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Digoxin Mediated Model for Rheumatic Fever and Recurrent Respiratory Infection - Hypodigoxinemic Immune Deficiency Syndrome

Introduction

The epidemiology of acute rheumatic fever is identical to that of group A streptococcal upper respiratory tract infections. As is the case for streptococcal sore throat, acute rheumatic fever most often occurs in children; the peak age related incidence is between 5 and 15 years. Studies have shown that approximately 3% of individuals with untreated group A streptococcal pharyngitis will develop rheumatic fever. The rheumatogenecity of specific strains is largely based upon epidemiologic evidence associating certain serotypes with rheumatic fever (5, 6 and 1 8).

Major efforts have focused on the abnormal immune response by the human host to one or more group A streptococcal antigens. The hypothesis of antigenic mimicry between human and bacterial antigens has been studied extensively and has concentrated on two interactions. The first is the similarity between the group specific carbohydrate of the group A streptococcus and the glycoproteins of heart valves; the second involves the molecular similarity between either streptococcal cell membrane or streptococcal M-protein and sarcolemma or other moieties of the human myocardial cell. The possibility of a predisposing genetic influence in some individuals is also postulated. Observations have been described that support the concept that this non-suppurative sequel to group A streptococcal infections results from an abnormal immune response by the human host. Thus differences in immune responses to streptococcal extracellular antigens have been reported as also the presence of a unique surface marker on non-T-lymphocytes of rheumatic fever patients.

The isoprenoidal pathway is a key regulatory pathway in the cell and produces important metabolites - digoxin, dolichol and ubiquinone. Archaeal digoxin is an endogenous membrane Na^+-K^+ ATPase inhibitor and can modulate immune activity. Lithium, an exogenous membrane Na^+-K^+ ATPase

inhibitor can produce immune activation. Elevated archaeal digoxin levels have been reported in Kawasaki's disease with cardiac involvement. Digoxin can also modulate neurotransmitter transport and dopaminergic hyperactivity has been reported in the chorea of acute rheumatic fever. Dolichol is important in N-glycosylation of proteins and glycoconjugate synthesis. Ubiquinone is an important free-radical scavenger and free radical mechanisms are important in phagocytic killing of bacteria by macrophages. Therefore it was considered pertinent to study the isoprenoid pathway in rheumatic fever to find out whether any dysregulation of the pathway can predispose to acute rheumatic fever with recurrent streptococcal infections. Hemispheric dominance has been related to immune mediated diseases. Therefore the pathway was also assessed in right hemispheric dominant, left hemispheric dominant and bihemispheric dominant individuals to find out whether hemispheric dominance has any role to play in the genesis of acute rheumatic fever.

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. 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 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 autoimmune disease.

Results

(1) The activity of HMG CoA reductase and the concentration of digoxin and dolichol were decreased in the serum of acute rheumatic fever cases. The concentration of serum ubiquinone, the activity of erythrocyte membrane Na^+-K^+ ATPase and serum magnesium were increased.

(2) The concentration of serum tryptophan, quinolinic acid and serotonin was decreased in the plasma of acute rheumatic fever patients while that of tyrosine, dopamine and noradrenaline was increased.

(3) Nicotine and strychnine were not detected in the plasma of acute rheumatic fever patients. Morphine was detected in the plasma of acute rheumatic fever patients.

(4) The concentration of total glycosaminoglycans (GAG) decreased in the serum of acute rheumatic fever patients with recurrent streptococcal infections. The concentration of heparan sulphate (HS) heparin (H), dermatan sulphate (DS), chondroitin sulphates (ChS) and hyaluronic acid (HA) was decreased in the serum. The concentration total hexose, fucose and sialic acid were decreased in the glycoproteins of the serum of acute rheumatic fever patients. The concentration of gangliosides, glycosyl-diglycerides, cerebrosides and sulphatides showed significant decrease in the serum of acute rheumatic fever patients.

