors producing hypotension in this group of patients.

It was therefore considered pertinent to study the role of endogenous digoxin in 4 sets of patients 1) cases of essential hypertension and patients presenting with low blood pressure and with a family history of hypotension 2) patients with coronary artery disease and thrombotic strokes during the acute phase of the illness 3) patients with lone-atrial fibrillation and embolic stroke 4) the isoprenoid pathway was also assessed the 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 vascular disease. Studies have shown that the endogenous digoxin like factor is in fact the steroidal glycoside, digoxin itself. Digoxin is synthesized by the isoprenoid pathway. Digoxin can regulate amino acid and neurotransmitter transport. The isoprenoidal pathway also produces two other important metabolites - ubiquinone involved in free radical scavenging and dolichol important in glycoconjugate metabolism. Therefore the isoprenoid pathway was assessed in the above mentioned group of patients along with tyrosine / tryptophan catabolic patterns.[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. 7 sets of patients were chosen for the study. (1) 15 cases of essential hypertension (2) 15 cases of familial hypotension (3) 15 cases of acute coronary artery disease (4) 15 cases of acute cerebrovascular occlusion-thrombotic (5) patients with lone-atrial fibrillation and embolic stroke (6) 15 cases of age and sex matched bihemispheric dominant controls (7) 15 cases each of right hemispheric, left hemispheric and bihemispheric dominant individuals diagnosed by the dichotic listening test. The patients' age ranged from 50-70 years. None of the subjects studied was 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 Wallach and Kamat was used. Digoxin in the plasma was determined by 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} 4.6x150 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 method described by Arun et al. Statistical analysis was done by 'ANOVA'.

Results

(1) The results showed that HMG CoA reductase activity, serum digoxin and dolichol were increased in essential hypertension, acute CAD, acute thrombotic stroke and lone atrial fibrillation with embolic stroke indicating upregulation of the isoprenoid pathway but serum ubiquinone, RBC membrane sodium-potassium ATPase activity and serum magnesium were reduced. The results showed that HMG CoA reductase activity, serum digoxin and dolichol were decreased in familial hypotension, indicating downregulation of the isoprenoid pathway but serum ubiquinone, RBC membrane sodium-potassium ATPase activity and serum magnesium were increased.

(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 essential hypertension, acute CAD, acute thrombotic stroke and lone atrial fibrillation with embolic stroke while that of tyrosine, dopamine, norepinephrine and morphine 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 patients with familial hypotension while that of tyrosine, dopamine, norepinephrine and morphine was higher.

(3) 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 / eft 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 Alteration in Membrane Structure and Membrane Formation in Relation to Cardiovascular 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 in essential hypertension, acute CAD, acute thrombotic stroke and lone atrial fibrillation with embolic stroke as evidenced by increased HMG CoA reductase activity. Studies in our laboratory have demonstrated that digoxin is synthesized by the isoprenoid pathway. In all the disorders studied, there was significant inhibition of RBC membrane Na^{+}-K^{+} ATPase and this inhibition appears to be a common feature in essential hypertension, acute CAD and acute thrombotic stroke. 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 site causes a decrease in the functional availability of Mg^{++}. This decrease in the availability of Mg^{++} can cause decreased mitochondrial ATP formation which along with low Mg^{++} can cause further inhibition of Na^{+}-K^{+} ATPase, since the ATP-Mg^{++} complex is the actual substrate for this reaction. There is thus a progressive inhibition of membrane Na^{+}-K^{+} ATPase activity first triggered by digoxin. Low intracellular Mg^{++} and high intracellular Ca^{++} consequent to membrane Na^{+}-K^{+} ATPase inhibition appear to be crucial to the pathophysiology of essential hypertension, acute CAD and acute thrombotic stroke. Increase in intracellular calcium can activate the G-protein coupled angiotensin receptor producing hypertension and the G-protein coupled thrombin receptor and platelet activating factor producing thrombosis observed in acute CAD and acute thrombotic stroke. Na^{+}-K^{+} ATPase inhibition related increased smooth muscle calcium and decreased magnesium can contribute to vasospasm and ischaemia observed in acute thrombotic stroke and CAD. Thus increased secretion of hypothalamic or endothelial archaeal digoxin could lead on to acute vasospasm and thrombosis. Thus a neural dysfunction could contribute to acute CAD and thrombotic stroke.

