4

Archaeal Digoxin Mediated Model for Rheumatoid Arthritis

Introduction

The cause of rheumatoid arthritis (RA) remains unknown. It has been suggested that RA might be a manifestation of the response to an infectious agent in a genetically susceptible host. A number of possible causative agents have been suggested including mycoplasma, ebstein barr virus, cytomegalovirus, parvo virus and rubella virus. One possibility is that there is persistent infection of articular structures or retention of microbial products in the synovial tissue which generates a chronic inflammatory response. Rheumatoid arthritis presents with a characteristic constellation of features-which include hyperplasia and hypertrophy of the synovial lining cells; focal and segmental vascular changes, including thrombosis, microvascular injury and neovascularisation, edema and infiltration with mononuclear cells which aggregates around small blood vessels. The predominant infiltrating cell is the T-lymphocyte. CD_4+ T-cells predominate over CD_8+ T-cells and are frequently found in close proximity to HLA-DR+ macrophages and dendritic cells. These cells produce both polyclonal immunoglobulin and the autoantibody rheumatoid factor that results in the formation of immune complexes. The rheumatoid factor is antoantibodies reactive with the Fc portion of IgG. Cytokines and chemokines derived from T-lymphocytes such as interleukin-2, interferon gamma, IL-6, IL-10, granulocyte-macrophage colony stimulating factor, tumour necrosis factor alpha and TGF-beta play, a role in immunopathology of rheumatoid arthritis. The vascular granulation tissue produces IL-1 and TNF alpha that play a role in stimulating the pannus cells to produce degradative enzymes including collagenase, neutral proteases and stromelysin which facilitate tissue damage. The same two cytokines stimulate the chondrocyte to produce proteolytic enzymes that degrade cartilage locally. The earliest event appears to be a non-specific inflammatory response against the unknown stimulus which leads

to T-cell activation and a subsequent B-cell activation and proliferation. As tissue damage occurs additional autoantigens are revealed resulting in nonspecific T-cell activation. Finally as a result of persistent exposure to the inflammatory milieu the function of the synovial fibroblast is altered and acquires a destructive potential which no longer requires stimulation from T-cells of macrophages. Geschwind has postulated a relationship between cerebral lateralization and immune function. For example, they observed a higher frequency of left-handedness in patients with some immune disorders. There are no reports on the role of hemispheric dominance in the pathogenesis of rheumatoid arthritis.

The archaea produces an endogenous membrane Na^+-K^+ ATPase inhibitor, digoxin which is a steroidal glycoside. Digoxin is synthesized by the isoprenoid pathway. Increased level of digoxin has been documented in immune diseases like Kawasaki's disease. A viral infective theory for Kawasaki's disease has been postulated by several groups of workers. Membrane Na^+-K^+ ATPase inhibition leads to immune stimulation and increased in CD_4/CD_8 ratios as exemplified by the action of lithium. Digoxin can also modulate amino acid and neurotransmitter transport and regulated synaptic transmission, Saito has reported increased activities of the tryptophan catabolic kynurenine pathway in various tissues following systemic immune stimulation, in conjunction with macrophage infiltration of the affected tissues. These results suggest that kynurenine metabolites may have some connection with immune response. Previous reports have demonstrated induction of indoleamine 2,3 dioxygenase and increased production of quinolinic acid in immune complex disease like systemic lupus mediated by interferons. The isoprenoid pathway produces two other metabolites - ubiquinone and dolichol important in cellular metabolism. Ubiquinone functions as a free radical scavenger and dolichol is important in N-glycosylation of proteins. Free radicals are involved in immune activation.

Digoxin being a modulator of synaptic transmission could play a role in hemispheric dominance.

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.

It was therefore considered pertinent to study digoxin status and digoxin synthesis in rheumatoid arthritis. The glycoconjugate, free radical metabolism and RBC membrane composition were also studied. The patterns were also studied in individuals with differing hemispheric dominance for comparison with those in rheumatoid arthritis. The results are presented in this paper.

Results

(1) The results showed that HMG CoA reductase activity, serum digoxin and dolichol were increased in rheumatoid arthritis indicating upregulation of the isoprenoid pathway but serum ubiquinone was reduced.

(2) The results showed that the concentration of tryptophan, quinolinic acid, serotonin, strychnine and nicotine was found to be higher in the plasma of patients with rheumatoid arthritis while that of tyrosine, dopamine, norepinephrine and morphine was lower.