(5) The activity of glycosaminoglycan (GAG) degrading enzymes - beta glucuronidase, beta N-acetyl hexosaminidase, hyaluronidase and cathepsin-D - was decreased in the serum of acute rheumatic fever

patients when compared to the controls. The activity of beta galactosidase, beta fucosidase and beta glucosidase decreased in the serum of acute rheumatic fever cases.

(6) The concentration of total GAG and hexose and fucose residues of glycoproteins in the RBC membrane increased significantly in acute rheumatic fever cases. The concentration of RBC membrane cholesterol decreased while that of phospholipid increased in acute rheumatic fever patients. The ratio of RBC membrane cholesterol phospholipids decreased in acute rheumatic fever cases.

(7) The activity of superoxide dismutase (SOD), catalase, glutathione reductase and glutathione peroxidase in the erythrocytes increased significantly in the serum of acute rheumatic fever cases. The concentration of malon dialdehyde (MDA), hydroperoxides, conjugated dienes and nitric oxide (NO) decreased significantly in the serum of acute rheumatic fever cases. The concentration of reduced glutathione increased in acute rheumatic fever cases.

(8) The results showed that HMG CoA reductase activity serum digoxin and dolichol were increased and serum ubiquinone, RBC membrane sodium-potassium ATPase activity and serum magnesium were reduced in left handed / right hemispheric dominant individuals. The results showed that HMG CoA reductase activity serum digoxin and dolichol were decreased and serum ubiquinone, RBC membrane sodium-potassium ATPase activity and serum magnesium increased in right handed / left hemispheric dominant individuals. The results showed that the concentration of tryptophan, quinolinic acid, serotonin, strychnine and nicotine was found to be higher in the plasma of left handed / right hemispheric dominant individuals while that of tyrosine, dopamine,

morphine and norepinephrine was lower. The results showed that the concentration of tryptophan, quinolinic acid serotonin, strychnine and nicotine was found to be lower in the plasma of right handed / left hemispheric dominant individuals while that of tyrosine, dopamine, morphine and norepinephrine was higher.

Discussion

Archaeal Digoxin and Membrane Na^+-K^+ ATPase Inhibition in Relation to Rheumatic Fever

The archaeaon steroidelle DXP pathway and the upregulated pentose phosphate pathway contribute to digoxin synthesis. The decrease in the activity of HMG CoA reductase in the acute rheumatic fever patients with recurrent streptococcal infection suggests a downregulation of the isoprenoid pathway. There is a marked decrease in plasma digoxin and dolichol and this decrease may be a consequence of decreased channelling of intermediates of the isoprenoid pathway for their biosynthesis. Studies have shown that digoxin is synthesized by the isoprenoid pathway. The decrease in endogenous digoxin, a potent inhibitor of membrane of Na^+-K^+ ATPase, can increase this enzyme activity. In acute rheumatic fever patients with recurrent streptococcal infection there was significant stimulation of the RBC membrane of Na^+-K^+ ATPase. The stimulation of Na^+-K^+ ATPase by low levels of digoxin is known to cause a decrease in intracellular calcium resulting from decreased Na^+-Ca^{++} exchange, decreased entry of calcium via the voltage gated calcium channel and decreased release of calcium from intracellular endoplasmic reticulum calcium stores. This decrease in intracellular calcium by not displacing magnesium from its binding sites causes an increase in the functional availability of magnesium. This increase in the availability of magnesium can cause increased mitochondrial. ATP formation which along with increased magnesium can cause further

stimulation of Na^+-K^+ ATPase, since ATP-magnesium complex is the actual substrate for this reaction. There is thus a progressive stimulation of Na^+-K^+ ATPase activity. The increased intracellular magnesium related mitochondrial ATP synthesis results in increased calcium extrusion from the cell. High intracellular magnesium and low intracellular calcium consequent to Na^+-K^+ ATPase stimulation appear to be crucial to the pathophysiology of rheumatic fever with recurrent streptococcal infection. The intracellular negative calcium signal and positive magnesium signal can regulate diverse cellular process. Serum magnesium was assessed in rheumatic fever patients with recurrent streptococcal infection and was found to be increased.