This vasospasm could also contribute to hypertension. Increased intracellular calcium can open up the mitochondrial PT pore producing endothelial cell mitochondrial dysfunction. This results in altered membrane fluidity of endothelium and increased permeability of endothelial cells to lipoproteins. Increased intracellular calcium within the endothelial cell leads to altered arterial wall elastin synthesis, turnover and composition, configuration change in arterial wall elastin exposing the elastin's hydrophobic sites resulting in increased cholesterol absorption and fragmentation of arterial wall elastic membrane with calcification. Decreased intracellular magnesium can produce dysfunction of lipoprotein lipase producing defective catabolism of triglycerides rich lipoproteins and hypertriglyceridemia. Hypomagnesemia leads to decreased Lecithin cholesterol acyl transferase (LCAT) activity and reduced formation of cholesterol esters in HDL as also increased LDL cholesterol levels. Nicotine administration is known to produce vasospasm. It can also produce autonomic ganglionic stimulation, adrenal medullary stimulation and carotid / aortic body stimulation leading to hypertension. Nicotine administration can lead on to increased tissue cholesterogenesis, decreased hepatic degradation of cholesterol and increased triglycerides synthesis. Plasma LCAT and lipoprotein lipase activity is reduced on nicotine administration leading on to decreased HDL cholesterol and increased LDL+VLDL cholesterol. Thus increased endogenous nicotine synthesis can contribute to the atherosclerosis and hypertension. Morphine can act as a vasodilator and its deficiency could contribute to the vasospasm. Intracellular magnesium deficiency can lead on to protein tyrosine kinase dysfunction and an insulin receptor defect. Increase in intracellular calcium and reduction in intracellular magnesium can lead on to increased secretion of insulin from the beta cell of the islet of Langerhans. This leads on to hyperinsulinism. The vascular tissues remain sensitive to insulin. Hyperinsulinism can contribute to hypertension by its action on the renal

tubules resulting in sodium retention and mitogenic action on the vascular smooth muscle cell. On the other hand the decrease in the activity of HMG CoA reductase in familial hypotension cases suggests a downregulation of the isoprenoid pathway. There is a marked decrease in plasma digoxin consequent to its reduced synthesis. The stimulation Na^+-K^+ ATPase by reduced digoxin levels is known to cause a decrease in intracellular calcium and increase in intracellular magnesium by mechanisms described before. High intracellular magnesium and low intracellular calcium consequent to Na^+-K^+ ATPase stimulation could contribute to vasodilatation and hypotension.

Increased digoxin levels can affect atrial conduction leading on to atrial fibrillation. The hypomagnesemia consequent to increased digoxin levels and membrane Na^+-K^+ ATPase inhibition can also lead on to atrial fibrillation. Increase in intracellular calcium as already indicated can activate the G-protein coupled thrombin receptor and platelet activating factor producing thrombosis observed in patients with lone atrial fibrillation and embolic stroke. This can lead on to formation of an LA (left atrial) thrombus. Thus a neural dysfunction could contribute to the formation of an LA thrombus and atrial fibrillation resulting in a embolic stroke.