(3) There was an increase in lipid peroxidation as evidenced from the increase in the concentration of MDA, conjugated dienes, hydroperoxides and NO with decreased antioxidant protection as indicated by a decrease in ubiquinone and reduced glutathione in rheumatoid arthritis. The activity of enzymes involved in free radical scavenging like superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase and catalase is decreased in rheumatoid arthritis suggesting reduced free radical scavenging.

(4) The results show an increase in the concentration of the serum total and individual GAG fractions, glycolipids and carbohydrate components of glycoproteins in rheumatoid arthritis. The activity of GAG degrading enzymes and that of glycohydrolases showed significant increase in the serum rheumatoid arthritis.

(5) The cholesterol phospholipid ratio of the RBC membrane was increased in rheumatoid arthritis. The concentration of total GAG, hexose and fucose content of glycoprotein decreased in the RBC membrane and increased in the serum in rheumatoid arthritis.

(6) 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 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 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 Rheumatoid Arthritis

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 in rheumatoid arthritis. There was increased synthesis of digoxin as evidenced by increased HMG CoA reductase activity. The inhibition of Na^+-K^+ ATPase by digoxin is known to cause an increase in intracellular calcium resulting from increased Na^+-Ca^{++} exchange, which displaces magnesium from its binding site and causes a decrease in the functional availability of magnesium. This decrease in the availability of magnesium can cause decreased mitochondrial ATP formation which along with low magnesium can cause further progressive inhibition of Na^+-K^+ ATPase, since ATP-magnesium complex is the actual substrate for this reaction. Low intracellular magnesium and high intracellular calcium consequent to Na^+-K^+ ATPase inhibition appear to be crucial to the pathophysiology of rheumatoid arthritis.

Archaeal Digoxin and Immune Activation in Rheumatoid Arthritis

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. In rheumatoid arthritis increased intracellular calcium consequent to membrane Na^+-K^+ ATPase inhibition activates the calcium dependent calcineurin signal transduction pathway, which can produce T-cell activation and secretion of interleukin-2, 6, 10 and TNF alpha. This immune activation can contribute to the genesis of rheumatoid arthritis.

Archaeal Digoxin and Regulation of Neurotransmitter Synthesis and Function in Relation to Rheumatoid Arthritis

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 rheumatoid arthritis. 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. In the presence of hypomagnesemia, the magnesium block on the NMDA receptor is removed leading to NMDA excitotoxicity. The elevated levels of quinolinic acid, strychnine and serotonin can also contribute to NMDA excitotoxicity as they are positive modulators of the NMDA receptor. NMDA excitotoxic mechanisms have been postulated to contribute to immune activation in immune complex disorders and could possibly due the same in rheumatoid arthritis. Quinolinic acid has been implicated in immune activation in autoimmune diseases like SLE. Gamma interferons important in mediating immune injury in rheumatoid arthritis and SLE act by promoting tryptophan catabolism along the kynurenine pathway. Increased amounts of quinolinic acid

suggest increased activity of gamma interferons. Serotonin, dopamine and noradrenaline receptors have been demonstrated in the lymphocytes. It has been reported that during immune activation serotonin is increased with a corresponding reduction in dopamine and noradrenaline and this can contribute to the immune activation in rheumatoid arthritis. The schizoid neurotransmitter pattern of reduced dopamine, noradrenaline and morphine and increased serotonin, strychnine and nicotine is common to schizophrenia and rheumatoid arthritis and could predispose to its development. A schizoid type of personality could predispose to the development of rheumatoid arthritis.

Archaeal Digoxin and Regulation of Golgi Body / Lysosomal Function in Relation to Rheumatoid Arthritis

The archaeaon glycosaminoglycoid and fructosoid contributes to glycoconjugate synthesis and catabolism by the process of fructolysis. The elevation in the level of dolichol in rheumatoid arthritis may suggest its increased availability for N-glycosylation of proteins. Magnesium deficiency can lead to increased glycolipid and glycosaminoglycan synthesis. 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 inspite of increased activity of many glycohydrolases may be due to their possible resistance to cleavage by glycohydrolases / GAG degrading enzymes consequent to qualitative change in their structure. The protein processing defect can result in defective glycosylation of endogenous synovial glycoprotein antigens and exogenous viral glycoprotein antigens with consequent defective formation of