Archaeal Digoxin and Immune Dysfunction in Relation to Rheumatic Fever

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. Decreased intracellular calcium consequent to membrane Na^+-K^+ ATPase inhibition in rheumatic fever with recurrent streptococcal infection inactivates the calcium dependent calcineurin signal transduction pathway involved in T-cell activation. This results in decreased secretion of interleukin-3, 4, 5, 6 and TNF alpha (tumour necrosis factor alpha). Low levels of TNF alpha can lead to immunosuppression which could also contribute to increased incidence of rheumatic fever with recurrent streptococcal infection.

Archaeal Digoxin and Regulation of Neurotransmitter Synthesis and Function in Relation to Rheumatic Fever

The archaeaon neurotransminoid shikimic acid pathway contributes to tryptophan and tyrosine synthesis and catabolism generating neurotransmitters and neuroactive alkaloids. The concentration of tryptophan, quinolinic acid and

serotonin was found to be lower in the plasma of patients with rheumatic fever with recurrent streptococcal infection while that of tyrosine, dopamine, morphine and norepinephrine was higher. Thus there is a decrease in tryptophan and its catabolites and an increase in tyrosine and its catabolites in the patient's serum. This could be due to the fact digoxin can regulate neutral amino acid transport system with preferential promotion of tryptophan transport over tyrosine and that digoxin levels are low in patients with rheumatic fever with recurrent streptococcal infection. Quinolinic acid has been implicated in immune activation and low levels of it can lead to immunosuppression. It has been reported that during immunosuppression serotonin is decreased with a corresponding increase in dopamine and noradrenaline and this can contribute to the immunosuppression in rheumatic fever patients with recurrent streptococcal infection. Morphine is also an immunosuppressive alkaloid. The increased level of morphine noted in patients with rheumatic fever patients with recurrent streptococcal infection is significant. The low level of quinolinic acid, serotonin and strychnine can contribute to reduce excitatory glutamatergic transmission as they are all positive modulators of the NMDA receptor. In the presence of hypermagnesemia, the magnesium block on the NMDA receptors is strengthened leading on to reduced NMDA transmission. The decreased presynaptic neuronal calcium can produce reduced cyclic AMP dependent dephosphorylation of synapsins resulting in decreased glutamate release into the synaptic junction and vesicular recyling. Decreased intracellular calcium in the post synaptic neuron can also inhibit the calcium dependent NMDA signal transduction. The plasma membrane glutamate transporter (on the surface of the glial cell and presynaptic neuron) is coupled with a sodium gradient which is activated by the stimulation of Na^+-K^+ ATPase, resulting in increased clearance of glutamate by presynaptic and glial uptake at the end of synaptic transmission. By these mechanisms, stimulation of Na^+-K^+ ATPase can inhibit glutamatergic

transmission. The increase in membrane Na^+-K^+ ATPase activity in rheumatic fever patients with recurrent streptococcal infection could be due to the fact that the hyperpolarising neurotransmitters (dopamine, morphine and noradrenaline) are increased and the depolarising neuroactive compounds (serotonin, strychnine, nicotine, quinolinic acid and glutamate) are decreased. Decreased serotonin can lead to depression and obsessive disorder. Such a psychopathology can lead to rheumatic fever with recurrent streptococcal infection. In obsessive compulsive disorder recurrent streptococcal infections are common. Both these movement disorders have been related to hyperdoparninergic transmission in basal ganglia and dopamine receptor supersensitivity.