Archaeal Digoxin, Shikimic Acid Pathway and Regulation of Neurotransmitter Synthesis and Function in Relation to Cardiovascular 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 reduction in tyrosine and its catabolites in the serum of patients with essential hypertension, acute CAD and acute thrombotic stroke. 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 hypertension, acute CAD and acute thrombotic stroke could be due to the fact that the hyperpolarising neurotransmitters (dopamine, morphine and noradrenaline) are reduced and the depolarising neuroactive compounds (serotonin, glutamate (increased N-methyl-D-aspartate activity - NMDA owing to intracellular magnesium depletion), strychnine, nicotine and quinolinic acid) are increased. The schizoid neurotransmitter pattern of reduced dopamine, noradrenaline and morphine and increased serotonin, strychnine (blocks inhibitory brain glycinergic transmission), glutamate and nicotine (promotes dopaminergic transmission despite reduced dopamine levels) is common to all the disorders studied and could predispose to their development. A schizoid type of personality could predispose to the development of hypertension, acute CAD and acute stroke. On the other hand the results showed that the concentration of tryptophan and its metabolites - quinolinic acid, nicotine, strychnine and serotonin was found to be lower in the plasma of patients with familial hypotension while that of tyrosine, dopamine, morphine and norepinephrine was higher consequent to low digoxin levels promoting tyrosine transport over tryptophan. The increase in membrane Na^{+}-K^{+} ATPase activity in familial hypotension could be due to the fact that the hyperpolarising neurotransmitters (dopamine, morphine and noradrenaline) are increased and the d ĝpolarising neuroactive compounds neuroactive compounds [serotonin, strychnine, nicotine, quinolinic acid and glutamate (decreased NMDA transmission owing to hypermagnesemia)] are decreased. Decreased serotonin can lead on to depression and obsessive neurosis. Such a psychopathology can coexist with familial hypotension.

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 archaeaon steroidelle, glycosaminoglycoid and fructosoid contributes to cell membrane formation synthesizing cholesterol by the DXP pathway and glycosaminoglycans by fructolysis. The membrane Na^{+}-K^{+} ATPase inhibition related decreased intracellular magnesium level in acute CAD, acute stroke and essential hypertension can stimulate the synthesis of vessel wall glycosaminoglycans and glycolipids. The increase in the level of dolichol may suggest its increased availability for N-glycosylation of proteins. The increase in glycoconjugate levels despite increased activity of lysosomal degrading enzymes suggests a qualitative change in the glycoconjugate structure making it resistant to the action of lysosomal enzymes. Altered glycoproteins and GAG (heparan sulphate and chondroitin sulphate) accumulate in the vessel wall and complex with lipoproteins leading on to arteriosclerosis and atherosclerosis consequent to reduced proteolytic digestion of these complexes. Increased fucoligands and sialoligands can also lead on to arterial wall immune infiltration by monocytes leading on to atherogenesis. The altered cell surface glycoconjugate can produce arterial wall smooth muscle proliferation consequent to defective contact inhibition. Structurally abnormal glycoproteins and proteoglycans resist catabolism by lysosomal enzymes and accumulate leading on to formation of amyloid deposits. Amyloid is a defectively processed protein. Accumulation of amyloid within the conducting tissue in old age can lead on to lone atrial fibrillation.

Archaeal Digoxin and Mitochondrial Dysfunction in Relation to Cardiovascular 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 acute CAD, thrombotic stroke and essential hypertension which maybe the result of decreased tyrosine levels, consequent to increased digoxin promoting tryptophan transport over tyrosine. The aromatic ring portion of the ubiquinone is synthetised from lyrosine. The opening of the mitochondrial PT pore by the increase in intracellular calcium and decreased ATP synthase activity owing to intracellular hypomagnesemia leads to decreased efficiency of mitochondrial oxidative phosphorylation and increased free radical production. Increased intracellular calcium can stimulate nitric oxide synthase leading on to increased NO generation as well as stimulation of phospholipase A_2 resulting in increased arachidonic acid release and free radical generation. Increased generation of free radicals can produce lipid peroxidative damage of the cell membrane and inhibit the membrane Na^+-K^+ ATPase further. There is decreased antioxidant protection as indicated by a decrease in free radical scavenger ubiquinone in acute CAD, thrombotic stroke and essential hypertension. Increased free radical production could contribute to increased incidence of arteriosclerosis and atherosclerosis in acute CAD, thrombotic stroke and essential hypertension. This leads to LDL oxidation, macrophage rupture by the oxidised LDL and plaque rupture by the released lysosomal enzymes. The increased intracellular calcium and ceramide related opening of the mitochondrial PT pore also leads to release of cyto C into the cytoplasm, caspase-9 activation and apoptosis contributing to atherosclerosis in acute CAD, thrombotic stroke and essential hypertension. The concentration of ubiquinone