MHC-antigen complex. The MHC linked peptide transporter, a P-glycoprotein which transports MHC-antigen complex to the antigen presenting cell surface, has an ATP binding site. The peptide transporter is dysfunctional in the presence of magnesium deficiency. This results in defective transport of MHC class-1 synovial glycoprotein antigen complex to the antigen presenting cell surface for recognition by CD4 or CD cell. Defective presentation of the endogenous synovial / viral glycoprotein antigen can explain the immune dysregulation and autoimmunity in rheumatoid arthritis. This can also explain the autoantibodies developed against Fc portion of IgG as this glycoprotein is also altered consequent to the protein processing defect. Defective presentation of exogenous viral antigens can produce immune evasion by the virus. Viral and bacterial persistence has been implicated in the development of rheumatoid arthritis. A number of fucose and sialic acid containing natural ligands are involved in trafficking of leukocytes and similar breaches in the blood brain barrier and resultant adhesion and trafficking of the lymphocyte and extravasation in to the perivascular space have been described in rheumatoid arthritis.

Archaeal Digoxin and Alteration in Membrane Structure and Membrane Formation in Relation to Rheumatoid Arthritis

The archaeaon steroidelle, glycosaminoglycoid and fructosoid contribute to cell membrane formation synthesizing cholesterol by the DXP pathway and glycosaminoglycans by fructolysis. The upregulation of the isoprenoid pathway can lead to increased cholesterol synthesis and magnesium deficiency can inhibit phospholipid synthesis in rheumatoid arthritis. Phospholipid degradation is increased owing to increase in intracellular calcium activating phospholipase A_2 and D. The cholesterol: phospholipid ratio of the RBC membrane was increased in rheumatoid arthritis. The concentration of total GAG, hexose and fucose of glycoprotein decreased in the RBC membrane and increased in the

serum suggesting their reduced incorporation into the membrane and defective membrane formation. This trafficking of the glycoconjugates and lipids which are synthesized in the endoplasmic reticulum - golgi complex to the cell membrane depends upon GTPases and lipid kinases which are crucially dependent on magnesium and are defective in magnesium deficiency. The change in membrane structure produced by alteration in glycoconjugates and cholesterol: phospholipid ratio can produce changes in the conformation of Na^+-K^+ ATPase resulting in further membrane Na^+-K^+ ATPase inhibition. The same changes can affect the structure of lysosomal membrane. The results in defective lysosomal stability and leakage of glycohydrolases and GAG degrading enzymes into the serum. Increased lysosomal release of neutral proteases and collagenase by the pannus cell and chondrocyte can contribute to tissue destruction in rheumatoid arthritis.

Archaeal Digoxin and Mitochondrial Dysfunction in Relation to Rheumatoid Arthritis

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 rheumatoid arthritis, which may be the result of low tyrosine levels, reported in most of the disorders, 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 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 this leads to defects in mitochondrial oxidative phosphorylation, incomplete reduction of oxygen and generation of superoxide which produces lipid peroxidation. Ubiquinone deficiency also leads to reduced free radical scavenging. The increase in intracellular calcium may lead to increased generation of NO by inducing the enzyme nitric oxide synthase which combines with superoxide radical to form peroxynitrite. Increased intracellular calcium can also 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. Magnesium deficiency can affect glutathione synthetase and glutathione reductase function. The mitochondrial superoxide dismutase leaks out and becomes dysfunctional with calcium related opening of the mitochondrial PT pore and outer membrane rupture. The peroxisomal membrane is defective owing to membrane Na^+-K^+ ATPase inhibition related defect in membrane formation and leads to reduced catalase activity. Mitochondrial dysfunction related free radical generation has been implicated in the pathogenesis of immune mediated diseases like rheumatoid arthritis. Free radicals have been implicated in immune activation.

Archaeal Digoxin and Hemispheric Dominance in Relation to Rheumatoid Arthritis

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 hyperdigoxinemic state. The hyperdigoxinemic state is associated with immuno

activation and viral persistence. There is an increased tendency for autoimmune diseases like rheumatoid arthritis in the hyperdigoxinemic state. The patterns in rheumatoid arthritis correlated with those obtained in right hemispheric dominance. In right hemispheric dominant individuals there is an upregulated isoprenoid pathway, increased digoxin synthesis and increased tryptophan catabolites over tyrosine. In left hemispheric dominant individuals there is a downregulated isoprenoid pathway, reduced digoxin synthesis and increased tyrosine catabolites over tryptophan. This correlates with previous reports on the relationship between left handedness and immune mediated disorders. Hemispheric dominance arid hypothalamic archaeal digoxin may play an important role in the pathogenesis of rheumatoid arthritis.

References

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