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

The archaeaon glycosaminoglycoid and fructosoid contributes to glycoconjugate synthesis and catabolism by the process of fructolysis. The membrane Na^+-K^+ ATPase stimulation related increased the intracellular magnesium level in rheumatic fever patients with recurrent streptococcal infection can affect the metabolism of glycosaminoglycans, glycoproteins and glycolipids. The decrease in the level of dolichol may suggest its decreased availability for N-glycosylation of proteins. Magnesium excess can lead to increased catabolism of sphinganine leading to decreased cerebroside and ganglioside synthesis. In magnesium excess the glycolysis, citric acid cycle and oxidative phosphorylation are activated and less of glucose 6-phosphate is channelled for the synthesis of glycosaminoglycans (GAG). The results show a decrease in the concentration of serum total GAG, glycolipids (ganglioside, glycosyl-diglyceride, cerebrosides and sulphatides) and carbohydrate components of glycoproteins (hexose, fucose and sialic acid) in rheumatic fever patients with recurrent streptococcal infection. The individual GAG fractions in the serum heparan sulphate (HS), chondroitin

sulphates (ChS), heparin (H), hyaluronic acid (HA) and dermatan sulphate (DS) are decreased. The activity of GAG degrading enzymes (beta glucuronidase, beta N-acetyl hexosaminidase, hyaluronidase and cathepsin-D) and that of glycohydrolases (beta galactosidase, beta fucosidase and beta glucosidase) showed a significant decrease in the serum in rheumatic fever patients with recurrent streptococcal infection. Intracellular magnesium excess also results in increased ubiquitin dependent proteolytic processing of glycoconjugates as it requires magnesium for its infections have been described. Increased dopamine can lead to chorea and tic syndrome associated with recurrent streptococcal function. The decrease in the activity of glycohydrolases and GAG degrading enzymes could be due to increased lysosomal stability.

The altered glycoconjugates of the heart valves can make them prone to damage in rheumatic fever. There is a similarity between specific carbohydrate antigens of group A streptococcus and the glycoproteins of the heart valve. This similarity is probably accentuated by reduced N-glycosylation of valve proteins consequent to reduced dolichol levels. The protein processing defect can result in defective glycosylation of exogenous bacterial glycoprotein antigens with consequent defective formation of MHC class-1 bacterial glycoprotein antigen complex. This results in defective transport of MHC class-1 bacterial glycoprotein antigen complex to the antigen presenting cell surface for recognition by CD_4 or CD_8 cell. Defective presentation of exogenous bacterial antigens can produce immune evasion by the bacteria and its persistence. The reduction in the synthesis of glycoconjugates can impair the integrity of the mucosal barrier in the respiratory system leading to rheumatic fever with recurrent streptococcal infection. The increased lysosomal stability also impairs the defence against the invading bacteria / virus. Phagocytosis by macrophages requires the activity of lysosomal enzymes. The increased stability of the lysosomes in patients with hypodigoxinemic state leading on to rheumatic fever

with recurrent streptococcal infection inhibits the pathogocytic lysosomes mediated killing of bacteria / virus. The decrease in fucoligands and sialoligands can also contribute to immunosuppression and streptococcal infection.

Archaeal Digoxin and Alteration in Membrane Structure and Membrane Formation in Relation to Rheumatic Fever

The archaeaon steroidelle, glycosaminoglycoid and fructosoid contribute to cell membrane formation synthesizing cholesterol by the DXP pathway and glycosaminoglycans by fructolysis. The downregulation of the isoprenoid pathway in rheumatic fever patients with recurrent decrease can lead to decreased cholesterol synthesis and magnesium excess can stimulate phospholipid synthesis. Phospholipid degradation is inhibited by a decrease in intracellular calcium inhibiting phospholipase A_2 and D. The cholesterol: phospholipid ratio of the RBC membrane was decreased in rheumatic fever patients with recurrent streptococcal infection. The concentration of total GAG, hexose and fucose content of glycoprotein increased in the RBC membrane and decreased in the serum suggesting their increased incorporation into the membrane and defective membrane formation. This is due to intracellular hypermagnesemia upregulating the trafficking of membrane components. The change in membrane structure produced by alteration in glycoconjugates and cholesterol: phospholipid ratio can produce changes in the conformation of Na^+-K^+ ATPase resulting in farther membrane Na^+-K^+ ATPase stimulation. The same changes can affect the structure of organelle membrane. This results in increased lysosomal stability. The alteration in the mucosal cell membranes can also increase the risk of penetration by bacteria and virus by eroding the mucosal barrier.