increased significantly in familial hypotension which may be the result of increased tyrosine levels, consequent to digoxin deficiency promoting tyrosine transport over tryptophan. The stabilisation of the mitochondrial PT pore by the decrease in intracellular calcium and increase an ATP synthase activity owing to intracellular hypermagnesemia leads to improved efficiency in mitochondrial oxidative phosphorylation and reduced free radical production. Decreased intracellular calcium can inhibit nitric oxide synthase leading to decreased NO generation as well as inhibition of phospholipase A_2 resulting in decreased arachidonic acid release and free radical generation. Decreased generation of free radicals can stabilise the cell membrane and stimulate membrane Na^+-K^+ ATPase further. There is increased antioxidant protection as indicated by the increase in free radical scavengers (ubiquinone and increased reduced glutathione) and increased free radical scavenging enzymes in familial hypotension, Stable peroxisomal membranes owing to alteration in membrane formation leads to increased catalase activity. Glutathione synthetase and glutathione reductase are activated in intracellular hypermagnesemia. Reduced intracellular calcium related stabilisation of the mitochondrial PT pore produces increased efficiency of superoxide dismutase activity. Decreased free radical production could contribute to reduced incidence of arteriosclerosis and atherosclerosis in familial hypotensive cases. The decreased intracellular calcium and ceramide related stabilisation of the mitochondrial PT pore also leads to downregulation of the apoptotic program and reduced atherosclerosis in familial hypotension. The synthesis of vasodilatory NO in the two groups increased NO synthesis in essential hypertension acute CAD and stroke and decreased NO synthesis in familial hypotension is a paradox. Probably NO synthesis occurs as a late event in vascular thrombosis where it generates the toxic free radical peroxynitrite damaging the vascular endothelium. This mechanism probably overrides its vasodilatory function.

Archaeal Digoxin and Immunoregulation in Relation to Cardiovascular Disease - The Fructosoid, Steroidelle and Viroidelle

The archaeaon fructosoid contributes to fructolysis and immune activation. Fructose can contribute to induction of NFKB and immune activation. The archaeaon steroidelle synthesized digoxin induces NFKB producing immune activation. The archaeaon secreting RNA viroids is called the viroidelle. The RNA viroids can block mRNAs and modulate immune function. In essential hypertension, acute CAD and acute stroke increased intracellular calcium activates the calcium dependent calcineurin signal transduction pathway which can produce T-cell activation and secretion of interleukin - 3, 4, 5, 6 and TNF alpha (Tumour necrosis factor alpha). This immune activation can contribute to the genesis of the atheromatous plaque. Increased intracellular calcium activates phospholipase C beta with increased diacyglycerol production and protein kinase C / MAP kinase cascade activation resulting in vascular smooth muscle proliferation. Increased generation of farnesyl phosphate owing to an upregulated isoprenoid pathway and decreased intracellular magnesium producing dysfunction of GTPase activity of the alpha-subunit of G-protein can result in ras oncogene activation and vascular smooth muscle proliferation contributing to atherogenesis. In familial hypotension decrease intracellular calcium can inhibit the calcium dependent calcineurin signal transduction pathway of the T-cell resulting in immunosuppression. In the presence of reduced intracellular calcium / increased intracellular magnesium the ras oncogene is inactivated and protein kinase C / MAP kinase cascade is inhibited resulting in decreased vascular smooth muscle proliferation and reduced atherogenesis.

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

The archaeaon related organelle - steroidelle, viroidelle, neurotransminoid and vitaminocyte contribute to hemispheric dominance. The patterns obtained in right hemispheric dominance correlated with patients of acute CAD, acute thrombotic stroke and hypertension. In right hemispheric dominant individuals there were increased digoxin and dolichol levels with reduced ubiquinone levels. The tryptophan catabolites were increased and tyrosine catabolites reduced. In left hemispheric dominant individuals there was a hypodigoxinemic state and the biochemical patterns were reversed. The hypodigoxinemic state was associated with familial hypotension and reduced risk for vascular thrombosis. Hemispheric dominance may thus regulate the risk for developing vascular thrombosis and hypertension.[1-13]

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