Archaeal Digoxin and Mitochondrial Dysfunction in Relation to Rheumatic Fever

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 increased significantly in rheumatic fever patients with recurrent streptococcal infection which may be the result of increased tyrosine levels, consequent to digoxin deficiency promoting tyrosine transport over tryptophan. The decrease in intracellular calcium can stabilise the mitochondrial PT pore and improve mitochondrial function. Intracellular magnesium excess can lead to an increase in the activity of ATP synthase. All this leads to improved efficiency of mitochondrial oxidative phosphorylation and reduced free radical generation. Ubiquinone excess also leads to increased free radical scavenging. Intracellular magnesium excess due to membrane Na^+-K^+ ATPase stimulation leads to decrease in defence against an invading bacteria / virus. The decrease in intracellular calcium may lead to decreased generation of NO by inhibiting the enzyme nitric oxide synthase and reduced peroxynitrite formation. Decreased calcium also can inhibit phospholipase A_2 resulting in decreased generation of arachidonic and free radical formation. Decreased generation of free radicals like the superoxide ion and hydroxyl radical can stabilise the cell membrane and stimulate membrane Na^+-K^+ ATPase. There was decrease in lipid peroxidation as evidenced from the decrease in the concentration of MDA, conjugated dienes, hydroperoxides and NO with increased antioxidant protection as indicated by an increase in ubiquinone and increased reduced glutathione levels. The activity of enzymes involved in free radical scavenging like superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase is increased in rheumatic fever patients with recurrent streptococcal infection suggesting increased free radical

scavenging. The peroxisomal membrane is stablised owing to membrane Na^+-K^+ ATPase stimulation related alteration in membrane formation and leads to increased catalase activity. Glutathione is synthesized by the enzyme glutathione synthetase which needs magnesium and ATP. The high intracellular magnesium consequent to Na^+-K^+ ATPase stimulation and the resulting increased ATP can result in increased synthesis of glutathione. Glutathione peroxidase, a selenium containing enzyme oxidises reduced glutathione (GSH) to oxidised glutathione (GSSG) which is then rapidly reduced to GSH by glutathione reductase. There is also a concomitant conversion of H_2O_2 to H_2O. The activity of glutathione reductase needs NADPH for the increased formation of glucose 6-phosphate and upregulation of the pentose phosphate pathway with a consequent increased generation of NADPH. Thus the glutathione system of free radical scavenging is activated in the presence of membrane Na^+-K^+ ATPase stimulation. The stabilisation of the mitochondrial PT pore consequent to reduced intracellular calcium produces increased efficiency of superoxide dismutase activity. Decreased free radical production could contribute to increased incidence of rheumatic fever with recurrent streptococcal infection. Phagocytic killing of bacteria / virus are mediated by free radicals in the phagosomes. Reduced free radical production will grossly impair phagocytic function leading on to rheumatic fever patients with recurrent streptococcal infection.

Archaeal Digoxin and Hemispheric Dominance in Relation to Rheumatic Fever

The archaeaon related organelle - steroidelle, neurotransminoid and vitaminocyte contribute to hemispheric dominance. Thus the immune mechanisms and the response to an invading bacteria / virus differ in the hypo and hyperdigoxinemic state. The hypodigoxinemic state is associated with immunosuppression and rheumatic fever with recurrent streptococcal infection.

Hypodigoxinemia is related to left hemispheric dominance and hyperdigoxinemia with right hemispheric dominance. Recurrent transient respiratory infection and immunosuppression is associated with left hemispheric dominance and hypodigoxinemia. Geschwind has postulated a relationship between cerebral lateralization and immune function. Hypothalamic archaeal digoxin and hemispheric dominance may thus regulate immune function.

References

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